# MCRA Documentation

***Release 10***

**Biometris, Wageningen University and Research**

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# USER GUIDE


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# Part I

# User Guide

CHAPTER

ONE

# INTRODUCTION TO MCRA

Humans are exposed to a mixture of multiple chemicals via food intake, inhalation and dermal contact. The risk to health that may result from this depends on the effects of different chemicals in the mixture and how they combine.

MCRA is the model and data toolbox developed in the EuroMix project. It implements methods for exposure, hazard and risk assessment, following guidelines from a.o. the Joint Research Centre (JRC) of the European Commission and the European Food Safety Authority (EFSA). The toolbox should provide computational tools for future risk management decisions on the safety of chemicals in mixtures to be taken by the European Commission and the Codex Alimentarius.

MCRA is a collection of data and models. The system consists of modules that are arranged in eight categories according to a *modular design*. See *Modules overview*.

Each module represents a certain type of data, which can be computed from data provided by other (sub)modules, or the data may be obtained from a dataset selected from the *data repository*. Likewise, each module may be of interest by its own merit, or may just be required as a sub-part of larger calculations. The modular design of MCRA reveals a network of data and models, and shows how data of types and from various sources can be combined in overarching modules. The most overarching module is *Risks or health impact estimates*. The toolbox allows the user to start in any of the modules in the modular design for performing calculations.

For each module, an *action* can be created to configure and run the module. For data modules, such as the *concentrations module*, such an action comprises specifying the dataset, specifying the scope (i.e., *foods* of interest, *substances* of interest, etc.), and perhaps specifying specific selections or model settings for data manipulations (e.g., *imputation of water concentrations* in the concentrations module). For calculation modules, when calculating the data of the module based on other data, configuration of an action comprises specification of the model settings and selection of the calculation inputs, which is data provided by other (sub-)modules. While running an action in MCRA, the module produces output of its associated data type (which can be used as input for other modules), and a report will be generated of the selected data, the selection and model settings, and the module and all intermediate (i.e., sub-modules) results.

## 1.1 User interface

This section describes the user interface of the MCRA Web Application.

The following sections give an overview of the general functionality of MCRA, broken down into subjects.

### 1.1.1 Welcome page

The MCRA welcome page contains general information on MCRA, links to the documentation and login and registration functionality.

In the top right corner the ‘person’ dropdown menu is expanded and contains the ‘Log in’ and ‘Register’ menu items. At the bottom of the page the current version of MCRA is shown.

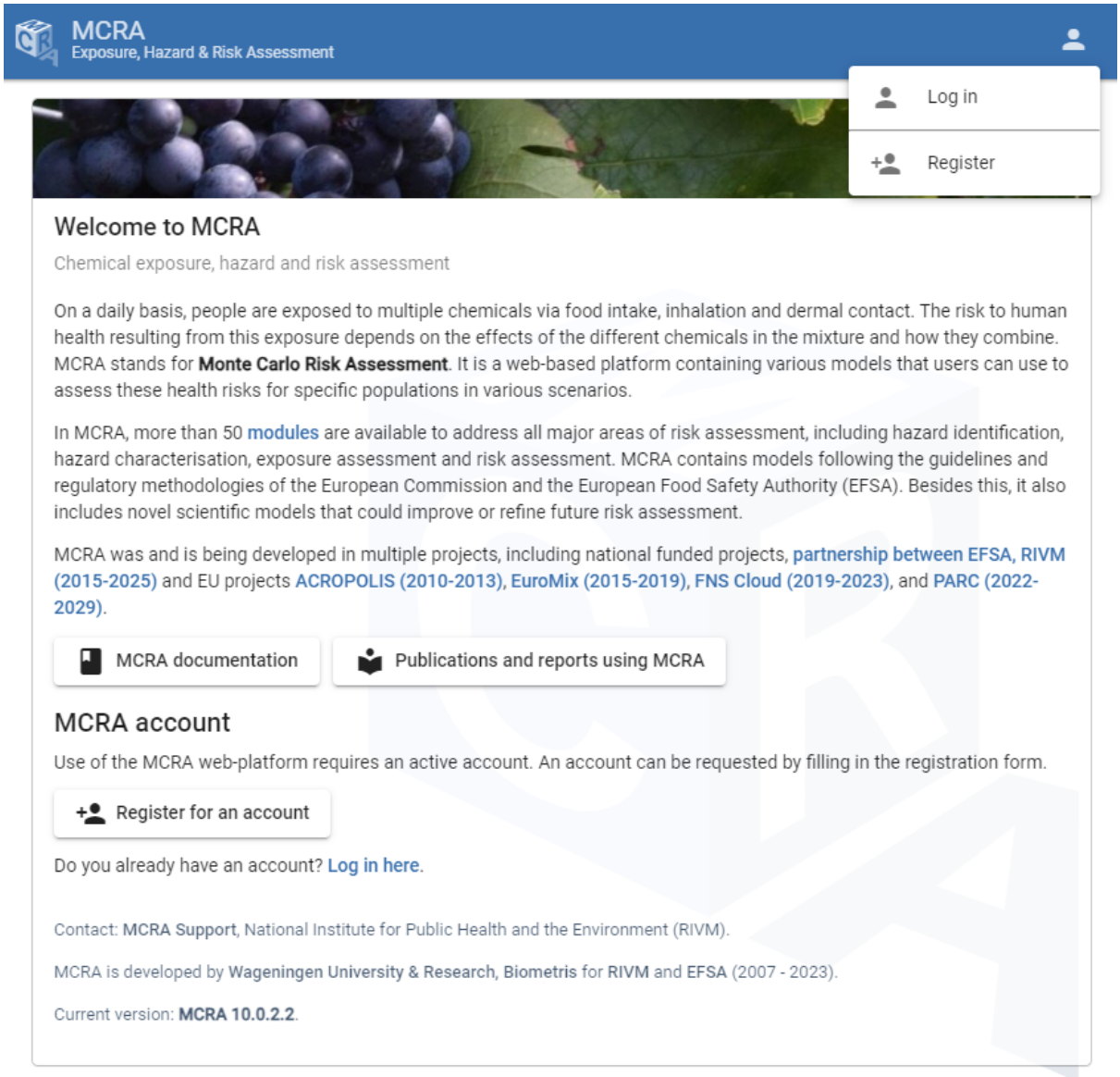


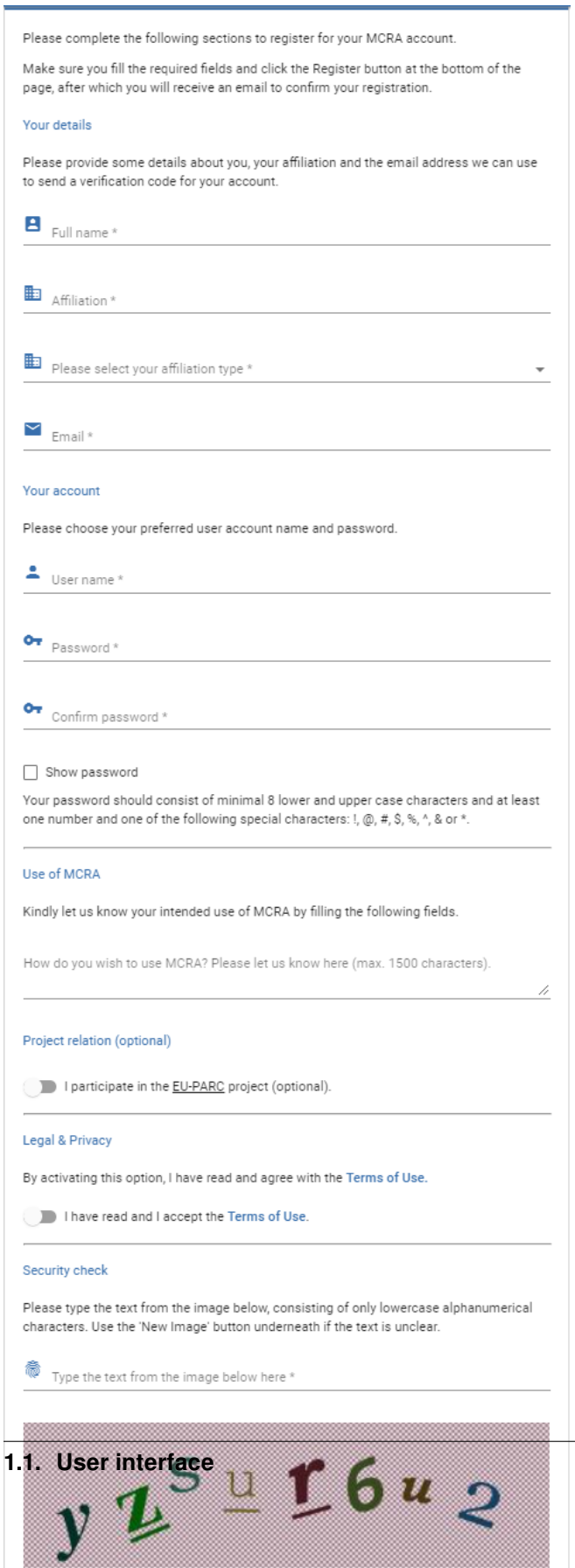

Figure 1.1: MCRA welcome screen

### 1.1.2 Registering

If you don't have an MCRA account, the registration procedure is as follows.

In the MCRA welcome screen, click on the 'Register for an account' button, which opens the following screen.

The screen consists of a number of sections which contains several required and optional items to complete before the register button is activated at the bottom of the input form (you need to scroll down on the page to see all options).




The following fields are required:

- Full name: your full name
- Affiliation: please provide the organisation you are affiliated with
- Affiliation type: select an option from the drop-down list to specify the type of your organisation
- Email: please provide a valid email address, if you use your email address as your user name, please repeat it here
- User name: choose a user name to use to log in to MCRA, you may use your email address also. The user name cannot contain spaces - only upper and lower case letters, numbers, or the characters @ (at), - (dash), . (dot) or _ (underscore) are allowed with a length between 8 and 50 characters.
- Password: provide a secure password, it should consist of minimal 8 lower and upper case characters and at least one number and one of the following special characters: !, @, #, $, %, ^, & or *.

You can type a short message on how you wish to use MCRA in the text field under 'Use of MCRA'

Optionally you can specify whether you want to use MCRA specifically for the EU-PARC project.

You are required to accept MCRA's Terms of Use to be able to register.

For security reasons, please type the characters that show up in the image at the bottom of the page, which consists of all lowercase letters and digits.

Clicking the 'Register' button submits the filled form to MCRA. You will receive an email at the email address you provided, containing a link to confirm your registration. This will verify your email account and confirm your registration request. The screen will show a verification message, as shown below.

Your registration request still needs to be approved by RIVM. You will receive another email when your account has been approved, after which you can log in to MCRA with your new account.

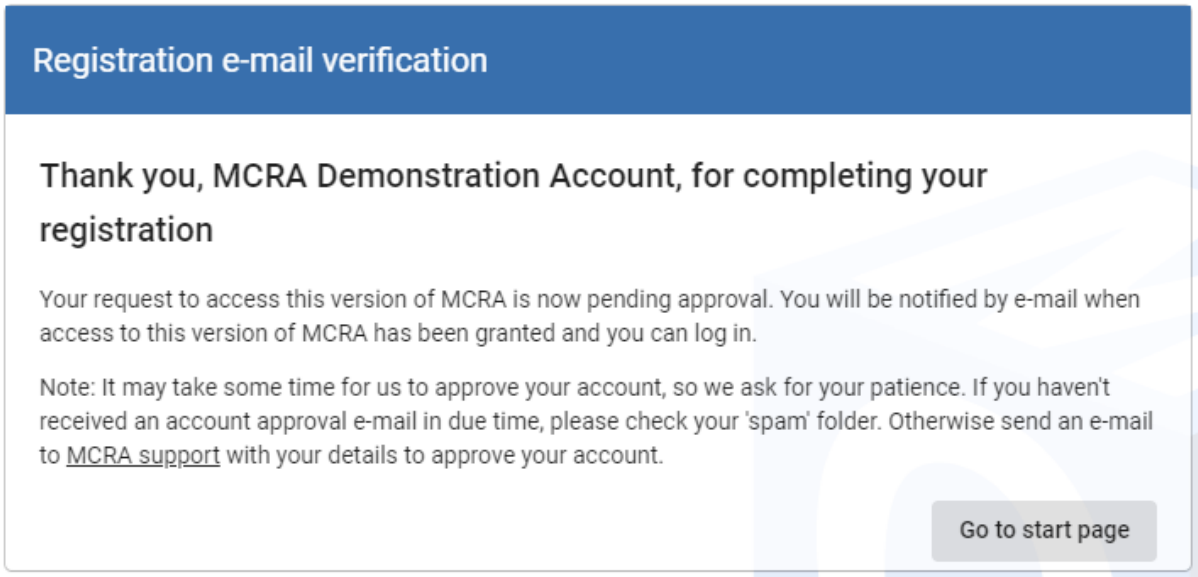



Figure 1.3: MCRA registration request has been verified

### 1.1.3 Logging in

MCRA requires logging in with a valid user account and a password. In addition, two-factor authentication is required for the MCRA production environment on RIVM.

After you enter your name and correct password and click on 'Login', you will need to enter a 6-digit security code which is required for two-factor authentication. You will receive this security code using a so-called authenticator app on a (mobile) device.

#### Setting up two-factor authentication

If you log in for the first time and/or have not set up two-factor authentication for your account, you are presented with the following screen.

Setting up two-factor authentication for your account consists of the following steps:

- Install an authenticator app on your device, to do so use one of the links on the page to install the desired app on your device. See the next paragraph for a list of commonly used apps.
- Request the authenticator QR code for your account. You will receive an email containing the personal QR code which is needed to register your MCRA account in the authenticator app. Once this is done, your authenticator app will show a 6-digit number you need to log in to MCRA.

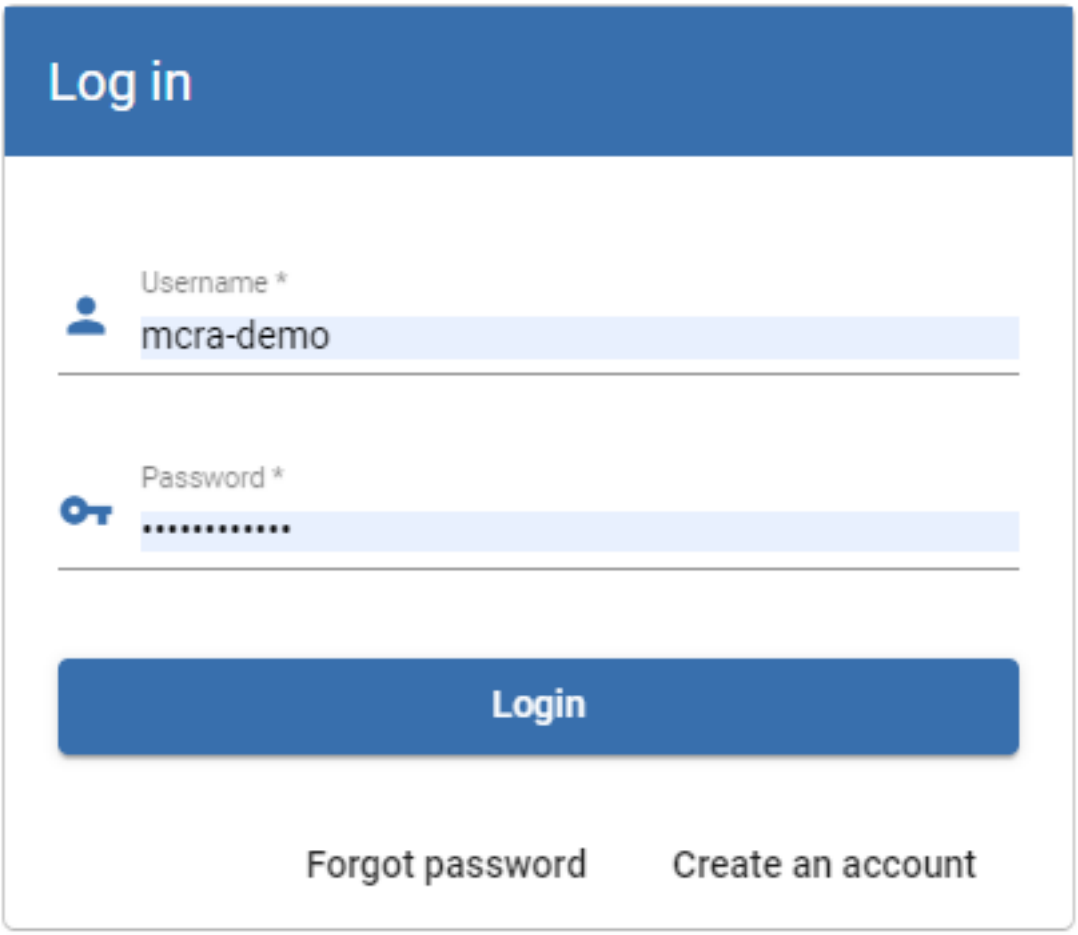



Figure 1.4: The MCRA login dialog

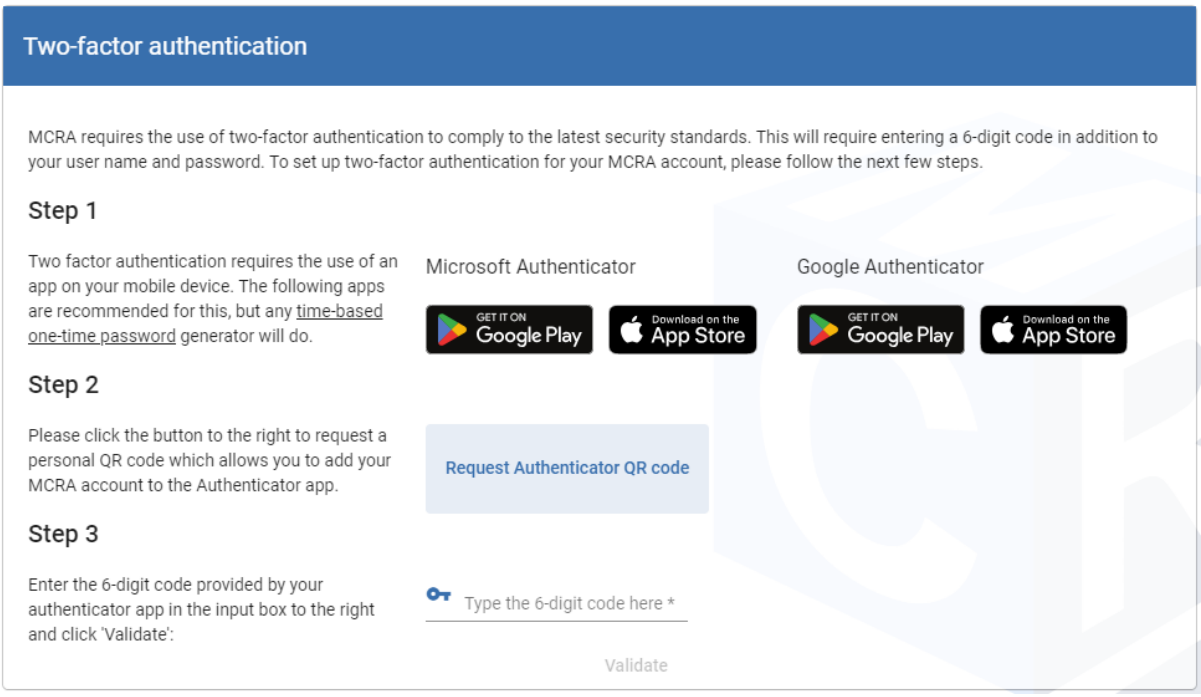



Figure 1.5: Set up two-factor authentication

#### Authenticator apps

Two factor authentication requires the use of an app on your (mobile) device. The following authenticator apps are commonly used to log in to systems which require two-factor authentication.

Use one of the links below to navigate to the website where you can install the app of your choice. Note that there are many other apps offering time-based one-time password authentication, simply search for two-factor (2FA) apps in your favourite search engine.

#### Google Authenticator

#### Microsoft Authenticator

#### Windows app: 2Fast Authenticator

#### Request an authenticator QR code

When you request the authenticator QR code, the following screen appears:

Here you need to type your password and a verification code. Click the 'Send' button to finish the request. You will receive an email containing your personal QR code

The image above shows an example of a QR code email. The Authenticator app allows you to add an account and scan the QR code. Alternatively, a readable code is also given as a way to add the account to your authenticator app.

After the authenticator has been set up correctly, you can return to the MCRA login screen and log in using your user name and password, and continue to enter the 6-digit code you get from your authenticator app to access MCRA.

If you should somehow lose your QR code, you can always request to send it to your email address using the 'I lost my authenticator code' button on the two-factor authentication page.

### 1.1.4 Main user interface

The MCRA main page contains general information on MCRA, links to the data, workspaces and documentation.

## 1.2 Data and calculation model

### 1.2.1 Modular design

The modular design distinguishes between three types of modules: primary entity modules, data modules, and calculation modules. For an overview see *Modules*.

- The primary entity modules are data modules determining the scope of the assessments in MCRA. That is, in each assessment, the scope specifies the *foods*, *substances*, *effects*, *populations*, *responses*, and/or *test systems* that are of interest.
- The data modules give summaries of the available data which depend on (some of) the primary entities. For example *consumptions* data.

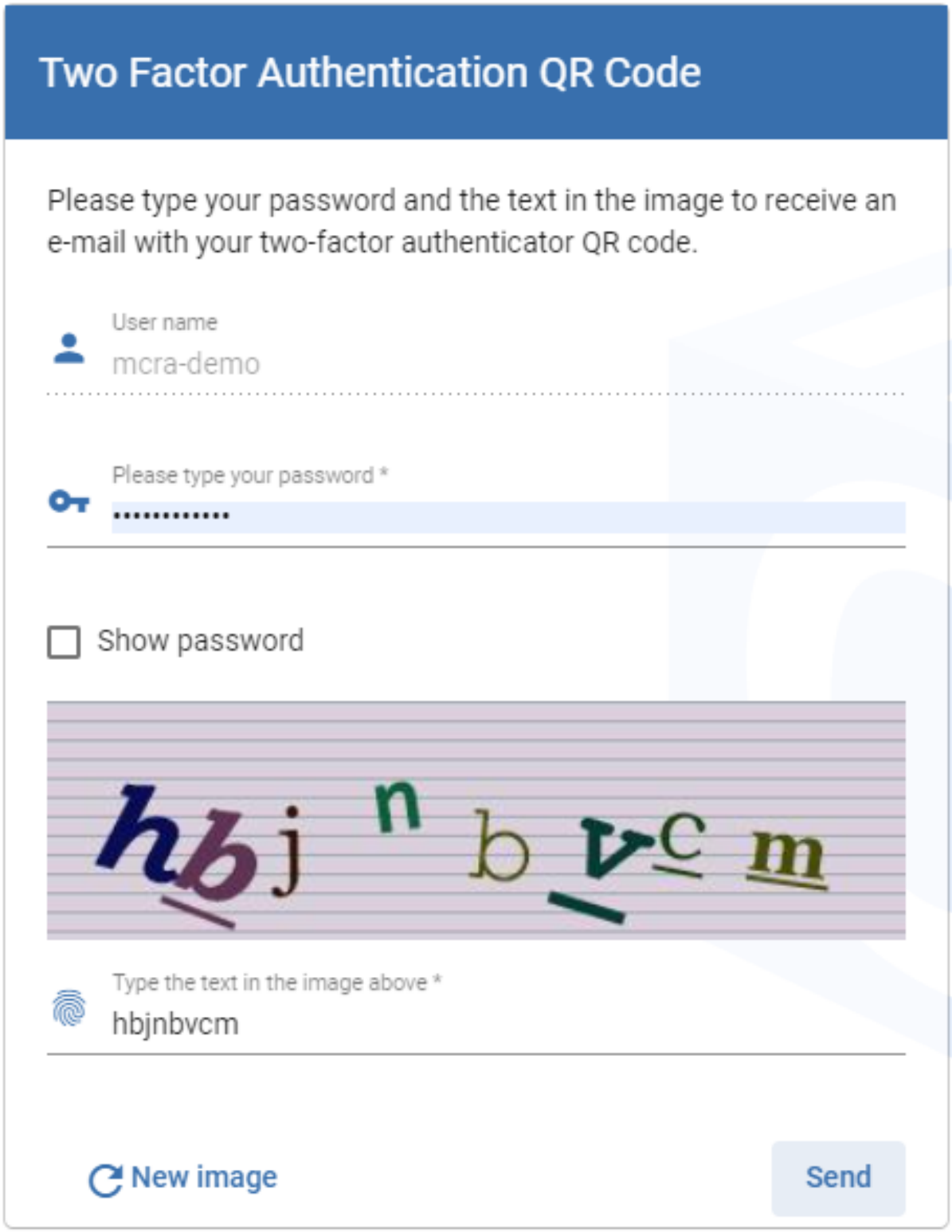



Figure 1.6: Request your personal two-factor QR code

**From:** No-Reply mcra-test <noreply.mcra-test@wur.nl>
**Sent:** donderdag 2 november 2023 10:46
**To:**
**Subject:** MCRA - Authenticator QR Code

**Your MCRA two-factor authenticator QR code**

You requested the Authenticator QR code for account **mcra-demo** (MCRA Demonstration Account)

Using your Authenticator app, please scan the following QR code to add 'MCRA':

Alternatively, you may enter the following code into your Authenticator app:

DEMODEMODEMO123456789DEMODEMODEMO

Figure 1.7: QR code email example

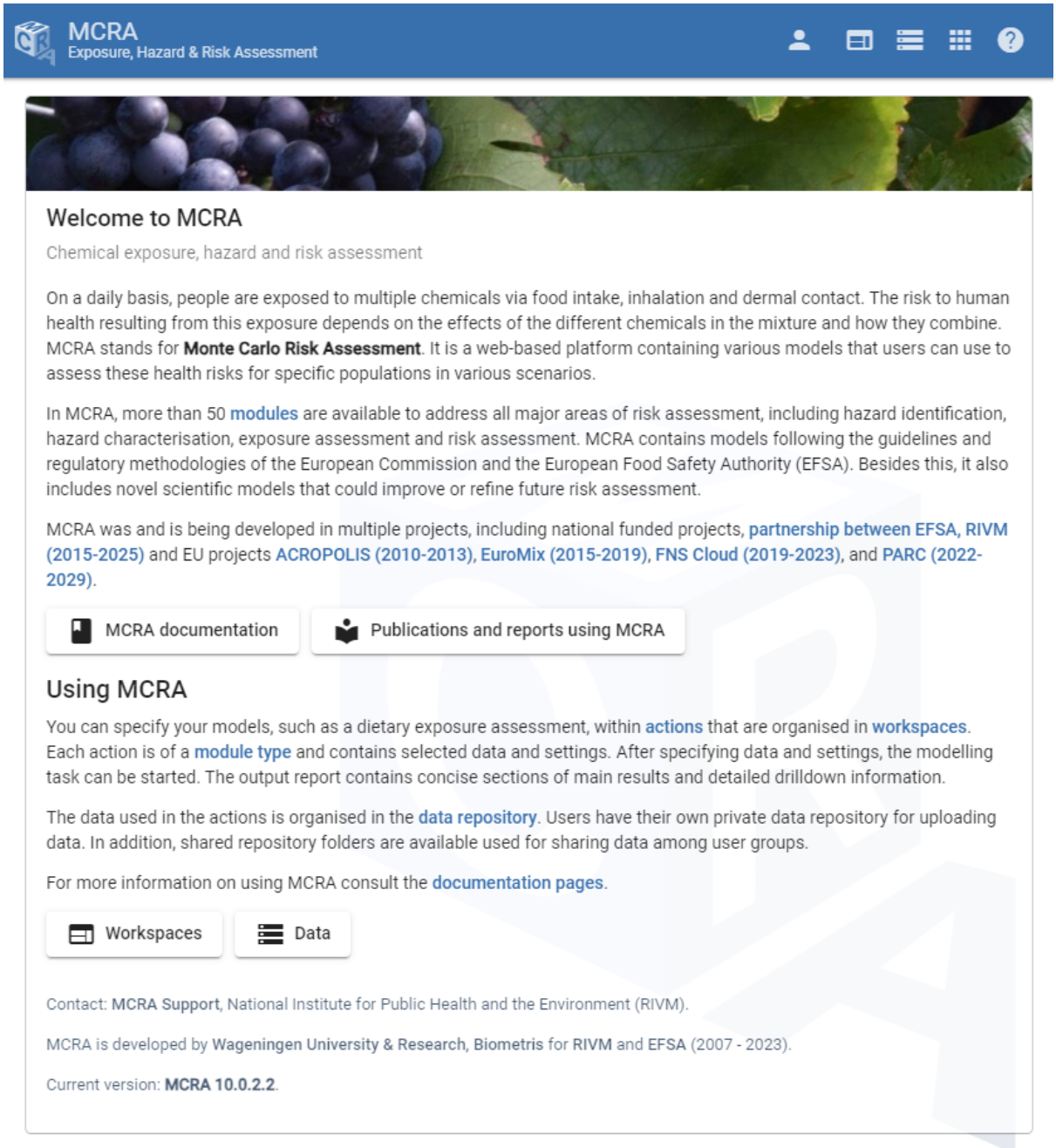



Figure 1.8: MCRA main user interface

- The calculation modules perform calculations on input data to produce data on another type, as specified by the module name. E.g. the *dietary-exposures* calculation module calculates dietary exposures from consumption and occurrence data. Some calculation modules can also act as a data module, in which case the data are directly specified rather than calculated. Examples are, the *relative potency factors* module: relative potency factors can be supplied as such (*Data*) or computed based on *hazard characterisations* (*Compute*); the *single value consumptions* module: Large Portions can be supplied as such (*Data*) or computed based on consumption distribution data of a population (*Compute*).

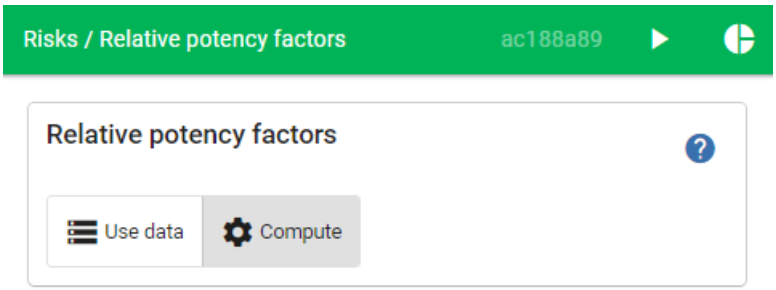



Figure 1.9: Relative potency factors supplied as data or computed based on hazard characterisations.

### 1.2.2 Nominal run and uncertainty analysis

Within MCRA two types of simulation runs are distinguished: the nominal run and the uncertainty analysis loop.

The nominal run represents a single simulation which is aimed to compute the most likely, unbiased estimates for the specified model. E.g., when a *dietary exposure assessment* is requested, in the nominal run a single exposure distribution is estimated using nominal values for all data and parameters.

In the *uncertainty analysis* loop, each simulation run is repeated a large number of times. Each run starts with a different scenario using data obtained with bootstrapping, parametric resampling and/or re-calculation of uncertain values. As a result, a large number of uncertain dietary exposure distributions is estimated which are used to estimate uncertainty limits (p5, p95).

Running a nominal run first has the advantage that the user may evaluate these modelling results before doing the final analysis. The model specification of rather complex simulation models and the corresponding output results are evaluated to detect any errors or misspecifications. Possible errors in the data and/or model settings are identified and corrected. In the final exposure assessment, the uncertainty analysis is included and the uncertainty of estimates is assessed.

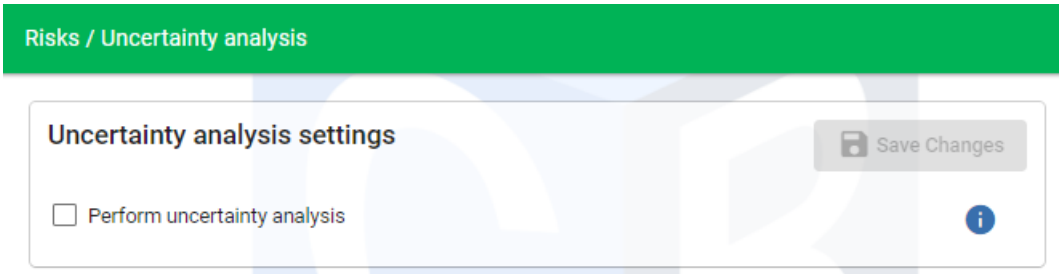



Figure 1.10: Uncertainty analysis settings.

### 1.2.3 Variability diagnostics

In MCRA, the nominal run might be followed by an uncertainty analysis to assess the uncertainty limits (e.g. 2.5 and 97.5%) of the nominal percentiles (e.g. p50, p95, p99, p99.9, p99.99) of the exposure or risk distribution. For these percentiles, the nominal run of an acute assessment consists of preferably 100.000 iterations, the uncertainty analysis preferably of 100 runs with 10.000 iterations each. Note that for the percentile p99.99 the minimal number of iterations should be 10.000. Likewise, to estimate uncertainty limits of 2.5 and 97.5%, the minimal number of bootstrap runs should be 100.

In general, the number of iterations and bootstrap runs will be restricted due to limited computational resources or simulation runs that are time consuming. MCRA offers a diagnostic tool to visualize whether the estimated percentiles and uncertainty limits are stable or vary due to small simulation runs with limited number of iterations and uncertainty runs.

The diagnostic tool focus on the stability of the percentiles or, re-frasing, quantify 1) the amount of Monte Carlo variability and 2) the amount of variability due to resampling e.g. consumption and monitoring data or others sources of uncertainty. By quantifying both quantities, the influence of both sources of variability on the estimated value of the percentiles is assessed.

The diagnostics are displayed in a number of graphs (as many as the number of specified percentiles). For each percentile, the graph is used to draw inference about the optimal number of MC-iterations, the number of uncertainty runs and the number of iterations in each uncertainty run.

In the section below it is assumed that the nominal run consists of 100.000 iterations and uncertainty (95% confidence) is assessed with 100 uncertainty runs of 10.000 iterations each.

To make inference, the set of nominal (Monte Carlo) values is split in 2 samples of 50.000 iterations each, 4 samples of 25.000 each, 8 samples of 12.500 each etc. By doing so, we get $n$ partitions of samples and in each partition we have $2^n$ samples of size $100.000/2^n$. In each partion, the percentiles of the available samples are estimated and the standard deviation of the percentiles. So in partition $n$ = 1, the estimate of the standard deviation is based on 2 percentiles derived from samples of size 50.000; in partition $n$ = 2, the estimate of the standard deviation is based on 4 percentiles derived from samples of size 25.000, etc. The estimated standard deviations are plotted against the number of MC-iterations per sample of each partition. It is expected that the standard deviation decreases as a function of sample size, so for larger sample sizes MC-variability decreases. For each standard deviation the 90% confidence limits are calculated.

A similar procedure is applied to the 100 uncertainty runs (of size 10.000). In each uncertainty run the percentiles are estimated. Then, in partition $n$ = 1, percentiles are estimated on the first 10.000/2 = 5000 iterations of each sample; in partition $n$ = 2 percentiles are estimated on the first 10.000/4 = 2500 iterations of each sample, etc. Then standard deviations of the percentiles of the partitions of 100 x 10.000, 100 x 5000, 100 x 2500, etc are estimated and plotted against the number of iterations in each partition. It is expected that the standard deviation decreases as a function of sample size.

In Figure 1.12, the estimates and uncertainty limits are displayed. In Figure 1.11, the diagnostics are dlotted

- Red dots: standard deviation (sd) of percentile estimates between subsets of simulations. Error bars indicate parametric 90% confidence interval for the sd.
- Blue dots: standard deviation of percentile estimates between uncertainty iterations of subsets of simulations. The red square indicates the specified number of iterations (10000) of an uncertainty run.
- Each blue dot represents the standard deviation of 100 percentiles

For percentages, p50, p90, p95 and p99 the curves of the nominal estimates are smooth. For the extreme percentiles, p99.9 and p99.99, patterns do not monotonically decrease and vary, indicating that percentile estimates are variable. Also the 90% confidence interval around the sd's are much larger than for the smaller percentiles. An general conclusion is that percentiles and uncertainty limits for p50, p99, p95 and p99 are stable. The percentile of the p99.99 is unstable meaning that running the simulation with a different initialisation seed estimates will vary. The percentile p99.9 is an intermediate case.

The boxplots for uncertainty show the p25 and p75 as edges of the box, and p2.5 and p97.5 as edges of the whiskers. The reference value is indicated with the dashed black line, the median with the solid black line within the box. Outliers are displayed as dots outside the wiskers.

### 1.2.4 Retain & Refine and tiered approaches

A basic idea of Retain & Refine is that entities (e.g., substances) can be handled in different ways (more or less refined) while still being considered together in the same risk assessment (retain). We refer to such different approaches as tiers.

In the modular design, a tier is defined as a specific set of settings for a module or a group of modules. Tiers differ in many aspects, and there is no single dimension to rank tiers as low vs. high. In risk assessment, typical tiers contrast deterministic to probabilistic approaches, conservative to realistic approaches, approaches using restricted data to

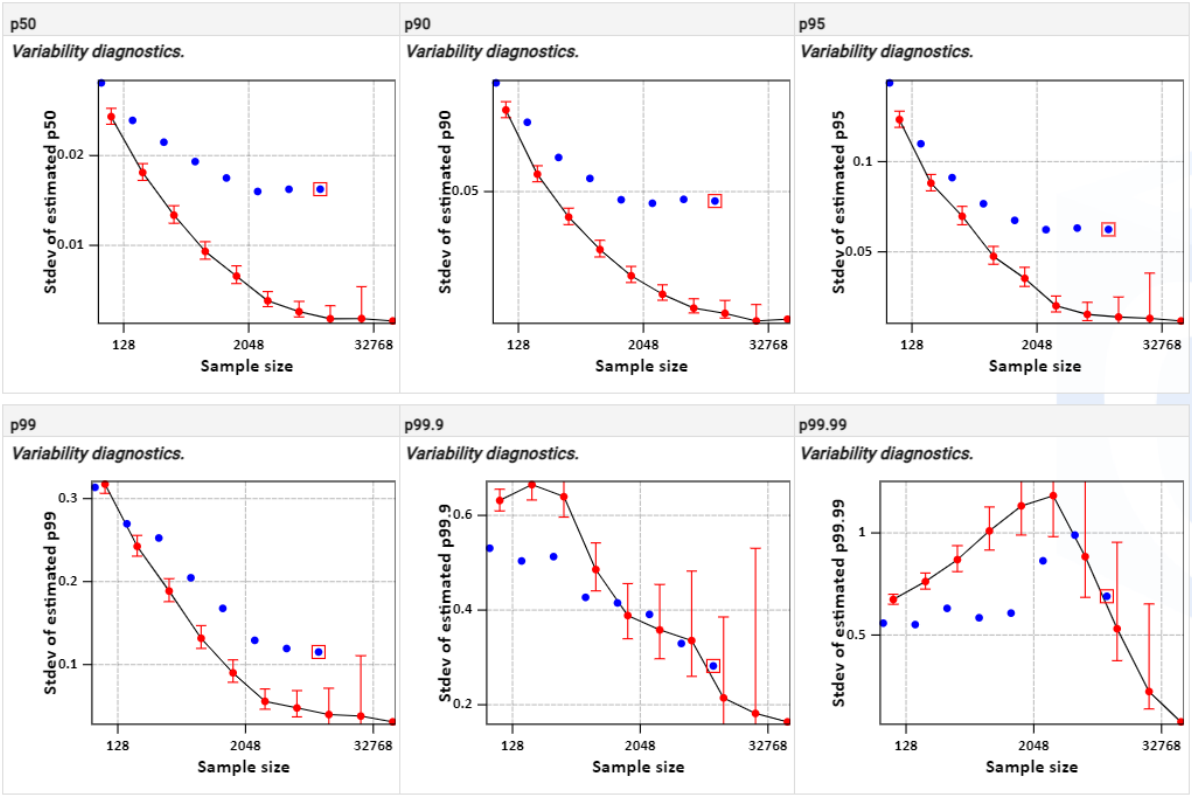



Figure 1.11: Variability diagnostics for percentiles p50, p90, p95, p99, p99.9 and p99.99.

| Percentage | Exposure (µg/kg bw/day) | Median (p50) | Uncertainty lower bound (p2.5). | Uncertainty upper bound (p97.5). |
|---|---|---|---|---|
| 50.00 | 0.2278 | 0.2026 | 0.1837 | 0.2395 |
| 90.00 | 0.6236 | 0.56 | 0.4896 | 0.653 |
| 95.00 | 0.82 | 0.7339 | 0.6417 | 0.8664 |
| 99.00 | 1.339 | 1.217 | 1.035 | 1.438 |
| 99.90 | 2.439 | 2.128 | 1.693 | 2.743 |
| 99.99 | 3.752 | 3.13 | 2.411 | 4.777 |

Figure 1.12: Exposure estimates for percentiles p50, p90, p95, p99, p99.9 and p99.99 with 95% confidence limits

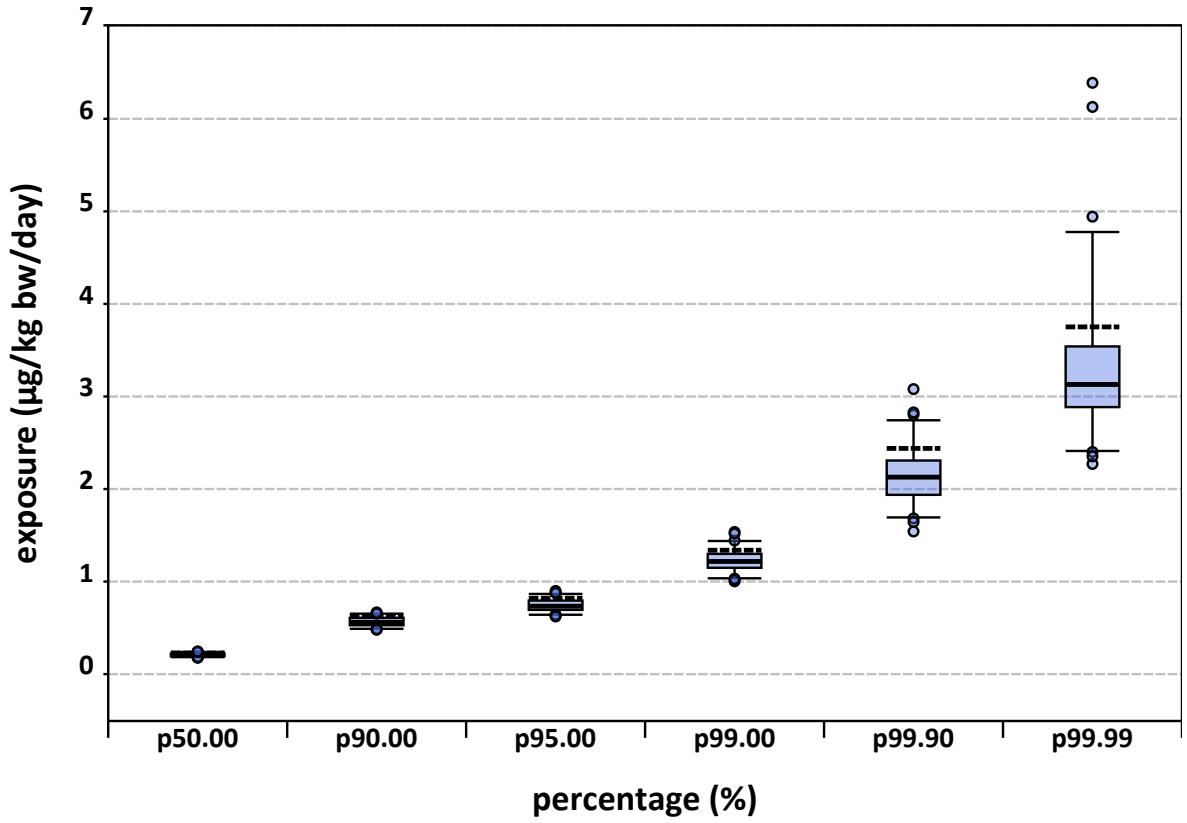



Figure 1.13: Boxplots for summary statistics for percentiles p50, p90, p95, p99, p99.9 and p99.99 with 95% confidence limits

approaches using more extensive data, and approaches using different degrees of model complexity. For each of the modules of MCRA, as many tiers are implemented as considered useful for the practice of risk assessment.

Each calculation in the modular design may involve multiple, nested, calculations of sub-modules. A *risk* (or health impact) assessment builds on an *exposure assessment* and a *hazard assessment*, the exposure assessment builds on a *dietary* and a *non-dietary exposure* assessment, the dietary exposure assessment builds on a *consumption assessment* and an *occurrence assessment*, etc. Tiers can be defined at each node of the assessment network.

Each calculator has as a main output entities that can be specified to have different tiers (tiered entities). For example, in a *hazard assessment*, some substances may be assessed using a tier 'Hazard Dose from dose-response data', other substances may be assessed using a tier 'TTCx100' or 'sample from general NOAEL distribution x100' (which only requires knowledge of the Cramer class of the substance). As another example, in dietary exposure assessment some food-substance combinations may be recognised as risk drivers for which a more complex approach (e.g. probabilistic modelling) is required, whereas a simpler approach (e.g. *deterministic modelling*) may be sufficient for all other food-substance combinations. So in this case the tiered entity is 'food-substance'. A typical risk assessment will start at a tier that is simple to perform for all tiered entities (potential risk drivers). Note that, based on data availability and ease of application, the initial assessment can already include more complex elements, such as probabilistic modelling. If the initial calculations produce risk estimates that do not exclude concern, refinement of the modelling for the perceived risk drivers is useful for checking whether this concern is real.

### 1.2.5 Uncertainty

Uncertainties arise in different forms in many of the models and data of MCRA.

- uncertainty in the data values (e.g., uncertain NOAELs, uncertain RPFs, or uncertain processing factors),
- uncertainty due to limited data (e.g., a limited number of food samples),
- uncertainty due to a lack of data (e.g., missing concentration data for some foods/substances or missing processing factors),
- uncertainty of the models, (e.g., due to a lack of detail).

MCRA offers the following options to handle uncertainty:

- for many types of data, the possibility to provide data including quantifications of uncertainty,
- imputation methods for filling in missing data in various types of models, and
- a generic uncertainty analysis method that providing uncertainty estimates of the modelling results for many of the modules, which are based on bootstrapping, parametric resampling, and/or re-calculation on all sub-modules for which this is possible.

#### Uncertainty due to limited sampled data

For some type of data, e.g., processing factors, it is possible to not only provide nominal estimates of the data values, but also to provide quantified estimates of the uncertainties of these values. Occasionally, quantifications of the uncertainties of these estimates are not available. MCRA provides the possibility to work with both quantified and unquantified uncertainties: include uncertainties in a quantitative uncertainty analysis when available, or, when not available, use nominal estimates, followed by an offline qualitative uncertainty analysis.

Uncertainties of data values are available in different forms. For some data values, uncertainty may be quantified by means of parametric distribution parameters (e.g., *processing factor uncertainties*, or kinetic model instance parameter uncertainties). Alternatively, uncertainty values may be provided in the form of an empirical set of uncertainty values (e.g., *relative potency factor uncertainties*, or *points of departure uncertainties*).

For each data sub-module that has quantified uncertainties, it is optional to include the source of uncertainty in the uncertainty analysis of the main module. Then, when specified, data values are resampled in each *uncertainty analysis cycle*.

The basic *acute exposure* distribution is estimated in a Monte Carlo simulation by combining dietary consumption records (person-days) with sampled residue values. The resulting distribution represents a combination of variability in consumption within the population and between residues in a food lot. Percentiles may be used for further quantification e.g. the median or 99th percentile. Due to the limited size of the underlying data, these outcomes

are uncertain. Confidence (or uncertainty) intervals reflect the uncertainty of these estimates, where MCRA uses bootstrap methodology and/or, depending on the available data, parametric methods to estimate the uncertainty.

### Empirical method, resampling

The empirical bootstrap is an approach to estimate the accuracy of an outcome. In its most simple, non-parametric form, the bootstrap algorithm resamples a dataset of n observations to obtain a *bootstrap sample* or *resampled set* of again n observations (sampling with replacement, that is: each observation has a probability of $1/n$ to be selected at any position in the new resampled set). By repeating this process $B$ times, one can obtain $B$ resampled sets, which may be considered as alternative data sets that might have been obtained during sampling from the population of interest. Any statistic that can be calculated from the original dataset (e.g. the median, the standard deviation, the 99th percentile, etc.) can also be calculated from each of the $B$ resampled sets. This generates a *uncertainty distribution* for the statistic under consideration. The uncertainty distribution characterises the uncertainty of the inference due to the sampling uncertainty of the original dataset: it shows which statistics could have been obtained if random sampling from the population would have generated another sample than the one actually observed (Efron (1979) and Efron and Tibshirani (1993)).

### Parametric methods

Instead of bootstrapping the observed data, inference about parameters is based on parametric methods. For processing, where factors are specified through a nominal and/or upper value this is the natural choice. For concentration data, where the lognormal model is used to represent less conservative scenario's (EFSA (2012)), the *parametric bootstrap* may be an alternative, especially when data are limited and the empirical bootstrap fails.

According to Cochran's theorem, sample variance $\hat{\sigma}_y^2$ follows a scaled chi-square distribution. In the parametric bootstrap for the *lognormal* distribution, the sample variance $\hat{\sigma}_y^2$ is replaced by a random draw from a chi-square distribution with $n_1 - 1$ degrees of freedom; the sample mean $\hat{\mu}_y$ is replaced by a random draw from a normal distribution with parameters $\hat{\mu}_y$ and $\hat{\sigma}_y^{*2}/n_1$, giving a new set of parameters $\hat{\mu}_y$ and $\hat{\sigma}_y^{*2}$. This is repeated $B$ times.

For the *truncated lognormal* and *censored lognormal*, large sample maximum likelihood theory is used to derive new parameters $\hat{\mu}_y$ and $\hat{\sigma}_y^{*2}$. This is repeated $B$ times.

The binomial fraction of the censored values for the *mixture lognormal* and *mixture truncated* distribution is sampled using the beta distribution with uniform priors $a = b = 1$ (with the *beta* distribution as the empirical Bayes estimator for the binomial distribution). This is repeated $B$ times.

### Uncertainty due to missing data

In some cases, data are only available for specific (primary) entities and missing for others. E.g., points of departure (such as NOAELs or BMDs) may only be available for some of the substances of interest.

### Uncertainty due to modelling approach

Model uncertainty or uncertainty of model outcomes arise by applying different modelling approaches or applying alternative model assumptions.

**Note**

TODO

## 1.3 Data repository

The data used for the *modelling actions* of MCRA is organised in the data repository. All users have their own (personal) repository folder in which they can *upload* their own data files and organise these in folders and subfolders to their own preference. In addition, there are shared repository folders that are specifically created for sharing data sources among user groups. Users may be granted access to one or more shared repositories: shared, maintained, and used by multiple users. Shared repositories and their contents are free to use by granted users in their own calculations.

Each data source in the data repository contains data of one or more data groups, indicating the module(s) for which the data set can be used as data. Each primary entity module and data module of the *modular design* is linked to a data group. If a data source is recognized as a data source belonging to a module, then it can be used as a data source of this module in a modelling action. The data groups of a data source are automatically recognized when the data is uploaded, based on whether the data matches with the specified data format(s) of the data group.

Figure 1.14 shows the data repository browser. The repository browsers allows users to browse through the data repository, upload and organise their own datasets and share these with other users. The central panel of the repository browser shows the data sources and sub-folders of the currently opened folder/repository. The top bar of the repository browser shows the path of the currently opened repository, buttons to collapse/expand the repository folder tree-view sidebar on the left ☰ and the info-sidebar on the right ⓘ, and a button to open the action menu ⋮. The tree-view sidebar shows the hierarchical structure of the repositories and sub-repositories to which the user has access. The info panel shows the details of the selected data source or folder. If the selected item is a data source, then the info panel shows the types of data available in the data source and the different data source versions of the data source. If the selected item is a folder, then the info panel shows info about the owner of the repository, the *access level* of the user, and info about the other users and user groups that have access to this repository.

Users with read-write access (or higher) may upload new data source files by pressing the add button + on the bottom right and selecting the *upload new file(s)* item. A new sub-repository can be created by pressing the same add button and selecting the *create new folder* item. A third option is to create an external Proast link, which can be seen as a data source repository folder in which the data sources link to datasets (outputs) available on Proast web.

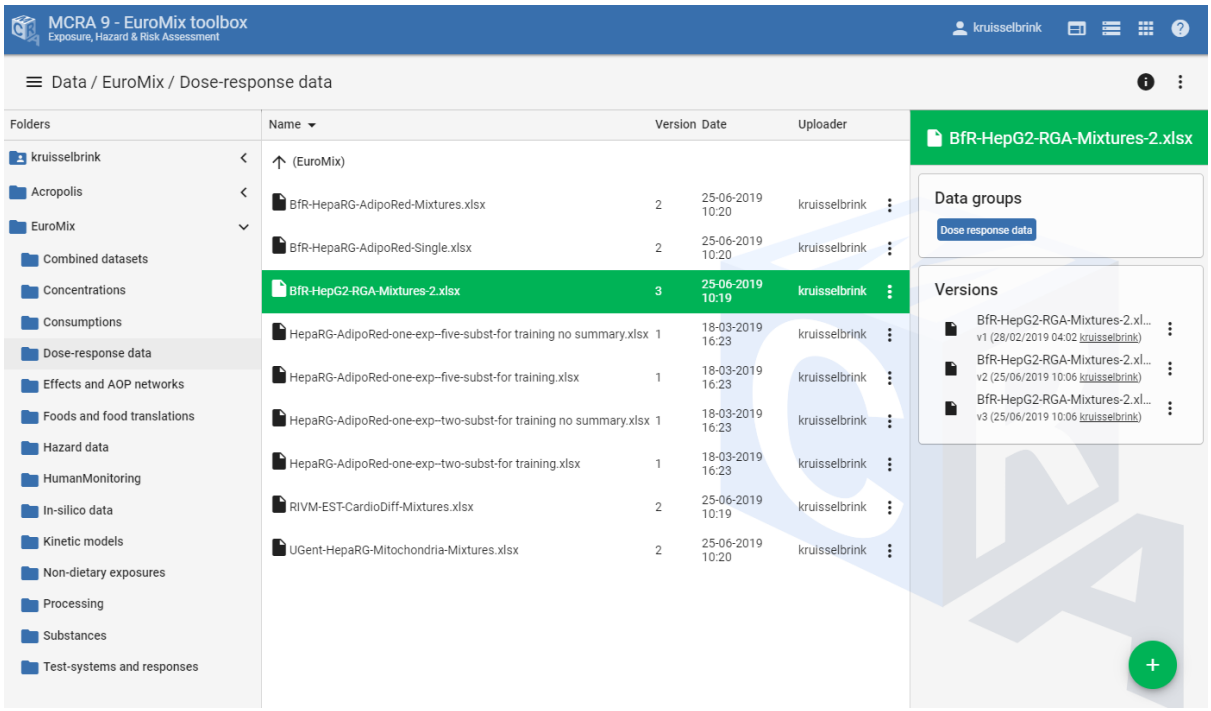



Figure 1.14: The data repository browser.

### 1.3.1 Creating and uploading data files

Users with an access level of read-write (or higher) are allowed to upload new data source files to a repository folder. This can be done by pressing the add button + on the bottom right and selecting the *upload new file(s)* item.

Accepted upload file types are:

- **Microsoft Excel files (.xlsx):** An Excel file contains one or more sheets, each sheet containing tabular data. The sheet names and the fields of the data tables must comply with the conventions as specified in the data format section of the module(s) for which the data is presented.
- **Microsoft Access files (.mdb):** An Access file contains one or more tables. The table names and the fields of the data tables must comply with the conventions as specified in the data format section of the module(s) for

which the data is presented.

- **Zip archives with CSV files (.zip):** A CSV file (.csv) is a comma-separated values file containing data in tabular format. One or more CSV files are archived in a zipped file format (.zip) to facilitate the upload of collections of multiple CSV files. The names of the CSV files in the zip archive must follow the accepted table names of the module(s) for which the data is presented and the tables in the CSV files must follow the data format of that/those module(s). Note, that it is not allowed to upload single CSV files.

### 1.3.2 Moving repositories and data sources

The data repository browser (Figure 1.14) supports moving files (data sources) and folders (sub-repositories) via drag-and-drop functionality.

Click on a folder or file item in the browser and drag it to another folder while holding the primary mouse button. The mouse icon will change and the item will be visibly moving while dragging. Release the mouse button over the desired destination folder. MCRA will ask for confirmation before the move is executed.

The following rules apply:

- You **can** move items within the tree-view, list-view and between both, vice versa.
- You **cannot** move a root repository folder, a root repository folder is not draggable.
- You **cannot** move a repository to one of it's descendants.
- If you have insufficient privileges for the source or destination folder, MCRA will show an error message.

Note that moving a data source or any of it's parent repositories to a different folder does **not** affect any actions which use this data source (or any of it's versions). The action's data source will reflect the new location correctly after the data source or any of it's parent repositories has been moved.

### 1.3.3 Repository access levels

Shares and access rights can be granted on the level of repositories and sub-folders. Data sources inherit the access rights of the repository/folder in which these are located. The following access rights are available:

- **visible:** the user can only see that the repository exists, but cannot see its contents, except for sub-folders that may also visible to the user.
- **use:** the user is only allowed to use the data sources in this repository, but is **not** allowed to download the original data of the data sources of the repository.
- **read:** the user can use data sources in this repository **and** is allowed to download the original data files of the data sources of the repository.
- **read/write:** the user can use and download data sources in this repository and is allowed to add/remove files and folders to/from this repository.
- **admin:** the is considered as an administrator of this repository and has full control over it, including the rights to add/remove files and folders to/from this repository and to add/remove user and group shares.
- **owner:** the user is considered to be the owner of this repository and therefore has full control over it.

Users with administrator or owner rights on a repository/folder are allowed to add/remove user and group access using the *edit shares dialog* (Figure 1.15) that can be opened by pressing the *edit shares* button .

### 1.3.4 Linking remote data repositories

MCRA also offers to link external data repositories . These are remote websites not part of MCRA, but contain data sources that can be used for calculations. Currently, only one remote source can be linked as external repository in MCRA, the PROASTweb (https://proastweb.rivm.nl/). PROASTweb users may link directly the outputs of their PROAST analyses (i.e., dose response models) as an external repository to MCRA.

Figure 1.16 shows how PROAST outputs of a PROASTweb user are linked to an external repository in MCRA. Data sources of remote repositories have to be explicitly imported in MCRA before they can be used in analyses. Initially,

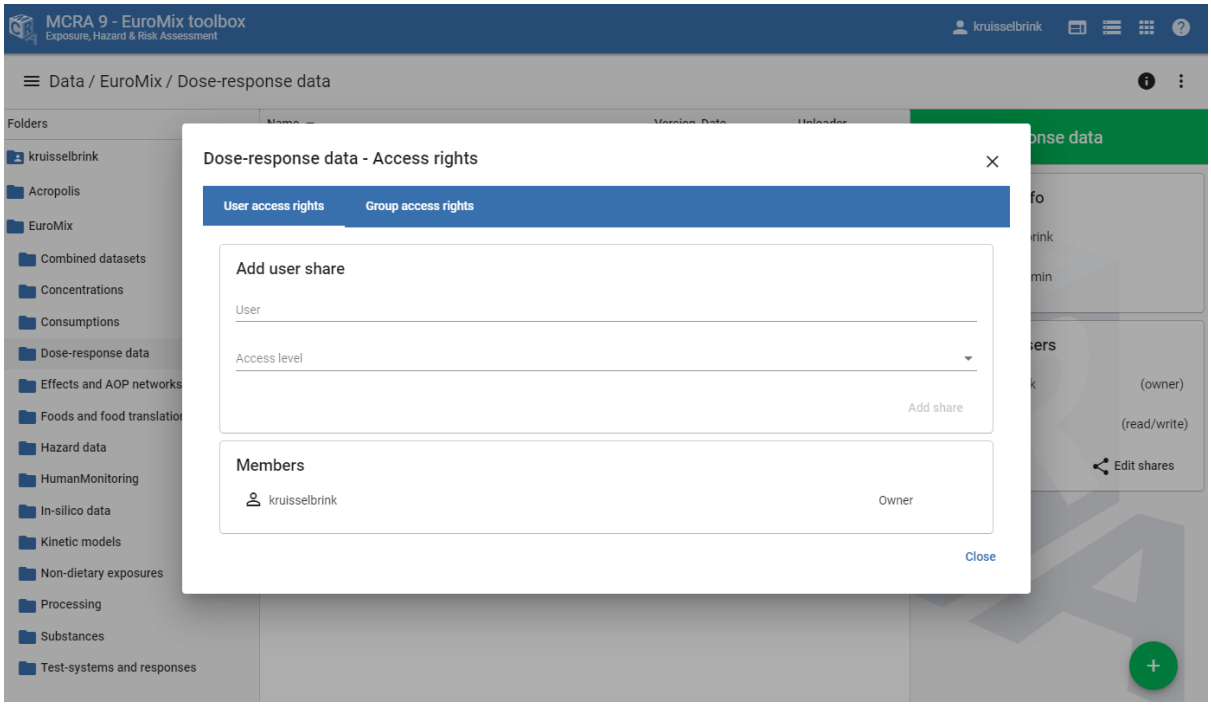



Figure 1.15: The edit-shares dialog of the data repository browser: user and group access rights are added and removed by repository owners and administrators.

all data sources in a remote repository have a status of not-imported. Pressing the import button, MCRA will attempt to import the data source and once that is finished, the data source is ready to be used in analyses.

A new PROAST remote repository link is created by pressing the add button + on the bottom right and selecting the *Create Proast link* option. A dialog (Figure 1.17) opens asking for the local name of the external repository/folder, the PROASTweb username of the user of which the outputs should be linked, and the PROASTweb access key of the user, which is required as authentication token to access the analyses of the specified user.

## 1.4 Workspaces and actions

In MCRA, user work is organised in workspaces. A workspace is collection of work items (actions) and data that are logically grouped together. Each workspace has a name and can be given a description and tags. The *workspace browser* page provides users with an overview of all available workspaces and allows for creation of new workspaces. The *workspace overview page* page is shown when opening a workspace and provides an overview of the actions, data and tasks of the workspace.

The modelling tasks of MCRA are specified through actions. Each action is of a certain action type, which is the *main module* for which this action specifies the modelling task. Depending on the type of action, the user can configure the settings and the data sources of the main module and all relevant/linked sub-modules in the *action area* or, if it is a so-called standard action, in the *standard action page*. When all required settings and data sources of an action are configured and the action is in a valid state, then the modelling task described by the action can be started by pressing the run button. The status of this modelling task (which, depending on the complexity, may take some time to run) is shown in the results page and when the task has completed, output is available in the form of reports or in the form of data that can be used as input in other actions. Note that users are free to change the settings of an action at any time. Actions can therefore have multiple outputs from multiple tasks created with different settings.

A special kind of action is a so-called standard action. In a full action, the user has to link up all data and configure all settings to run the action. To get an action up and running can be quite cumbersome and the result is an output report which can be quite detailed. Although output sections follow the modular design, specific sections are not instantly available. To encourage users to explore MCRA, *standard actions* are implemented to facilitate an easy introduction to the use of MCRA. The actions can be specified with only a few settings that are important within the scope of the standard action, and the output report contains a limited selection of main sections only.

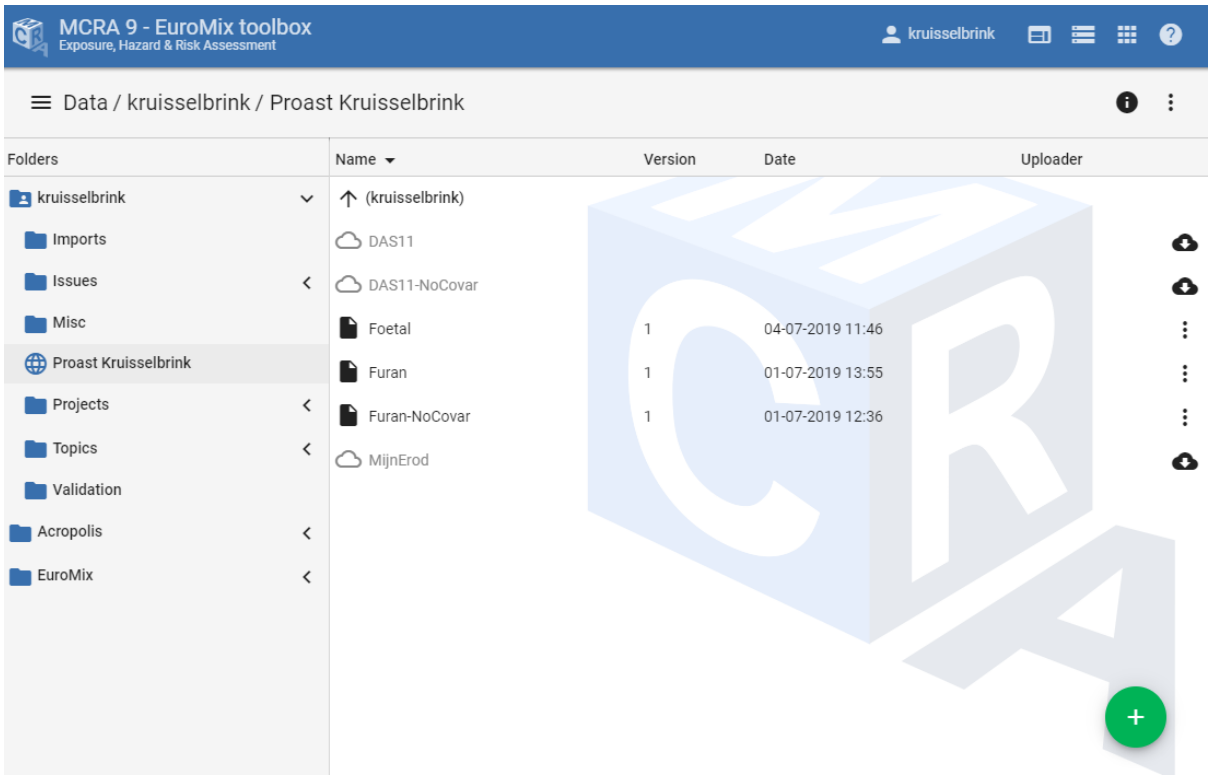



Figure 1.16: The remote (PROASTweb) repository in the data repository browser.

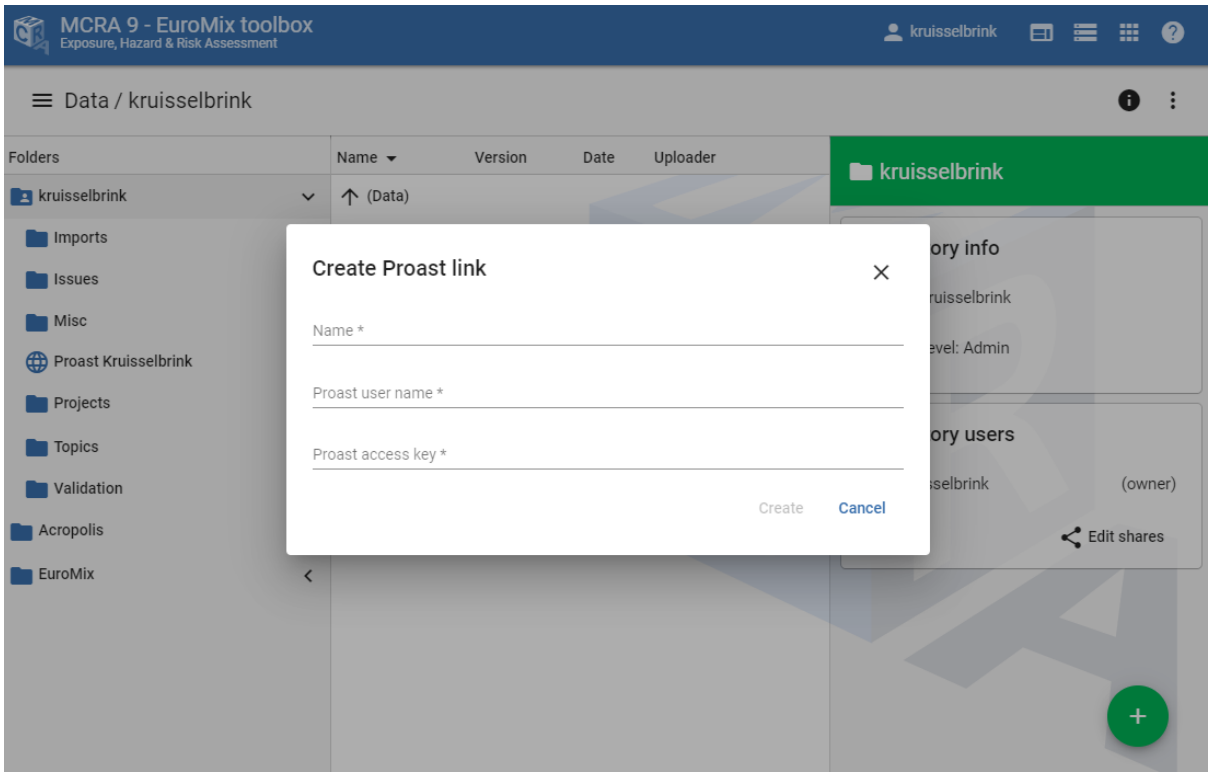



Figure 1.17: The dialog for creating a new PROASTweb remote repository link.

A new action can be added to a workspace by clicking the + button at the bottom right of the *workspace overview page*. This will present an action menu with three options (see Figure 1.18):

- **Create a new action:** will open a wizard to create a (full) *action* by selecting the desired action type, specifying name, description and tags, and, depending on the action type, some main action settings.
- **Create a new standard action:** will open a dialog to create a *standard action* by selecting one of the available standard actions.
- **Import an action from zip file:** will open a local file browser that lets the user *import* a specifically formatted zip-file containing an action definition.

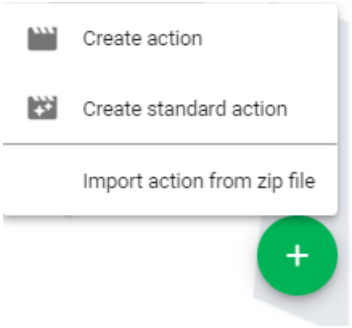



Figure 1.18: Three options to add an action to the workspace: create new action, create new standard action, and import action from zip file.

### 1.4.1 Workspace browser

Figure 1.19 shows the workspace browser. Users scroll through their workspaces and select the workspace which they want to work with. Detailed information about the selected item in the browser is shown in the info panel, which can be expanded/collapsed using the info button on the right of the toolbar. The *filter text box* is used to quickly find/filter workspaces by name or tag. A workspace is opened by clicking on the workspace name or selecting the *open workspace* option of the *action menu* of the workspace. Opening a workspace will redirect you to the *workspace overview page*.

A new workspace is added by pressing the add button + on the bottom right of the screen. Delete workspaces by opening the *action menu* of the workspace item in the browser and selecting the delete option.

### 1.4.2 Workspace overview page

Figure 1.20 shows the workspace overview page. This page provides an overview of the actions, data, tasks, and results of a workspace, shown as four tabs at the top of the page. The actions tab shows all actions of the workspace, and from this tab, actions are opened. The data tab shows all data sources used in this workspace. I.e., all data sources that are used by the actions of the workspace. The results tab shows all tasks and results of simulation jobs that have been submitted by the actions of the workspace. The properties tab shows the general information of the workspace (i.e., name, descriptions, and tags) and edit functionality.

In the actions tab, all actions of the workspace are listed. The list of actions can be filtered by action type or by filter text using the controls on the toolbar. An action is opened by clicking on the action name or by selecting the *open action* option of the action menu of the selected action item. Opening a workspace will redirect you to the *action area*. A new action is added to the workspace by pressing the *add button* + at the bottom right of the page.

### 1.4.3 Action area

After opening an action, the user is directed to the main panel of the action. Each action has its own specific panel. In the main action page and sub-action pages, an action is configured, simulation jobs started, and output results are evaluated. The panel in Figure 1.21 shows the following sections:

- **Scope:** Links to the scope-panels in which the scope entities of the action are set (e.g., foods or substances).
- **Inputs:** Links are shown for panels in which the calculation inputs or selection inputs are set (e.g., concentration models that are inputs for computing dietary exposures).

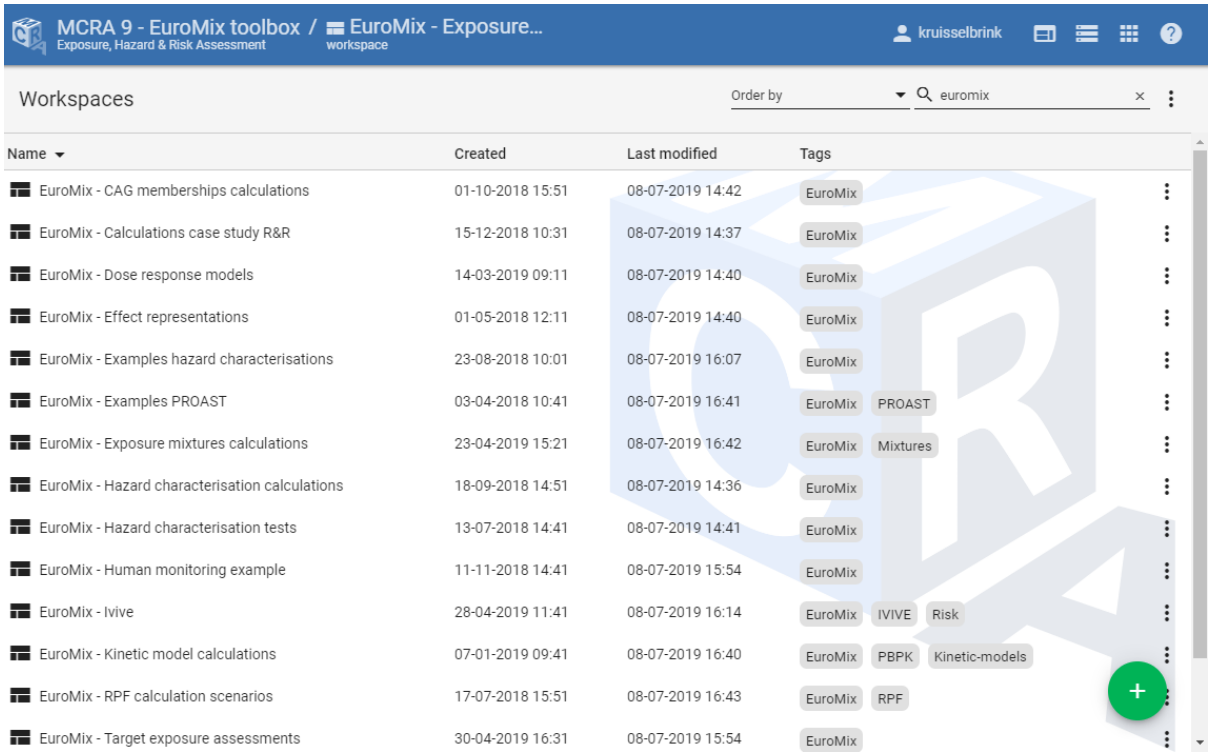



Figure 1.19: The workspace browser.

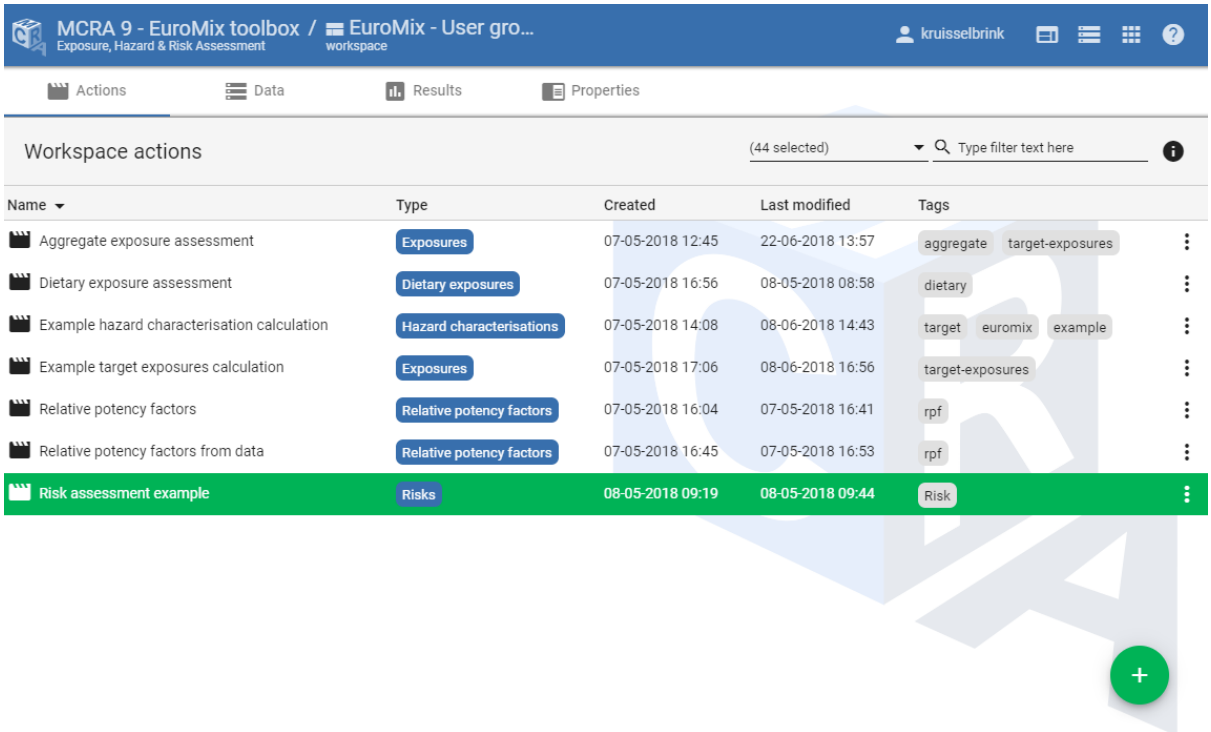



Figure 1.20: The workspace overview page.

- **Data source:** If the action is a data action, then a form is shown in which the data source should be specified (e.g., selection of the concentration data source in a concentrations action).
- **Settings:** A form is shown in which the calculation and/or selection settings of the action are set/changed (e.g., specify the exposure type, chronic/acute, of an exposure assessment).

All modules of MCRA have equally structured panels. In each panel, data sources and settings for the action are specified and the scope and input sub-module links that are relevant are shown. This presentation reflects the modular design and allows the user to select the data and settings required for running the action. In the summary panel the main settings and data of the action are summarized. The output settings panel is used to specify general output settings. In the uncertainty settings panel the number of uncertainty runs and uncertainty sources is specified. In the results panel running tasks and output results of the actions are shown. An alternative form of navigating from action to sub-action is provided by the navigation menu in the left sidebar that can be expanded/collapsed by clicking the menu button on the top left in the Action bar. In this menu, all required modules for the action are shown in one list, allowing a linear way of navigation.

An action is valid and ready to run when all scopes and inputs are valid and all required data and settings are configured. For each sub-action, the check symbol ✓ indicates that it has been configured correctly and is ready to run. In case a sub-action has a warning symbol ⚠, some user action is required. When the main action is ready to run, a simulation job is started by clicking the run button ▶ in the grey action bar on the top right. Optionally, sub-actions can be started by clicking the run button ▶ in the green (sub)action bar on the top right. Clicking the run button will send the simulation task of this (sub)action to the job-scheduler, and the progress of the task is shown in the results panel . After completing the task, output is available in the form of a screen report, download as pdf, or as an html report with tables (csv) and charts (svg) in a downloadable zip file.

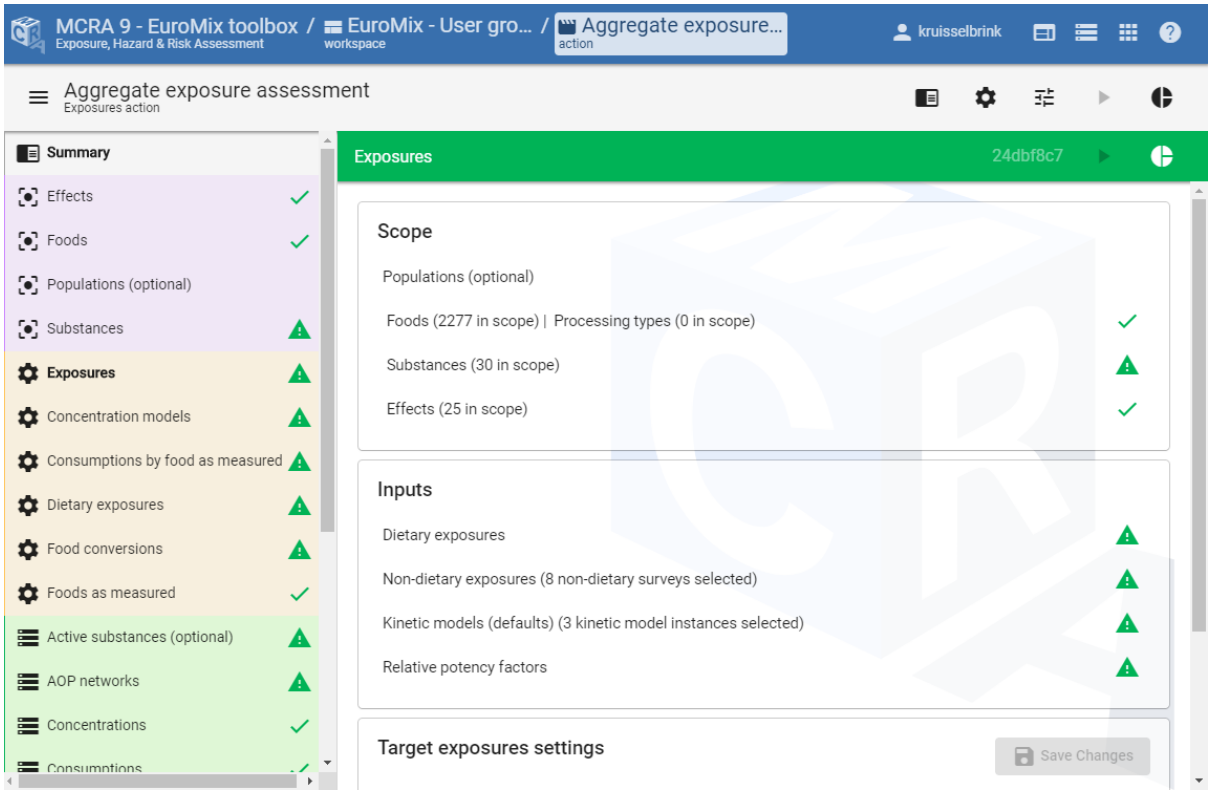



Figure 1.21: The main page of an action.

### Scoping: entity selection

Each action starts with the selection of the relevant primary entities. In this context, entity selection or scoping plays an important role. Scoping of the action is defining the members for its primary entities, and, occasionally, also for other entities.

As an example, Figure 1.22 shows the substances module panel. At the top, the data source file with substances is selected containing the primary entity data of substance codes. In the selection card, a selection is made of the entities

in the dataset that are relevant for the current action (3 in scope). Note that if no explicit selection is made, the scope is set to all entities by default. In the settings form, additional (selection) settings are shown, e.g., selection of the index substance (relevant for a cumulative assessment). In this way, the scope of the action is specified by selection of the primary entities.

The panels for the data modules have a similar structure and selection is essentially the same. The only difference is that data actions always have a scope. I.e., data modules always relate to one or more primary entities.

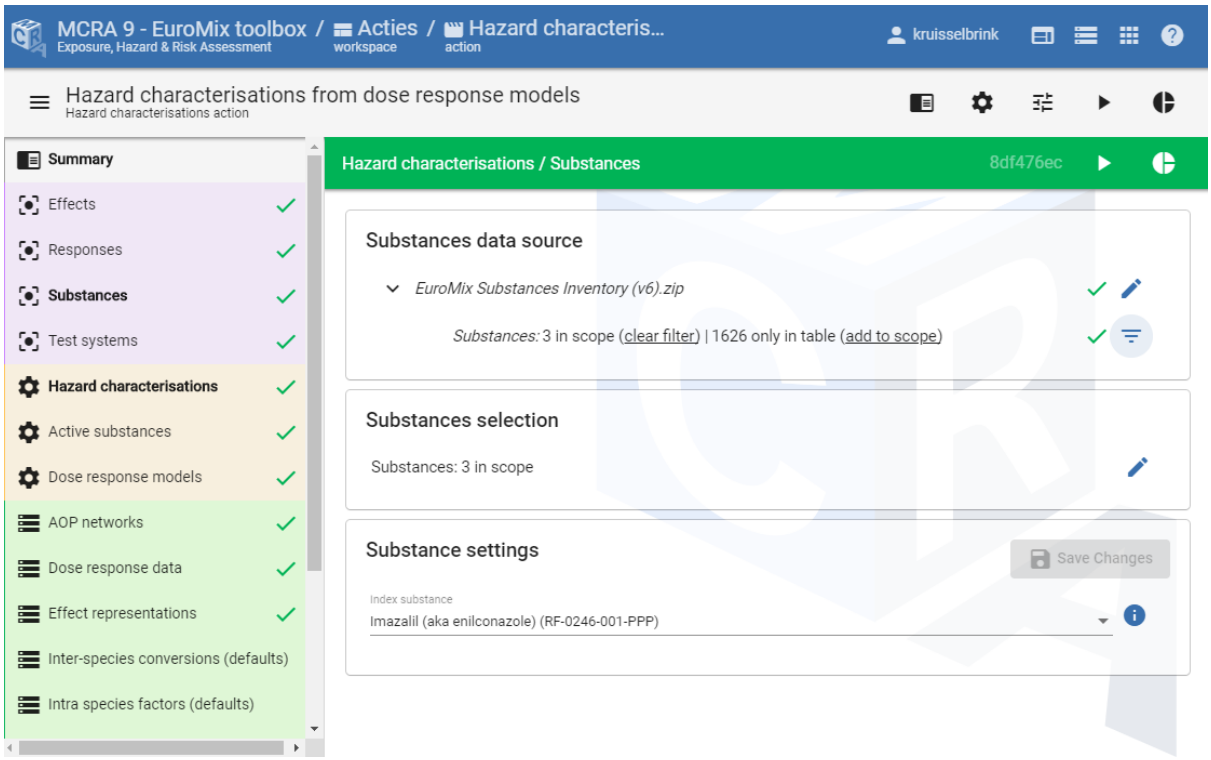



Figure 1.22: The substances module panel as an example of a primary entity module panel.

### Implicit versus explicit scoping

MCRA distinguishes between implicit and explicit selection of entities (scoping). By default, the selection is defined implicitly as 'all entities' found in all data are linked to the action. For instance, the substance scope will contain all substance codes found. That is, not only substances as specified in the substance data source, but also all other substances found in data sources that link to substances like concentration sample data or points of departure data. These are implicit selections. Explicit selections are made in the specific module panel of this data type (e.g., by selecting the substances in the substances panel). Once made explicit, selections are no longer automatically expanded when new data sources are linked to the action.

For example, the substances scope shown in Figure 1.22 is defined explicitly, having three substances in the scope, and excluding 1626 substances also present provided through substances data source and/or other linked data sources like concentration samples. By pressing the *clear filter* button, the explicit scope is cleared and is made implicit again. Then, the scope contains all substances found as primary entities and found in all linked data sources, in total 1629 (1626 + 3) substances.

### Comparing new data to set scopes

After linking a data source to an action, MCRA performs a check whether the new data links well to the current scope (selected entities) of the action and reports the results. For instance, after linking new substance concentration data to an action which already has an implicit or explicit substance scope, it should be checked whether the substance codes used in the concentration data match with the current substances in scope. Note that this check is also performed after linking a primary entity substances data source to an action which already has a set of substances in scope, i.c. substances already specified in other selected data sources.

After linking a data table from a new data source to an action which already has a defined scope for one of the entities in the table, there are three possible states for entity codes:

- codes included in both the scope and the data source
- codes included in the scope, but not present in the data source
- codes included in the data source, but not present in the scope

The first case represents a successful link, no further action is required. For the second and third type of mismatch, it depends on the type of data link whether this is considered a serious problem (red flag ⚠) or merely a point of attention (green flag ⚠). For instance, in the case of concentration data, for some substances no concentrations are available, and therefore MCRA allows missing concentration data for part of the substances in the scope: a green warning symbol is shown. The concentration data source may equally well contain codes that are not in the scope (e.g., concentrations for substances that are not specified in the primary entity data for substances). It may be desirable to extend the scope with these substances found in the concentration data. Also this situation is flagged with a green warning symbol.

Figure 1.23 shows an example of a point of departure action. The substances scope has already been defined by other data in the action (in this case points of departure data), and subsequently a substances data source is selected. Here, there are 140 substances in the current scope (explicitly defined). However, 132 of these 140 substances are not present in the substances data source (*not in table*). Hence, we are missing the definitions of these substances. This is considered a critical linking issue that should be solved by updating the substances data source to include these substances, therefore a red warning symbol is shown. On the other hand, the substances data source also contains 3 substances that are not part of the current scope (*only in table*). This is a non-critical error, normally leading to a green warning symbol, but in this case, it is overruled by the red warning symbol.

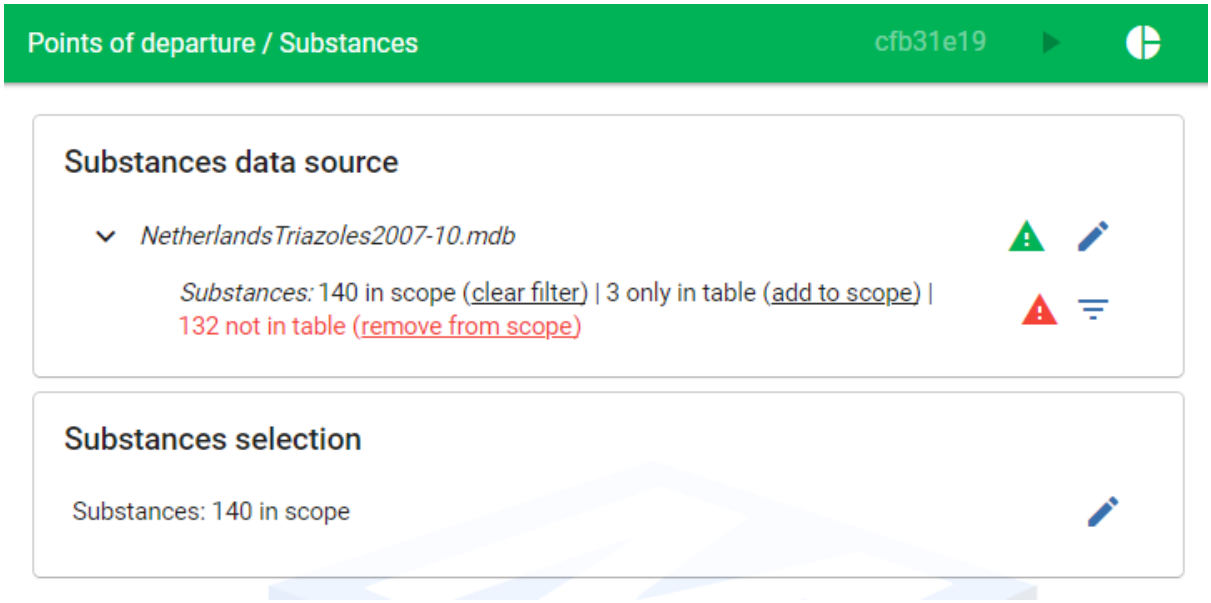



Figure 1.23: Checking substances data in a substances data source against an already set substances scope.

Another example is shown in Figure 1.24. The primary entities effects and substances are selected and in the scope. Then, a points of departure data source is selected containing effect and substance codes. For effects, no linking errors are observed, hence the new data source matches perfectly with the effects already in scope. For substances, we see that there are 7 substances that are in the points of departure data source but not in the substances scope (*new*) and for 3 substances in the scope no points of departure are available (*not in table*). The former is fine, but it might be needed to extend the scope with these 7 substances (*add to scope*). The latter, in general, is not a problem but just a point of consideration. These substances might be removed from the scope (*remove from scope*) or not.

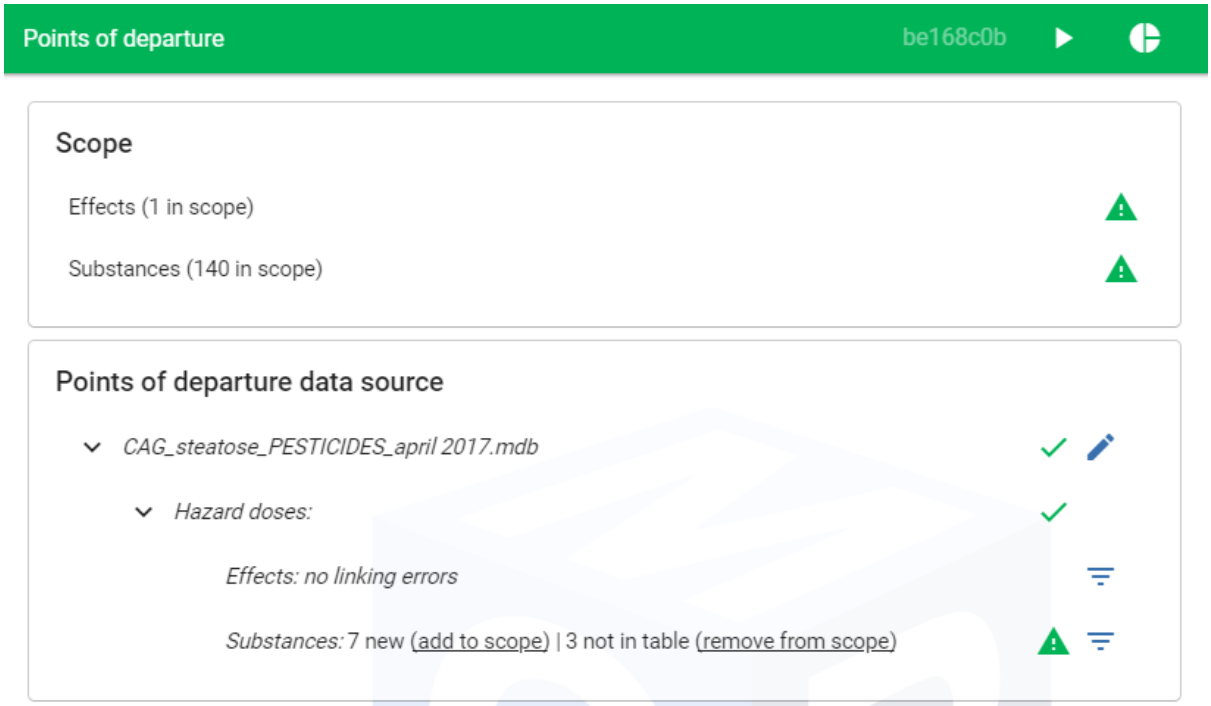



Figure 1.24: Checking substances data in a POD data source against an already set substances scope.

### 1.4.4 Standard action area

Standard actions facilitates MCRA users in organizing the data and configuring all setting to run an action. Some standard actions are for demonstration purposes only, other standard actions are realistic examples of risk assessment or dietary exposure assessment using real data.

#### Creating a standard action

A new standard action is added to the workspace by pressing the *add button* + at the bottom right of the workspace page, see *workspace overview page*. Select the *Create standard action* option.

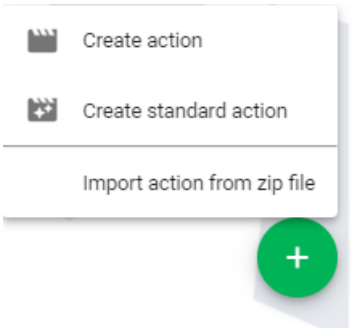



Figure 1.25: Add standard action.

Then a pop-up appears, see Figure 1.26 and after clicking one of the available panes the standard action is created. Currently, a limited number of standard actions is available for authorized users. Please contact the MCRA system administrator at https://rivm.nl for more information. New standard actions will be developed in the near future.

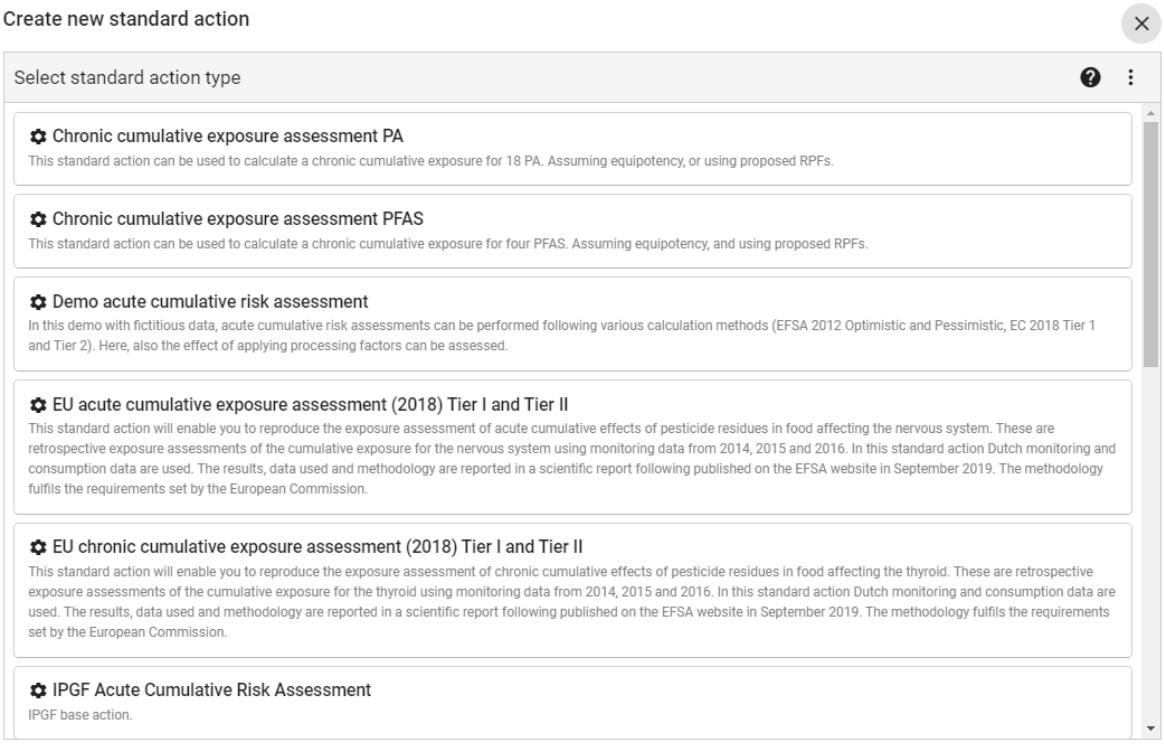



Figure 1.26: Create standard action.

### Standard action reports

Although a standard action produces a short output report, see Figure 1.27, by clicking the *Show detailed report* the full report becomes available. By clicking *Show short report*, the short output report is returned.

### Converting a standard action to a full action

A standard action is easily converted to a full action by opening the *action menu* ⋮ in the white bar of the standard workspace in your browser and selecting the 🎬 *Convert to full action* or 🎬 *Clone to full action* option. The first option replaces the standard action by a full action, the second option makes a clone to a full action and the standard action is still available.

## 1.4.5 Action zip files

MCRA also provides the functionality to import and export actions (with or without data) as specially formatted zip files (.zip) containing 'ready to run' actions. This special file archive contains two XML files (.xml) named *_ActionSettings.xml* and *_ActionData.xml* that respectively describe the action's settings and linked data sources. In addition, this zip archive may include the action data itself, either in their original form, located in a sub-folder (data) or in the form of (.csv) files.

These action zip files can be imported into and workspace by pressing the *add button* + at the bottom right of the workspace page, see *workspace overview page* and then selecting the *Import action from zip file* option. Once uploaded, the action doesn't require further user interaction and is ready to run.

An action can be exported as a zip archive by by clicking the *action menu* ⋮ located in the white bar on top of the panel. Currently, this allows export in three different formats (see Figure 1.29):

- A link **Edit metadata** to clone the current action to a new action (change action type) and to add a description.
- The **download action (no data)** option will create a zip archive containing only the two xml files defining the action, but will not include the data.

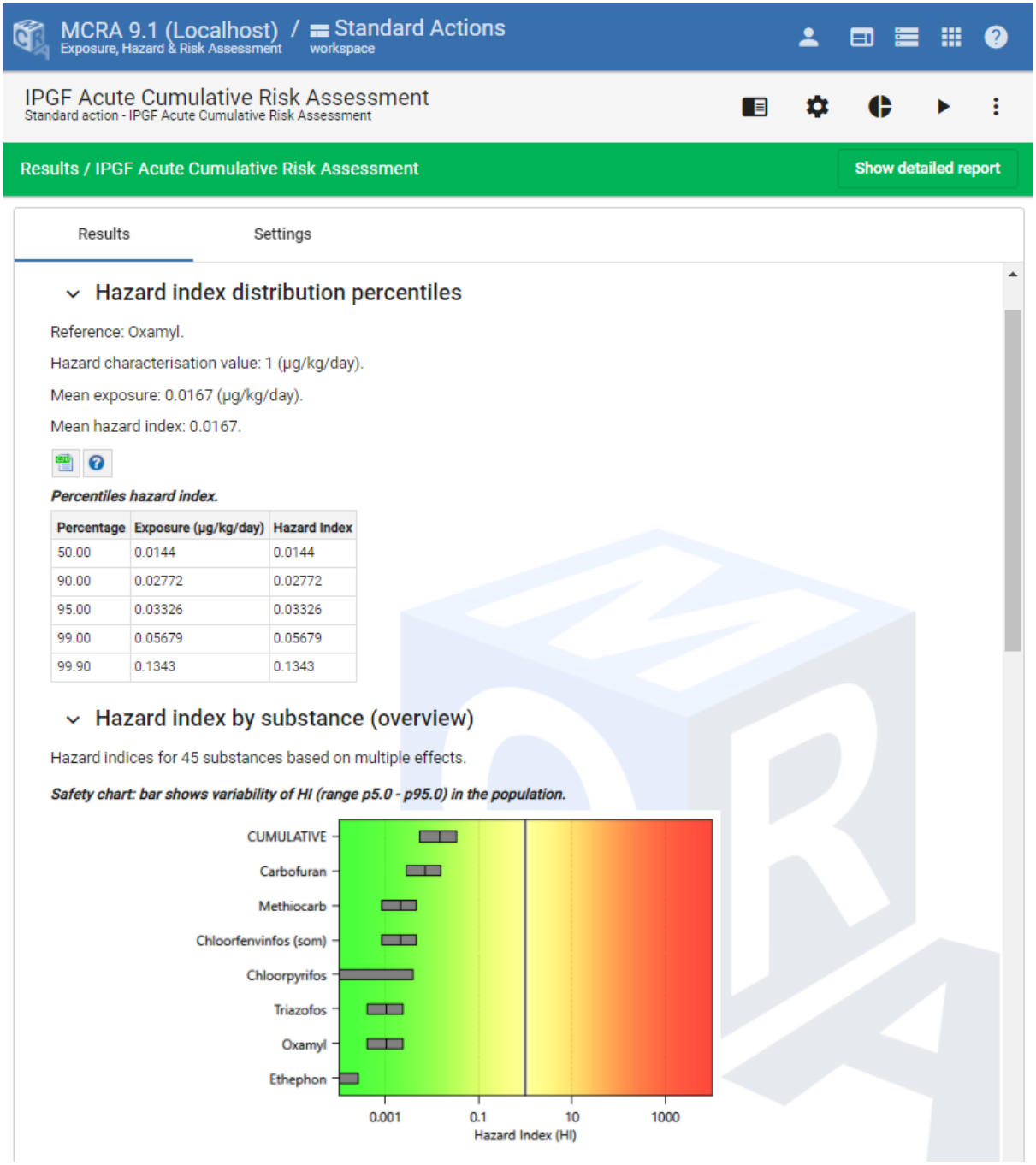



Figure 1.27: Short output report.

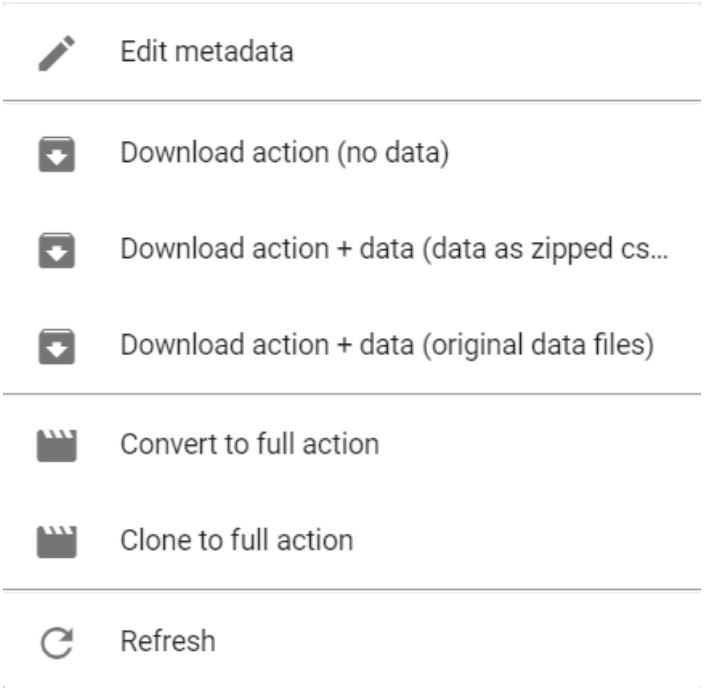



Figure 1.28: Convert to full action.

- The **download action + data (data as zipped cvs)** option will create a zip archive containing the action definition xml files and also the action data in the form of csv files of the internally used data table formats.
- The **download action + data (data as zipped cvs)** option will create a zip archive containing the action definition xml files and also the original action data files (i.e., the files that were originally uploaded in the repository).
- The **download action diagram (.svg)** option will create a plot of the modular design of the current action (scalable vector graphics, SVG). Open the SVG file and it will launch in your browser. Most browser support SVG files. The nodes in the diagram contain hyperlinks to the documentation.

## 1.5 MCRA web and core

The Monte Carlo Risk Assessment (MCRA) platform, developed by Wageningen University & Research (WUR, Biometris) for the Dutch National Institute for Public Health and the Environment (RIVM), is a web-based system for risk assessment of chemicals, which brings together statistical models, shared data and data uploaded by the users.

*EFSA* and *RIVM* previously agreed on the use of this MCRA system for the cumulative risk assessment of pesticides. This agreement was formalised in two framework partnership agreements for the periods 2015-2016 and 2017-2020. As part of these partnership agreements, the MCRA system was continuously improved in terms of capacity and functionality, in accordance with requirements defined by EFSA. In response to needs on transparency and data accessibility, the MCRA system was further developed into a transparent, collaborative, EU harmonised, interoperable, open-source accessible platform.

### 1.5.1 MCRA core

Source codes of the statistical models are open source (i.e., freely accessible and re-usable) and made more flexible to allow for cooperation and co-creation. The source code of MCRA core is available at a repository located at https://github.com/rivm-syso/mcra-core/. RIVM is the owner of the MCRA core, with co-ownerships of specific parts by WUR Biometris, FERA, INERIS and possibly others in the future. RIVM will manage MCRA core, such that it is available as open source.

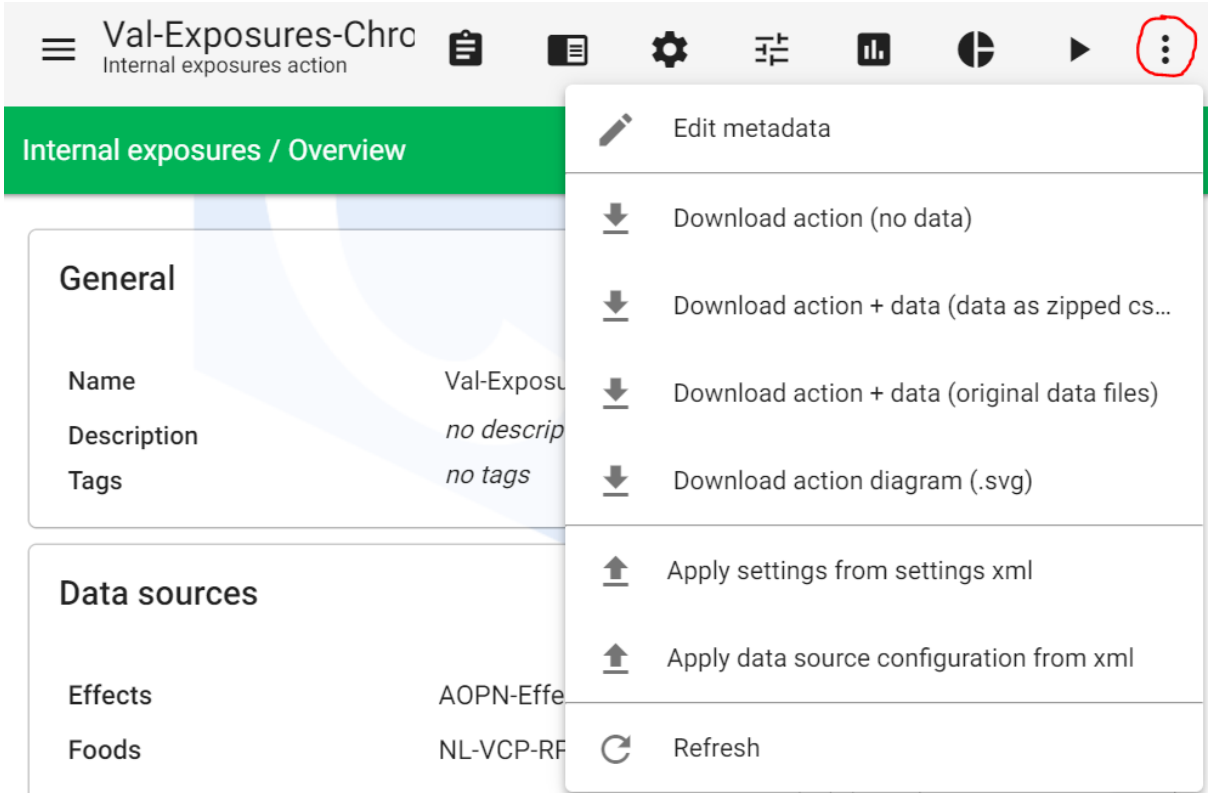



Figure 1.29: Export an action zip archive and other down/up-loads

### 1.5.2 MCRA web

The MCRA web portal provides tailored access to the MCRA core actions. In the web portal, each module of MCRA can be accessed as a starting point to perform the corresponding action. RIVM is the owner and manager of the MCRA web platform. The source code of the MCRA web platform is maintained at a dedicated RIVM github site. Access (both for reading and contributing) is restricted to the MCRA development and operations team. It is not anticipated that co-developers will contribute to the code of the web platform.

### 1.5.3 Running MCRA core using the command line interface

The MCRA core library is supplied with a *command line interface* (CLI) utility to run MCRA actions using input files and producing output files.

## 1.6 Results panel

The output of all runs is shown in the results panel. By clicking the hyperlink of an output section the output is opened in the browser. Most output tables have three icons. Click the left icon to download the table in csv format, click the middle icon to sort table columns or multiple columns (sort column, press/hold shift and sort next column) or to filter (search box). Press the question mark for additional information about the table headers.

All plots and charts can be saved by right clicking the picture.

An easy way to compare multiple outputs is to select a few outputs as shown in Figure 1.30, then click om the three dots and click Compare selected.

A new panel pops up and each output section can be reached by clicking the output name, e.g., *PARC Exposure mixtures training 0.8*. Expand the tree on the left side and select the sections you want to compare. In Figure 1.31, *Concentrations by substance* is selected in the Human monotoring analysis sub-action. Navigate to the output by clicking name of the output sections e.g., *PARC Exposure mixtures training 0.8*.

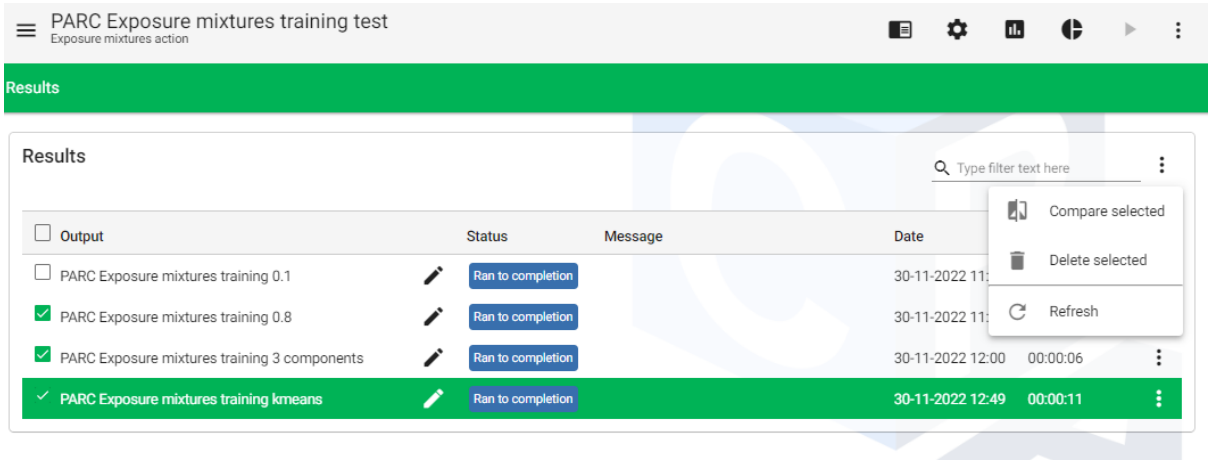



Figure 1.30: Compare selected outputs

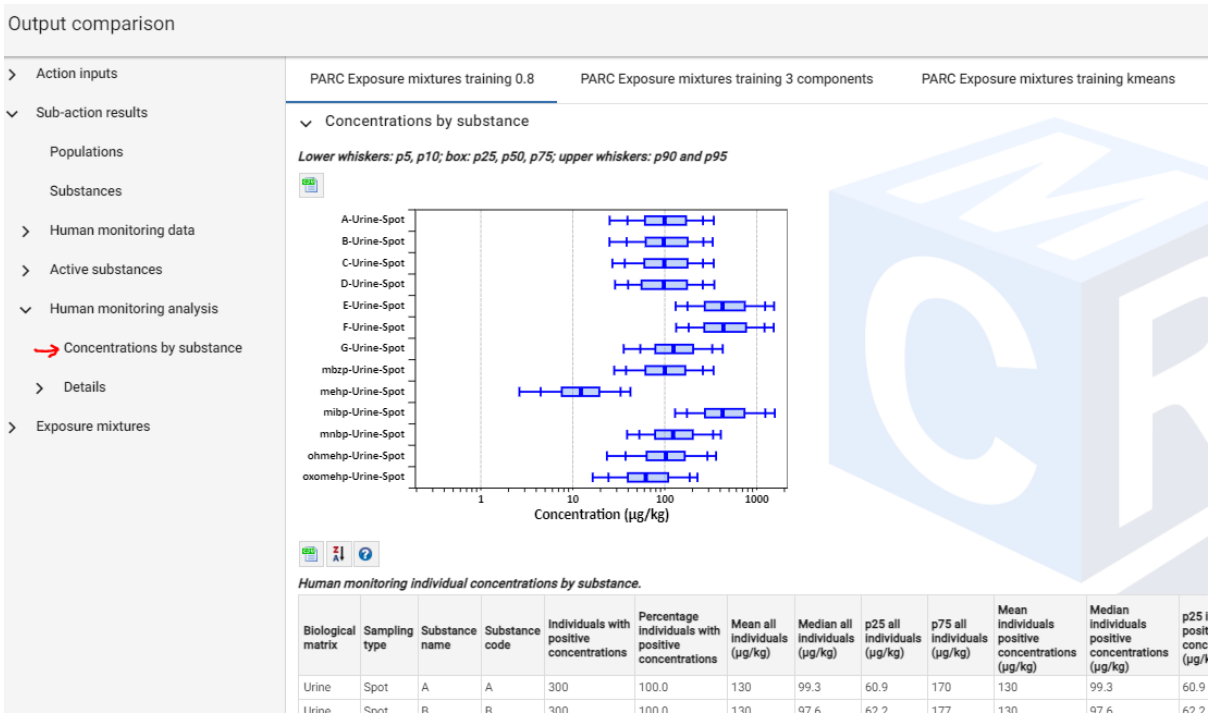



Figure 1.31: Output comparison panel

CHAPTER

TWO

# EXAMPLES

**Note**

This section is under construction.

Guidance notes used in PARC training sessions:

- Guidance how to use PARC HBM data in MCRA
- Guidance how to perform mixture analysis on PARC HBM data in MCRA
- Example HBM data

Training materials used in EuroMix training sessions:

- EuroMix dietary exposure
- RPF-exercise 1-for training-draft

There are a few exercises prepared that you could follow to get started.

## 2.1 Cumulative dietary exposure assessment

### 2.1.1 Introduction

The goal of this exercise is to perform a probabilistic cumulative dietary exposure assessment, illustrating all data needed. In Example 1 we will upload and use nine different files containing the data. In Example 2 we will upload and use a single data file for the same purpose. In the example the exposure will be characterised by upper tail percentiles, and the risk driving substances and foods can be examined. In Example 3 an uncertainty analysis is added.

### 2.1.2 Preparation

In the workspace browser ( icon), create a new workspace *Examples*, using the + button in the bottom right corner.

### 2.1.3 Example 1

Calculate a cumulative chronic dietary exposure for Dutch young adults in 2003 regarding a group of eight triazole substances according to the basic optimistic model of the EFSA 2012 guidance document. Use liver steatosis as a focal effect and Cyproconazole as an index substance. The data files are already available in the data folder *Documentation-Examples / Exercise Dietary Exposure Assessment.*

Detailed steps are as follows.

- In the *Examples* workspace, create a new action using the + button in the bottom right corner.
  - Select action type *Dietary exposures*
    - Name it, e.g. *Triazoles exposures*

- (Optional) You can also add tags (e.g. triazoles, NL, steatosis) as labels that can be used later to find similar actions
- (Optional) You can add a description for further information
- Click Next

- Specify Dietary exposures settings
  - Tier: *EFSA 2012 Optimistic*
  - Risk type *Chronic*
  - Click *Create*

You are now directed to the main page of the new action. You can always return to this main page by clicking Action settings ⚙ or the action type name (*Dietary exposures*) in the green bar.

The main page contains at least three blocks of information: Scope, Inputs and Settings. We will now first link all nine data files needed for this cumulative assessment. For most settings we will use default values in accordance with the chosen tier (*EFSA 2012 Optimistic*).

Scope of the assessment:

- Click *Effects* (path in the green bar changes Total *Dietary exposures / Effects*)
  - At *Effects data source*, click ✎ and browse to the file *Effect - Steatosis.xlsx*, then click *Select*
  - At *Effect Settings* for *focal effect* select *Steatosis-liver* and click 🖫 *Save Changes*
  - In the green navigation bar, click *Dietary exposures* to go up one level.
- Click *Foods* (path: *Dietary exposures / Foods*)
  - At *Foods data source*, click ✎ and browse to the file *Foods.xlsx*, then click *Select*
  - In the green navigation bar, click *Dietary exposures* to go up one level
- Click *Populations (optional)* (path: *Dietary exposures / Populations*)
  - At *Populations data source*, click ✎ and browse to the file *Populations.xlsx*, then click *Select*
  - This file contains two populations, only one is allowed. Click ✎ under Populations selection, this opens a pop-up window. Deselect *NL_2006*, then click *Save*. The red warning signs ⚠ should now be gone. (Note: green warning signs ⚠ point at details and can usually be ignored)
  - In the green navigation bar, click *Dietary exposures* to go up one level.
- Click *Substances* (path: *Dietary exposures / Substances*)
  - At *Substances data source*, click ✎ and browse to the file *Substances - Triazoles.xlsx*, then click *Select*
  - At *Substance settings* for *Index substance* select *Cyproconazole* and click 🖫 *Save Changes*
  - In the green navigation bar, click *Dietary exposures* to go up one level

Next we choose the other input data:

- Click *Consumptions by modelled foodd* (path: *Dietary exposures / Consumptions by modelled food*)
  - Click *Consumptions* (path: *Dietary exposures / Consumptions by modelled food / Consumptions*)
    - At *Consumptions data source*, click ✎ and browse to the file *FoodConsumptions.xlsx* and *Select*
    - At *Consumptions data selection*, with ✎ open the food consumption surveys selection.
      - The file contains two surveys, but only one is allowed. Click ✎ under Consumptions data selection, this opens a pop-up window. Deselect *VCP-kids*, then click *Save* (the red warning ⚠ should now be gone)
    - In the green navigation bar, click *Consumptions by modelled food* to go up one level
  - Click *Food conversions* (path: *Dietary exposures / Consumptions by modelled food / Food conversions*)

- Click *Modelled foods* (path: *Dietary exposures / Consumptions by modelled food / Food conversions / Modelled foods*)
  - Click *Concentrations* (path: *Dietary exposures / Consumptions by modelled food / Food conversions / Modelled foods / Concentrations*)
    - At *Concentrations data source*, click ✎ and browse to the file *ConcentrationData.xlsx*, then click *Select*
    - In the green navigation bar, click *Food conversions* to go up two levels
  - Click *Food recipes* (path: *Dietary exposures / Consumptions by modelled food / Food conversions / Food recipes*)
    - At *Food recipes data source*, click ✎ and browse to the file *FoodTranslations.xlsx*. then click *Select*
    - In the green navigation bar, click *Dietary exposures* to go up three levels
- Click *Concentration models* (path: *Dietary exposures / Concentration models*)
  - Click *Relative potency factors* (path: *Dietary exposures / Concentration models / Relative potency factors*)
    - At *Relative potency data source*, click ✎ and browse to the file *RPFs.xlsx*, then click *Select*
    - In the green navigation bar, click *Dietary exposures* to go up two levels
- Click *Processing factors* (path: *Dietary exposures / Processing factors*)
  - At *Processing factors data source*, click ✎ and browse to the file *ProcessingFactors.xlsx*, then click *Select*
  - In the green navigation bar, click *Dietary exposures* to go up one level
- Click *Active substances (optional)* (path: *Dietary exposures / Active substances*)
  - In this example we have a fixed list of relative potency factors for the eight substances, and don't need point of departure (POD) data to decide which substances are active with respect to the health effect and therefore belong to the cumulative assessment group. Deselect the setting "Derive memberships from POD presence", then click 🖫 *Save Changes*
  - In the green navigation bar, click *Dietary exposures* to go up one level

Now run the model, either by clicking the ▶ run icon in the grey bar, or by clicking the ▶ run icon in the green bar (Note: ▶ in the green bar can also be used to run subactions on their own).

The ▶ icon is replaced by the text "Running". When the run has finished, the interface automatically changes to the Results screen. You can also click the Results icon ◔ to go there.

As an exercise, try find the following results:

1. The 99th percentile of cumulative exposure
2. The substance(s) with highest contribution to the total exposure
3. The food(s)-as-measured with the highest contribution to the upper tail of the exposure distribution

Answers:

- In the grey bar, browse to the results panel by clicking the ◔ icon and click on the latest output (path: *Results / Dietary exposures*)
  - In the *Dietary exposures* tab, browse in the tree (unfold by clicking › where necessary) to ˅ *Dietary exposures* ˅ *Distribution (OIM)* ˅ *Percentiles*
    - In the table it states that the 99% exposure percentile is at an exposure of 0.02127 µg/kg bw/day.
  - In the *Dietary exposures* tab, browse in the tree (unfold by clicking › where necessary) to ˅ *Dietary exposures* ˅ *Details* ˅ *Exposures by substance* ˅ *Total distribution*
    - From the pie chart it is clear that Tebuconazole contributes the most to the total exposure distribution with 32.7%. In the table below the graph more details can be found.

- In the *Dietary exposures* tab, browse in the tree (unfold by clicking › where necessary) to ˅ *Dietary exposures* ˅ *Details* ˅ *Exposures by food and substance* ˅ *Risk drivers upper tail*
  - From the pie chart it is clear that Flusilazole in grapefruit contributes the most (16.7%) to the upper tail exposure distribution

### 2.1.4 Example 2

We will create a new action to demonstrate uploading all the data at once. All data is now contained within one file, *MCRA-Documentation Example Dietary exposures.xlsx*.

Detailed steps are as follows.

- In the *Examples* workspace, create a new action (using +)
  - Select action type *Dietary exposures*
  - Name it, e.g. *Triazoles exposures from one data file*
  - Click Next
- Specify Dietary exposures settings
  - Tier: *EFSA 2012 Optimistic*
  - Risk type *Chronic*
  - Click *Create*
- Then go to the actions settings ⚙ of this action (path: *Dietary exposures*)
  - Click *Effects* (path: *Dietary exposures / Effects*)
    - At *Effects data source*, click ✎ and browse to the file *MCRA-Documentation Example Dietary exposures.xlsx*. Click *Toggle all*, then *Select*. This will load all available data tables for all subactions of *Dietary exposures*.

You still need to specify the focal effect (under *Effects*), index substance (under *Substances*), and food surveys (under *Consumptions by modelled food / Consumptions*). You also need to deselect the "Derive memberships from POD presence" setting under *Active substances*. Navigate to the subaction where these changes have to be made using the green bar.

You now have achieved the same as in Example 1, only with the upload of one single file. You can now run the model, and inspect the results, which should be the same as for Example 1.

### 2.1.5 Example 3

Repeat the run of the previous task, but in addition to the nominal run, perform an uncertainty analysis as well.

- Click on the ⚟ icon (in the grey bar) to open the uncertainty settings panel
  - At *Uncertainty settings*, check ✓ *Perform uncertainty analysis*
    - For *Monte Carlo iterations per uncertainty run* choose *100*, and press 🖫 *Save Changes*
- Now run the model, by pressing the ▶ run icon in the grey bar. Note that the run will take much more time.

Compare with the previous results, to find:

1. 95% uncertainty bounds for the 99% exposure percentile
2. 95% uncertainty bounds for the highest contribution from a substance to the total exposure distribution
3. 95% uncertainty bounds for the highest contribution from a food to the total exposure distribution

## 2.2 TDS-based exposure and risk assessment

Total Diet Studies (TDS) monitor chemical levels in representative consumed foods as eaten (e.g. bread, pizza), so after processing steps (Lee et al. (2015)). TDSs contrast to the common chemical monitoring studies on raw primary commodities (e.g. wheat, tomato). In some TDSs, samples are analysed directly, in other TDSs samples of similar food products are pooled before chemical analysis. Pooling of samples means that average concentrations can be well estimated, but that less or no infromation is available about variability. Therefore, in the context of risk assessment, TDS data are used for the assessment of chronic risks from long-term exposure.

This section contains three demonstrators (*MCRA standard actions*) on how to use TDS data for exposure and risk assessment. The demonstrators were developed in the FNS-Cloud project. Two examples illustrate simple TDS data on consumed foods. The first demonstrator shows the exposure to methyl-mercury and the risk for German children. The second demonstrator shows the exposure to nickel and the risk for several Belgian age groups. DON for Dutch children. The third demonstrator contains the previous two as specific cases, but also includes a case where foods are pooled before analysis, for the exposure to the mycotoxin DON and the risk for Dutch children. In this last case additional data are included to describe the TDS sample compositions in terms of the modelled foods.

After trying out the standard actions, prospective users can convert or clone these standard actions to full actions for use with other data or using other exposure or risk models.

### 2.2.1 Standard actions

The following standard actions are available as TDS exposure and risk assessment demonstrators:

- *TDS-based long-term exposure and risk assessment of methylmercury for German children*
- *Long-term dietary exposure and risk of nickel for the Belgian population*
- *TDS-based long term dietary exposure and risk assessment*

## 2.3 Aggregate exposure assessment

### 2.3.1 Introduction

The goal of this exercise is to assess aggregate exposure assessment.

### 2.3.2 Preparation

If you haven't done so, in the workspace browser (use the icon), create a new workspace named *Examples*, using the +.

The data files used in the example(s) in this section, are located in the data folder *Documentation-Examples / Exercise Aggregate Exposure Assessment*.

### 2.3.3 Example 1

- In the *Examples* workspace, create a new action (using +)
  - Then select ✓ *Show all action types*, select *Exposures*
  - Name it *exposures*
  - At *Exposure settings* choose:
    - As *Risk type Chronic*
    - Check ✓ *Include dietary and non-dietary routes of exposure*
  - Press *Create*
- Then go to the Actions settings of this action (path: *Exposures*)
  - At *Scope*, click *Effects* (path: *Exposures / Effects*)
    - At *Effects data source* with browse to the file *Effect - Steatosis.xlsx* and *Select*

- At *Effect settings* for *Focal effect* select *Steatosis-liver* and press 🖫 *Save Changes*
- In the green navigation bar, click *Exposures* to go up one level

- At *Scope*, click *Foods* (path: *Exposures / Foods*)
  - At *Foods data source* with ✎ browse to the file *Foods.xlsx* and *Select*
  - In the green navigation bar, click *Exposures* to go up one level
- At *Scope*, click *Substances* (path: *Exposures / Substances*)
  - At *Substances data source* with ✎ browse to the file *Substances.xlsx* and *Select*
  - At *Substance settings*
    - for *Index substance* select *Cyproconazole* and press 🖫 *Save Changes*
  - In the green navigation bar, click *Exposures* to go up one level
- At *Inputs*, click *Dietary exposures* (path: *Exposures / Dietary exposures*)
  - At *Inputs*, click *Consumptions by modelled food* (path: *Exposures / Dietary exposures / Consumptions by modelled food*)
    - At *Inputs*, click *Consumptions* (path: *Exposures / Dietary exposures / Consumptions by modelled food / Consumptions*)
      - At *Consumptions data source* with ✎ browse to the file *Consumptions.xlsx* and *Select*
      - At *Consumptions data selection* with ✎ open the food consumption surveys selection.
        - The file contains two surveys, but only one is allowed. So deselect everything by clicking ✓ on the first line, next to the word *Code*
        - Now select *DNFCS_2003* and press *Save* (the red warning ⚠ should now be gone)
      - In the green navigation bar, click *Consumptions by modelled food* to go up one level
    - At *Inputs*, click *Food conversions* (path: *Exposures / Dietary exposures / Consumptions by modelled food / Food conversions*)
      - At *Inputs*, click *Modelled foods* (path: *Exposures / Dietary exposures / Consumptions by modelled food / Food conversions / Modelled foods*)
        - At *Inputs*, click *Concentrations* (path: *Exposures / Dietary exposures / Consumptions by modelled food / Food conversions / Modelled foods / Concentrations*)
          - At *Concentration data source* with ✎ browse to the file *ConcentrationData.xlsx* and *Select*
          - In the green navigation bar, click *Food conversions* to go up two levels
      - At *Inputs*, click *Food recipes* (path: *Exposures / Dietary exposures / Consumptions by modelled food / Food conversions / Food recipes*)
        - At *Food recipes data source*, with ✎ browse to the file *FoodRecipes.xlsx* and *Select*
        - In the green navigation bar, click *Dietary exposures* to go up three levels
    - At *Inputs*, click *Concentration models* (path: *Exposures / Dietary exposures / Concentration models*)
      - At *Inputs*, click *Relative potency factors* (path: *Exposures / Dietary exposures / Concentration models / Relative potency factors*)
        - At *Relative potency factors data source* with ✎ browse to the file *RelativePotencyFactors.xlsx* and *Select*
        - In the green navigation bar, click *Dietary exposures* to go up two levels
    - At *Inputs*, click *Processing factors* (path: *Exposures / Dietary exposures / Processing factors*)
      - At *Processing factors data source* with ✎ browse to the file *ProcessingFactors.xlsx* and *Select*
      - In the green navigation bar, click *Dietary exposures* to go up one level

- At *Inputs*, click *Active substances (optional)* (path: *Exposures / Dietary exposures / Active substances*)
  - At *Inputs*, click *Points of departure* (path: *Exposures / Dietary exposures / Active substances / Points of departure*)
    - At *Points of departure data source* with ✎ browse to the file *HazardDoses - Triazoles.xlsx*
    - In the green navigation bar, click *Dietary exposures* to go up two levels
  - At *Dietary exposure settings*, for *Dietary exposure calculation tier* select *EFSA 2012 Optimistic*, and press 🖫 *Save Changes*
  - In the green navigation bar, click *Exposures* to go up one level
- At *Inputs*, click *Non-dietary exposures* (path: *Exposures / Non-dietary exposures*)
  - At *Non-dietary exposures data source* with ✎ browse to the file *NonDietaryExposures.xlsx* and *Select*
- Now run the model, by pressing the ▶ run icon in the grey bar.

Try to find the following results:

1. Exposure percentiles daily intakes with uncertainty bounds
2. Substance with highest contribution to the total exposure distribution
3. The modelled food measured with the highest contribution to the upper tail of the exposure distribution

### 2.3.4 Example 2

In this example we will elaborate on the previous one with kinetic models.

- Go to the Actions settings ⚙ of this action (path: *Exposures*)
  - At *Inputs*, click *Kinetic models (default)* (path: *Exposures / Kinetic models*)
    - At *Kinetic models data source* with ✎ browse to the file *UserGroupDemo-KineticModelsArtificial.xlsx* and *Select*
    - At *Kinetic model settings* for *Kinetic model* select *Cosmos Version 5*
- Now run the model, by pressing the ▶ run icon in the green bar.

## 2.4 Hazard characterisations from PoDs

### 2.4.1 Introduction

The goal of this exercise is to try to establish hazard characterisations from PoDs (NOAELs).

### 2.4.2 Preparation

If you haven't done so, in the workspace browser (use the 🗔 icon), create a new workspace named *Examples*, using the +.

The data files used in the example(s) in this section, are located in the data folder *Documentation-Examples / Exercise Hazard characterisations*.

### 2.4.3 Example 1

In this example, Imazalil target dose from NOAEL will be calculated.

- In the *Examples* workspace, create a new action (using +)
  - Then select ✓ *Show all action types*, and select *Hazard characterisations*
  - Name it *TargetDoseImazalil*
  - Use as Hazard characterisation settings

- Risk type: *Chronic*
- Target level: *External*

- Press Create

- Then go to the Actions settings ⚙ of this action.
  - At *Scope*, click *Effects* (path: *Hazard characterisations / Effects*)
    - At *Effects data source* with ✎ browse to the file *Effects and AOP Network Steatosis.xlsx* and *Select*
    - At *Effects selection* with ✎
      - Deselect everything by clicking ✓ on the first line, next to the word *Code*
      - On the second page, select only *Steatosis-liver*, and 🖫 Save
    - At *Effect Settings* for *focal effect* select *Steatosis-liver* and press 🖫 Save Changes.
    - In the green navigation bar, click *Hazard characterisations* to go up one level
  - At *Scope*, click *Substances* (path: *Hazard characterisations / Substances*)
    - At *Substances data source* with ✎ browse to the file *TargetDosescalculation-Substances.xlsx* and *Select*
    - At *Substances selection* with ✎
      - Deselect everything, by clicking the ✓ on the first line, next to the word *Code*
      - Select only *Imazalil*, and 🖫 Save
      - In the green navigation bar, click *Hazard characterisations* to go up one level
  - At *Inputs*, click *Points of departure* (path: *Hazard characterisations / Points of departure*)
    - At *Points of departure data source* with ✎ browse to the file *TargetDosesCalculation-HazardDoses.xlsx* and *Select*
    - In the green navigation bar, click *Hazard characterisations* to go up one level
  - At *Hazard characterisations settings*, for *Expression type* select *NOAEL (convert all hazard characterisations as NOAELs)*
  - At *Hazard characterisations settings*, Select ✓ Use inter-species conversions
  - At *Hazard characterisations settings*, Select ✓ Use intra-species factors, and press 🖫 Save Changes
- Now run the model, by pressing the ▶ run icon in the grey bar.

Try to find the following results:

1. The NOAEL for Imazalil used as point of departure.
2. The target hazard dose based on the default assessment factors 1/10 and 1/10 for inter-species and within-species conversion.

Answers:

- In the grey bar, browse to the results panel by clicking the ◔ icon and click on the latest output (path: *Results / TargetDoseImazalil*)
  - In the *Hazard characterisations* tab, browse in the tree (unfold by clicking › where necessary) to ˅ *Available hazard characterisations*
    - The NOAEL for Imazalil is 40 µg/kg bw/day.

## 2.5 Health impact estimates

### 2.5.1 Introduction

The goal of this exercise is to assess a health impact estimate.

### 2.5.2 Preparation

If you haven't done so, in the workspace browser (use the icon), create a new workspace named *Examples*, using the +.

The data files used in the example(s) in this section, are located in the data folder *Documentation-Examples / Exercise Health Impact*.

### 2.5.3 Example 1

- In the *Examples* workspace, create a new action (using +)
  - Then select ✓ *Show all action types*,select *Risks*
  - Name it *Risks*
  - Press *Create*
- Then go to the Actions settings of this action (path: *Risks*)
  - At *Scope*, click *Effects* (path: *Risks / Effects*)
    - At *Effects data source* with browse to the file *Effects and AOP Network Steatosis.xlsx* and *Select*
    - At * Effect settings*, for *focal effect* select *Steatosis-liver* and press *Save Changes*
    - In the green navigation bar, click *Risks* to go up one level
  - At *Scope*, click *Foods* (path: *Risks / Foods*)
    - At *Foods data source* with browse to the file *Foods.xlsx* and *Select*
    - In the green navigation bar, click *Risks* to go up one level
  - At *Scope*, click *Substances* (path: *Risks / Substances*)
    - At *Substances data source* with browse to the file *Substances.xlsx* and *Select*
    - At *Substance settings*, for *index substance* select *Cyproconazole*, and press *Save Changes*
    - In the green navigation bar, click *Risks* to go up one level
  - At *Inputs*, click *Exposures* (path: *Risks / Exposures*)
    - At *Inputs*, click *Dietary exposures* (path: *Risks /Exposures / Dietary exposures*)
      - At *Inputs*, click *Consumptions by food measured* (path: *Risks /Exposures / Dietary exposures / Consumptions by modelled food*)
        - At *Inputs*, click *Consumptions* (path: *Risks /Exposures / Dietary exposures / Consumptions by modelled food / Consumptions*)
          - At *Consumptions data source* with browse to the file *Consumptions.xlsx* and *Select*
          - At *Consumptions data selection* with open the food consumption surveys selection.
            - The file contains two surveys, but only one is allowed. So deselect everything by clicking ✓ on the first line, next to the word *Code*
            - Now select *DNFCS_2003* and press *Save* (the red warning ⚠ should now be gone)
          - At *Consumptions settings* for *Food survey* select *DNFCS_2003* and press *Save Changes*
          - In the green navigation bar, click *Consumptions by modelled food* to go up one level

- At *Inputs*, click *Food conversions* (path: *Risks /Exposures / Dietary exposures / Consumptions by modelled food / Food conversions*)
  - At *Inputs* click *Food as modelled* (path: *Risks /Exposures / Dietary exposures / Consumptions by modelled food / Food conversions / Food as modelled*)
    - At *Inputs*, click *Concentrations* (path: *Risks /Exposures / Dietary exposures / Consumptions by modelled food / Food conversions / Food as modelled / Concentrations*)
      - At *Concentrations data source* with ✎ browse to the file *UserGroupDemo-ConcentrationData.xlsx* and *Select*
      - In the green navigation bar, click *Food conversions* to go up two levels
    - At *Inputs*, click *Food recipes* (path: *Risks /Exposures / Dietary exposures / Consumptions by modelled food / Food conversions / Food recipes*)
      - At *Food recipes data source* with ✎ browse to the file *UserGroupDemo-FoodRecipes.xlsx* and *Select*
      - In the green navigation bar, click *Dietary exposures* to go up three levels
- At *Inputs*, click *Processing factors* (path: *Risks /Exposures / Dietary exposures / Processing factors*)
  - At *Processing factors data source* with ✎ browse to the file *UserGroupDemo-ProcessingFactors.xlsx* and *Select*
  - In the green navigation bar, click *Risks* to go up three levels

- At *Inputs*, click *Hazard chararcterisations* (path: *Risks / Hazard chararcterisations*)
  - At *Inputs*, click *Active substances* (path: *Risks / Hazard chararcterisations / Active substances*)
    - At *Inputs*, click *Points of departure* (path: *Risks / Hazard chararcterisations / Active substances / Points of departure*)
      - At *Points of departure data source* with ✎ browse to the file *UserGroupDemo-HazardDoses.xlsx* and *Select*
      - In the green navigation bar, click *Active substances* to go up one level
    - At 'Active substances' click ⚙ Compute

## 2.6 Assessment group membership probabilities

### 2.6.1 Introduction

The goal of this exercise is to assess group membership probabilities.

### 2.6.2 Preparation

If you haven't done so, in the workspace browser (use the 🗔 icon), create a new workspace named *Examples*, using the +.

The data files used in the example(s) in this section, are located in the data folder *Documentation-Examples / Exercise Dietary Exposure Assessment*.

### 2.6.3 Example 1

- In the *Examples* workspace, create a new action (using +)
  - Then select *Dietary exposures*
  - Name it *Dietary exposures*

- Use as Dietary exposures settings
  - Tier: *EFSA Guidance Optimistic*
  - Risk type *Chronic*
  - Select ✓ *Cumulative*
- Press *Create*

- Then go to the actions settings ⚙ of this action (path: *Dietary exposures*)
  - At *Scope*, click *Foods* (path: *Dietary exposures / Foods*)
    - At *Foods data source* with ✎ browse to the file *UserGroupDemo-Foods.xlsx* and *Select*
    - In the green navigation bar, click *Dietary exposures* to go up one level
  - At *Scope*, click *Substances* (path: *Dietary exposures / Substances*)
    - At *Substances data source* with ✎ browse to the file *UserGroupDemo-Substances.xlsx* and *Select*
    - At *Substance settings* for *Index substance* select *Cyproconazole* and press 🖫 *Save Changes*
    - In the green navigation bar, click *Dietary exposures* to go up one level
  - At *Scope*, click *Effects* (path: *Dietary exposures / Effects*)
    - At *Effects data source* with ✎ browse to the file *Effect - Steatosis.xlsx* and *Select*
    - At *Effect Settings* for *focal effect* select *Steatosis-liver* and press 🖫 *Save Changes*
    - In the green navigation bar, click *Dietary exposures* to go up one level.
  - At *Inputs*, click *Consumptions by modelled food* (path: *Dietary exposures / Consumptions by modelled food*)
    - At *Inputs*, click *Consumptions* (path: *Dietary exposures / Consumptions by modelled food / Consumptions*)
      - At *Consumptions data source* with ✎ browse to the file *UserGroupDemo-Consumptions.xlsx* and *Select*
      - At *Consumption settings* for *Food survey* select *DNFCS_2003* and press 🖫 *Save Changes*
      - In the green navigation bar, click *Consumptions by modelled food* to go up one level
    - At *Inputs*, click *Food conversions* (path: *Dietary exposures / Consumptions by modelled food / Food conversions*)
      - At *Inputs*, click *Modelled foods* (path: *Dietary exposures / Consumptions by modelled food / Food conversions / Modelled foods*)
        - At *Inputs*, click *Concentrations* (path: *Dietary exposures / Consumptions by modelled food / Food conversions / Modelled foods / Concentrations*)
          - At *Concentrations data source* with ✎ browse to the file *UserGroupDemo-ConcentrationData.xlsx* and *Select*
          - In the green navigation bar, click *Food conversions* to go up two levels
      - At *Inputs*, click *Food recipes* (path: *Dietary exposures / Consumptions by modelled food / Food Food recipes*)
        - At *Food recipes data source*, with ✎ browse to the file *UserGroupDemo-FoodRecipes.xlsx*
        - In the green navigation bar, click *Dietary exposures* to go up three levels
  - At *Inputs*, click *Concentration models* (path: *Dietary exposures / Concentration models*)
    - At *Inputs*, click *Relative potency factors* (path: *Dietary exposures / Concentration models / Relative potency factors*)

        - At *Relative potency data source* with ✎ browse to the file *UserGroupDemo-RelativePotencyFactors.xlsx* and *Select*
        - In the green navigation bar, click *Dietary exposures* to go up two levels
    - At *Inputs*, click *Processing factors* (path: *Dietary exposures / Processing factors*)
        - At *Processing factors data source* with ✎ browse to the file *UserGroupDemo-ProcessingFactors.xlsx* and *Select*
        - In the green navigation bar, click *Dietary exposures* to go up one level
    - At *Inputs*, click *Active substances (optional)* (path: *Dietary exposures / Active substances*)
        - At *Inputs*, click *Points of departure* (path: *Dietary exposures / Active substances / Points of departure*)
            - At *Points of departure data source*, with ✎ browse to the file *HazardDoses - Triazoles.xlsx*
            - In the green navigation bar, click *Dietary exposures* to go up two levels
- Now run the model, by pressing the ▶ run icon in the grey bar.

Try to find the following results:

1. Exposure percentiles daily intakes
2. Substance with highest contribution to the total exposure distribution
3. The food-as-measured with the highest contribution to the upper tail of the exposure distribution

### 2.6.4 Example 2

Repeat the run of the previous task, but instead of the nominal run, now do an uncertainty analysis loop.

- Click on the ⚙ icon (in the grey bar) to open the uncertainty settings panel, and check ✓ *Perform uncertainty analysis*
    - For *Monte Carlo iterations per uncertainty run* choose *100*, and press 🖫 *Save Changes*
- Now run the model, by pressing the ▶ run icon in the grey bar.

Compare with the previous results, to find:

1. Exposure percentiles daily intakes with uncertainty bounds
2. Substance with highest contribution to the total exposure distribution
3. The food-as-measured with the highest contribution to the upper tail of the exposure distribution

# Part II

# Reference Manual

CHAPTER

THREE

# MODULES

MCRA is a modular system. The diagram in Figure 3.1 shows the modules and their relations. Each module is associated with its own type of data, and is linked to one or more other modules. Note that not all details can be fully shown in the scheme, for details consult the table below, which specifies all relations between the modules in MCRA.

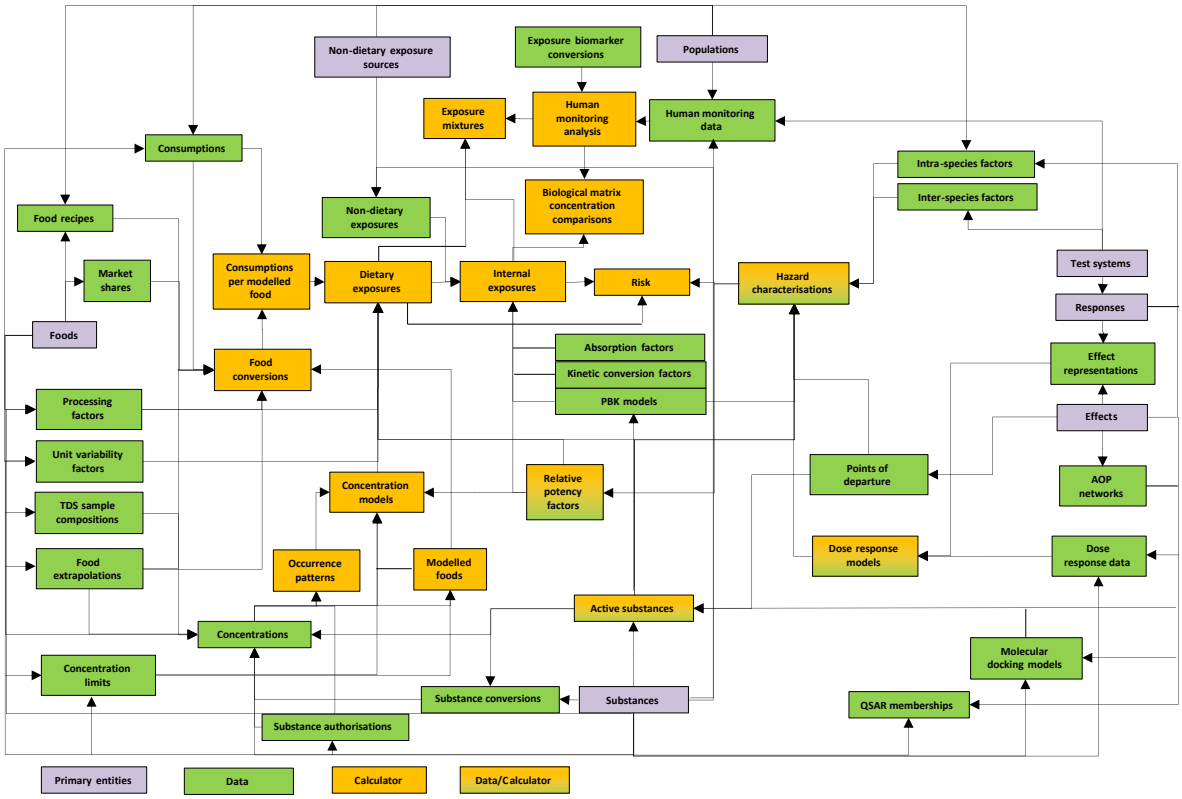



Figure 3.1: Modular design of MCRA.

## 3.1 Primary entity modules

The MCRA modular system is based on six primary entities, defining who (*Populations*) is to be protected against what impact (*Effects*) caused by what agent (*Substances*) originating from where (*Foods*), with an indication how the effects are quantified (*Responses* in *Test systems*).

### 3.1.1 Effects

Effects are biological or toxicological consequences for human health, that may result from chemical exposure and are the focus of hazard or risk assessment.

Output of this module is used by: *Food concentration models High exposure food-substance combinations Dietary exposures Exposure mixtures QSAR membership models Molecular docking models Active substances Relative potency factors Hazard characterisations Points of departure Effect representations Inter-species conversions Intra species factors AOP networks Exposure response functions Burden of disease Risks Single value risks*

#### Effects from data

#### Effects calculation

Option *Multiple effects analysis* selects multiple selects. Effects are selected using **Effects selection**. Press **Clear filter** and/or **change selection** and select multiple effects in the scroll down box. If both this option and *Include related effects of AOP network* is unchecked, it is obligatory to select one and only one effect. If *Include related effects of AOP network* is checked, a **Focal effect** is specified and all related effects in the *AOP network* are selected as well.

#### Effects data formats

Effects are primary entities of the data model. Health effects are defined as (critical) changes relative to a treatment or exposure.

Download empty dataset template: Zipped CSV Excel

#### Effects

Effects are uniquely identified by a code (idEffect). Optionally, a name and description can be added. Health effects are commonly distinguished in two types, acute and chronic. Further properties may be specified, e.g. in relation to decision schemes such as the use of thresholds of toxicological concern (TTCs).

Table 3.1: Table definition for Effects.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idEffect | AlphaNumeric (50) | Unique identification code of the effect. | idEffect, EffectId, CodeFocalEffect, Id, Code, KeyEvent, idKeyEvent | Yes |
| CodeSystem | AlphaNumeric (100) | Identifier of the coding system of the effect code. | CodeSystem | No |
| Name | AlphaNumeric (100) | Name of the effect. | Name | No |
| Description | AlphaNumeric (200) | Additional description or label of the effect. | Description | No |
| BiologicalOrganisation | *BiologicalOrganisationType* | Biological organisation of the effect: Molecular, Cellular, Tissue, Organ, Individual, Population. This is in line with AOP wiki terminology and can be used for grouping. | BiologicalOrganisation | No |
| KeyEventProcess | AlphaNumeric (100) | Description of AOP Key event component process. E.g., receptor signalling. | Process | No |
| KeyEventObject | AlphaNumeric (100) | Description of AOP Key event component object. E.g., PPAR-alpha. | Object | No |
| KeyEventAction | AlphaNumeric (100) | Description of AOP Key event component action. E.g., decreased. | Action | No |
| KeyEventOrgan | AlphaNumeric (100) | Description of AOP Key event organ. E.g., liver. | Organ | No |
| KeyEventCell | AlphaNumeric (100) | Description of AOP Key event organ. E.g., hepatocyte. | Cell | No |
| AOPwikiKE | AlphaNumeric (200) | Key event ID number in AOP wiki https://aopwiki.org/events Several ID possible Some effects might not be in the wiki, and this field will be empty. | AOPWikiIds, AOPwikiKE | No |
| Reference | AlphaNumeric (200) | External reference(s) to sources containing more information about the AOP key event. E.g., the AOP wiki, and the associated AOP wiki Ids. | References | No |

Accepted table names: Effects, Effect, KeyEvents, KeyEvent.

### Effects settings

#### Selection settings

Table 3.2: Selection settings for module Effects.

| Name | Type | Description |
|---|---|---|
| Multiple effects analysis | Boolean | Specifies whether the analysis should consider multiple effects. Otherwise, a single focal effect should be selected. |
| Focal effect | AlphaNumeric | The main (health) effect of interest. |
| Include related effects of AOP network | Boolean | Include all related key events of the AOP network. |

#### Effects as data

Effect definitions are provided as lists/catalogues of effect definitions.

- *Effects data formats*
- *Effects from data*
- *Effects calculation*

### 3.1.2 Foods

Foods are uniquely defined sources of dietary exposure to chemical substances. Foods may refer to 1) foods as eaten, foods as coded in food consumption data (e.g. pizza); 2) modelled foods, foods as coded in concentration data (e.g. wheat, tomato); 3) any other type of food (e.g. ingredients like flour, tomato sauce).

Output of this module is used by: *Consumptions Single value consumptions Market shares Food recipes Food concentrations Food concentration distributions Single value concentrations Processing factors Unit variability factors Occurrence patterns Occurrence frequencies Substance authorisations Deterministic substance conversion factors Concentration limits Food concentration models Modelled foods Focal food concentrations Total diet study sample compositions Food extrapolations Food conversions Consumptions by modelled food High exposure food-substance combinations Dietary exposures Single value dietary exposures*

#### Foods from data

#### Foods data formats

Foods are of interest in (dietary) consumption assessments and the sources of exposure within exposure assessments. The foods table is the main table of the food definitions. Relevant food related data, such as processing types, additional properties (e.g., unit weight and brand loyalty), facets, and hierarchies, can be described in the food properties, food hierarchies, and faces and facet descriptors tables.

Download empty dataset template: Zipped CSV Excel

#### Foods

Each food is identified by a unique code (idFood) in a code system of choice, a name, and a description. Food codes can have a hierarchical structure (as in the FoodEx1 coding systems), using '.' or '$' as separator between adjacent hierarchical levels, e.g. 'A.05' is fruits and fruit products, 'A.05.01' is citrus fruits, and 'A.05.01.001' is grapefruit (citrus paradisi). Additional forms of foods, such as foods in processed form, can be specified via food facets according to the FoodEx2 system of EFSA.

Table 3.3: Table definition for Foods.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFood | AlphaNumeric (50) | The unique identification code of the food. | idFood, Code, FoodId, FoodCode, Food, Id | Yes |
| Name | AlphaNumeric (100) | The name of the food. | Name, FoodName | No |
| Description | AlphaNumeric (200) | Food description. | Description | No |

Accepted table names: Foods, Food.

### Food properties

Additional food properties. This table is deprecated. See table FoodUnitWeights which partly replaces this table for data on food unit weights.

Table 3.4: Table definition for Food properties.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFood | AlphaNumeric (50) | The code of the food to which the property is attached. The provided food code should match with a code of the foods table. | idFood, FoodId, Food, FoodCode, Code | Yes |

Accepted table names: FoodProperties, FoodProperty.

### Food unit weights

Food unit weights as specified for a food, and possibly a location.

Table 3.5: Table definition for Food unit weights.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFood | AlphaNumeric (50) | The unique identification code of the food. | idFood, Code, FoodId, FoodCode, Food, Id | Yes |
| Location | AlphaNumeric (50) | The location for which this food unit weight is defined. If not specified, then the value is considered a default unit weight that can be used when there is no location specific unit weight. | Location | No |
| ValueType | *UnitWeightValueType* | The value type of the unit weight value (i.e., raw agricultural commodity or edible portion). Controlled terminology. | ValueType, UnitWeightValueType | No |
| Qualifier | *ValueQualifier* | Qualifier of the unit weight value, e.g. equal-to (=) or smaller-than (<). If omitted, = is assumed. | Qualifier, QualifierType | Yes |
| Value | Numeric | Unit weight value in grams. | Value, UnitWeightValue, UnitWeight | Yes |
| Reference | AlphaNumeric (200) | External reference(s) to source of the unit weight value. | Reference, References | No |

Accepted table names: FoodUnitWeights, UnitWeights.

### Food hierarchies

Food items are commonly categorised in hierarchies, e.g. oranges and mandarins are citrus fruits. For example FoodEx is a food description and food classification (FDFC) system consisting of a large number of individual food items aggregated into food groups and broader food categories in a hierarchical structure of parent-child relationships.

Table 3.6: Table definition for Food hierarchies.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFood | AlphaNumeric (50) | Food node. | idFood, FoodId, Food, Code | Yes |
| idParent | AlphaNumeric (50) | Parent node of the food. | idParent, ParentId, Parent, ParentCode | Yes |

Accepted table names: FoodHierarchies, FoodHierarchy, FoodsHierarchy.

### Facets

Food codes can be linked to facets, as e.g. in FoodEx2. FoodEx2 is a comprehensive food classification and description system aimed at covering the need to describe food in data collections across different food safety domains.

See the EFSA catalogue browser for facets currently used e.g. the facet to describe processing technology is: F28 process.

Table 3.7: Table definition for Facets.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFacet | AlphaNumeric (10) | The food code of the food to which the facet is attached. | idFacet, Code, Id, FacetCode, FacetId | Yes |
| Name | AlphaNumeric (200) | Facet name | Name, FacetName | No |
| Description | AlphaNumeric (200) | Additional description of the facet. | Description | No |

Accepted table names: Facets, Facet, FoodFacets, FoodFacet.

### Facet descriptors

Facet descriptors are elements of additional information on a facet such as processing.

Table 3.8: Table definition for Facet descriptors.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFacet-Descriptor | AlphaNumeric (10) | The identification code of the facet descriptor. | idFacet-Descriptor, Code, Id, FacetCode, FacetId | Yes |
| Name | AlphaNumeric (200) | The name of the facet descriptor. | Name, Facet-DescriptorName | No |
| Description | AlphaNumeric (200) | Additional description of the facet descriptor. | Description | No |

Accepted table names: FacetDescriptors, FacetDescriptor, FoodFacetDescriptors, FoodFacetDescriptor.

### Processing types

Table 3.9: Table definition for Processing types.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idProcessing-Type | AlphaNumeric (50) | The unique identification code of the processing type. | idProcessing-Type, ProcessingType-Id, ProcType, Id | Yes |
| Name | AlphaNumeric (100) | The processing name. | ProcName, Name | No |
| Description | AlphaNumeric (200) | The processing type description. | Description | No |
| Distribution-Type | *Processing-DistributionType* | The distribution type. Simulated processing factors are restricted to the interval (0,1) using a logistic-normal distribution (default) or simulated processing factors are restricted to positive values using a log-normal distribution. | Distribution-Type, DistType | No |
| Bulking-Blending | Boolean | For types of processing applied on large batches, e.g., juicing, sauce/puree. Default is no bulking blending. | Bulking-Blending, BulkBlending, IsBulkBlending | No |

Accepted table names: ProcessingTypes, ProcessingType.

### Food consumption quantifications

Food consumption quantifications record information about food consumption quantities that are associated with unit-consumptions of foods.

Table 3.10: Table definition for Food consumption quantifications.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFood | AlphaNumeric (50) | The food code of the quantification. | idFood, FoodId, Food | Yes |
| idUnit | AlphaNumeric (50) | The code of the unit of consumption. E.g spoon, plate, cup. Units may depend on food. | idUnit, UnitId, Unit | Yes |
| UnitWeight | Numeric | The unit weight/portion size of the food, specified in grams. | UnitWeight | Yes |
| UnitWeight-Uncertainty | Numeric | The uncertainty in unit weight/portion size (%). | UnitWeight-Uncertainty, UnitWeight% | No |
| Amount-Uncertainty | Numeric | The uncertainty in amount consumed (%). The label 'general' specifies a default value for the uncertainty when specific information for combinations of food and unit in food consumptions table is not available. | Amount-Uncertainty, Amount% | No |

Accepted table names: FoodConsumptionQuantifications, FoodConsumptionQuantification.

### Foods as data

Food definitions are provided as lists/catalogues of food definitions, optionally with encompassing processing type definitions, facet definitions, hierarchy definitions, and additional food property information.

- *Foods data formats*
- *Foods from data*

### Food coding systems

MCRA is intended to retain complete transparence of the results of risk assessment in terms of the foods that were actually consumed (foods-as-eaten). In many cases measurements of substances have not been made on the **food-as-eaten**, e.g. pizza, but on a raw agricultural commodity (RAC), e.g. tomato, onion etc. The food on which the concentration measurements have been made is termed the **modelled food**. MCRA implements a *recursive search algorithm* to link foods-as-eaten to modelled foods. This means that there can be intermediate steps, e.g. if unpeeled *apple* and *grapes* are the modelled foods, the food-as-eaten *apple pie* contains *peeled apple* and *raisins*, *peeled apple* is linked to unpeeled *apple*, and *raisins* are dried *grapes*. *Peeled* and *dried* are the *processing types*.

### Food classification: FoodEx1

### Food code definition

In MCRA, a food code is a string consisting of symbols. Some special symbols (., $, -, #) are reserved for special use (see below), and can not be used freely in own codes.

Codes can be hierarchical. Any code can be followed by $ or . plus a subtype code. This can be repeated any number of times, e.g. A$B$C$D, or A.B.C.D.

Codes can specify the food processing type (e.g. peeling). Any code can be followed by a hyphen ('-') plus a processing type code (e.g. FP0226-2). More than one level of processing code is allowed (e.g. FP0226-2-13). Subtype codes should precede processing codes (e.g. NL005$123$456-2).

### Food codes in consumption surveys

Any coding system for foods-as-eaten can be used in MCRA. For example, in Europe EFSA develops a Food Classification and Description System for exposure assessment named FoodEx 2 (EFSA (2011a), EFSA (2011b)), featuring a hierarchical system of a core list of foods, an extended list, and domain-specific hierarchies.

### Food codes in concentration data

Any coding system for modelled foods can be used in MCRA.

### Food processing

Concentrations of substances in foods may change when foods are processed. Examples of *processing types* are peeling (e.g. of apples), cooking (e.g. of spinach), drying (e.g. of grapes), juicing (e.g. of oranges). In MCRA a processing factor can be specified for any food. Processing factors specify the ratio of concentrations in the processed and unprocessed food. The food code of the processed food (e.g. FP0226-2) will be converted to the food code of the unprocessed food (FP0226) and a processing type (2). In an exposure assessment, the concentration in the unprocessed food will then be multiplied by the processing factor. Special attention is needed when food processing also includes changes of the weight of the food. Traditionally, processing factors combine the effects of chemical alteration and weight change, so the weight change should not be double-counted. The *processing correction factor* is introduced to correct processing factors that combine both effects, e.g. when 100g *raisins* (dried grapes) are translated to 300g *grape* (modelled food) and the processing factor for drying combines both effects, the processing correction factor is 3.

### Recipes and food translation

*Recipes* specify the composition of composite foods, e.g. *pizza*, in terms of relevant ingredients, e.g. 100g pizza contains 10g *tomato*, 5g *cheese* and 50g *flour*. Recipes are also used to specify weight changes, e.g. to obtain 100g *raisins* (dried grapes) 300g of the modelled food *grape* is needed, see also *processing correction*.

A special use of recipes and food translation is found in *Total Diet Studies*. Here, the composition of a Total Diet Study food is specified, e.g. TDS-food *FruitMix* is composed of *apple*, *orange* and *pear* with a default translation proportion of 100%. So in MCRA, the food-as-eaten *apple* is converted to *FruitMix* (100%) and *FruitMix* is considered as the modelled food (TDS-food). A conversion from *apple-pie* (food-as-eaten) to *FruitMix* (modelled food) is based on a recipe for apple-pie and a TDS composition for FruitMix.

Another use of converting foods (as-eaten or as an intermediate step), is through the specification of so-called food extrapolations (read across translations), e.g. for *pineapple* no measurements are found but by specifying that *pineapple* is converted to *FruitMix* (with a default proportion of 100%), the TDS sample concentration value of *FruitMix* will be used for *pineapple* (as-eaten or as ingredient).

### Market shares and brand loyalty

Sometimes measurements of substances in food are available at a more detailed food coding level than consumption data. For example, measurements may have been made for specific brands of a food whereas the consumption survey did not record the brand. MCRA allows to specify market share data for subtypes of a food (e.g. A$1, A$2, A$3 are three brands of food A), and to calculate acute exposure based on such *market shares*.

### Supertypes

Sometimes measurements of substances on food are available at a less detailed food coding level than consumption data. MCRA allows to use the concentration data of a supertype for all underlying food codes. However, this is not the default, and an explicit permission should be given to allow this feature.

### Maximum Residue Levels

Maximum residue levels are the upper legal levels of a concentration for substance residues in a food, e.g. pesticide, or feed based on good agricultural practices and to ensure the lowest possible consumer exposure.

### MCRA food code conversion algorithm

The conversion algorithm links food as eaten codes to modelled food codes using a *7-step procedure*.

### Food classification: FoodEx2

'The collection and evaluation of data on levels of chemical occurrence or presence of biological agents in food and feed are important tasks of *EFSA*. By combining the data with information on food consumption allows for detailed intake and exposure estimates crucial to any food and feed safety risk assessment or nutrient adequacy analysis. The EU Member States provide an increasing volume of data to EFSA and other European bodies. To provide a common link to all the diverse food and feed databases, a system for the unique and universal identification and characterisation of food and feed items is essential. *EFSA* has developed a preliminary standardised food classification and description system called FoodEx2 (version 2 of the EFSA Food Classification and Description System [FCDC] for exposure assessment). The system consists of descriptions of a large number of individual food items aggregated into food groups and broader food categories in a hierarchical parent-child relationship. Central to the system is a common 'core list' of food items or generic food descriptions that represent the minimum level of detail needed for intake or exposure assessments. More detailed terms may exist in addition to the core list and these are identified as the 'extended list'. A parent-child relationship exists between a core list food item and its related extended list food items. The terms of the core and extended list may be aggregated in different ways according to the needs of the different food safety domains. In the present version four hierarchies are proposed: three domain-specific and a general purpose one. Facets are used to add further detail to the information provided by the food list term. Facets are collections of additional terms describing properties and aspects of foods from various perspectives'. For more information visit: http://www.efsa.europa.eu/en/datex/datexfoodclass.htm.

For MCRA, having a different set of food codes is in itself not a problem. That is, for MCRA, it does not matter how foods are coded, as long as they can be linked to consumptions and concentrations within an exposure assessment. What makes FoodEx2 different from other food coding systems is that it provides additional food hierarchies, food facets, and a combined food/facet coding system. Below follows a brief summary of these main features of the FoodEx 2 coding system from the perspective of exposure assessment using MCRA.

### Foods and food hierarchies

FoodEx 2 contains different food hierarchy definitions and allows for creation of custom food hierarchy definitions. These hierarchies could, for exposure assessment, allow to assess intake or consumption data based on the groups defined by these hierarchies.

Table 3.11: Food hierarchy export from FOODEX 2.0 Browser version 0.1.3

| Code | Level | Name | ParentCode | Scopenotes |
|---|---|---|---|---|
| A000J | 1 | Grains and grain-based products | ROOT | The category covers all … |
| A000K | 2 | Cereals and similar | A000J | … |
| A000l | 3 | Cereal and cereal-like grains | A000K | … |
| A000M | 4 | Amaranth grain | A000L | … |
| A000N | 5 | Buckwheat grain | A000L | … |
| A000P | 6 | Barley grain | A000L | … |
| … | … | … | … | … |

### Facets and facet descriptors

FoodEx 2 allows to provide supplementary details on specific aspects of foods by means of so-called facets and facet descriptors. Facets are collections of terms defining specific characteristics of food from particular points of view and facet descriptors describe specific characteristics foods. For example, *processing technology* is a facet, and *baking* is a facet descriptor belonging to this facet. Currently, 26 facets are defined, containing in total 2172 descriptors see EFSA (2011b). Facets are also defined in a hierarchical system. For instance, *cooking in fat (A07GR)* and *baking (A07GX)* are sub-items of the descriptor *cooking and similar thermal preparation processes (A0BA1)*. Facets are coded as small strings that consist of a facet code and a facet descriptor code separated by a '.'-character. For example, the facet code *F28.A07GX* holds

1. the facet code *F28*, which is the facet code for *process technology*, and
2. *A07GX* , which is the descriptor code for *baking*.

Table 3.12: Part of the FoodEx 2 facet descriptor codes of the source facet (F01).

| Code | Level | Name | ParentCode | Scopenotes |
|---|---|---|---|---|
| A04SF | 1 | Animals | ROOT | … |
| A056H | 2 | Mammals (food source animal) | A04SF | … |
| A056Z | 3 | Farmed / non-game mammals (food source animal) | A056H | … |
| A057A | 4 | African buffalo (food source animal) | A056Z | … |
| A057B | 4 | American buffalo (food source animal) | A056Z | … |
| A057C | 4 | Buffalo (food source animal) | A056Z | … |
| A057D | 4 | Cape buffalo (food source animal) | A056Z | … |
| A057E | 4 | Cattle (food source animal) | A056Z | … |
| … | … | … | … | … |

### Implicit facets

Implicit facets are facets of a product that are already implied by the food product itself. Consider, for example, *potato boiled (A011P)*, where *boiling (A011P)* is an implicit facet, because boiling is already implied by the product. According to EFSA (EFSA (2011a)) 'inclusion of implicit facets in the string recorded for each food database record is not encouraged' and it is suggested to identify and record the implicit facet descriptors in a separate table.

### Foods as facets

Foods and facet descriptors share the same unique alphanumerical coding system; in some cases, like *characterising ingredient or sweetening agent* food list elements may be used as facet descriptors.

### The FoodEx 2 coding system

In the coding system, facets can be added to the primary food codes to provide supplementary detailed information of particular data records. The structure of the FoodEx 2 codes is:

*idFood#idFacet.idFacetDescriptor$idFacet.idFacetDescriptor$….*

The code starts with the primary FoodEx2 food code. Then, when there are supplementary facets, the food code is followed by a '**#**'-character and the facets string. The facets string is constructed as a concatenation of the individual facets strings, separated by means of the '**$**' character. As an example, consider the string *A011P#F28.A07GL$F28.A07KQ* which is composed of:

- Food: *A011P - Potato boiled*
- Facet 1: *F28.A07GL - Process technology - Boiling*
- Facet 2: *F28.A07KQ - Process technology - Freezing*

### FoodEx2

For MCRA, FoodEx 2 introduces the following points of attention:

- Reading and dealing with FoodEx 2 coded data sets
- Reading and dealing with food facets
- Reading and exploiting food hierarchy data

### Reading and dealing with FoodEx 2 codes

All data entities that contain foods data are potentially affected by the introduction of FoodEx 2. In MCRA, the following data tables are adapted to allow for input of full FoodEx 2 food codes:

- Foods
- Consumptions
- Concentrations

For these tables, the food code is allowed to be the complete FoodEx 2 food code and automatically recognized as such. As an example, Table 3.13 shows how the FoodEx 2 coded consumptions should be provided to the system. On important note: the maximum field length of the food code is 50. This means that there is a maximum of five facets that can be specified for a food.

Table 3.13: Integrated coding of the facets in the consumed foods field of food consumptions. Implementation.

| Individual | DayOfSurvey | Food | Amount | FoodSurvey |
|---|---|---|---|---|
| 14233701 | 1 | A011R# F28.A07GX | 153.43 | FS01 |
| 18843004 | 1 | A011R# F28.A07GX | 125.23 | FS01 |
| 34025701 | 1 | A011R# F28.A07GX | 153.60 | FS01 |
| 14720005 | 2 | A011R# F28.A07GX | 105.00 | FS01 |
| 49174010 | 1 | A011R# F28.A07GX | 140.00 | FS01 |
| 62794010 | 1 | A011R# F28.A07GX | 67.00 | FS01 |
| 61392002 | 1 | A011P# F28.A07GL$F28.A07KQ | 104.72 | FS01 |
| 61281231 | 1 | A011P# F28.A07GL$F28.A07KQ | 109.72 | FS01 |

### Reading and dealing with facets data

Within MCRA, the following facets related aspects are accounted for:

- Reading facets data
- Dealing with facets
- Facets in concentration data
- Facets in food conversion
- Using facets as processing factors
- Using hierarchy data in the output

### Reading facets data

To incorporate input of facets data in MCRA, two tables Facets and FacetDescriptors are introduced as optional tables of the Foods data group. See table *Facets* and *Facet descriptors*.

Within MCRA, the facets of FoodEx 2 coded foods, consumptions, and concentrations are automatically linked to the provided facets and facet descriptors. Also, the facet descriptor names are added automatically to the foods containing these facets.

### Dealing with facets

The introduction of food facets allows for much more detailed specifications of consumption and concentration data. However, it introduces the problem of deciding on which level of detail the exposure assessment should be performed. That is, should concentration models be generated on the level of foods-without-facets or on the level of foods-with-facets? E.g., should the concentrations of *clementine peeled (A01CE#F28.A07LC)* and *clementine unprocessed (A01CE#F28.A0C0S)* be modelled separately or should one model be constructed for *clementine (A01CE)*? Treating all clementine's as equal may yield over-simplified conversions, whereas treating all separately may lead to many concentration models based on only few measurements. In MCRA, no implicit grouping of concentrations of equal foods with different facets is applied. If concentrations are provided for both *clementine peeled (A01CE#F28.A07LC)* and *clementine unprocessed (A01CE#F28.A0C0S)*, then these are modelled separately. Another question is whether the order of the facets is relevant or not. E.g., is *A0BYV#F02.A06GF$F03.A06HY* the same as *A0BYV#F03.A06HY$F02.A06GF*? Regarding this matter, MCRA considers the facet order to be important. I.e., *A0BYV#F02.A06GF$F03.A06HY* is not the same as *A0BYV#F03.A06HY$F02.A06GF*.

### Facets in food conversion

For conversion of foods-as-eaten to modelled foods, MCRA considers foods with different facet strings as different foods. I.e., there is no implicit conversion of foods-with-facets to foods-without-facets and also the order of the facets is important. However, as it is realistic to convert food-with-facets to the base food without facets, an additional (explicit) conversion step remove-all-facets is added that converts foods with facets to the base foods. I.e., the action is "remove all". There is no conversion step for "stripping off one facet at a time". The reason for this is that there

is no good way of deciding which facet to strip off first. This new conversion step is somewhat equivalent to the already existing default processing conversion step (step 6), and is therefore implemented as step 6b of the conversion algorithm. Particular rules followed by this step:

- Conversion of food-with-facets to food-without-facets.

### Using facets that reveal processing data

Facets containing processing information, such as *part-consumed-analysed (F20)* and *processing technology (F28)* could be integrated with processing data. As an example, consider *clementine peeled (A01CE#F28.A07LC)*. This could be linked to *clementine (A01CE)*, with processing type *removal of external layer (A07LC)*. Linking to processing data could be achieved by entering processing data using the facet codes. As an alternative to the current processing factor tables, a facet-based processing factors table is defined for processing facets. That is, the codes for food processed and unprocessed are implicitly defined for FoodEx 2.

Table 3.14: Example of a MCRA processing factors table using FoodEx 2 foods and facets codes.

| FacetCode | Substance | FoodCode | ProcNom | ProcUpp | ProcNomUncUpp | ProcUppUncUpp |
|---|---|---|---|---|---|---|
| A07LC | SubstanceX | A01CE | 0.5 | 0.6 | 0.05 | 0.06 |
| F28.A07GV | SubstanceX | A0BY | 0.2 | 0.1 | 0.03 | 0.04 |

Note that in the example, the facet code could be specified as the full facet code, or just the code of the facet descriptor. As a more elaborate example consider

*French fries from cut potato (A0BYV#F02.A06GF$F03.A06HY$F04.A00ZT$F28.A07GR)*

For this food code, the substring of the processing facet is extracted from the list of facets.

- *A0BYV#F02.A06GF$F03.A06HY$F28.A07GR$F04.A00ZT* with processing facet link A07GR
- *A0BYV#F02.A06GF$F03.A06HY$F04.A00ZT*

In MCRA, a table *Processing factors* is introduced that allows for specification of processing factors by means of facets. This table has the following structure:

Table 3.15: Table FacetDescriptors of the Food data group.

| Column name | Key | Required | Type | Size | Description |
|---|---|---|---|---|---|
| idProcessingType | Yes | Yes | String | 5 | The facet code of this processing factor definition. May be specified as full facet code, i.e., facet code plus facet descriptor code, or as the facet descriptor code. |
| idFood | Yes | Yes | String | 200 | The food code |
| idCompound | Yes | No | String | 50 | The substance for which this processing factor is defined. |
| Nominal | No | Yes | Double | | Nominal value (best estimate of 50th percentile) of processing factor (defines median processing factor) |
| Upper | No | Yes | Double | | Upper value (estimate of 95th percentile or "worst case" estimate) of processing factor due to variability |
| NominalUncertaintyUpper | No | Yes | Double | | Upper 95th percentile of nominal value (Nominal) due to uncertainty. A standard deviation for uncertainty of the nominal value (Nominal) is derived using the nominal value (Nominal) and upper 95th percentile (NominalUncertaintyUpper) |
| UpperUncertaintyUpper | No | Yes | Double | | Upper 95th percentile of upper value (Upper) due to uncertainty. From the nominal value (Nominal), upper value (Upper) and the specified uncertainties of these values (NominalUncertaintyUpper and UpperUncertaintyUpper, respectively) the degrees of freedom of a chi-square distribution describing the uncertainty of the standard |

The integration with the food conversion algorithm is as follows: Conversion step 2 (*processing*) is extended with a step 2c (*processing facet*) that attempts to match facets of a food code to processing data provided in the processing facets table. The following important rules are followed:

- Processing factors can be defined for base-food-code/facet-code combinations and translate as food-with-processing-facet to food-without-processing-facet.
- If multiple processing facets are present in the food-as-eaten code, then the last processing facet is used first for conversion.
- Facet processing factors can be specified using the full facet code (i.e., facet-code plus facet-descriptor-code) or just the facet descriptor code. If both are specified for the same food, the full facet code is used.
- Facet processing factors can be defined substance-specific, and non-substance-specific. Processing factors that are defined substance-specific always precede non-substance specific processing factors.
- Processing factors defined by a food-processed/food-unprocessed combination precede processing factors defined through facets.

Weight reduction factors for processing factors defined for facets should be included in table *Recipes* should match exactly.

## Food hierarchies

### Reading and dealing with food hierarchy data

Within MCRA, the following hierarchy related aspects are accounted for:

- Reading food hierarchy data
- Using hierarchical data for conversion of foods
- Using hierarchy data in the output

### Reading food hierarchy data

A new data group named *Foods data formats* is added. In this group, a new table *Food hierarchies* is used for input of food hierarchies. This table contains food hierarchy node-definition records that reflect a hierarchical structure. For foods that are not in this list as idFood, it is implicitly assumed that these foods are root items.

Note: It is common practice to describe hierarchies using tree structures. Here, the elements of the tree are named *nodes*, the lines connecting the nodes are named *branches*, and nodes without children are *leaf nodes/end-nodes*. This terminology is also used throughout the remainder of this document.

### Using food hierarchies for food conversion

The introduction of the hierarchy structure allows for integration with step 4 and step 5 of the food conversion algorithm; the *subtype* and *supertype* linking steps. That is, when no concentration data is found for a certain product, the concentration data of a (according to the hierarchy) related product could be used. In MCRA, the *supertype* conversion step also contains a *hierarchy-supertype* step based on the food hierarchy.

**Supertype link (step 5)**:

a) **Supertype**: Try to find supertypes base on '$'-coded strings, e.g., 'xxx$yyy' is converted to 'xxx'

b) **Hierarchy-supertype**: try to find the supertype of the current food based on the food hierarchy (i.e., convert the current food to its parent).

Note 1: the *supertype* conversion step is optional and should be specified in the conversion settings panel.

Note 2: the *hierarchy-supertype* step only applies for foods-without-facets. The reason for this is that for the conversion, the base type of a food-with-facets can be considered as a better conversion candidate than the parent food with the same facets.

### Using hierarchy data in the output

Food hierarchy information could be used in presentation of various tables of the output of MCRA. That is, in the tables in which foods data is presented, these records could be grouped based on the hierarchy and/or a tree-like display can be built for the presentation of this data. Tables that are candidate for being extended are, for example, the input data tables foods-as-eaten/modelled foods and the exposure by food-as-eaten/modelled food output tables.

Summarizing over the food hierarchy is many cases not a straightforward task. Consider, for instance, the statistic *number of consumption days* given the artificial hierarchy of *Citrus Fruits* containing two child-nodes *Mandarin* and *King Mandarin*: the number of consumption of *Citrus Fruits* is not "just" the sum of the consumption day of *Mandarin* and *King Mandarin*. A difficulty for summarizing based on a hierarchy arises when a node contains both data and child-nodes with data. E.g., concentrations are defined on the level of *Citrus Fruits* and on the level of *Mandarin*. In this case, the hierarchy view should ideally summarize for both *Citrus Fruits* as data record and *Citrus Fruits* as summary node. An additional complication is the status of facet-coded foods within the hierarchy. In a hierarchical view, foods-with-facets should ideally be added to their base-foods for visualization.

In MCRA, an alternative view (treetable) is added that can display hierarchical data. This alternative view is used to present a hierarchical view based on the foods hierarchy for the consumption input summary tables food as eaten and modelled food. The data summary methods for these tables are updated such that the data is also summarized per hierarchy-node.

If a node contains both data and a child record, then this node is split-up in two nodes: a summary node that summarizes the data of the node and all of its child nodes, and a data record with the string "(unspecified)" added as a child

| Food name | Food code | Mean consumption (g) | Mean consumption days (g) | Consumption days | Percentage consumption days | Total weights consumption days | Percentage total weights consumption days |
|---|---|---|---|---|---|---|---|
| Fruit and fruit products | A01BS | 167 | 200 | 5 | 83.3 % | 5.0 | 83.3 % |
| Fresh fruit | A04RK | 167 | 200 | 5 | 83.3 % | 5.0 | 83.3 % |
| Starchy roots or tubers and products thereof, sugar plants | A00ZR | 100 | 600 | 1 | 16.7 % | 1.0 | 16.7 % |
| Starchy root and tuber products | A011B | 66.7 | 400 | 1 | 16.7 % | 1.0 | 16.7 % |
| Processed root and tuber products | A04MJ | 66.7 | 400 | 1 | 16.7 % | 1.0 | 16.7 % |
| Potato boiled | A011P | 66.7 | 400 | 1 | 16.7 % | 1.0 | 16.7 % |
| Potato boiled Tuber (as part-nature) | A011P#F02.A067V | 16.7 | 100 | 1 | 16.7 % | 1.0 | 16.7 % |
| Potato boiled Tuber (as part-nature), Potatoes, Boiling | A011P#F02.A067V$F27.A00ZT$F28.A07GL | 16.7 | 100 | 1 | 16.7 % | 1.0 | 16.7 % |
| Potato boiled Tuber (as part-nature), Potatoes, Boiling | A011P#F02.A067V$F28.A07GL$F27.A00ZT | 16.7 | 100 | 1 | 16.7 % | 1.0 | 16.7 % |
| Potato boiled Tuber (as part-nature), Potatoes, Boiling, Baking | A011P#F02.A067V$F27.A00ZT$F28.A07GL$F28.A07GX | 16.7 | 100 | 1 | 16.7 % | 1.0 | 16.7 % |
| Starchy roots and tubers | A00ZS | 33.3 | 200 | 1 | 16.7 % | 1.0 | 16.7 % |
| Tubers | A04MC | 33.3 | 200 | 1 | 16.7 % | 1.0 | 16.7 % |
| Potatoes | A00ZT | 33.3 | 200 | 1 | 16.7 % | 1.0 | 16.7 % |
| Potatoes Potatoes (food source plant), Tuber (as part-nature) | A00ZT#F01.A05KG$F02.A067V | 16.7 | 100 | 1 | 16.7 % | 1.0 | 16.7 % |
| Potatoes Potatoes (food source plant), Tuber (as part-nature), Baking | A00ZT#F01.A05KG$F02.A067V$F28.A07GX | 16.7 | 100 | 1 | 16.7 % | 1.0 | 16.7 % |

Figure 3.2: Hierarchy view for the foods as eaten input summary table.

of this summary node. See Figure 3.2 for an example (*Citrus Fruits* versus *Citrus Fruits (unspecified)*). In MCRA, foods-with-facets are added as child nodes of the foods-without-facets.

### Food unit weights

Food unit weights specify the standard weights of food units. E.g., the standard weight of an apple. This unit weight may be specified as the weight of the whole food (raw agricultural commodity/RAC) or the weight of the edible portion (EP), e.g., without peel. Unit weights are specified in the table *Food unit weights* and used in combination with *unit variability factors* to account for unit-to-unit variation in concentrations between single units of the same food in *single value dietary exposures assessments* and *(individual) dietary exposures assessments*.

Food unit weights can be location specific or specified as overall (default) unit weights. For some models, e.g., the *IESTI model*, location specific unit weights are preferred over overall unit weights. The overall unit weights are then used when no location specific uses are available. For other methods, only overall unit weights are used. If, for a food, an overall unit weight is not available, but there are location specific unit weights available, then the overall unit weight is computed as the average weight of the location specific unit weights (similar to *EFSA PRIMo* revision 3 EFSA (2018)).

**Note**

Note that in earlier versions of the software, food unit weights were specified in the *table for Food properties*. Although this is still possible, the recommended way of specifying unit weights is in the *table for Food unit weights*. If, for a food, unit weights are specified in both tables, then the unit weights specified in table *Food unit weights* have priority. The unit weights specified in table *Food properties* are then only used as fallbacks for the overall unit weight when no overall unit weight is specified in the *table for Food unit weights*.

## 3.1.3 Consumer products

Consumer products are uniquely defined sources of (personal care) products.

Output of this module is used by: *Consumer product exposure determinants Consumer product use frequencies Consumer product concentrations Consumer product concentration distributions Consumer product exposure estimates Consumer product exposures*

#### Consumer products from data

#### Consumer products data formats

Consumer products are primary entities of the data model.

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#### ConsumerProducts

Each consumer product is identified by a unique code (id), a name, description and/or product group (parent). Consumer products codes are not harmonised.

Table 3.16: Table definition for ConsumerProducts.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| Id | AlphaNumeric (50) | The unique identification code of the consumer product. | idConsumer-Product, Consumer-ProdufctId, Id | Yes |
| Name | AlphaNumeric (100) | The name of the consumer product. | Name, Consumer-ProductName | No |
| Description | AlphaNumeric (200) | Description of the consumer product. | Description | No |
| idGroup | AlphaNumeric (50) | Identifier of the parent product (i.e., the product group of which this product is a part). | idGroup, GroupId | No |

Accepted table names: ConsumerProducts, ConsumerProduct.

#### Consumer products as data

Consumer products definitions are provided as lists/catalogues of food definitions or hierarchy definitions.

- *Consumer products data formats*
- *Consumer products from data*

### 3.1.4 Non-dietary exposure sources

Non-dietary exposure sources are the sources containing chemical substances to which individuals in a population are exposed via any of three non-dietary routes: dermal, inhalation or oral, per day.

#### Non-dietary exposure sources from data

#### Non-dietary exposure sources data formats

Non-dietary exposure sources are defined in the non-dietary sources table.

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#### Non-dietary exposure sources

Each non-dietary exposure source is identified by a unique code in a code system of choice, a name, and a description.

Table 3.17: Table definition for Non-dietary exposure sources.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idNonDietary-ExposureSource | AlphaNumeric (50) | The unique identification code of the non-dietary exposure source. | idNonDietary-ExposureSource, idSource, Code, Id | Yes |
| Name | AlphaNumeric (100) | The name of the non-dietary exposure source. | Name | No |
| Description | AlphaNumeric (200) | Description of the non-dietary exposure source. | Description | No |

Accepted table names: NonDietaryExposureSources.

#### Non-dietary exposure sources as data

Non-dietary exposure sources are lists/catalogues of definitions of non-dietary sources through which people can be exposed to chemical substances (e.g., personal care products and plant-protection products).

- *Non-dietary exposure sources data formats*
- *Non-dietary exposure sources from data*

### 3.1.5 Populations

Populations are groups of human individuals that are the scope of exposure or risk assessments. Optional descriptors of populations are location (e.g. a country), time period (with a start and end date), age range (with a minimum and maximum age) and gender. Example: the French population in 2005-2007 (= time period) of women (= gender) of child-bearing age 18-45 yr (= age range).

Output of this module is used by: *Consumptions Single value consumptions Consumer product use frequencies Food concentrations Consumptions by modelled food Dietary exposures Single value dietary exposures Single value non-dietary exposures Non-dietary exposures Internal exposures HBM concentrations HBM analysis Exposure comparisons Dust exposures Soil exposures Air exposures Individuals Consumer product exposures HBM single value exposures Hazard characterisations Burden of disease Risks Single value risks Environmental burden of disease*

#### Populations from data

#### Populations calculation

In an exposure or risk assessment, the population of interest is implicitly or explicitly defined. An implicit definition is made by selecting one of the available food consumption surveys in the **Compute** option. For example, by selecting the food survey 'NL-Toddlers' with corresponding consumption data, the Dutch population of toddlers is implicitly considered as the population of interest.

After selecting a survey, the population is further defined by checking *Define population based on specified individual properties* in the *Population definition from dietary surveys panel*. Include implicitly defined individual(day) properties in the population definition. E.g., the Dutch population of toddlers is restricted to females by including the property *gender* with level *'Female'* in the population definition. The implicitly defined population becomes the Dutch female toddlers.

Although implicit definition of the population of interest works fine, there is a need to make more explicit that the focus of an assessment is on the population. The user should be aware that assessments are about assessing the exposure or risk in a specific population of interest. This becomes even more urgent when dietary exposures are combined

with non-dietary exposures. Without explicitly specifying the population of interest, the exposure of Dutch toddlers may unintentionally be combined with non-dietary exposures of e.g. adult operators. The explicit definition of a population is made by selecting a population datasource in the **Use data** option. By specifying population properties like age, gender or any other property in the data, the population may be further restricted.

For the **Compute** option:

- Setting *Population definition from dietary surveys* Check *Define populations based on specified individual properties* for including individual properties.

When the population of interest is explicitly defined, (**Use data** option), the population definitions are based on the data in the *IndividualProperties table* referring to populations in the *Populations table.*.

### Population definition from dietary surveys

This panel is only available when the population of interest is implicitly defined, use the *Compute* option. Currently, population definitions are based on dietary surveys. It is foreseen that the population definition will be extended as soon as Human Biomonitoring (HBM) data and/or non-dietary survey data become available.

Specify the *nominal population bodyweight*, needed for single value calculations, e.g. 70 kg (default).

After checking *Define populations based on specified individual properties* in Figure 3.3, include individual properties for the population definition.

Select the requested levels for each property.

See also the *consumption panel documentation* for further information on population definition based on a selection of individual properties.

For individual day properties, an extra option is available to include the records without date data. Currently, the default value is to include records without dates.

### Populations data selection

This option is only available when the population of interest is explicitly defined, use the *Use data* option and select a data source. Select one of the available populations in the *Populations selection* pane.

Selecting two or more populations, initiates a loop over multiple populations. Check the *Loop over multiple populations* checkbox. See also Figure 3.8

### Populations data formats

Populations are primary entities of the data model.

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### Populations

Populations identify human groups in e.g. dietary, nondietary and human monitoring surveys. Optionally, a name and description can be added. Specify a standard bodyweight (optional) as a descriptor of the average or nominal bodyweight in the population. Use table PopulationIndividualPropertyValues to specify descriptors/properties that characterise the population. These population individual property values will be used to restrict the population to e.g. a certain time period (through specifying a start and end date, both dates are inclusive), age (through specifying a minimum and maximum age, both limits are inclusive) or gender (male or female). To facilitate the user, dynamic properties may be added to the table. Three kind of additional properties are available: alphanumeric properties (property name and level), numeric properties (a range through specifying a minimum and maximum using suffixes Min and Max, both bounds are inclusive) and datetime properties (a range through specifying a start and end date using prefixes Start and End, both dates are inclusive). Dynamic or additional properties are ignored when table PopulationIndividualPropertyValues is present in the upload. In table IndividualProperties each property used in the Populations table is described.

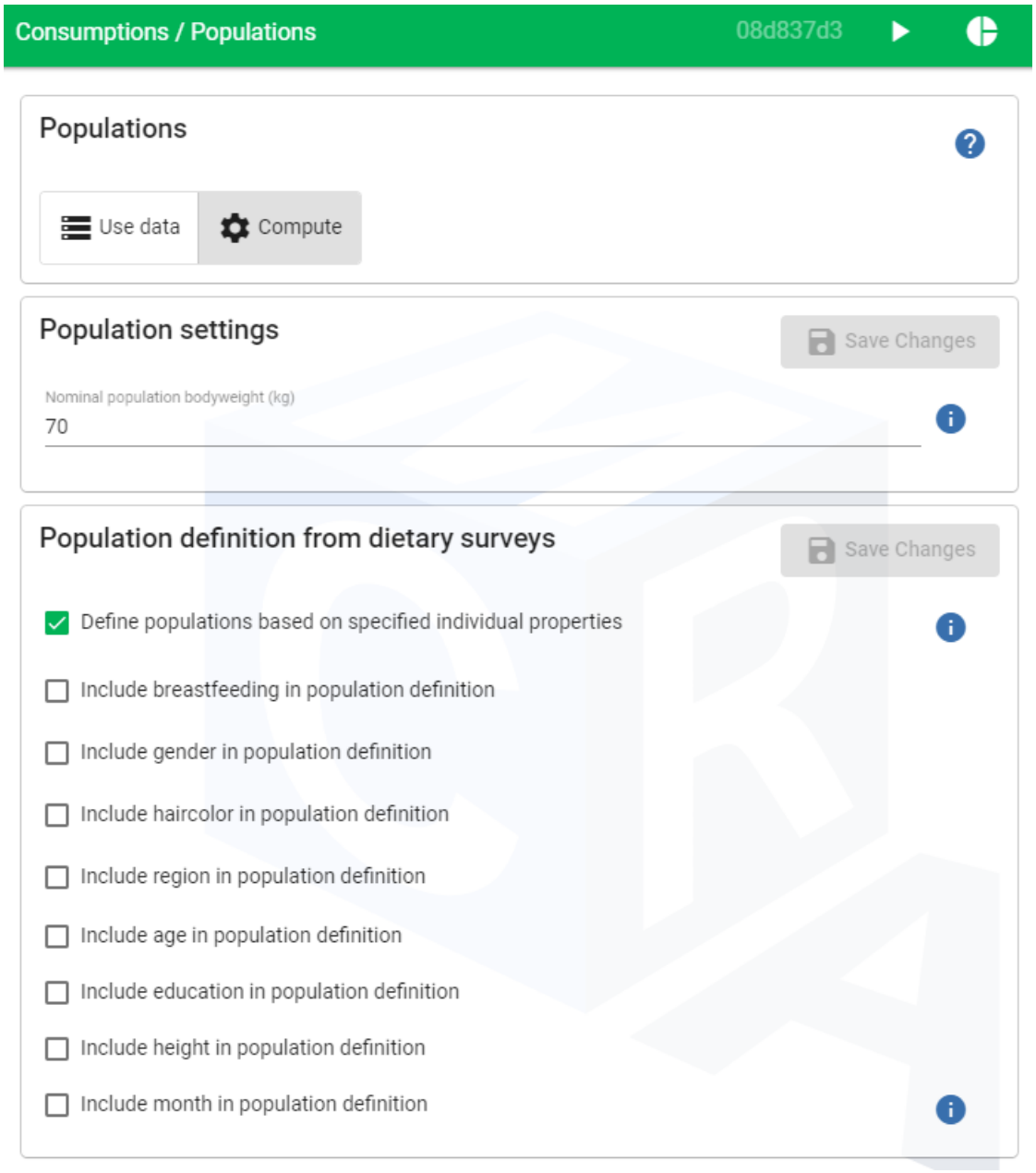


Figure 3.3: Define populations by including individual properties.

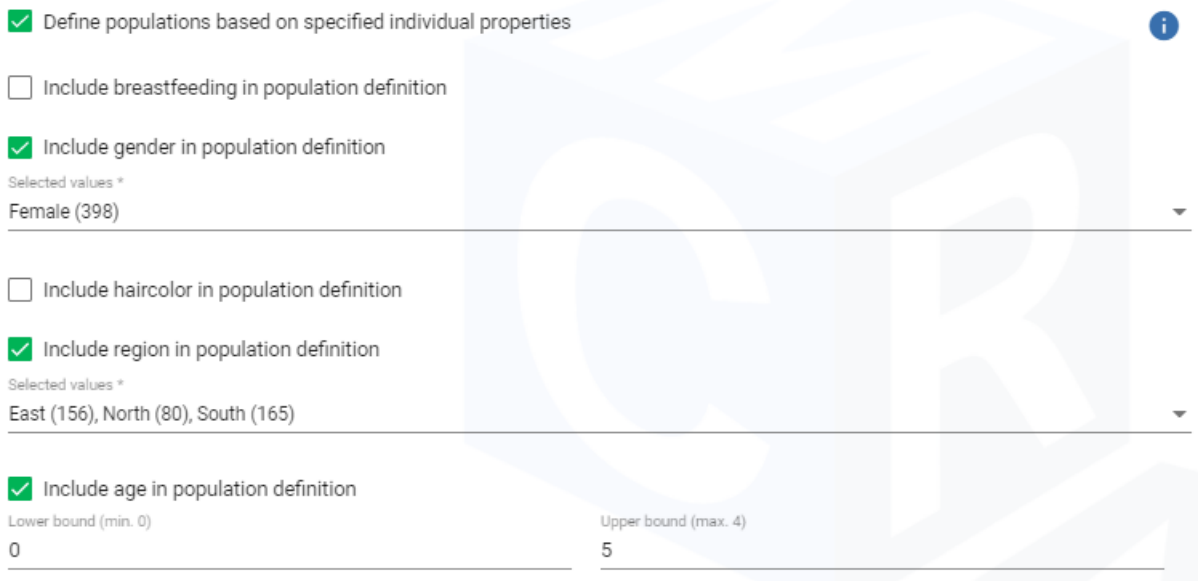


Figure 3.4: Check *gender*, region and age and select the requested levels Female, East, North and South and age min = 0, age max = 5, resp.

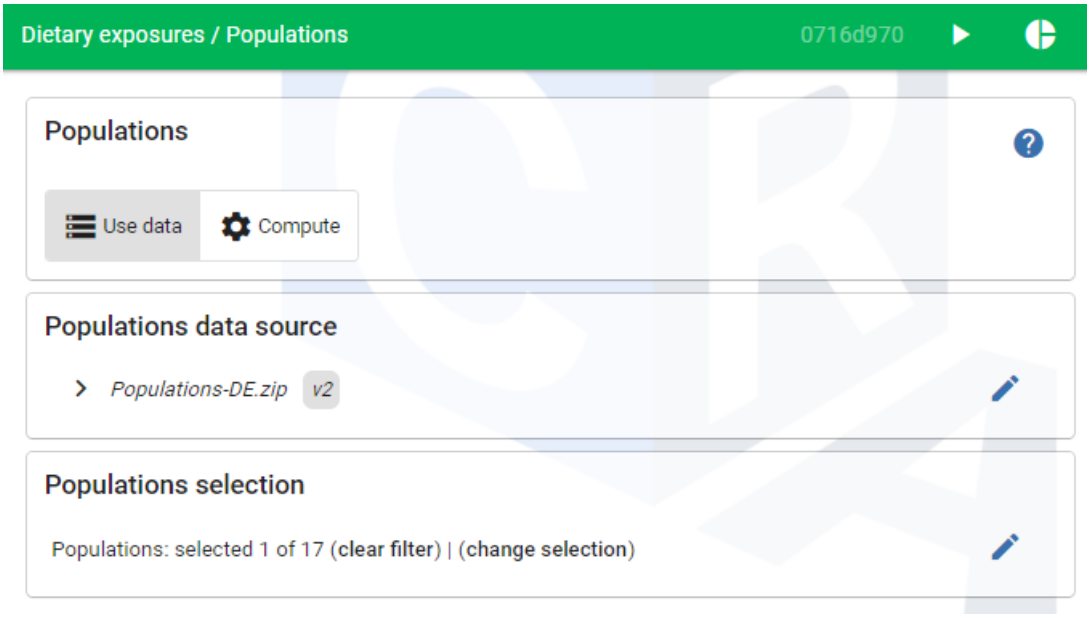


Figure 3.5: Population data selection (*Use Data*).

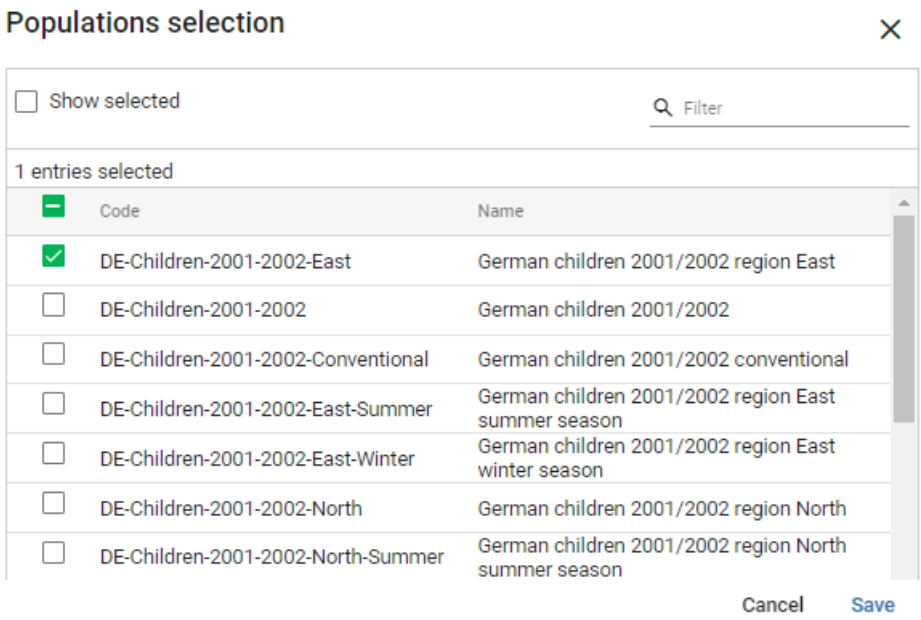


Figure 3.6: Available population data: **change selection**.

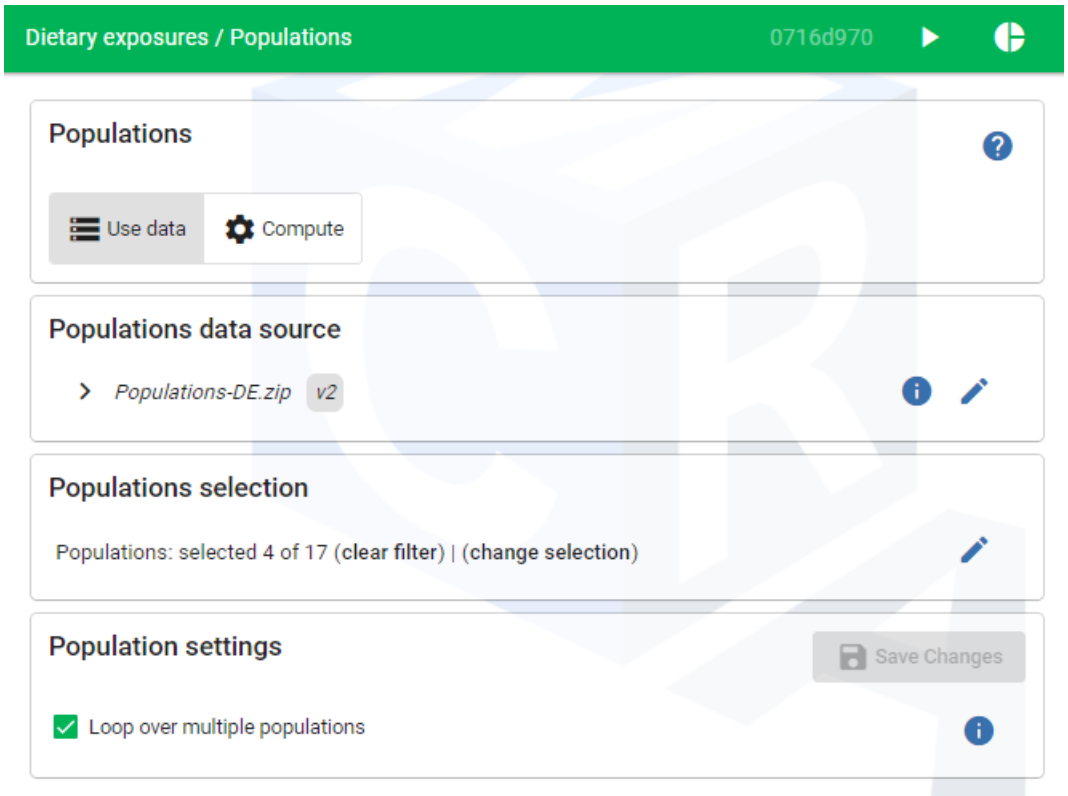


Figure 3.7: Loop over multiple populations (*Use Data*).

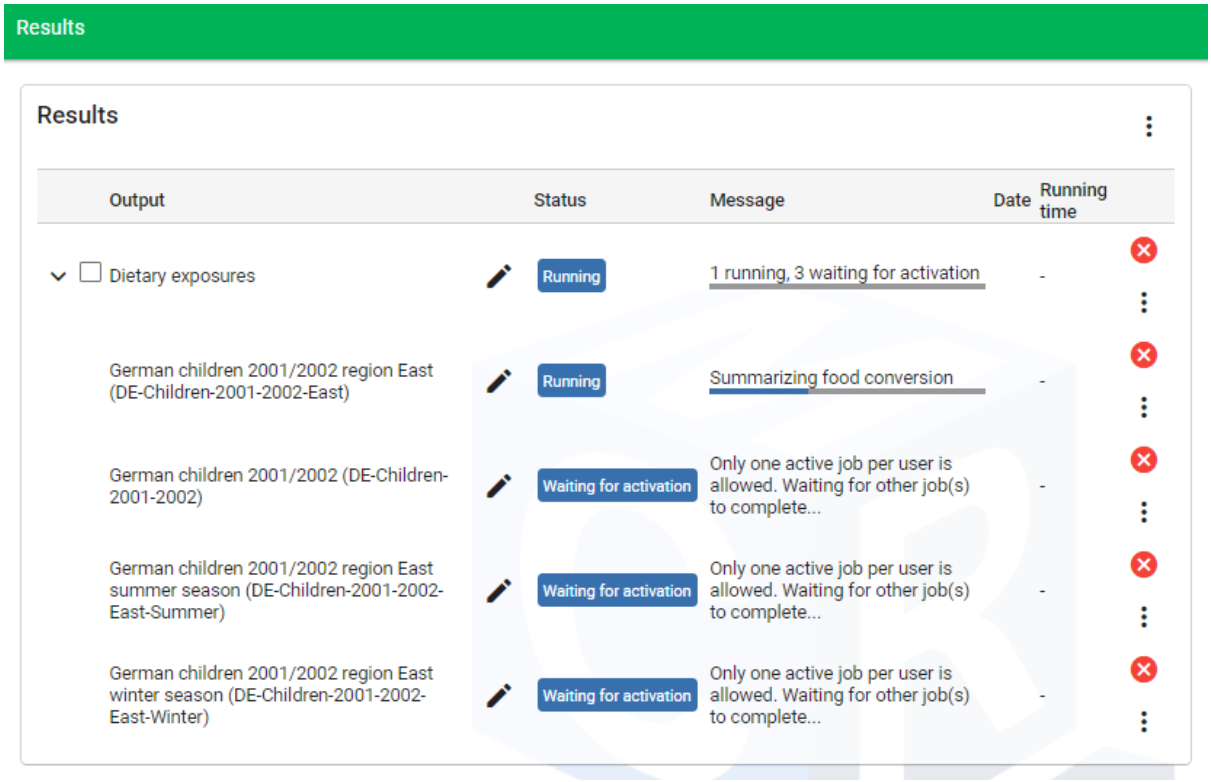


Figure 3.8: Results pane with loop over multiple populations (*Use Data*).

Table 3.18: Table definition for Populations.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idPopulation | AlphaNumeric (50) | Unique identification code of the population. | IdPopulation, PopulationId, Code, Id | Yes |
| Name | AlphaNumeric (100) | The name of the population. | Name, PopulationName | No |
| Description | AlphaNumeric (200) | Description of of the population. | Description | No |
| Location | AlphaNumeric (50) | Location. | Location, Country | No |
| StartDate | DateTime | Starting date of the specific time window marking this population. | StartDate | No |
| EndDate | DateTime | End date of the specific time window marking this population. | EndDate | No |
| NominalBody-Weight | Numeric | Nominal body weight (in kg) of the individuals of this population. | NominalBody-Weight, BodyWeight | No |
| Size | Numeric | The number of individuals of this population. | Size, PopulationSize, Value | No |
| Size-Uncertainty-Distribution | *PopulationSize-DistributionType* | Distribution type (Uniform, or Normal). If not specified, the population size is assumed to be a constant factor. | SizeUncertainty-Distribution, SizeDistribution | No |
| SizeLower | Numeric | The lower value of the distribution. If the distribution is triangular then it is the lower bound of the uniform distribution. This value should be smaller than the population size. | SizeLower, SizeUncertainty-Lower | No |
| SizeUpper | Numeric | The upper value of the | SizeUpper, | No |

Accepted table names: Populations, Population.

### Individual properties

This table is used to describe the properties used in the Populations or PopulationIndividualPropertyValues table characterising the population (table Populations) and/or the properties used in the Individuals table characterising an individual. Properties like Age, Gender, Region are describing an individual (PropertyLevel = Individual). Properties like Period (for populations) or Month (sampling date for an individual day) are describing an individual day (PropertyLevel = IndividualDay).

Table 3.19: Table definition for Individual properties.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual-Property | AlphaNumeric (50) | The code of the property. | idIndividual-Property, Individual-PropertyId, Individual-Property | Yes |
| Name | AlphaNumeric (100) | The name of the property. | Name | No |
| PropertyLevel | *PropertyLevelType* | The level of the property. This type follows a controlled terminology, with possible values: Individual or IndividualDay. | PropertyLevel, LevelProperty | No |
| Description | AlphaNumeric (200) | Description of the property. | Description | No |
| Type | *IndividualProperty-Type* | This field specifies the type of the values of this individual property. This type follows a controlled terminology, with possible values: Boolean, Categorical (default), Numeric, Nonnegative, Integer, NonnegativeInteger, Month, Datetime, Gender. | Type | No |

Accepted table names: IndividualProperties, IndividualProperty.

### Population individual property values

This table describes population individual properties, such as Age, Gender, Period, Region or Breastfeeding. Population individual property values are used to restrict the population to, for example, a range of ages, a gender, a certain time period, a geographical location or women who are breastfeeding. For numerical properties, use MinValue and MaxValue to specify a range. To specify a time period, use StartDate and EndDate. For Gender, Region and Breastfeeding use Value to specify the gender, categorical level or boolean value, respectively. In the IndividualProperties table, each property used in the PopulationIndividualPropertyValues table is described. NOTE: the individual property ID (idIndividualProperty) must be unique for a population (specified by idPopulation), i.e., the combination idPopulation - idIndividualProperty may occur only once in the table Population individual property values. You may list multiple values in the 'Value' field by separating them with a comma (e.g., 'Summer, Autumn').

Table 3.20: Table definition for Population individual property values.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idPopulation | AlphaNumeric (50) | The code of the population to which the property is attached. The provided population code should match with a code of the populations table. | idPopulation, PopulationId, Population, PopulationCode, Code | Yes |
| idIndividual-Property | AlphaNumeric (50) | The name or reference of the individual property. | idIndividual-Property, Individual-PropertyId, Individual-Property | Yes |
| Value | AlphaNumeric (50) | The value(s) of the property. Multiple values should be comma separated. | Value | No |
| MinValue | Numeric | Minimum value of the value of the property for a numeric range. | MinValue, ValueMin | No |
| MaxValue | Numeric | Maximum value of the value of the property for a numeric range. | MaxValue, ValueMax | No |
| StartDate | DateTime | Start date value of the property for a time period. | StartDate, MinDate | No |
| EndDate | DateTime | End date value of the property for a time period. | EndDate, MaxDate | No |

Accepted table names: PopulationIndividualPropertyValues, PopulationIndividualPropertyVal, PopulationPropertyValues.

### Population characteristics

Characteristics describing specifics of a population, e.g. IQ or average birth weight.

Table 3.21: Table definition for Population characteristics.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idPopulation | AlphaNumeric (50) | Unique identification code of the population. | IdPopulation, PopulationId | Yes |
| Characteristic | *PopulationCharacteristicType* | Population characteristic type. | Characteristic, idCharacteristic, PopulationCharacteristic, IdPopulationCharacteristic | Yes |
| Unit | AlphaNumeric (50) | Unit of the population characteristic. | Unit, CharacteristicUnit | No |
| Value | Numeric | Mean of the distribution. | Mean | Yes |
| PopulationCharacteristicDistributionType | *PopulationCharacteristicDistributionType* | Distribution type (Normal, Uniform, or LogNormal). If not specified, the characteristic is assumed to be constant. | DistributionType, PopulationCharacteristicDistributionType, Distribution | No |
| CvVariability | Numeric | Coefficient of variation. | CvVariability, CV | No |

Accepted table names: PopulationCharacteristics, PopulationCharacteristic.

### Populations settings

### Selection settings

Table 3.22: Selection settings for module Populations.

| Name | Type | Description |
|---|---|---|
| Define populations based on specified individual properties | Boolean | Define a population by selecting specific ranges/values of individual properties. E.g., the female population between ages and 45 is composed of the properties gender (female) and age (between 18 and 45). |
| Individuals subset definitions | IndividualsSubsetDefinition | Contains a list of subset definitions to filter the population's individuals based on an individual's properties, by property nam and a custom filter query, for example a value range or a list of keywords. |
| Individual day subset | IndividualDaySubsetDefinition | Individual day subset definition. |
| Nominal population bodyweight (kg) | Numeric | Nominal population bodyweight in kg (needed for single value calculations). |

### Calculation settings

Table 3.23: Calculation settings for module Populations.

| Name | Type | Description |
|---|---|---|
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |

#### Uncertainty settings

Table 3.24: Uncertainty settings for module Populations.

| Name | Type | Description |
|---|---|---|
| Resample population sizes | Boolean | Specifies whether the population size is resampled from a parametric uncertainty distribution. |

#### Populations as data

Populations are provided as data. When the population of interest is explicitly defined, subset selections are based on the data in the IndividualProperties and PopulationIndividualPropertyValues table.

- *Populations data formats*
- *Populations from data*

Settings used

- *Calculation Settings*

#### Calculation of populations

Populations are implicitly defined by the individuals as used in the dietary consumption module and/or the non-dietary module and/or the human based monitoring module.

- *Populations calculation*

Settings used

- *Calculation Settings*

### 3.1.6 Responses

Responses are measurable entities in test systems. Responses are used to represent effects (see effect representations) and their measured values are collected in dose response data.

This module has as primary entities: *Test systems*

Output of this module is used by: *Dose response models Dose response data Effect representations*

#### Responses from data

#### Responses data formats

A response is a measurable endpoint on in a test system. E.g., in a rat test system a response may be the percentage of fatty hepatocytes observed after 90 days. Responses are defined in the responses table.

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#### Responses

Each response is identified by a unique code (idResponse) in a code system of choice, a name, and a description. Also, each response should be linked to a test system (idTestSystem) on which the response is measured. Responses can be of various types (ResponseType), e.g., ContinuousMultiplicative (= non-negative real values using a ratio scale), ContinuousAdditive (= real values using an interval scale), Ordinal, Quantal, or Binary. For continuous variables,

the response unit (ResponseUnit) is also relevant. Additionally, also a reference to the test method guideline, e.g., standardised assay kit may also be specified (GuidelineMethod).

Table 3.25: Table definition for Responses.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idResponse | AlphaNumeric (50) | Unique identification code of the response. In the EuroMix data collection, a EuroMix coding system has been set up in which the id of the test system prefixes the id of the response. E.g., 'HepaRG-PCR-PPARA', 'RatWEC-PCR-CYP26a1' and 'MouseDevelopmental-FacialPrimordia-malformed-E9'. | idResponse, ResponseId, Response, Id | Yes |
| CodeSystem | AlphaNumeric (100) | Identifier of the coding system of the response code. | CodeSystem | No |
| Name | AlphaNumeric (100) | Name of the response. | Name | No |
| Description | AlphaNumeric (200) | Additional description or label of the response. | Description | No |
| idTestSystem | AlphaNumeric (50) | Unique identification code of the test system. | idTestSystem, idSystem, SystemId, TestSystem | Yes |
| Guideline-Method | AlphaNumeric (200) | Reference to the test method guideline, e.g., standardised assay kit. | Guideline-Method | No |
| ResponseType | *ResponseType* | The data type of the response measurements (e.g., continuous multiplicative, continuous additive, binary, quantal, count, ordinal, categorical). Controlled terminology. | ResponseType | Yes |
| ResponseUnit | AlphaNumeric (100) | If the response type is Continuous, then this should be the unit of the response, e.g., kg. | ResponseUnit | No |

Accepted table names: Responses, Response.

### Responses as data

A response is a measurable endpoint defined in a test system. It has a unit and a measurement type (e.g., continuous non-negative, quantal).

- *Responses data formats*
- *Responses from data*

## 3.1.7 Substances

Substances are chemical entities that can refer to: 1) active substances such as investigated in toxicology; 2) measured substances such as defined in specific analytical methods. MCRA assessments can have one or more substances as

the scope. When more than one substance is specified, there is an option to perform a cumulative assessment. In that case one of the substances has to be indicated as the index/reference substance, and results will be expressed in equivalents of the index substance.

Output of this module is used by: *Dust exposure determinants Soil exposure determinants Air exposure determinants Consumer product exposure determinants Food concentrations Food concentration distributions Dust concentrations Dust concentration distributions Soil concentrations Soil concentration distributions Air concentration distributions Indoor air concentrations Outdoor air concentrations Single value concentrations Processing factors Unit variability factors Occurrence patterns Occurrence frequencies Substance authorisations Substance approvals Substance conversions Deterministic substance conversion factors Concentration limits Food concentration models Modelled foods Focal food concentrations Consumer product concentrations Consumer product concentration distributions Food conversions Consumptions by modelled food High exposure food-substance combinations Dietary exposures Single value dietary exposures Single value non-dietary exposures Non-dietary exposures Internal exposures Exposure mixtures HBM concentrations Consumer product exposure estimates HBM analysis Exposure comparisons Dust exposures Soil exposures Air exposures Consumer product exposures HBM single value exposures Occupational task exposures Occupational exposures Exposure biomarker conversions QSAR membership models Molecular docking models Absorption factors PBK model parametrisations Kinetic conversion factors Active substances Relative potency factors Hazard characterisations Points of departure Dose response models Dose response data Inter-species conversions Intra species factors Exposure response functions Risks Single value risks Environmental burden of disease*

### Substances from data

### Substances data formats

Substances are primary entities of the data model. Substance intakes are of main interest in exposure assessments and the effect of intake on human health is of interest in risk assessments. In the substances table, the substance entities and other relevant substance properties that are relevant for the assessment at hand should be defined.

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### Substances

Each substance should have a unique identification code (idSubstance), and optionally, a name and description may be used for a more detailed description of the entity. Additional properties, such as the molecular mass (MolecularMass) and Cramer class (CramerClass) may also be specified. Example: Captan (idSubstance RF-0061-001-PPP) has MolecularMass 300.5922 and CramerClass 3.

Table 3.26: Table definition for Substances.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubstance | AlphaNumeric (50) | The unique identification code of the substance. This code may be from an existing coding system, such as CAS-codes or Param codes of EFSA, or it may be a used-defined code. | idSubstance, SubstanceId, SubstanceCode, Substance, Code, Id | Yes |
| Name | AlphaNumeric (100) | The substance name. | Name, SubstanceName, PesticideName | No |
| Description | AlphaNumeric (200) | Substance description. | Description | No |
| Concentration-Unit | *ConcentrationUnit* | Contains a coding to determine the default unit in which concentrations for this substance are expressed. | Concentration-Unit, Unit, Reference-Concentration-Unit | No |
| CramerClass | Integer | The Cramer class of the substance. | CramerClass | No |
| MolecularMass | Numeric | The molecular (molar) mass. | MolecularMass, Mass, MolarMass, Molecular-Weight, MolarWeight | No |
| IsLipidSoluble | Boolean | States whether the substance is soluble in lipid (0 = no, 1 = yes). | IsLipidSoluble, IsSoluble | No |

Accepted table names: Substances, Substance.

### Substances settings

### Selection settings

Table 3.27: Selection settings for module Substances.

| Name | Type | Description |
|---|---|---|
| Compute cumulative exposures | Boolean | Specifies whether the assessment involves multiple substances a results should be cumulated over all substances. |
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Index substance | AlphaNumeric | The substance of interest or index substance. |

### Substances as data

Substances are provided as data (code, name).

- *Substances data formats*
- *Substances from data*

### 3.1.8 Test systems

Test systems are biological or artificial systems used for assessing hazard in relation to chemical exposure from substances in varying doses. Test systems may refer to 1) in-vivo test systems (e.g. a rat 90-day study, a human biomonitoring study); 2) in-vitro test systems (e.g. HepaRG cells).

Output of this module is used by: *Responses Dose response models Dose response data*

#### Test systems from data

#### Test systems data formats

Test systems are the biological systems (e.g., animals) or in-vitro systems on which responses related to health effects can be measured.

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#### Test Systems

Each test system should have a unique identification code (idSystem), and (optionally) a name and a description. The test system's type (TestSystemType) indicates the type whether the test system is an in-vivo test system (in which case it is a model for external exposure) or any of a range of other, in-vitro, options (cell-line, etc., which all will be interpreted as models for internal exposure). Additionally, if applicable, the organ (e.g., liver) of the test system and the route of exposure (RouteExposure) for in-vivo test systems (oral, dermal or inhalation) may be specified.

Table 3.28: Table definition for Test Systems.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idTestSystem | AlphaNumeric (50) | Unique identification code of the test system. | idTestSystem, idSystem, Id, Code | Yes |
| CodeSystem | AlphaNumeric (100) | Identifier of the code system of the test systems. | CodeSystem | No |
| Name | AlphaNumeric (100) | Name of the test system. | Name | No |
| Description | AlphaNumeric (200) | Additional description or label of the test system. | Description | No |
| TestSystem-Type | *TestSystemType* | The type of the test system, i.e., in-vivo, cell-line, primary cells, tissue, organ. Controlled terminology. | TestSystem-Type, SystemType | No |
| Organ | AlphaNumeric (100) | If applicable, the organ that the cells originate from associated with the in vitro test-system. | Organ | No |
| Species | AlphaNumeric (100) | If applicable, the species associated with the test-system. | Species | No |
| Strain | AlphaNumeric (100) | If applicable, the strain of the species associated with the test-system. | Strain | No |
| RouteExposure | *ExposureRoute* | If applicable, the route of exposure associated with the in vivo test-system, oral, dermal, inhalation, s.c., i.v. Controlled terminology. | ExposureRoute-Type, ExposureRoute, RouteExposure | No |
| Guideline-Method | AlphaNumeric (200) | Reference to test guideline. | GuidelineStudy | No |
| Reference | AlphaNumeric (200) | External reference(s) to other sources containing more information about the test system. E.g., publications, website, documents. | Reference | No |

Accepted table names: TestSystems, TestSystem, Systems, System.

### Test systems as data

Test systems are provided as data.

- *Test systems data formats*
- *Test systems from data*

## 3.2 Consumption modules

Consumption modules specify the *consumptions* or *single value consumptions* of *foods* by surveyed individuals in *populations*. Foods can be related to each other using *food recipes*.

### 3.2.1 Consumptions

Consumptions data are the amounts of foods consumed on specific days by individuals in a food consumption survey. For acute exposure assessments, the interest is in a population of person-days, so one day per individual may be sufficient. For chronic exposure assessments, the interest is in a population of persons, so preferably two or more days per individual are needed.

This module has as primary entities: *Populations Foods*

Output of this module is used by: *Food conversions Consumptions by modelled food*

#### Consumptions from data

#### Consumptions calculation

The consumptions module offers a number of options and filters that specify how the consumption data should be included in the assessment.

- After including individual properties for defining a population in the *populations panel* an option becomes available *Match consumption data to population definition options*. Use all populations definitions (default), ignore all populations definitions or use a selection of properties to define the population.
- When individual sampling weights have been recorded in the *data*, the option *ignore sampling weights* specifies whether sampling weights are ignored or not in all calculations.
- It is possible to *restrict to consumptions of specific foods*.
- Depending on the *exposure type* (acute or chronic), the individuals (chronic) or individual-days (acute) can be filtered in several ways. It is possible to restrict the consumers or consumer days to consumers that consume or consumer days with a consumption. Use option *consumers or consumer days only*, and only consumers or consumer days with consumption of *specific (focal) products* are selected.
- For a chronic dietary or risk assessment (OIM, LNN or BBN), the individuals with less than N surveys days may be filtered out. Check setting *Exclude individuals with less than N days*, then./ option *N (number of days in survey)* appears. Specify a number, all individuals with a number of survey days less than N are filtered out.
- In general, one consumption data source is selected. However, the menu allows selection of multiple data-sources through the use of the *add another data source* option. Press the add button + on the right side of the panel and select a datasource. Then, in the settings panel a new checkbox appears *Loop over multiple surveys* and after checking it all red triangles in the left panel disappear. See also *multiple surveys*.

In Figure 3.9 the consumption panel is shown. The setting *Match consumption data to population definition* is selected as default. All properties that are included in the *populations definition* are used. See *other options* for more info.

#### Consumption population definition

In Figure 3.10 all options of setting *Match consumption data to population definition options* are shown.

- Match consumption data to population definition: all selected properties in the population definition are used (default),
- Ignore population definition (use all individuals in survey): all selected properties in the population definition are ignored,
- Match consumption data to population definition using selected properties only: a selection of individual properties is used to define the population.

In the *populations panel*, the population was defined by including individual properties. These properties are all used (default), ignored or *a subset is selected* for further restricting the population.

In Figure 3.12 the selected individual properties that are available are shown. Check one or more for restricting the population definition to the specified set.

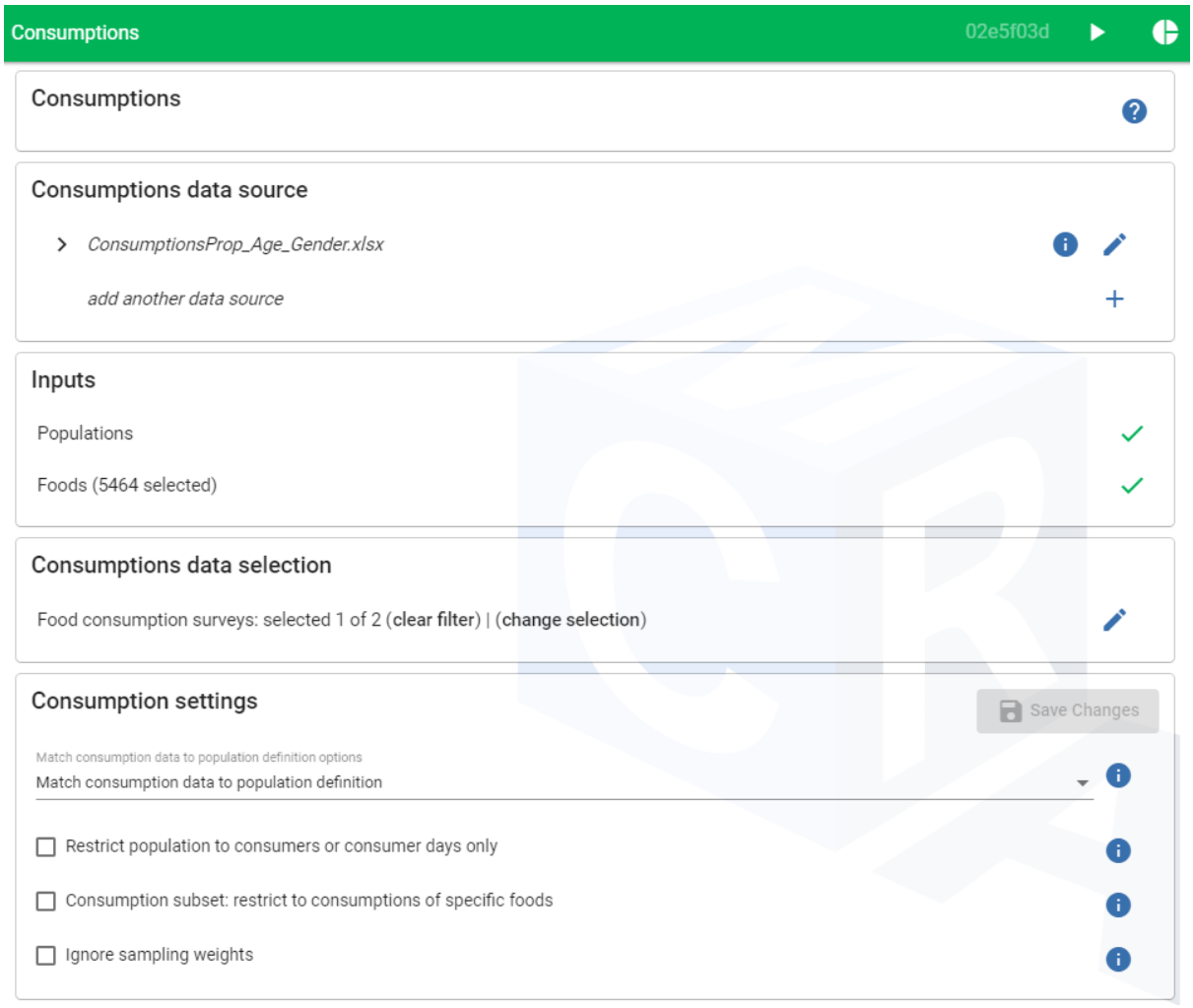


Figure 3.9: Consumption and consumption settings.

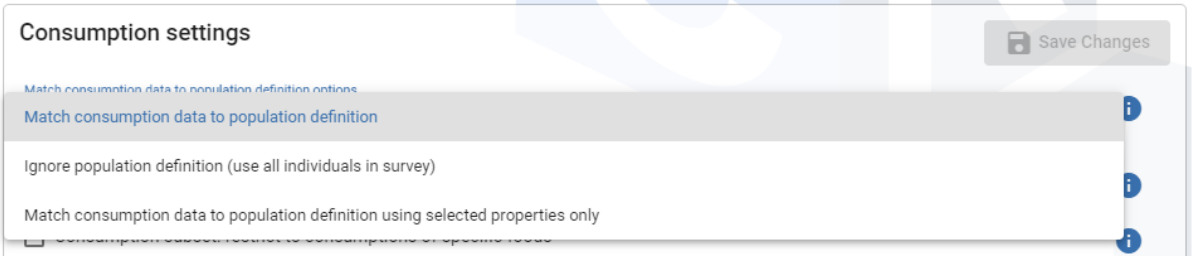


Figure 3.10: Consumption settings panel: Match consumption data to population definition options.

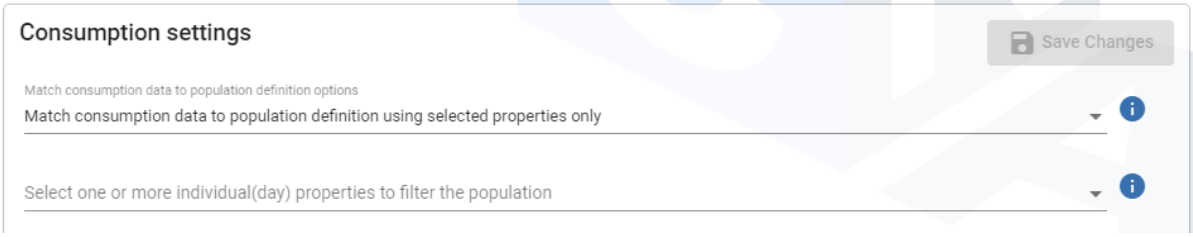


Figure 3.11: Match consumption data to population definition using selected properties only.

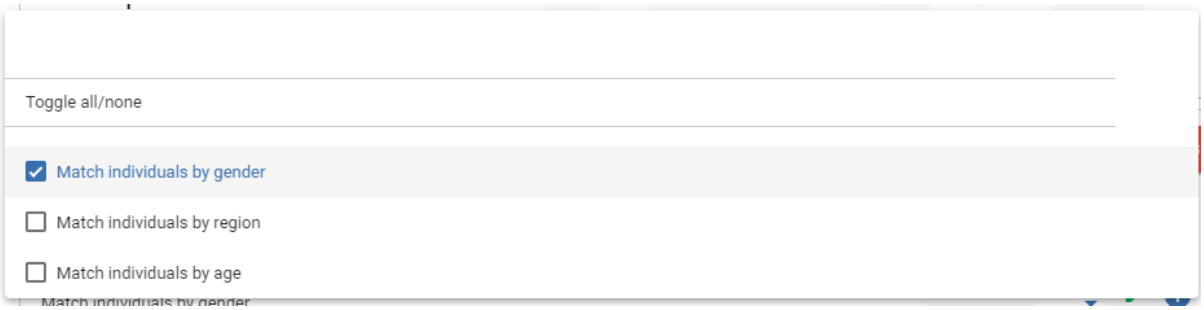


Figure 3.12: Check one or more of the available properties after selecting

### Multiple surveys

In the Consumption panel, consumption data sources are selected. After selecting two or more data sources (*add another data source*), MCRA performs a loop over the selected surveys, see Figure 3.13. Check *Loop over multiple surveys*.

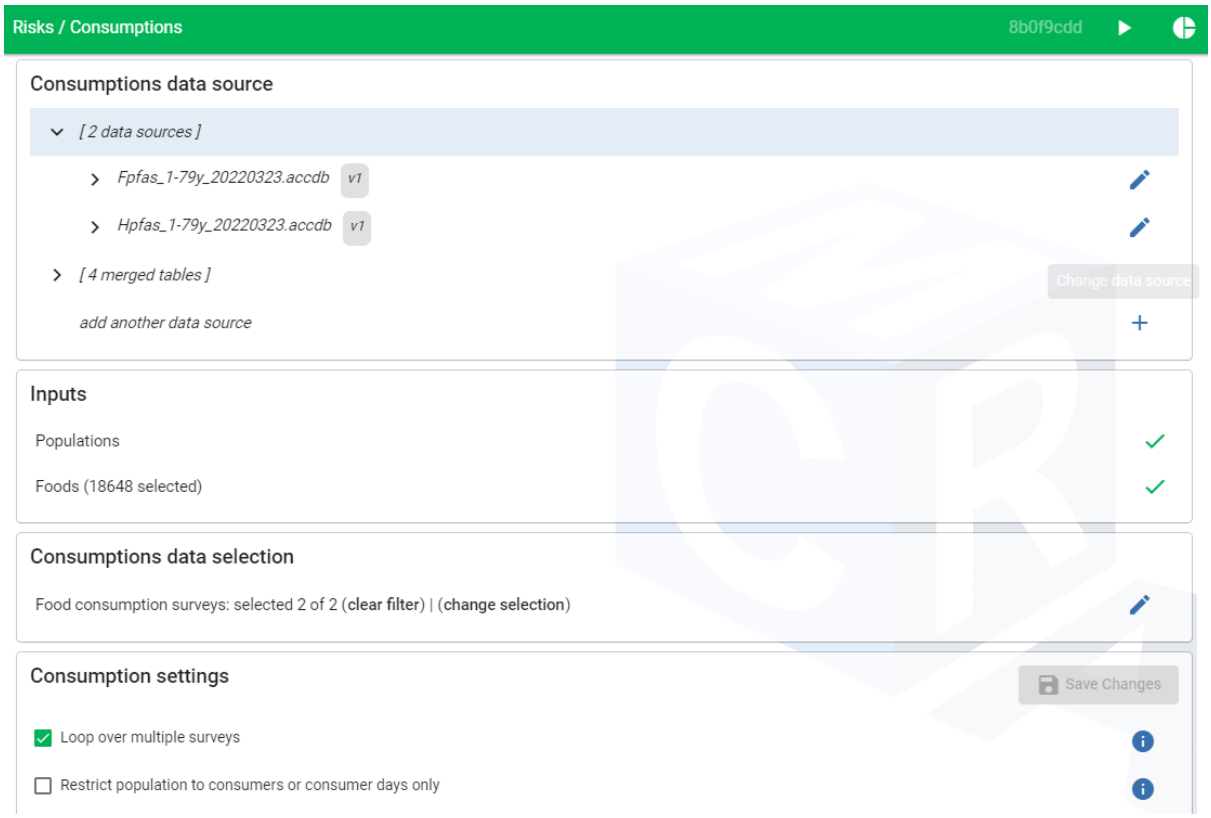


Figure 3.13: Loop over multiple surveys.

The advantage of running a multiple survey loop instead of running separate actions for each surveyn is that outputs are directly compared. In the Results panel, Figure 3.14, a toc appears containing links to the output of the risk or dietary exposure assessment (main action) for the selected surveys, but also a link to the combined output panel.

After clicking the link *2022 surveys*, the combined output is represented in violin plots and a table with percentiles for the specified percentages. Here a combined risks action is run and the p99 of the risk characterisation ratio (exposure/hazard) distribution is selected. For a dietary exposure action similar results are available.

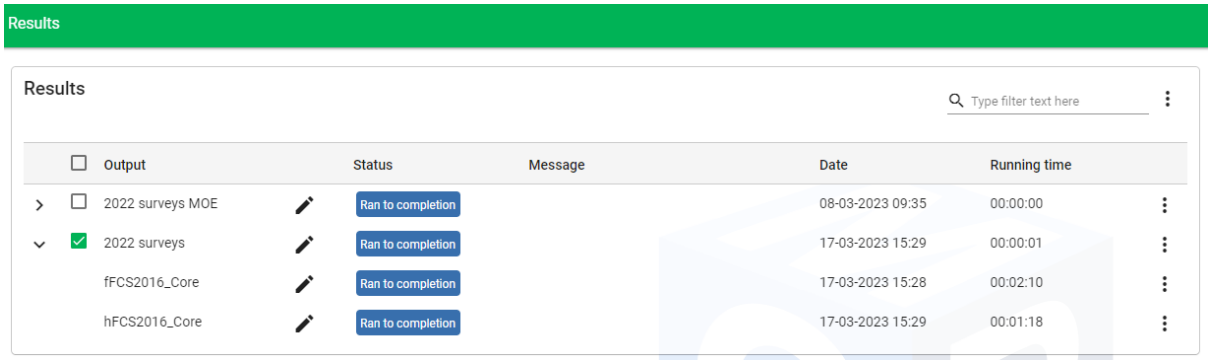


Figure 3.14: Results panel multiple surveys.

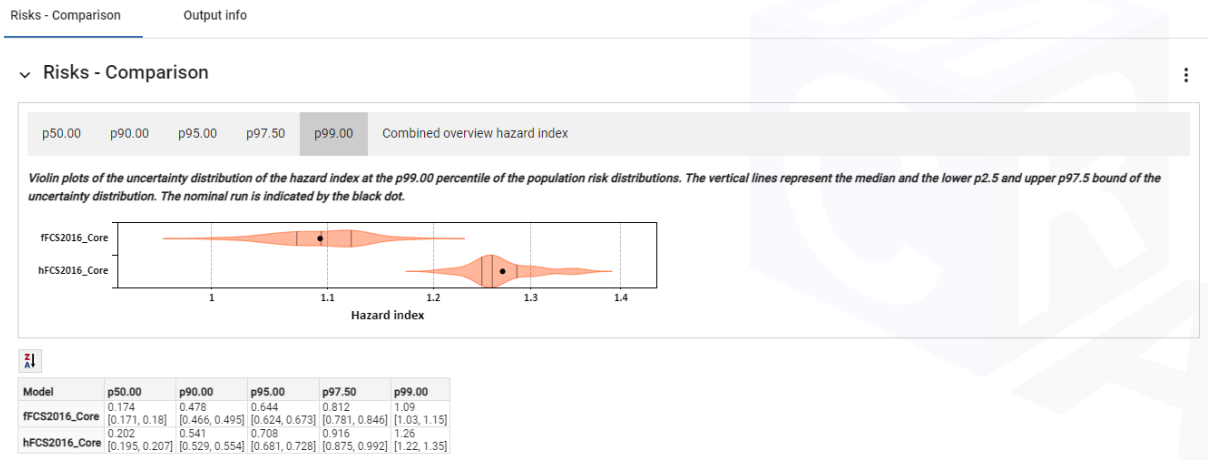


Figure 3.15: Risks comparison multiple surveys.

### Consumptions data formats

Consumption data is often collected in 24-hour dietary recall studies and contains the food consumptions and consumption amounts for a number of individuals on a number of days. For each of the individuals, the bodyweight should be specified, and optionally also age, sex, and other properties may be recorded. If applicable, sampling weights may also be specified that can be used to correct the sample of individuals in the survey to a more representative sample of the targeted population. The consumption amounts are usually expressed in grams, but may also be expressed in alternative units of plates, cups, or spoons. Optionally, the uncertainty of food consumption quantifications can be specified, see Souverein et al. (2011).

Consumption surveys are described using three tables: FoodSurveys, Individuals, and Consumptions. Individuals are linked to food surveys using the survey code (idFoodSurvey), and consumptions are linked to individuals using the individual codes (idIndividual). The food codes used to identify the consumed foods should match with the codes provided by the foods entity definitions.

Download empty dataset template: Zipped CSV Excel

### Food consumption surveys

The records of the food consumption surveys table contain the ids, names, descriptions, and other relevant metadata of consumption surveys.

Table 3.29: Table definition for Food consumption surveys.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSurvey | AlphaNumeric (50) | Unique identification code of the food consumption survey. | idSurvey, idFoodSurvey, Survey, FoodSurvey, SurveyId, FoodSurveyId, Code, Id | Yes |
| Name | AlphaNumeric (100) | The name of the food consumption survey. | Name, SurveyName | No |
| Description | AlphaNumeric (200) | Description of the food consumption survey. | Description | No |
| Location | AlphaNumeric (50) | The location or country where survey is held. It is recommended to use ISO Alpha-2 country codes. | Location, Country | No |
| BodyWeight-Unit | *BodyWeightUnit* | The unit of bodyweight of the individuals of the survey: kg (default) or g. | BodyWeight-Unit, UnitBody-Weight, WeightIn | No |
| Consumption-Unit | *ConsumptionUnit* | The unit of the use/consumption amounts of the consumptions of the survey: g (default) or kg or CustomUnit (see table food consumption quantifications table). | AmountUnit, UnitAmount, AmountUnit, Consumption-Unit | No |
| StartDate | DateTime | The start date of the survey. | StartDate | No |
| EndDate | DateTime | The end date of the survey. | EndDate | No |
| NumberOf-SurveyDays | Integer | The number of days each individual participated in the survey. | NumberOf-SurveyDays, NDaysInSurvey | Yes |
| idPopulation | AlphaNumeric (50) | Unique identification code of the population. | IdPopulation, PopulationId | No |

Accepted table names: FoodConsumptionSurveys, ConsumptionSurveys, FoodSurveys, Surveys.

### Individuals

The individuals of a survey are recorded in the Individuals table. Add additional properties like Region, Breastfeeding to further describe an individual. In table IndividualProperties, each property in the Individuals table is described (recommended way). Note that only those properties that are available in the Individuals table are used in module Populations, table Populations or PopulationIndividualPropertyValues to subset the individuals. This is only relevant when the UseData option in the population module is used.

Table 3.30: Table definition for Individuals.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual | AlphaNumeric (50) | Unique identification code of the individual. | idIndividual, IndividualId, Individual, Id | Yes |
| idFoodSurvey | AlphaNumeric (50) | The identification code / short name of survey. | idSurvey, idFoodSurvey, Survey, FoodSurvey, SurveyId, FoodSurveyId, SurveyCode, idSet, SetCode, Code | Yes |
| BodyWeight | Numeric | The body weight of the individual. | BodyWeight, Weight | No |
| Sampling-Weight | Numeric | The sampling weight for an individual (default = 1). | SamplingWeight | No |
| NumberOf-SurveyDays | Integer | The number of days the individual participated in the survey. | NumberOf-SurveyDays, NumberOfDays-InSurvey, DaysInSurvey, NDaysInSurvey | No |
| Name | AlphaNumeric (100) | Name or label of the individual. | Name | No |
| Description | AlphaNumeric (200) | Additional description of the individual. | Description | No |
| Individual properties | | Other individual properties can be added like the fields Age, Gender, Region etc. These properties are automatically parsed as co-factors or co-variables. | | No |

Accepted table names: Individuals, SurveyIndividuals, ConsumptionSurveyIndividuals, FoodConsumptionSurveyIndividuals.

### IndividualDays

The individuals and days in the survey are recorded in the individualDays table.

Table 3.31: Table definition for IndividualDays.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual | AlphaNumeric (50) | The identification code of the individual. | idIndividual, IndividualId, Individual, Id | Yes |
| idDay | AlphaNumeric (50) | Identification code of the day of consumption, sequential number | idDay, DayId, Day, DayOfSurvey | Yes |
| SamplingDate | DateTime | The date of the consumption. | Date, SamplingDate, SurveyDate | No |

Accepted table names: IndividualDays, SurveyIndividualDays, ConsumptionSurveyIndividualDays,

FoodConsumptionSurveyIndividualDays.

### Individual properties

This table is used to describe the properties used in the Populations or PopulationIndividualPropertyValues table characterising the population (table Populations) and/or the properties used in the Individuals table characterising an individual. Properties like Age, Gender, Region are describing an individual (PropertyLevel = Individual). Properties like Period (for populations) or Month (sampling date for an individual day) are describing an individual day (PropertyLevel = IndividualDay).

Table 3.32: Table definition for Individual properties.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual-Property | AlphaNumeric (50) | The code of the property. | idIndividual-Property, Individual-PropertyId, Individual-Property | Yes |
| Name | AlphaNumeric (100) | The name of the property. | Name | No |
| PropertyLevel | *PropertyLevelType* | The level of the property. This type follows a controlled terminology, with possible values: Individual or IndividualDay. | PropertyLevel, LevelProperty | No |
| Description | AlphaNumeric (200) | Description of the property. | Description | No |
| Type | *IndividualProperty-Type* | This field specifies the type of the values of this individual property. This type follows a controlled terminology, with possible values: Boolean, Categorical (default), Numeric, Nonnegative, Integer, NonnegativeInteger, Month, Datetime, Gender. | Type | No |

Accepted table names: IndividualProperties, IndividualProperty.

### Individual property values

Not recommended. This table describes individual property values. Property values are describing an individual for properties like e.g. Region, Breastfeeding. The recommended way is to add these columns as additional columns in the Individuals table. In table IndividualProperties, each property in the IndividualPropertyValues table is described.

Table 3.33: Table definition for Individual property values.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual | AlphaNumeric (50) | The identification number of the Individual. | Id | Yes |
| PropertyName | AlphaNumeric (50) | The name of the property. | Name | Yes |
| TextValue | AlphaNumeric (50) | The value of the property as text value. | | No |
| DoubleValue | Numeric | The value of the property as number. | | No |

Accepted table names: IndividualPropertyValues, IndividualPropertyValue.

### Consumptions

The individual consumptions are recorded in the consumptions table.

Table 3.34: Table definition for Consumptions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual | AlphaNumeric (50) | The unique identification code of the consumer (individual). | idIndividual, IndividualId, Individual | Yes |
| idFood | AlphaNumeric (50) | The food code (food as eaten code). | idFood, Food, FoodId, FoodConsumed, FoodAsEaten | Yes |
| Facets | AlphaNumeric | The codes of the facets/treatments recorded for this consumption. Multiple treatments are separated by a '$'. | Treatments, Treatment, Facets | No |
| idUnit | AlphaNumeric (50) | Identification code of the unit in which the food is consumed (e.g. plate, cup, spoon). | idUnit, Unit, UnitId | No |
| idDay | AlphaNumeric (25) | Identification code of the day of consumption, sequential number | idDay, DayId, Day, DayOfSurvey | Yes |
| idMeal | AlphaNumeric (25) | Identification code of the meal (eating occasion within a day). | idMeal, MealId, Meal | No |
| Amount | Numeric | The consumed portion of food in g (default) or kg or quantity of a plate, cup, spoon. Days without consumptions are not recorded. | Amount, Amount-Consumed | Yes |

Accepted table names: FoodConsumptions, FoodConsumption, Consumptions, Consumption.

### Consumptions settings

### Selection settings

Table 3.35: Selection settings for module Consumptions.

| Name | Type | Description |
|---|---|---|
| Selected tier | SettingsTemplateType | Specifies all module settings should be set according to a pre-defined tier or using custom settings. |
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Food survey | AlphaNumeric | The food consumption survey representative for the population interest. |
| Restrict population to consumers or consumer days only | Boolean | Specifies whether the population should be restricted to the individuals (chronic) or individual days (acute) that have non-ze consumption. |
| Restrict population to consumers or consumer days with consumptions of specific foods | Boolean | Specifies whether the population should be restricted to the individuals (chronic) or individual days (acute) consuming any the foods of the specified subset. |
| Selected foods-as-eaten | AlphaNumeric | Set of consumed foods that are of particular interest for restrict the consumers / consumption days. |
| Consumption subset: restrict to consumptions of specific foods | Boolean | If checked, then the consumptions are restricted to those of the specified food-as-eaten subset. |
| Selected foods-as-eaten | AlphaNumeric | Set of consumed foods that are of particular interest. |
| Match consumer selection to population definition options | *IndividualSubsetType* | Match consumption data to population definition. Use populati definitions (default), ignore all population definitions or use a selection of properties. |
| Select one or more individual(day) properties to filter the population | AlphaNumeric | Select one or more individual(day) properties to filter the individuals(days) in the population. |
| Ignore sampling weights | Boolean | If checked, individual sampling weights are not used (sampling weight = 1). If unchecked, the specified sampling weights are used. |
| Exclude individuals with less than N days | Boolean | Filter out all individuals with less than N survey days. |
| N (number of days in survey) | Numeric | Specify the nominal number of days in the survey to filter out a individuals with less than N survey days. |
| Cofactor name | AlphaNumeric | Specify the name of the cofactor. |
| Covariable name | AlphaNumeric | Specify the name of the covariable. |
| Individual day subset | IndividualDaySubsetDefinition | Individual day subset definition. |
| Individuals subset definitions | IndividualsSubsetDefinition | Contains a list of subset definitions to filter the population's individuals based on an individual's properties, by property nam and a custom filter query, for example a value range or a list of keywords. |

### Calculation settings

Table 3.36: Calculation settings for module Consumptions.

| Name | Type | Description |
|---|---|---|
| Define populations based on specified individual properties | Boolean | Define a population by selecting specific ranges/values of individual properties. E.g., the female population between ages and 45 is composed of the properties gender (female) and age (between 18 and 45). |

### Output settings

Table 3.37: Output settings for module Consumptions.

| Name | Type | Description |
|---|---|---|
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |

### Uncertainty settings

Table 3.38: Uncertainty settings for module Consumptions.

| Name | Type | Description |
|---|---|---|
| Resample individuals | Boolean | Individual data are resampled from the original database using t bootstrap methodology (Efron 1979, Efron & Tibshirani 1993) |
| Resample portion sizes | Boolean | Specifies whether portion sizes should be resampled based on food consumption quantification data, see (Souverein et al. 201 |

### Consumptions tiers

### Overview

Table 3.39: Tier overview for module Consumptions.

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec- tive Tier II | EFS 202 Chr Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| Ig no sa pl w | true | true | true | true | true | true | true | true | true | true |
| E cl in di vi u- al w le th N da | false | true | false | true | false | true | false | true | false | true |
| N (r bo of da in su ve | | 2 | | 2 | | 2 | | 2 | | 2 |

### Retrospective dietary CRA (EC 2018) - Acute / Tier I

Table 3.40: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier I.

| Name | Setting |
|---|---|
| Ignore sampling weights | true |
| Exclude individuals with less than N days | false |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier I

Table 3.41: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier I.

| Name | Setting |
|---|---|
| Ignore sampling weights | true |
| Exclude individuals with less than N days | true |
| N (number of days in survey) | 2 |

### Retrospective dietary CRA (EC 2018) - Acute / Tier II

Table 3.42: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier II.

| Name | Setting |
|---|---|
| Ignore sampling weights | true |
| Exclude individuals with less than N days | false |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier II

Table 3.43: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Ignore sampling weights | true |
| Exclude individuals with less than N days | true |
| N (number of days in survey) | 2 |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier I

Table 3.44: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier I.

| Name | Setting |
|---|---|
| Ignore sampling weights | true |
| Exclude individuals with less than N days | false |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I

Table 3.45: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I.

| Name | Setting |
|---|---|
| Ignore sampling weights | true |
| Exclude individuals with less than N days | true |
| N (number of days in survey) | 2 |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier II

Table 3.46: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier II.

| Name | Setting |
|---|---|
| Ignore sampling weights | true |
| Exclude individuals with less than N days | false |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II

Table 3.47: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Ignore sampling weights | true |
| Exclude individuals with less than N days | true |
| N (number of days in survey) | 2 |

### Prospective dietary CRA (EFSA 2023) - Acute / Tier II

Table 3.48: Tier definition for Prospective dietary CRA (EFSA 2023) - Acute / Tier II.

| Name | Setting |
|---|---|
| Ignore sampling weights | true |
| Exclude individuals with less than N days | false |

### Prospective dietary CRA (EFSA 2023) - Chronic / Tier II

Table 3.49: Tier definition for Prospective dietary CRA (EFSA 2023) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Ignore sampling weights | true |
| Exclude individuals with less than N days | true |
| N (number of days in survey) | 2 |

### Prospective dietary CRA (EFSA 2024) - Acute / Tier II

Table 3.50: Tier definition for Prospective dietary CRA (EFSA 2024) - Acute / Tier II.

| Name | Setting |
|---|---|
| Ignore sampling weights | true |
| Exclude individuals with less than N days | false |

### Prospective dietary CRA (EFSA 2024) - Chronic / Tier II

Table 3.51: Tier definition for Prospective dietary CRA (EFSA 2024) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Ignore sampling weights | true |
| Exclude individuals with less than N days | true |
| N (number of days in survey) | 2 |

#### Consumptions uncertainty

In MCRA, in an *acute exposure* assessments, individual consumption day data are *resampled*, thus preserving the multivariate consumption patterns and associated weights and/or other individual characteristics. In MCRA we re-sample the set of individuals x number of survey days. We think that this implementation better reflects the notion of acute exposure which is expressed as the normalized intake per day. For *chronic exposure* assessments the resampling algorithm remained unchanged and the set of individuals (with corresponding days) is *resampled*.

#### Consumptions as data

Consumptions data are the amounts of foods consumed on specific days by individuals in a food consumption survey.

- *Consumptions data formats*
- *Consumptions from data*
- *Consumptions calculation*

Settings used

- *Calculation Settings*

### 3.2.2 Dust exposure determinants

Dust exposure determinants specify the factors that determine the exposure of individuals to dust.

This module has as primary entities: *Substances*

Output of this module is used by: *Dust exposures*

#### Dust exposure determinants from data

#### Dust exposure determinants data formats

Distributions for exposure determinants of substances in dust.

Download empty dataset template: Zipped CSV Excel

#### Dust ingestions

Variability distributions specifying the intake/ingestions of dust, specified using a distribution type, a mean and a coefficient of variation (CV). Distributions may be specified for different subgroups of age and sex.

Table 3.52: Table definition for Dust ingestions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubgroup | AlphaNumeric (50) | The id of the subgroup. | idSubgroup | Yes |
| AgeLower | Numeric (50) | Specifies the lower bound of the age interval (in years) of the dust exposure determinant subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower bound of the next subgroup. | AgeLower, LowerAge | No |
| Sex | *GenderType* | The sex of the subgroup. | Sex, Gender | No |
| Value | Numeric | Distribution mean. | Mean | Yes |
| ExposureUnit | *ExternalExposureUnit* | The unit of the dust ingestion. If not specified, then a default unit of g/day is assumed. | Unit, DustIngestionUnit | No |
| DistributionType | *DustIngestionDistributionType* | Distribution type (Uniform, or LogNormal). If not specified, the dust adherence amount is assumed to be a constant factor. | DistributionType, Distribution | No |
| CvVariability | Numeric | Coefficient of variation of the distribution. | | No |

Accepted table names: DustIngestions, DustIngestion.

### Dust body exposure fractions

Variability distributions specifying the individual fractions of the body exposed to dust. The distributions are specified using a distribution type, a mean and a coefficient of variation (CV). Distributions may be specified for different subgroups of age and sex.

Table 3.53: Table definition for Dust body exposure fractions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubgroup | AlphaNumeric (50) | The id of the subgroup. | idSubgroup | Yes |
| AgeLower | Numeric (50) | Specifies the lower bound of the age interval (in years) of the dust body exposure fractions subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower bound of the next subgroup. | AgeLower, LowerAge | No |
| Sex | *GenderType* | The sex of the subgroup. | Sex, Gender | No |
| Value | Numeric | Mean. | Value, Mean, Mean | Yes |
| Distribution-Type | *DustBodyExposure-FractionDistribution-Type* | Distribution type (Uniform, or LogNormal). If not specified, the dust body exposure fraction is assumed to be constant. | Distribution-Type, Distribution | No |
| CvVariability | Numeric | Coefficient of variation. | CvVariability, Sd | No |

Accepted table names: DustBodyExposureFractions, DustBodyExposureFraction.

### Dust adherence amounts

Variability distributions specifying the dust adherence amounts. The distributions are specified using a distribution type, a mean and a coefficient of variation (CV). Distributions may be specified for different subgroups of age and sex.

Table 3.54: Table definition for Dust adherence amounts.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubgroup | AlphaNumeric (50) | The id of the subgroup. | idSubgroup | Yes |
| AgeLower | Numeric (50) | Specifies the lower bound of the age interval (in years) of the dust adherence fractions subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower bound of the next subgroup. | AgeLower, LowerAge | No |
| Sex | *GenderType* | The sex of the subgroup. | Sex, Gender | No |
| Distribution-Type | *DustAdherence-AmountDistribution-Type* | Distribution type (Uniform, or LogNormal). If not specified, the dust adherence amount is assumed to be a constant factor. | Distribution-Type, Distribution | No |
| Value | Numeric | Mean adherance amount (in g/m2). | Value, Mean | Yes |
| CvVariability | Numeric | Coefficient of variation. | CvVariability, CV | No |

Accepted table names: DustAdherenceAmounts, DustAdherenceAmount.

### Dust availability fractions

Distributions for fractions of substance in dust available for dermal contact can be dependent on e.g. age.

Table 3.55: Table definition for Dust availability fractions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubgroup | AlphaNumeric (50) | The id of the subgroup. | idSubgroup | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| AgeLower | Numeric (50) | Specifies the lower bound of the age interval (in years) of the dust exposure determinant subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower bound of the next subgroup. | AgeLower, LowerAge | No |
| Sex | *GenderType* | The sex of the subgroup. | Sex, Gender | No |
| Value | Numeric | Mean of the distribution. | Mean | Yes |
| Distribution-Type | *DustAvailability-FractionDistribution-Type* | Distribution type (Uniform, or LogNormal). If not specified, the dust availability fraction is assumed to be constant. | Distribution-Type, Distribution | No |
| CvVariability | Numeric | Coefficient of variation. | | No |

Accepted table names: DustAvailabilityFractions, DustAvailabilityFraction.

#### Dust exposure determinants as data

Dust exposure determinant data can be entered using the internal, relational data format.

- *Dust exposure determinants data formats*
- *Dust exposure determinants from data*

### 3.2.3 Soil exposure determinants

Soil exposure determinants specify the factors that determine the exposure of individuals to soil.

This module has as primary entities: *Substances*

Output of this module is used by: *Soil exposures*

#### Soil exposure determinants from data

#### Soil exposure determinants data formats

Distributions for exposure determinants of substances in soil.

Download empty dataset template: Zipped CSV Excel

#### Soil ingestions

Distributions for soil ingestions are dependent on e.g. age.

Table 3.56: Table definition for Soil ingestions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubgroup | AlphaNumeric (50) | The id of the subgroup. | idSubgroup | Yes |
| AgeLower | Numeric (50) | Specifies the lower bound of the age interval (in years) of the soil exposure determinant subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower bound of the next subgroup. | AgeLower, LowerAge | No |
| Sex | *GenderType* | The sex of the subgroup. | Sex, Gender | No |
| Value | Numeric | Mean of the distribution. | Mean | Yes |
| ExposureUnit | *ExternalExposureUnit* | The unit of the soil ingestion. If not specified, then a default unit of g/day is assumed. | Unit, SoilIngestionUnit | No |
| DistributionType | *SoilIngestionDistributionType* | Distribution type (Uniform, or LogNormal). If not specified, the soil adherence amount is assumed to be a constant factor. | DistributionType, Distribution | No |
| CvVariability | Numeric | Coefficient of variation. | | No |

Accepted table names: SoilIngestions, SoilIngestion.

#### Soil exposure determinants as data

Soil exposure determinant data can be entered using the internal, relational data format.

- *Soil exposure determinants data formats*
- *Soil exposure determinants from data*

### 3.2.4 Air exposure determinants

Air exposure determinant data are distributions of chemical substances occurring in air samples. The distributions can differ per age group.

This module has as primary entities: *Substances*

Output of this module is used by: *Air exposures*

#### Air exposure determinants from data

#### Air exposure determinants data formats

Distributions for exposure determinants of substances in air.

Download empty dataset template: Zipped CSV Excel

### AirIndoorFractions

Point estimates for indoor fractions,,can be dependent on e.g. age.

Table 3.57: Table definition for AirIndoorFractions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubgroup | AlphaNumeric (50) | The id of the subgroup. | idSubgroup | Yes |
| AgeLower | Numeric (50) | Specifies the lower bound of the age interval (in years) of the air exposure determinant subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower bound of the next subgroup. | AgeLower, LowerAge | No |
| Fraction | Numeric | Fraction indoors, between 0 and 1. | Fraction, FractionIndoors | Yes |

Accepted table names: AirIndoorFractions, AirIndoorFraction, FractionsAirIndoor.

### Air ventilatory flow rates

Distributions for air ventilatory flow rates (default m3/day) can be dependent on e.g. age.

Table 3.58: Table definition for Air ventilatory flow rates.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubgroup | AlphaNumeric (50) | The id of the subgroup. | idSubgroup | Yes |
| AgeLower | Numeric (50) | Specifies the lower bound of the age interval (in years) of air ventilatory flow rate subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower bound of the next subgroup. | AgeLower, LowerAge | No |
| Sex | *GenderType* | The sex of the subgroup. | Sex, Gender | No |
| Value | Numeric | Mean of the distribution. | Value, Mean | Yes |
| Distribution-Type | *VentilatoryFlow-RateDistributionType* | Distribution type (LogNormal). If not specified, the air ventilatory flow rate is assumed to be constant. | Distribution-Type, Distribution | No |
| CvVariability | Numeric | Coefficient of variation. | CvVariability, Sd | No |

Accepted table names: AirVentilatoryFlowRates, AirVentilatoryFlowRate.

### Air body exposure fractions

Variability distributions specifying the individual fractions of the body exposed to air. The distributions are specified using a distribution type, a mean and a coefficient of variation (CV). Distributions may be specified for different subgroups of age and sex.

Table 3.59: Table definition for Air body exposure fractions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubgroup | AlphaNumeric (50) | The id of the subgroup. | idSubgroup | Yes |
| AgeLower | Numeric (50) | Specifies the lower bound of the age interval (in years) of the air body exposure fractions subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower bound of the next subgroup. | AgeLower, LowerAge | No |
| Sex | *GenderType* | The sex of the subgroup. | Sex, Gender | No |
| Value | Numeric | Mean. | Value, Mean, Mean | Yes |
| Distribution-Type | *AirBodyExposure-FractionDistribution-Type* | Distribution type (Uniform, or LogNormal). If not specified, the air body exposure fraction is assumed to be constant. | Distribution-Type, Distribution | No |
| CvVariability | Numeric | Coefficient of variation. | CvVariability, Sd | No |

Accepted table names: AirBodyExposureFractions, AirBodyExposureFraction.

### Air exposure determinants

### Calculation settings

Table 3.60: Calculation settings for module Air exposure determinants.

| Name | Type | Description |
|---|---|---|
| Deposition velocity | Numeric | Deposition velocity of airborne particles onto the skin's surface (m/h). |
| Default air body exposure fraction | Numeric | Default fraction of total body surface area exposed to air. Used when no distributions (for specific sub-groups) are found in the data. |

### Air exposure determinants as data

Air exposure determinant data can be entered using the internal, relational data format.

- *Air exposure determinants data formats*
- *Air exposure determinants from data*

Settings used

- *Calculation Settings*

### 3.2.5 Consumer product exposure determinants

Consumer product exposure determinant data are distributions of chemical substances occurring in consumer products. The distributions can differ per age group.

This module has as primary entities: *Substances Consumer products*

Output of this module is used by: *Consumer product exposures*

#### Consumer product exposure determinants from data

#### Consumer product exposure determinants data formats

Distributions for exposure determinants of substances in consumer products.

Download empty dataset template: Zipped CSV Excel

#### Consumer product exposure fractions

Fractions of the substance used with the product to which a consumer is exposed.

Table 3.61: Table definition for Consumer product exposure fractions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idProduct | AlphaNumeric (50) | The consumer product. | idProduct, ProductId | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| ExposureRoute | *ExposureRoute* | The exposure route(s) (only applicable if exposure level is external) for which this exposure. | ExposureRoute, Route | Yes |
| Exposure-Fraction | Numeric | Fraction between 0 and 1. | Exposure-Fraction, Fraction | Yes |
| AgeLower | Numeric (50) | Specifies the lower bound of the age interval (in years) of the exposure fraction in case the distribution applies to a specific population age subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower age of the next subgroup. | AgeLower, LowerAge | No |
| Sex | *GenderType* | Specifies the sex associated with this exposure fraction in case the distribution applies to a specific population sex subgroup. | Sex, Gender | No |

Accepted table names: ConsumerProductExposureFractions, CPExposureFractions, ExposureFractions.

### Consumer product application amounts

Distributions of consumer product application amounts represent the quantities used or applied during a single use. These distributions can be characterized for the general population or for specific subgroups based on age and/or sex.

Table 3.62: Table definition for Consumer product application amounts.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idProduct | AlphaNumeric (50) | Identifier/code of the consumer product. | idProduct, ProductId | Yes |
| AgeLower | Numeric (50) | Specifies the lower bound of the age interval (in years) of the application amount in case the distribution applies to a specific population age subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower age of the next subgroup. | AgeLower, LowerAge | No |
| Sex | *GenderType* | Specifies the sex associated with this application amount in case the distribution applies to a specific population sex subgroup. | Sex, Gender | No |
| Amount | Numeric | Mean of the distribution. Amounts are in g (gram, default unit). | Amount, Mean | Yes |
| Distribution-Type | *ApplicationAmount-DistributionType* | Type of the distribution. If not specified, the application amount is assumed to be constant. | Distribution-Type, Distribution | No |
| CvVariability | Numeric | Coefficient of variation of the distribution. | Cv, CvVariability | No |
| Unit | *ApplicationAmount-Unit* | The unit for the consumer product application amount. When not specified, then a default unit of g (gram) is assumed. | Unit, Application-AmountUnit | No |

Accepted table names: ConsumerProductApplicationAmounts, CPApplicationAmounts, ApplicationAmounts.

### Consumer product exposure determinants as data

Consumer product exposure determinant data can be entered using the internal, relational data format.

- *Consumer product exposure determinants data formats*
- *Consumer product exposure determinants from data*

## 3.2.6 Consumer product use frequencies

Consumer product use frequencies specify the frequency of use for a consumer product (personal care, do-it-yourself, cleaning product) per day.

This module has as primary entities: *Populations Consumer products*

Output of this module is used by: *Consumer product exposures*

### Consumer product use frequencies from data

### Consumer product use frequencies data formats

Consumer product use frequencies are described by five table.

Download empty dataset template: Zipped CSV Excel

### Consumer product surveys

The records of the consumer product surveys table contain the ids, names, descriptions, and other relevant metadata of consumer product surveys.

Table 3.63: Table definition for Consumer product surveys.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSurvey | AlphaNumeric (50) | Unique identification code of the consumer product survey. | idSurvey, Survey, SurveyId, Id | Yes |
| Name | AlphaNumeric (100) | The name of the consumer product survey. | Name, SurveyName | No |
| Description | AlphaNumeric (200) | Description of the consumer product survey. | Description | No |
| Country | AlphaNumeric (50) | The location or country where the survey is held. It is recommended to use ISO Alpha-2 country codes. | Location, Country | No |
| BodyWeight-Unit | *BodyWeightUnit* | The unit of bodyweight of the individuals of the survey: kg (default) or g. | BodyWeight-Unit, UnitBody-Weight, WeightIn | No |
| AmountUnit | *ConsumptionUnit* | The unit of the amounts of consumer product use in the survey: g (default) or kg or CustomUnit (see table food consumption quantifications table). | AmountUnit, UnitAmount | No |
| StartDate | DateTime | The start date of the survey. | StartDate | No |
| EndDate | DateTime | The end date of the survey. | EndDate | No |
| idPopulation | AlphaNumeric (50) | Unique identification code of the population. | IdPopulation, PopulationId | No |

Accepted table names: ConsumerProductSurveys, CPSurveys.

### Individuals

The individuals of a survey are recorded in the Individuals table. Add additional properties like Region, Breastfeeding to further describe an individual. In table IndividualProperties, each property in the Individuals table is described (recommended way). Note that only those properties that are available in the Individuals table are used in module Populations, table Populations or PopulationIndividualPropertyValues to subset the individuals. This is only relevant when the UseData option in the population module is used.

Table 3.64: Table definition for Individuals.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual | AlphaNumeric (50) | Unique identification code of the individual. | idIndividual, IndividualId, Individual, Id | Yes |
| idFoodSurvey | AlphaNumeric (50) | The identification code / short name of survey. | idSurvey, idFoodSurvey, Survey, FoodSurvey, SurveyId, FoodSurveyId, SurveyCode, idSet, SetCode, Code | Yes |
| BodyWeight | Numeric | The body weight of the individual. | BodyWeight, Weight | No |
| Sampling-Weight | Numeric | The sampling weight for an individual (default = 1). | SamplingWeight | No |
| NumberOf-SurveyDays | Integer | The number of days the individual participated in the survey. | NumberOf-SurveyDays, NumberOfDays-InSurvey, DaysInSurvey, NDaysInSurvey | No |
| Name | AlphaNumeric (100) | Name or label of the individual. | Name | No |
| Description | AlphaNumeric (200) | Additional description of the individual. | Description | No |
| Individual properties | | Other individual properties can be added like the fields Age, Gender, Region etc. These properties are automatically parsed as co-factors or co-variables. | | No |

Accepted table names: Individuals, SurveyIndividuals, ConsumptionSurveyIndividuals, FoodConsumptionSurveyIndividuals.

### Individual properties

This table is used to describe the properties used in the Populations or PopulationIndividualPropertyValues table characterising the population (table Populations) and/or the properties used in the Individuals table characterising an individual. Properties like Age, Gender, Region are describing an individual (PropertyLevel = Individual). Properties like Period (for populations) or Month (sampling date for an individual day) are describing an individual day (PropertyLevel = IndividualDay).

Table 3.65: Table definition for Individual properties.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual-Property | AlphaNumeric (50) | The code of the property. | idIndividual-Property, Individual-PropertyId, Individual-Property | Yes |
| Name | AlphaNumeric (100) | The name of the property. | Name | No |
| PropertyLevel | *PropertyLevelType* | The level of the property. This type follows a controlled terminology, with possible values: Individual or IndividualDay. | PropertyLevel, LevelProperty | No |
| Description | AlphaNumeric (200) | Description of the property. | Description | No |
| Type | *IndividualProperty-Type* | This field specifies the type of the values of this individual property. This type follows a controlled terminology, with possible values: Boolean, Categorical (default), Numeric, Nonnegative, Integer, NonnegativeInteger, Month, Datetime, Gender. | Type | No |

Accepted table names: IndividualProperties, IndividualProperty.

### Individual property values

Not recommended. This table describes individual property values. Property values are describing an individual for properties like e.g. Region, Breastfeeding. The recommended way is to add these columns as additional columns in the Individuals table. In table IndividualProperties, each property in the IndividualPropertyValues table is described.

Table 3.66: Table definition for Individual property values.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual | AlphaNumeric (50) | The identification number of the Individual. | Id | Yes |
| PropertyName | AlphaNumeric (50) | The name of the property. | Name | Yes |
| TextValue | AlphaNumeric (50) | The value of the property as text value. | | No |
| DoubleValue | Numeric | The value of the property as number. | | No |

Accepted table names: IndividualPropertyValues, IndividualPropertyValue.

### Individual consumer product use frequencies

Individual consumer product use frequencies are specified as a number of use per day for a consumer product (>= 0).

Table 3.67: Table definition for Individual consumer product use frequencies.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual | AlphaNumeric (50) | The unique identification code of the consumer (individual). | idIndividual, IndividualId, Individual | Yes |
| idProduct | AlphaNumeric (50) | The consumer product id or code. | idProduct, ProductId, Product | Yes |
| Frequency | Numeric | The frequency of use, a value equal or higher than zero (freq >= 0). | Frequency | Yes |

Accepted table names: ConsumerProductUseFrequencies, CPUseFrequencies, UseFrequencies.

### Consumer product use frequencies settings

### Selection settings

Table 3.68: Selection settings for module Consumer product use frequencies.

| Name | Type | Description |
|---|---|---|
| Individuals subset definitions | IndividualsSubsetDefinition | Contains a list of subset definitions to filter the population's individuals based on an individual's properties, by property nam and a custom filter query, for example a value range or a list of keywords. |
| Define populations based on specified individual properties | Boolean | Define a population by selecting specific ranges/values of individual properties. E.g., the female population between ages and 45 is composed of the properties gender (female) and age (between 18 and 45). |
| Match consumer product individuals selection to population definition options | *IndividualSubsetType* | Match consumer product individuals selection to population definition. Use population definitions (default), ignore all population definitions or use a selection of properties. |
| Use sampling weights | Boolean | If checked, individual sampling weights are used. If unchecked the individual sampling weights are not in the calculations. |
| Select one or more individual properties to filter the population | AlphaNumeric | Select one or more individual properties to filter the individuals the population. |

### Output settings

Table 3.69: Output settings for module Consumer product use frequencies.

| Name | Type | Description |
|---|---|---|
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |

### Consumer product use frequencies as data

Consumer product use frequencies specify the frequency of use.

- *Consumer product use frequencies data formats*
- *Consumer product use frequencies from data*

## 3.2.7 Food recipes

Food recipes data specify the composition of specific foods (typically: foods-as-eaten) in terms of other foods (intermediate foods or modelled foods) by specifying proportions in the form of a percentage.

This module has as primary entities: *Foods*

Output of this module is used by: *Food conversions*

### Food recipes from data

### Food recipes data formats

Recipe data to specify the ingredients of foods. Food recipes can be used to describe the ingredients of a composite food (e.g., of apple pie), or to specify the amount of a primary ingredient needed to obtain 100g of the food (e.g., grapes to raisins). Recipe is commonly used recursively (e.g., apple pie contains apple and flour, flour contains wheat).

Download empty dataset template: Zipped CSV Excel

### Recipes

Table 3.70: Table definition for Recipes.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFromFood | AlphaNumeric (50) | The code of the composite food (from-code), i.e., the code of the food for which the ingredient(s) are specified. | idFromFood, FromFoodId, FromFood, FoodFrom, Food | Yes |
| idToFood | AlphaNumeric (50) | The code of the ingredient food (to-code). | idToFood, ToFoodId, ToFood, FoodTo, Ingredient | Yes |
| Proportion | Numeric | Proportion of each ingredient in the food (%). | Proportion, Proportion% | Yes |
| idPopulation | AlphaNumeric (50) | Unique identification code of the population. | IdPopulation, PopulationId | No |

Accepted table names: FoodTranslations, FoodTranslation, FoodCompositions, FoodComposition.

### Food recipes as data

Food recipes are provided as data in the form of simple composition tables.

- *Food recipes data formats*
- *Food recipes from data*

### 3.2.8 Market shares

Market shares data specify for a given food, percentages of more specific foods (subfoods, e.g. brands) representing their share in a market. Market shares are used when consumption data are available at a more generalised level than concentration data.

This module has as primary entities: *Foods*

Output of this module is used by: *Food conversions*

#### Market shares from data

#### Market shares data formats

Describes the shares (proportions) in a market.

Download empty dataset template: Zipped CSV Excel

#### Market shares

Market shares main table.

Table 3.71: Table definition for Market shares.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFood | AlphaNumeric (50) | The subtype of the food. | idFood, FoodId, Food, FoodType | Yes |
| Percentage | Numeric | Market share percentage of the subtype. | Percentage, Marketshare-Percentage, MarketShare, MarketShare-Percentage, MarketShare% | Yes |
| BrandLoyalty | Numeric | A parameter used in brand loyalty modelling, where 0 (default) specifies no brand loyalty (on each eating occasion a random selection of the next lower level in the hierarchy of food codes), and 1 specifies absolute brand loyalty (on subsequent eating occasions the same selection of the next lower level in the hierarchy of food codes). | BrandLoyalty | No |

Accepted table names: MarketShares, MarketShare, FoodMarketShares, FoodMarketShare.

#### Market shares as data

Market shares are provided as data in the form of percentages.

- *Market shares data formats*
- *Market shares from data*

### Market shares and brand loyalty

Sometimes measurements of substances in food are available at a more detailed food coding level than consumption data. For example, measurements may have been made for specific brands of a food whereas the consumption survey did not record the brand. MCRA allows to specify market share data for subtypes of a food (e.g. A$1, A$2, A$3 are three brands of food A), and to calculate acute exposure based on such market shares.

For chronic assessments **brand loyalty** should be specified according to a simple Dirichlet model (Goodhardt et al. (1984)). Technically, the Dirichlet model for brand choice needs nbrand parameters $\alpha_i$ (which should be positive real numbers). The average brand choice probability for each brand is

$$\alpha_i / S$$

where

$$S = \sum \alpha_i$$

By definition, the market shares $m_i$ should be proportional to the brand choice probabilities, and thus to the parameters $\alpha_i$. Thus means that $S$, the sum of the alphas, is the only additional parameter that should be specified, and indeed this is the parameter that determines brand loyalty. $S = 0$ corresponds to absolute brand loyalty, and brand loyalty decreases with increasing $S$. We define $L = (1 + S)^{-1}$ as an interpretable brand loyalty parameter, where now $L = 0$ and $L = 1$ correspond to the situations of no brand loyalty and absolute brand loyalty, respectively.

The multinomial distribution models the probability of counts and is a generalization of the binomial distribution. The Dirichlet does the opposite, it models for a number of counts the distribution of probabilities, so for numbers $\alpha_1 = x_1, ..., \alpha_k = x_k$ the distribution of $m_1, ..., m_k$ is modelled with $m_k$ the marketshare for brand $k$.

Given empirical or parametric distributions of consumption and concentration values, the algorithm for chronic exposure assessment now operates as follows:

1. Simulate consumptions for $n$ individual(day)s.
2. Simulate $n$ selection probabilities from the Dirichlet distribution.
3. For each individual, simulate $d$ brand choices from a multinomial distribution using the individual specific selection probabilities from step 2.
4. For all individuals and days simulate values from the appropriate concentration distribution.
5. Multiply consumption with concentration to obtain exposure.

## 3.2.9 Single value consumptions

Single value consumption data are the single value amounts (Large Portion, Mean Consumption, p97.5Consumption) of modelled foods (foods-as-measured) consumed in a population.

This module has as primary entities: *Populations Foods*

Output of this module is used by: *Single value dietary exposures*

### Single value consumptions from data

### Single value consumptions calculation

Single value consumptions can be supplied *as data* or computed. When single value consumptions are computed from *consumptions by modelled food*, then the mean, median and large portion (p97.5 percentile) are computed for all modelled food consumption distributions. Besides these statistics, also the mean bodyweight of the population is computed. The following options are relevant in this calculation:

- Set the *risk type* option to *acute* if the consumptions should be based on the individual-day distributions. Otherwise, choose *chronic* to base them on the distributions aggregated by individual.

- Checking the *apply processing factors* option will compute the single value consumptions for the processed foods. When using this option, the output will also show a reverse yield factor, that is the ratio of the quantity of the raw commodity required to to obtain the processed commodity. Note, when no processing factors are available, the single-value consumption amounts of processed foods are expressed in terms of the processed commodities. The yield factor, i.c. the factor for translating the processed amount to the unprocessed amount, is not applied. In the IESTI calculations (and also chronic single-value calculations), calculations are done using the processed amounts, this is on the level of raw processed foods.
- Check the *restrict population to consumers or consumer days only (modelled-food)* option to compute the single value consumption statistics for each food based on the food consumers only. Note that checking this option will also affect the computed bodyweight, which is then computed by food based on the food-consumers only and can be different for each food.
- There is also an option to *ignore sampling weights* in the calculation.
- Check the *standardise consumption with body weight before calculation of single values or afterwards (with mean bodyweight)* option to compute the single value consumptions from the per bodyweight distribution. If unchecked, the per-person distribution will be used for computing the statistics. Note that although the results are reported per-day, the statistics are established by multiplying the statistics obtained from the per bw distribution by the bodyweight.

### Single value consumptions data formats

Single value consumptions data provides a single per-individual-day and per-food consumption amount for a population. Also the bodyweight should be specified, and optionally also age, sex, and other properties may be recorded. The consumption amounts are usually expressed in grams, but may also be expressed in alternative units of plates, cups, or spoons. Optionally, the uncertainty of food consumption quantifications can be specified, see Souverein et al. (2011).

Single value consumptions are described using one table: PopulationConsumptionSingleValues.

Download empty dataset template: Zipped CSV Excel

### Population consumption single values

Population consumption single values describe population food consumptions in the form of single value statistics.

Table 3.72: Table definition for Population consumption single values.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idPopulation | AlphaNumeric (50) | Unique identification code of the population. | IdPopulation, PopulationId | Yes |
| idFood | AlphaNumeric (50) | The unique identification code of the consumed food. | idFood, FoodCode, Food | Yes |
| Value type of the single value consumption amount. | *ConsumptionValueType* | The value type of this consumption value. | ConsumptionType, ValueType, ConsumptionValueType, ConsumptionSingleValueType | Yes |
| Percentile | Numeric | The percentile (if consumption value type is a percentile). | Percentile | No |
| ConsumptionAmount | Numeric | The consumed amount. | Amount, Consumption, ConsumptionAmount, AmountConsumed | Yes |
| ConsumptionUnit | *ConsumptionIntakeUnit* | The unit of the consumption amount. | AmountUnit, UnitAmount, ConsumptionUnit | No |
| Reference | AlphaNumeric (200) | Reference to the source from which this value is obtained. | Reference, References, Source, Sources | No |

Accepted table names: ConsumptionSingleValues, SingleValueConsumptions, PopulationConsumptionSingleValues, PopulationConsumptionValues.

### Single value consumptions settings

### Calculation settings

Table 3.73: Calculation settings for module Single value consumptions.

| Name | Type | Description |
|---|---|---|
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Restrict population to consumers or consumer days only | Boolean | Specifies whether the population should be restricted to the individuals (chronic) or individual days (acute) that have non-ze consumption. |
| Ignore sampling weights | Boolean | If checked, individual sampling weights are not used (sampling weight = 1). If unchecked, the specified sampling weights are used. |
| Use standardised consumption distributions before calculation of single values | Boolean | Specifies whether single values are calculated on individual consumptions standardised with body weight and then multiplie by the mean body weight. Otherwise, single values are calculate on the original consumptions (per day). Note that both method lead to different estimates for the single value. |
| Apply processing factors | Boolean | Specified in table ProcessingFactor. If checked, processing fact are applied. Concentrations in the consumed food may be different from concentrations in the modelled food in monitorin programs (typically raw food) due to processing, such as peelin washing, cooking etc. If unchecked, no processing information used. This is in most (though not all) cases a worst-case assumption |
| Restrict population to consumers or consumer days only (food-as-measured) | Boolean | Specifies whether the population should be restricted to the individuals (chronic) or individual days (acute) with consumptio containing any of the modelled foods. |

### Single value consumptions as data

Single value consumption data are the single value amounts of modelled foods (foods-as-measured) consumed in a population.

- *Single value consumptions data formats*
- *Single value consumptions from data*

Settings used

- *Calculation Settings*

### Calculation of single value consumptions

Single value consumptions are calculated as a percentile (p97.5 or p99) or mean of the modelled food consumption distribution. For an acute single value dietary exposure assessment, this is the individual day consumption distribution, for chronic single value dietary exposure assessment, the individual consumption distribution is used.

- *Single value consumptions calculation*

Inputs used: *Consumptions by modelled food*

Settings used

- *Calculation Settings*

## 3.3 Occurrence modules

The basic occurrence data are *concentrations* for *substances* in *foods*, sometimes specified separately for a focal food as *focal food concentrations*. In some cases *concentration limits* are used as a stand-in when data are missing.

Concentration data are recalculated (if needed) as *active substance concentrations* in *modelled-foods*. If substance concentrations are not specified directly for the *active substances*, then they are converted using *substance conversions* and/or specified authorised *occurrence patterns*. The composition of mixed samples in total diet studies is described in *total diet study sample compositions*. *Food extrapolation rules* specify if insufficient data for a food can be suppleted with data from another food. From these basic data the list of *modelled-foods* is derived.

*Active substance concentrations* in *modelled-foods* are modelled in *concentration models*, optionally allowing for *occurrence pattern models*. In addition, *processing factors* and *unit variability factors* can be provided for further use in *dietary exposure assessment*.

### 3.3.1 Food concentration distributions

Food concentration distributions describe substance concentrations on foods in the form of summary statistics.

This module has as primary entities: *Foods Substances*

Output of this module is used by: *Food concentration models Dietary exposures*

#### Food concentration distributions from data

#### Food concentration distributions data formats

Concentration distributions describe substance concentrations on foods in the form of summary statistics. These distributions can be characterised by a mean and a dispersion factor, the standard deviation or, preferably, a percentile point e.g. p95.

Download empty dataset template: Zipped CSV Excel

#### Concentration distributions

Substance concentrations on foods specified in the form of summary statistics.

Table 3.74: Table definition for Concentration distributions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFood | AlphaNumeric (50) | Food code, the raw agricultural commodity. | idFood | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Mean | Numeric | The mean of (monitoring) samples, on the original scale (in mg/kg). | Mean | Yes |
| CV | Numeric | Coefficient of variation, for samples of the size of the TDS pooled amount. | CV | No |
| Percentile | Numeric | The percentile at the point specified by the percentage. | Percentile | No |
| Percentage | Numeric | The percentage that belongs to the given the percentile, e.g., 95 (in mg/kg). | Percentage | No |
| Limit | Numeric | The specified norm value or limit value (in mg/kg). | Limit | No |
| Concentration-Unit | *ConcentrationUnit* | The unit of the limit value (default mg/kg). | Concentration-Unit, Unit | No |

Accepted table names: ConcentrationDistributions, ConcentrationDistribution, FoodConcentrationDistribution.

#### Food concentration distributions as data

Food concentration distributions describe substance concentrations on foods in the form of summary statistics.

- *Food concentration distributions data formats*
- *Food concentration distributions from data*

### 3.3.2 Concentration limits

Concentration limits specify (legal) limit values for substance concentrations on foods and are sometimes used as conservative values for concentration data. In the framework of pesticides the legal Maximum Residue Limit (MRL) is the best known example.

This module has as primary entities: *Foods Substances*

Output of this module is used by: *Food concentrations Single value concentrations Food concentration models Modelled foods*

#### Concentration limits from data

#### Concentration limits data formats

The concentration limits table describes limit values (e.g., MRLs) for specific food/substance combinations. This data may be used, for instance, for the food/substance combinations for which no concentration data is available. The food codes (idFood) and substance codes (idSubstance) should match the codes of the foods and substances table respectively.

Concentration limits are concentration limit values for specific food and substance combinations originating from regulations (e.g., MRLs). This data may be used, for instance, for the food/substance combinations for which no concentration data is available.

Download empty dataset template: Zipped CSV Excel

#### Concentration limits

The food codes (idFood) and substance codes (idSsubstance) should match the codes of the foods and substances table respectively.

Table 3.75: Table definition for Concentration limits.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFood | AlphaNumeric (50) | Code of the food of this residue limit definition. | idFood, FoodId, Food | Yes |
| idSubstance | AlphaNumeric (50) | Code of the substance of this residue limit definition. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Value | Numeric | Residue limit value. | Value, Limit, MaximumResidueLimit, MaximumResidueLimits, MRL | Yes |
| StartDate | DateTime | Start date of the period during which the limit applies. | StartDate | No |
| EndDate | DateTime | End date of the period during which the limit applies. | EndDate | No |
| ConcentrationUnit | *ConcentrationUnit* | The unit of the limit value (default mg/kg). | ConcentrationUnit, Unit | No |
| ValueType | *ConcentrationLimitValueType* | Value type of the concentration value. | ValueType, ConcentrationLimitValueType, ConcentrationSingleValueType | No |
| Reference | AlphaNumeric (200) | Reference to the source from which this concentration single value is obtained. | Reference, References, Source, Sources | No |

Accepted table names: ResidueLimits, ResidueLimit, MaximumResidueLimits, MaximumResidueLimit, MRLs, MRL.

#### Concentration limits as data

Maximum Residue Limits (MRL) are provided as data.

- *Concentration limits data formats*
- *Concentration limits from data*

### 3.3.3 Food concentration models

Food concentration models are distributional models of substance concentrations on foods. They describe both the substance presence (yes/no, with no representing an absolute zero concentration) and the substance concentrations. Food concentration models are specified per food/substance combination.

This module has as primary entities: *Foods Substances Effects*

Output of this module is used by: *High exposure food-substance combinations Dietary exposures*

### Food concentration models calculation

There are a number of *concentration model types* are available. A basic distinction is between using the empirical concentration data (empirical model), fitting a statistical model to the concentration data (parametric model), or to construct a model from (conservative) limit values. Settings relevant for some of these model types as well as other settings are described under *food concentration model settings*.

Concentration data from *Total Diet Studies* does not include variability information. In order to include variability in the concentration models created for TDS samples, the variance of the TDS concentrations may be *estimated using variances of the foods making up the composite TDS food*.

### Concentration model types

### Empirical model

Data points are sampled at random from the available set. Censored values (non-detect, i.c. < LOD, non-quantifications, i.c. < LOQ) are handled by imputation. If *occurrence patterns* are used, a proportion $p_0/p_{ND}$ of censored values is set as 0. See also *concentration models*.

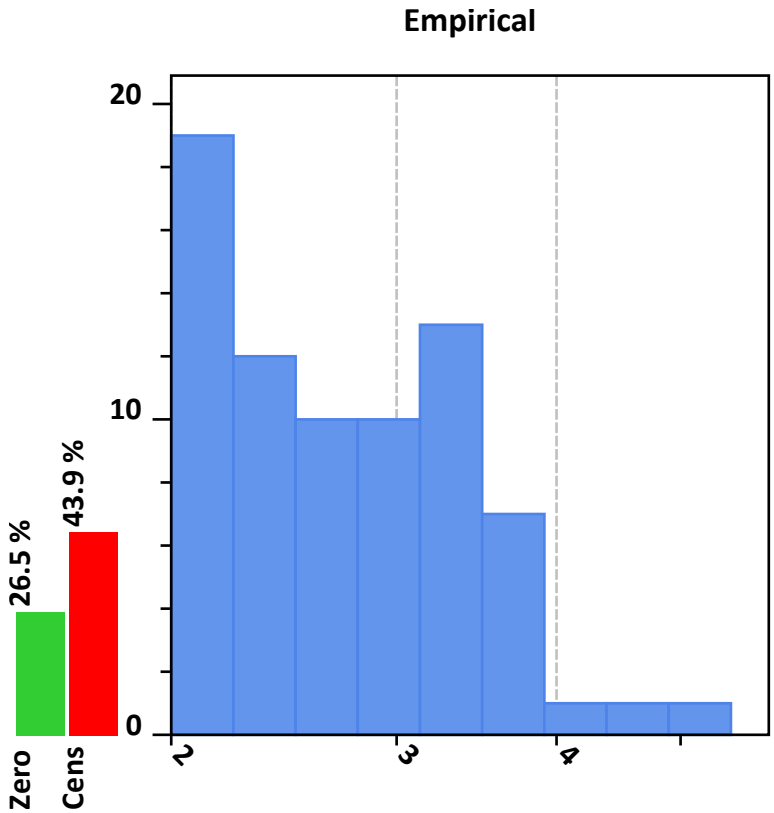


Figure 3.16: Empirical distribution

### Censored spike lognormal model

A binomial model is used to estimate the proportion $p$ of positive values (detects). This is just the proportion observed in the data (unless *agricultural use* data have been used to set a proportion of true zeroes). A lognormal model is fitted to the positive data. This provides estimates of $\mu$ and $\sigma$, which are the mean and standard deviation of the natural logarithm of the concentration. Simulated concentrations are a censored value with probability $p_{ND} = 1 - p$ or a value sampled from the fitted lognormal distribution with probability $p$. Censored values (non-detects or non-

quantifications) are handled by imputation. If occurrence patterns are used, a proportion $p_0/p_{ND}$ of censored values is set as 0. Minimum requirements: at least two positive concentration values. See also *concentration models*.

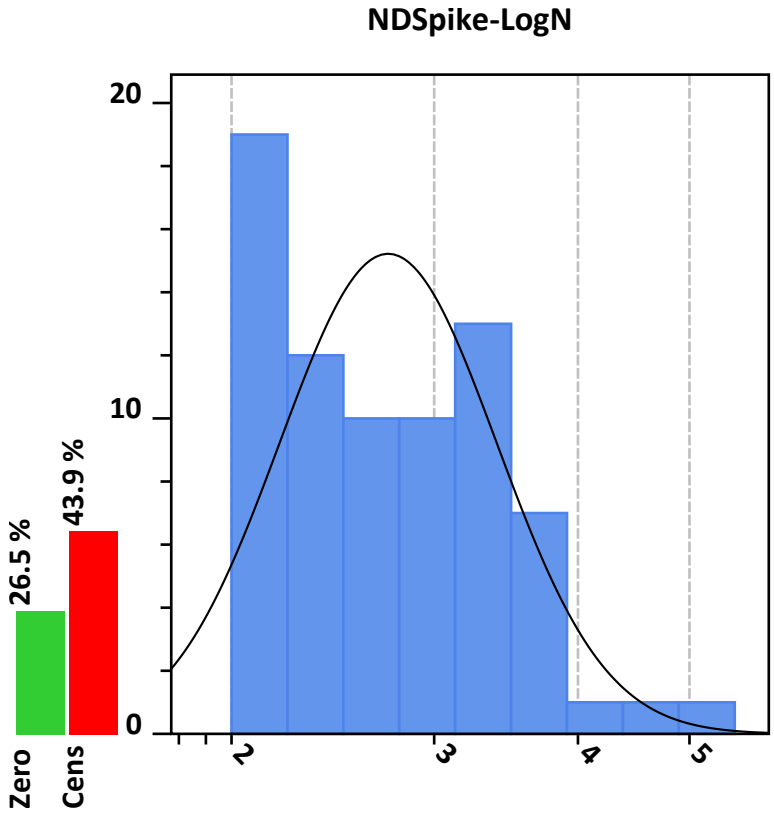


Figure 3.17: Censored Spike Lognormal distribution

### Censored-Spike Truncated lognormal model

A binomial model is used to estimate the proportion $p$ of positive values (detects). This is just the proportion observed in the data (unless agricultural use data have been used to set a proportion of true zeroes in which case $p$ is calculated on the remaining proportion). A truncated lognormal model, with LOR as the truncation limit, is fitted to the positive data, leading to estimates of $\mu$ and $\sigma$, which are the mean and standard deviation of the natural logarithm of the concentration. Simulated concentrations are a censored with probability $p_{ND} = 1 - p$ or a value sampled from the fitted lognormal distribution with probability $p$. Censored values (non-detects or non-quantifications) are handled by imputation. If occurrence patterns are used, a proportion $p_0/p_{ND}$ of censored values is set as 0. Minimum requirements: at least two positive concentration values, all censored values must have one LOR value. See also *concentration models*.

### Censored Lognormal model

A censored lognormal model, with LOR as the censoring limit, is fitted to the data, both positives and censored values. This provides estimates of $\mu$ and $\sigma$, which are the mean and standard deviation of the natural logarithm of the concentration. If agricultural use data are being used, then a proportion $p_0/p_{ND}$ of censored values will be excluded, where $p_0$ will be lowered to $p_{ND}$ if it would be higher. Simulated concentrations are sampled from the fitted lognormal distribution. If agricultural use data have been used, simulated concentrations are 0 with probability $p_0$ or are sampled from the fitted lognormal distribution with probability $1 - p_0$. Minimum requirements: at least one positive concentration value. See also *concentration models*.

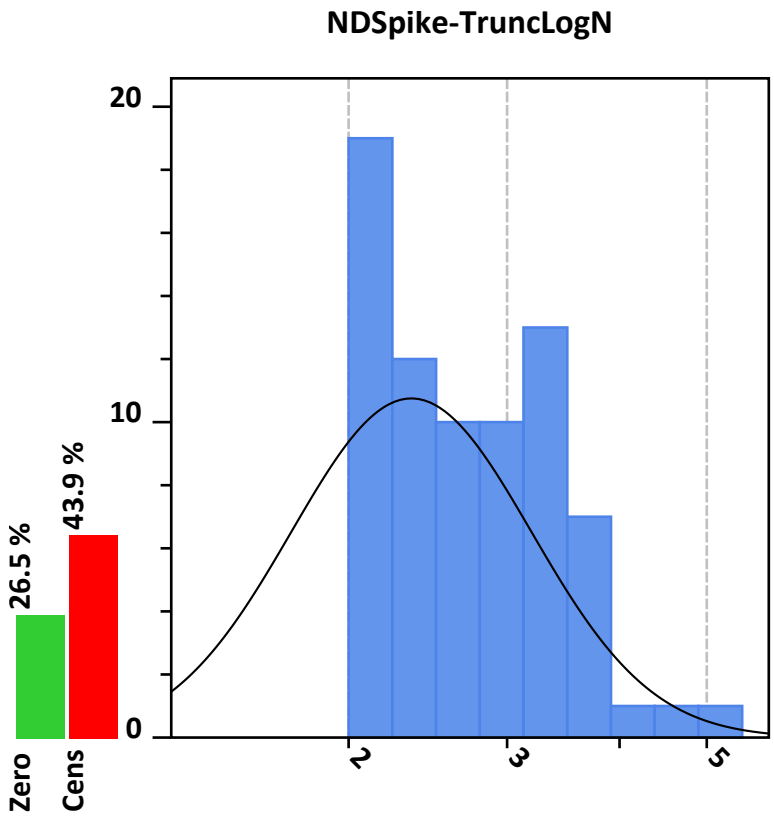


Figure 3.18: Censored Spike Truncated Lognormal distribution

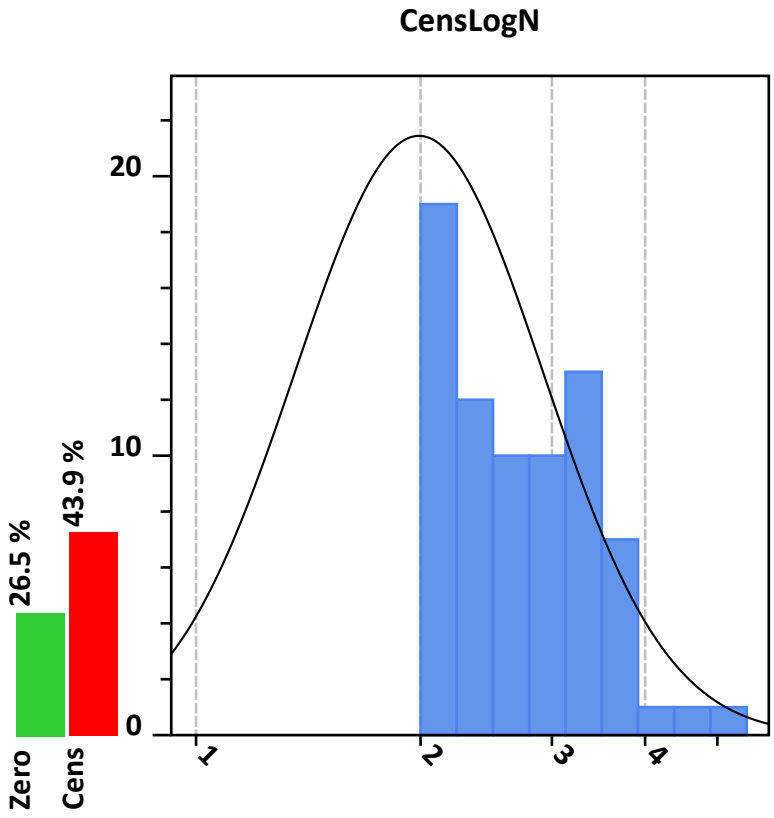


Figure 3.19: Censored Lognormal distribution

### Zero-spike censored lognormal model

A mixture distribution of a spike of true zeroes and a censored lognormal model, with LOR as the censoring limit, is fitted to the data (censored values and positives). This provides estimates of $p_0$, which is the proportion of true zeroes, and of $\mu$ and $\sigma$, which are the mean and standard deviation of the natural logarithm of the concentration. Simulated concentrations are 0 with probability $p_0$ and are sampled from the fitted lognormal distribution with probability $1-p_0$. Minimum requirements: at least one positive concentration value, no agricultural use data for the food-substance combination (which directly specify $p_0$, therefore it should not be estimated from the data). See also *concentration models*.

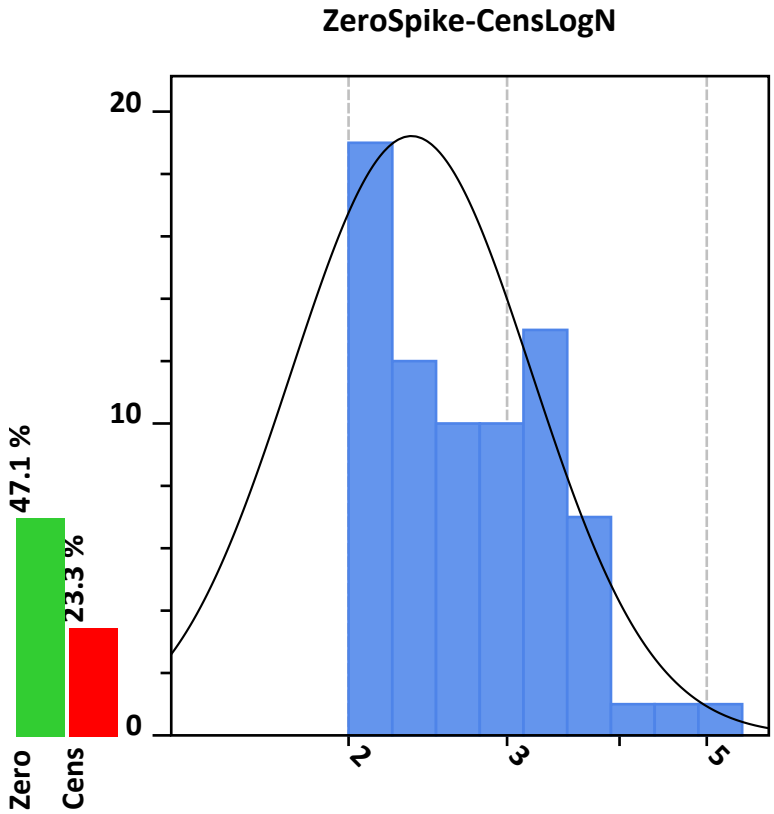


Figure 3.20: Zero Spike Censored Lognormal distribution

### Censored spike MRL model

This model simply takes values specified in an input table as *Maximum Residue Levels* (MRL) to be used for the proportion of positive values in the concentration dataset, and can be used to force the use of a pessimistic value.

### Summary statistics model

For this model, no individual measurements on raw agricultural commodities are needed. The final estimates of $\mu$ and $\sigma$ are simply provided or pooled or estimated using e.g. a coefficient of variation. Specific use of this model is found in *Total Diet Study* assessments. In general, each TDS food sample is prepared only once, yielding one measurement for a TDS food sample. The variability of the underlying distribution is unknown. However, a rough guess can be made using the e.g. coefficient of variation of the subsamples (in general raw agricultural commodities) that compose the TDS food sample. The estimated standard deviation is *calculated as a pooled estimate using the coefficient of variation and the count of each subsample in the TDS food*.

### Concentration models

Let $x$ denote a random variable from a lognormal distribution. Then, the log transformed variable $y = ln(x)$ is normally distributed with $\mu$ and variance $\sigma$. The probability density function (p.d.f.) of y may be expressed as:

$$f_y(y, p_0, \mu_y, \sigma_y^2) = p_0 I(y;0) + (1-p_0)(1-I(y;0)) \cdot \frac{1}{\sqrt{2\pi\sigma_y}} \exp \frac{(y-\mu_y)^2}{2\sigma_y^2}$$

where $p_0 = Pr(y < log(X_{lor}))$, $x_{lor}$ is the limit of reporting and $I(y;0)$ is an indicator function for $y < log(X_{lor})$. For $p_0 = 0$ the p.d.f. of $y$ reduces to the usual lognormal density. The left truncated density for $y \geq \log(X_{lor})$ may be expressed as:

$$f_y(y; \mu_y, \sigma_y^2) = \frac{1}{\sqrt{2\pi\sigma_y}} \exp \frac{(y-\mu_y)^2}{2\sigma_y^2} / (1 - \Phi(z))$$

with $\Phi(\cdot)$ the standard normal c.d.f. and $z = (\log(x_{lor}) - \mu_y)/\sigma_z$. Model parameters are estimated using maximum likelihood estimation based on the loglikelihood functions specified below. The loglikelihood functions are evaluated in R, using the **optim** algorithm to find estimates for $\mu_y, \sigma_y^2$ and $p_0$.

### Mixture zero spike and censored lognormal

The loglikelihood may be expressed as:

$$\log L(p_0, \mu_y, \sigma_y^2) = \sum_{i=1}^{n_0} \log(p_0 + (1-p_0)\Phi(z_i)) + n_1 \log(\frac{1-p_0}{\sqrt{2\pi\sigma_y}}) - \sum_{i=n_0+1}^{n} \frac{(y_i - \mu_y)^2}{2\sigma_y^2}$$

where $y_i = \log(x_i)$, $\Phi(\cdot)$ is the standard normal c.d.f., $z = (\log(x_{i,lor}) - \mu_y)/\sigma_y$, $z_{lor} = (\log(lor) - \mu_y)/\sigma_y$ with $n_0$ number of censored values $(x_i < x_{i,lor})$, $n_1$ number of uncensored values $(x_i \geq x_{i,lor})$ and $x_i, i = 1 \cdots n$.

Multiple values for LOR are allowed.

### Censored lognormal

When $p_0 = 0$ the loglikelihood reduces to:

$$\log L(\mu_y, \sigma_y^2) = \sum_{i=1}^{n_0} \log(\Phi(z)) + n_1 \log(\frac{1}{\sqrt{2\pi\sigma_y}}) - \sum_{i=n_0+1}^{n} \frac{(y_i - \mu_y)^2}{2\sigma_y^2}$$

Multiple values for LOR are allowed.

### Mixture censored spike and truncated lognormal

Ignoring the $n_0$ values below $x_{lor}$, the loglikelihood may be expressed as:

$$\log L(\mu_y, \sigma_y^2) = -n_1 \log(1 - \Phi(z)) + n_1 \log(\frac{1}{\sqrt{2\pi\sigma_y}}) - \sum_{i=n_0+1}^{n} \frac{(y_i - \mu_y)^2}{2\sigma_y^2}$$

Only one value for LOR is allowed.

### Mixture censored spike and lognormal

Ignoring the $n_0$ values below $x_{lor}$, the loglikelihood may be expressed as:

$$\log L(\mu_y, \sigma_y^2) = n_1 \log(\frac{1}{\sqrt{2\pi\sigma_y}}) - \sum_{i=n_0+1}^{n} \frac{(y_i - \mu_y)^2}{2\sigma_y^2}$$

Only one value for LOR is allowed.

### Imputation of non-detect measurements

A complication in concentration modelling occurs when concentration measurements are reported as below a certain limit. Different names may be used for such a limit, e.g. **limit of detection** (*LOD*), **limit of quantification** (*LOQ*) or the more general term **limit of reporting** (*LOR*). Results that are only reported to be below the LOD (non-detects) or below the LOQ (non-quantifications) are generally referred to as censored values or non-reports. Censored values are a very common phenomenon for some classes of substances like pesticides. When modelling the substance concentrations, they can be handled by incorporating them in a parametric model, or by replacing them with a given value (**imputation**). For imputation, different models are available:

- **Replace by zero**: All left censored measurement values are replaced by zero. This is an optimistic modelling choice.
- **Replace by factor x LOR**: Measurements reported below LOD or LOQ are replaced by a factor times LOQ. When the LOQ is unspecified, then the LOD is used. When the factor is equal to one, this method can be assumed to be a conservative approach.
- **Replace LOD by factor x LOD and LOQ by factor x (LOQ - LOD)**: Measurements reported below LOD are replaced by a factor times LOD and measurements reported below LOQ are replaced by a factor times LOQ-LOD (i.e., a value between LOD and LOQ). the factor is set between zero and one.
- **Replace non-detects by zero and non-quantifications by factor * LOQ**: the factor is set between zero and one.

See also *non-detects handling method*.

Note, when LOD is not available then it is assumed to be 0. When LOQ is not available then it is assumed to be LOD (or zero if LOD is also not available).

An additional option of the imputation methods that replace the left censored values with some positive value is to *use occurrence frequencies for imputation*. When this option is used, a part of the left-censored values are replaced by a positve value and another part is replaced by zero, based on the *occurrence frequencies* of the modelled foods and substances. Another option is to restrict imputation with positive values to only the authorised substances.

In Figure 3.21 to Figure 3.24, the various scenarios are displayed. Two substances, Fenamidine and Hexythiazox are indicated with a brown box, these substances are authorised.

### No imputation

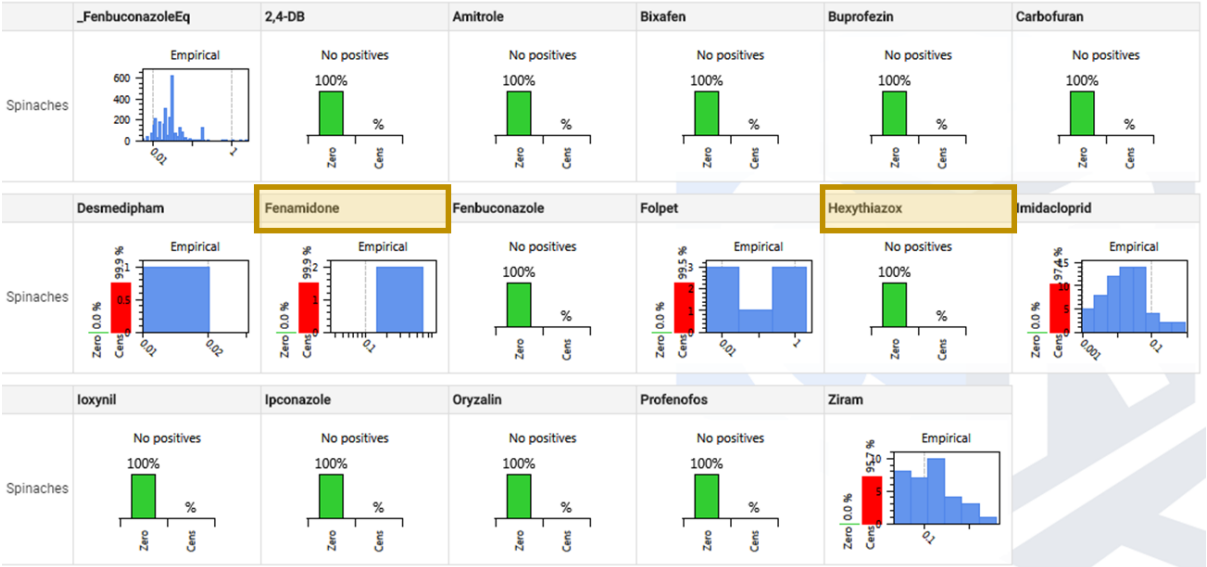


Figure 3.21: Tier 1: Censored values are replaced by zero. For Fenamidine and Hexythiazox (brown boxes) authorized use is assumed.

### Impute all censored values by factor times LOQ

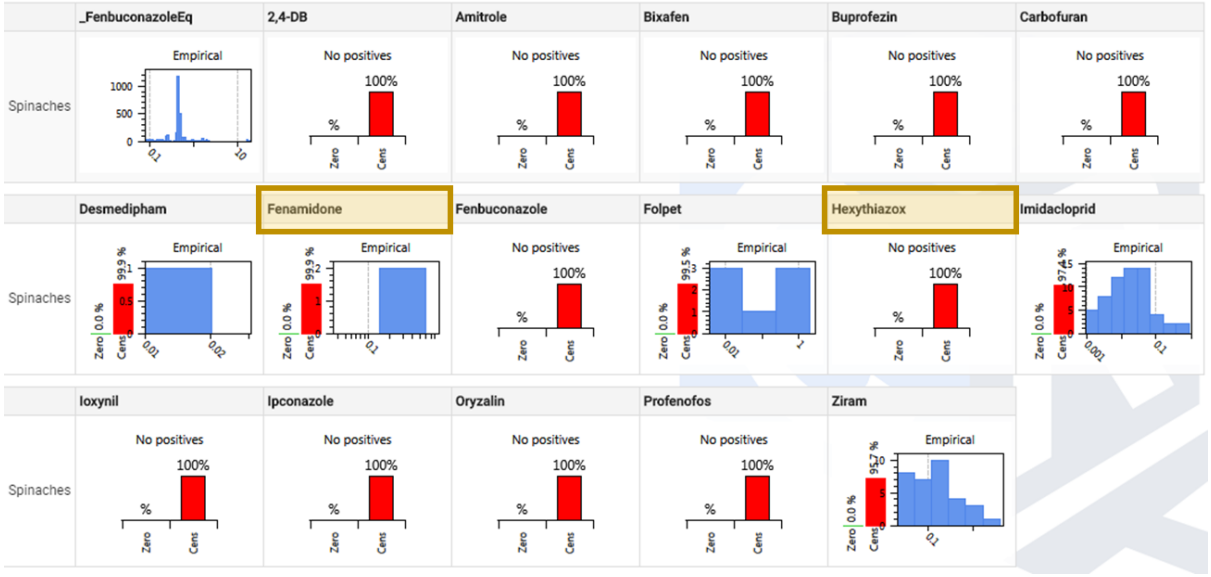


Figure 3.22: All censored values are replaced by a **constant** x LOR. For Fenamidine and Hexythiazox (brown boxes) authorized use is assumed.

### Impute censored values based on authorized uses

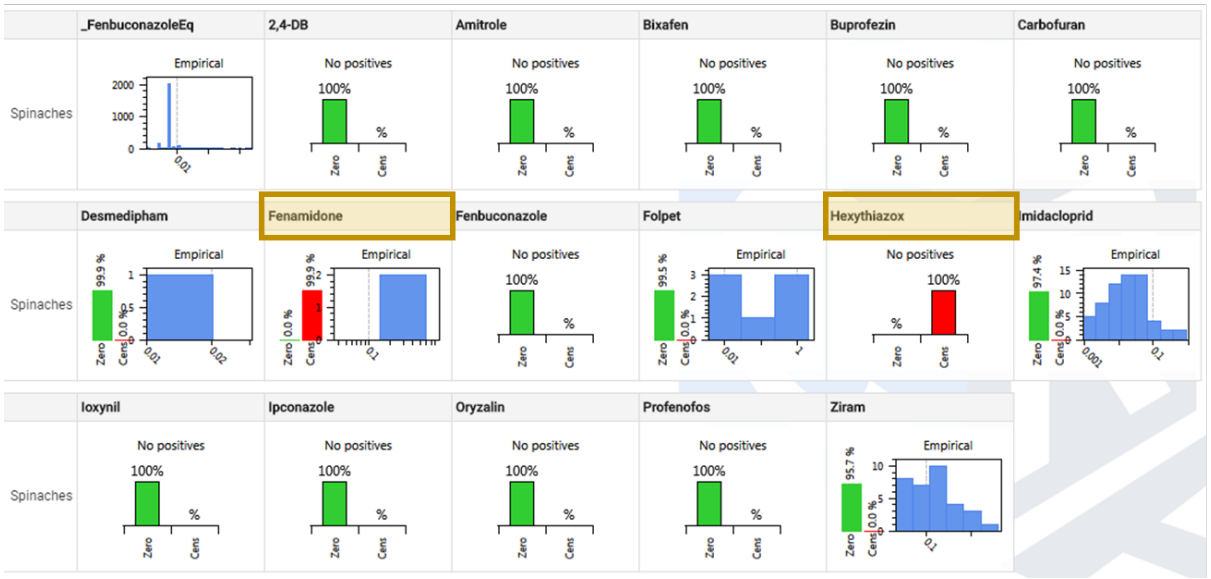


Figure 3.23: Censored values are replaced by a **constant** x LOR for authorized uses. For Fenamidine and Hexythiazox (brown boxes) authorized use is assumed.

### No imputation except for authorized uses

### Deriving the variance of TDS samples from monitoring

Variability of TDS food sample concentrations can be derived using *concentration distributions* for the sub-foods of the TDS food samples (defined by the *TDS compositions*). For each sub-food, e.g. *apple* (sub-food of TDS food *FruitMix*), a coefficient of variation (CV) is specified that is derived using the available monitoring samples. Note that monitoring samples may be composite samples. For *apple*, composite food samples are measured and each sample

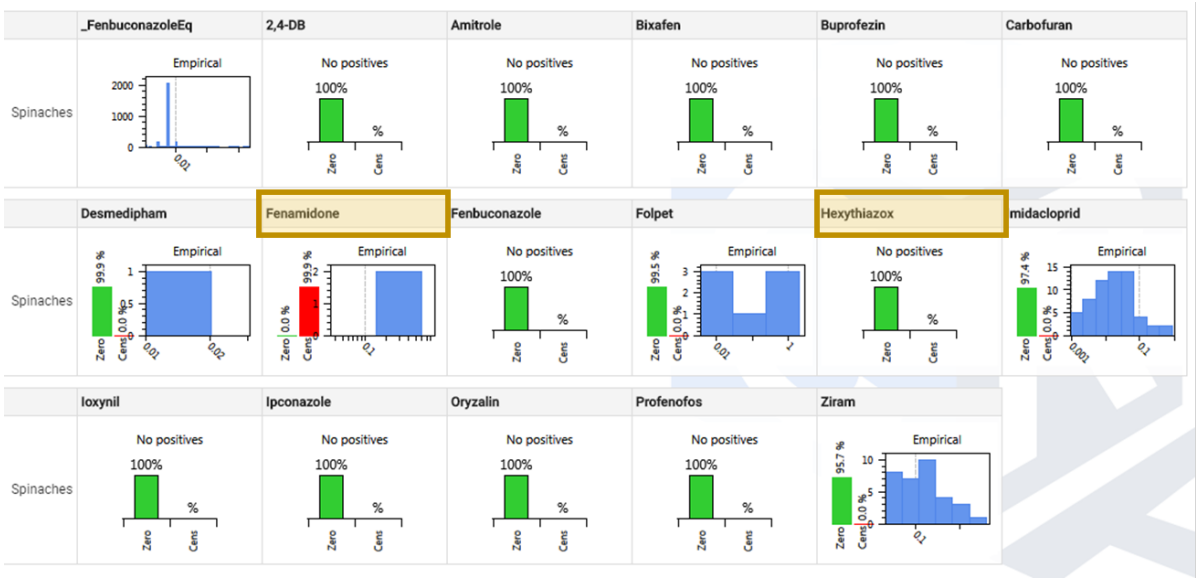


Figure 3.24: Tier 1: Censored values are not replaced except for authorized uses (replaced by a **constant** x LOR). For Fenamidine and Hexythiazox (brown boxes) authorized use is assumed.

contains, for instance, 12 apples with unit weight 200 g. So monitoring concentrations, $c_{mi}$, are based on composite samples with a total weight $w_{mi}$ = 2400 g each.

A TDS food sample is composed of $w_i$ g of food $i$ with $i = 1...k, w_i$ represents the *PooledAmount* in *TDS food sample compositions table*. Then, the concentration of a TDS food sample may be represented as:

$$c_{TDS} = \sum_{i=1}^{k}(w_i \cdot c_i) / \sum_{i=1}^{k} w_i$$

with variance:

$$var(c_{TDS}) = \sum_{i=1}^{k}(w_i \cdot var(c_i)) / \sum_{i=1}^{k} w_i$$

and $var(c_i)$ is the variance of concentrations $c_i$ of food $i$ with portion sample size $w_i$.

It is expected that increasing the number of units in a composite sample will have a reverse effect on the variation between concentrations. Suppose TDS food *FruitMix* is composed of 2 x 200 = 400 g *apple*. The expected variation between portion sizes of 400 g will be larger than between portion sizes of 2400 g:

$$var(c_i) = var(c_{mi}) \cdot w_{mi}/w_i$$

The variance of the monitoring samples are corrected as follows, calculate:

1. $var(c_{mi}) = \log(CV_{mi}^2 + 1)$
2. $var(c_i) = var(c_{mi}) \cdot w_{mi}/w_i$
3. $CV_i = \sqrt{\exp(var(c+i) - 1)}$

### Food concentration models settings

### Calculation settings

Table 3.76: Calculation settings for module Food concentration models.

| Name | Type | Description |
|---|---|---|
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Selected tier | SettingsTemplateType | Specifies all module settings should be set according to a pre-defined tier or using custom settings. |
| Concentration model types per food-substance combination | ConcentrationModelType-FoodSubstance | The concentration model types used for food/substance combinations. |
| Default concentration model | *ConcentrationModelType* | The concentration model type that will be used as default for al food/substance combinations. If this model type cannot be fitte e.g., due to a lack of data, a simpler model will be chosen automatically as a fall-back. |
| Include MRL fallback model | Boolean | Use the MRL as fallback model in case the occurrence data is insufficient for other concentration modelling options. |
| Restrict LOR imputation to authorised uses | Boolean | Specifies whether imputation of factor x LOR should be limited authorised uses only. |
| Censored values replacement | *NonDetectsHandlingMethod* | How to replace censored values (when not co-modelled, as in censored models). |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | Numeric | Replace censored values by Limit of reporting (LOR), Non-detects (LOD) or Non-quantifications (LOQ) times this factor. Constant (f), e.g. 0.5. |
| MRL Factor (f x MRL) | Numeric | Use f x MRL as concentration estimate of the MRL models. |
| Sample based | Boolean | Include co-occurrence of substances in samples in simulations. checked, substance residue concentrations are sampled using th correlations between values on the same sample. If unchecked, any correlation between substances is ignored, substance residu concentrations are sampled ignoring the correlations between values on the same sample. |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | Boolean | If checked, in procedure of EFSA Guidance 2012, Appendix 1 impute missing values using substance based concentration models. If unchecked, missing values are imputed by 0. |
| Correlate imputed values with sample potency | Boolean | If checked, in procedure of EFSA Guidance 2012, Appendix 1 correlate high imputed values with high cumulative potency samples. If unchecked, random imputation. |
| Use occurrence frequencies for imputation | Boolean | Use of occurrence frequencies (e.g., agricultural use frequencie is relevant for imputation of censored values in the concentratio data. Part of the observed censored values and missing values m be imputed with zero when the occurrence frequency is smaller than 100%. If checked, occurrence frequencies are expected as input of this action, otherwise 100% potential presence is assumed for all substances on all foods. |
| Total diet study concentration data | Boolean | Specifies whether exposure is based on sampling data from tota diet studies. |
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Compute cumulative exposures | Boolean | Specifies whether the assessment involves multiple substances a results should be cumulated over all substances. |

### Uncertainty settings

Table 3.77: Uncertainty settings for module Food concentration models.

| Name | Type | Description |
|---|---|---|
| Parametric uncertainty | Boolean | For resample concentrations: specifies whether the uncertainty assessment is based on a parametric approach. |
| Resample concentrations | Boolean | Specifies whether concentrations are resampled by empirical bootstrap or using a parametric uncertainty model. |

### Food concentration models tiers

In addition to the possibility for users to work with their own choices for all settings, MCRA implements four tiers from two documents:

- The optimistic and pessimistic basic assessments from the *EFSA 2012 Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues* (EFSA (2012)).
- Tier 1 and 2 from the *European Commission working document SANTE-2015-10216 rev. 7 (2018)* on risk management aspects related to the assessment of cumulative exposure (EC (2018)).

### Overview

Table 3.78: Tier overview for module Food concentration mo

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| D fa co ce tr ti m | Empirical | Empirical | Empirical | Empirical | Empirical | NonDetect-SpikeLog-Normal | NonDetect-SpikeLog-Normal | Empirical | Empirical | Emp |
| In cl M fa ba m | false | false | false | false | false | true | true | false | false | false |
| R st L in pr ta ti to au th ri us | false | false | false | false | | false | false | false | false | false |

Table 3.78 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| C sc va ue re pl m | Replace-ByLOR | Replace-ByLOR | Replace-ByLOR | Replace-ByLOR | Replace-ByZero | Replace-ByLOR | Replace-ByLOR | Replace-ByLOR | Replace-ByLOR | Repl ByL |
| F tc f (f x L or f x L or L + f x (I - L | 0.5 | 0.5 | 0.5 | 0.5 | | 1 | 1 | 0.5 | 0.5 | 0.5 |
| S pl ba | true | true | true | true | true | true | true | true | true | true |

Table 3.78 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| In p m in va uc fr av al va uc (i u m in va uc ar in p w 0 | true | true | true | true | false | true | true | true | true | true |
| C re la in p va uc w sa pl p te | true | true | false | false | false | true | true | true | true | false |
| U oc cu re fr qu ci fo in pu ta ti | true | true | true | true | false | | | true | true | true |

Table 3.78 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| P m ri u c ta | false | false | false | false | false | true | false | false | false | false |
| F te sa pl ex ce in th co ce tr ti li it | false | false | false | false | | false | false | false | false | false |
| U su st co ve si ru | true | true | true | true | | | | true | true | true |
| S st co ve si m | UseMostToxic | UseMostToxic | DrawRandom | DrawRandom | | | | UseMostToxic | UseMostToxic | Draw dom |

Table 3.78 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| R ta al al lc ca su st af te ac ti su st al lc ca ti | true | true | true | true | | | | true | true | true |
| A co fo su st au th ri sa ti in su st co ve si | false | false | true | true | | | | false | false | true |
| F du pl ca su st al lc ca ti in co si te ci | false | false | false | false | | | | false | false | false |

Table 3.78 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| U ex tr o- la ti ru | true | true | true | true | | | | false | false | false |
| T ol fc ex tr o- la ti | 10 | 10 | 10 | 10 | | | | | | |
| R st ex tr o- la ti tc ec M | true | true | true | true | | | | | | |
| R st ex tr o- la ti tc au th ri us | true | true | true | true | | | | | | |
| Ir pr w te cc cc tr ti | true | true | true | true | | | | true | true | true |

Table 3.78 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| W te co ce tr ti va (μ | 0.1 | 0.1 | 0.05 | 0.05 | | | | 0.1 | 0.1 | 0.05 |
| R st w te ir pr ta ti to th fi m to su st | true | true | true | true | | | | true | true | true |
| R st w te ir pr ta ti to au th ri us | false | false | false | false | | | | false | false | false |
| R st w te ir pr ta ti to ap pr su st | false | false | false | false | | | | true | true | true |

Table 3.78 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| A pl oc cu re pa te pe ce ag | false | false | true | true | | | | false | false | true |
| T ge le | External | External | External | External | External | External | External | External | External | Exte |
| S up us fr qu to 1( | | | true | true | | | | | | true |
| R st us pe ce ag up sc to au th ri us | | | true | true | | | | | | true |
| M F to (f x M | | | | | | 1 | 1 | | | |
| C ce tr ti li fi te ex ce fa to | | | | | | | | | | |

Table 3.78 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| In cl fo ca co m it co ce tr ti | | | | | | | | | | |
| F ca co m it su st oc cu re p ce ag | | | | | | | | | | |
| A ju m fa to fo th fo ca fo co ce tr ti | | | | | | | | | | |

Table 3.78 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| U de te m is ti su st co ve si fo fo ca co m it | | | | | | | | | | |
| In cl pr ce de ti of th fo ca fo in m su m re pl m | | | | | | | | | | |

The sections below describe the settings specified by each tier in detail.

### Retrospective dietary CRA (EC 2018) - Acute / Tier I

Table 3.79: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | | |
| Include MRL fallback model | false | | |
| Restrict LOR imputation to authorised uses | false | | |
| Censored values replacement | ReplaceByLOR | | |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | | |
| Sample based | true | | |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | | |
| Correlate imputed values with sample potency | true | | |
| Use occurrence frequencies for imputation | true | | |
| Parametric uncertainty | false | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) -* | *Food concentrations* |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier I

Table 3.80: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | | |
| Include MRL fallback model | false | | |
| Restrict LOR imputation to authorised uses | false | | |
| Censored values replacement | Replace-ByLOR | | |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | | |
| Sample based | true | | |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | | |
| Correlate imputed values with sample potency | true | | |
| Use occurrence frequencies for imputation | true | | |
| Parametric uncertainty | false | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) -* | *Food concentrations* |

### Retrospective dietary CRA (EC 2018) - Acute / Tier II

Table 3.81: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | | |
| Include MRL fallback model | false | | |
| Restrict LOR imputation to authorised uses | false | | |
| Censored values replacement | ReplaceByLOR | | |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | | |
| Sample based | true | | |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | | |
| Correlate imputed values with sample potency | false | | |
| Use occurrence frequencies for imputation | true | | |
| Parametric uncertainty | false | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) -* | *Food concentrations* |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier II

Table 3.82: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | | |
| Include MRL fallback model | false | | |
| Restrict LOR imputation to authorised uses | false | | |
| Censored values replacement | ReplaceByLOR | | |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | | |
| Sample based | true | | |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | | |
| Correlate imputed values with sample potency | false | | |
| Use occurrence frequencies for imputation | true | | |
| Parametric uncertainty | false | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) -* | *Food concentrations* |

### Retrospective dietary CRA (EFSA 2012) - Optimistic

Use the optimistic model settings according to the EFSA Guidance 2012. Concentration values are sampled using a sample-based empirical distribution. Available processing factors are applied. No unit variability model should be applied.

Table 3.83: Tier definition for Retrospective dietary CRA (EFSA 2012) - Optimistic.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | | |
| Include MRL fallback model | false | | |
| Censored values replacement | Replace-ByZero | | |
| Sample based | true | | |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | false | | |
| Correlate imputed values with sample potency | false | | |
| Use occurrence frequencies for imputation | false | | |
| Parametric uncertainty | false | | |
| Target level | External | *Retrospective dietary CRA (EFSA 2012) - Optimistic* | *Hazard characterisations* |

### Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic

Acute probabilistic exposure assessment using the pessimistic model settings according to the EFSA Guidance 2012. Only processing factors > 1 are applied. For unit variability, the Beta distribution is applied.

Table 3.84: Tier definition for Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | NonDetectSpikeLogNormal | | |
| Include MRL fallback model | true | | |
| Restrict LOR imputation to authorised uses | false | | |
| Censored values replacement | ReplaceByLOR | | |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 1 | | |
| MRL Factor (f x MRL) | 1 | | |
| Sample based | true | | |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | | |
| Correlate imputed values with sample potency | true | | |
| Parametric uncertainty | true | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Food concentrations* |
| Target level | External | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Hazard characterisations* |

### Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic

Chronic probabilistic exposure assessment using the pessimistic model settings according to the EFSA Guidance 2012. Only processing factors > 1 are applied.

Table 3.85: Tier definition for Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | NonDetectSpikeLogNormal | | |
| Include MRL fallback model | true | | |
| Restrict LOR imputation to authorised uses | false | | |
| Censored values replacement | ReplaceByLOR | | |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 1 | | |
| MRL Factor (f x MRL) | 1 | | |
| Sample based | true | | |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | | |
| Correlate imputed values with sample potency | true | | |
| Parametric uncertainty | false | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food concentrations* |
| Target level | External | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Hazard characterisations* |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier I

Table 3.86: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | | |
| Include MRL fallback model | false | | |
| Restrict LOR imputation to authorised uses | false | | |
| Censored values replacement | Replace-ByLOR | | |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | | |
| Sample based | true | | |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | | |
| Correlate imputed values with sample potency | true | | |
| Use occurrence frequencies for imputation | true | | |
| Parametric uncertainty | false | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Substance conversion method | UseMost-Toxic | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I

Table 3.87: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | | |
| Include MRL fallback model | false | | |
| Restrict LOR imputation to authorised uses | false | | |
| Censored values replacement | Replace-ByLOR | | |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | | |
| Sample based | true | | |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | | |
| Correlate imputed values with sample potency | true | | |
| Use occurrence frequencies for imputation | true | | |
| Parametric uncertainty | false | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier II

Table 3.88: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | | |
| Include MRL fallback model | false | | |
| Restrict LOR imputation to authorised uses | false | | |
| Censored values replacement | Replace-ByLOR | | |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | | |
| Sample based | true | | |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | | |
| Correlate imputed values with sample potency | false | | |
| Use occurrence frequencies for imputation | true | | |
| Parametric uncertainty | false | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II

Table 3.89: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | | |
| Include MRL fallback model | false | | |
| Restrict LOR imputation to authorised uses | false | | |
| Censored values replacement | ReplaceByLOR | | |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | | |
| Sample based | true | | |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | | |
| Correlate imputed values with sample potency | false | | |
| Use occurrence frequencies for imputation | true | | |
| Parametric uncertainty | false | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |

### Prospective dietary CRA (EFSA 2023) - Acute / Tier II

Table 3.90: Tier definition for Prospective dietary CRA (EFSA 2023) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | | |
| Include MRL fallback model | false | | |
| Restrict LOR imputation to authorised uses | false | | |
| Censored values replacement | Replace-ByLOR | | |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | | |
| Sample based | true | | |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | | |
| Correlate imputed values with sample potency | false | | |
| Use occurrence frequencies for imputation | true | | |
| Parametric uncertainty | false | | |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |

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Table 3.90 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |

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Table 3.90 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |

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Table 3.90 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Occurrence patterns* |
| Target level | External | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Hazard characterisations* |

### Prospective dietary CRA (EFSA 2023) - Chronic / Tier II

Table 3.91: Tier definition for Prospective dietary CRA (EFSA 2023) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | | |
| Include MRL fallback model | false | | |
| Restrict LOR imputation to authorised uses | false | | |

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Table 3.91 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Censored values replacement | ReplaceByLOR | | |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | | |
| Sample based | true | | |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | | |
| Correlate imputed values with sample potency | false | | |
| Use occurrence frequencies for imputation | true | | |
| Parametric uncertainty | false | | |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |

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Table 3.91 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |

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Table 3.91 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |

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Table 3.91 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Occurrence patterns* |
| Target level | External | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Hazard characterisations* |

### Prospective dietary CRA (EFSA 2024) - Acute / Tier II

Table 3.92: Tier definition for Prospective dietary CRA (EFSA 2024) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | | |
| Include MRL fallback model | false | | |
| Restrict LOR imputation to authorised uses | false | | |
| Censored values replacement | ReplaceByLOR | | |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | | |
| Sample based | true | | |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | | |

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Table 3.92 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Correlate imputed values with sample potency | false | | |
| Use occurrence frequencies for imputation | true | | |
| Parametric uncertainty | false | | |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |

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Table 3.92 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |

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Table 3.92 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Include processed derivatives of the focal food in measurement replacement | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |

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Table 3.92 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Occurrence patterns* |
| Target level | External | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Hazard characterisations* |

### Prospective dietary CRA (EFSA 2024) - Chronic / Tier II

Table 3.93: Tier definition for Prospective dietary CRA (EFSA 2024) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | | |
| Include MRL fallback model | false | | |
| Restrict LOR imputation to authorised uses | false | | |
| Censored values replacement | ReplaceByLOR | | |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | | |
| Sample based | true | | |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | | |

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Table 3.93 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Correlate imputed values with sample potency | false | | |
| Use occurrence frequencies for imputation | true | | |
| Parametric uncertainty | false | | |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |

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Table 3.93 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |

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Table 3.93 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Include processed derivatives of the focal food in measurement replacement | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |

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Table 3.93 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Occurrence patterns* |
| Target level | External | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Hazard characterisations* |

### Food concentration models uncertainty

When using empirical distributions, concentration model uncertainty is covered by the the inputs. I.e., concentration models can be recomputed from *resampled/bootstrapped* concentration data. This happens for both the univariate concentration models, being recomputed from the bootstrapped residue collections for each food and substance, and also for the samples of the sample-based approach that are re-generated from the bootstrapped samples (including the necessary steps of missing value imputation and imputation of censored values).

When parametric uncertainty is preferred over empirical bootstrapping, the parameters of the univariate concentration models fitted as a parametric distributions can be *resampled parametrically*.

Let $x$ denote a random variable from the specified distribution. The log transformed variable $y = ln(x)$ is normally distributed with mean $\mu_y$ and variance $\sigma_y$. The maximum likelihood estimates are $\hat{\mu}_y$ and $\hat{\sigma}_y$. In each bootstrap sample, values are drawn from a normal distribution where the maximum likelihood estimates are replaced by ( $\hat{\mu}^*_y$, $\hat{\sigma}^*_y$).

### Calculation of food concentration models

Concentration models can be computed from concentration data.

- *Food concentration models calculation*

Inputs used: *Food concentrations Concentration limits Active substances Modelled foods Substance authorisations Occurrence frequencies Relative potency factors Food concentration distributions Total diet study sample compositions*

Settings used

- *Calculation Settings*

### 3.3.4 Food concentrations

Food concentrations data are analytical measurements of chemical substances occurring in food samples. In their simplest form, food concentration data can just be used as provided by datasets. Optionally, food concentrations data can be manipulated for active substances, extrapolated to other foods, and/or default values can be added for water.

This module has as primary entities: *Foods Substances Populations*

Output of this module is used by: *Single value concentrations Occurrence patterns Food concentration models Modelled foods*

#### Food concentrations from data

#### Food concentrations calculation

Occasionally, food concentrations of substances measured in food samples are exceeding a specified concentration limit e.g. the *Maximum Residue Limits* (MRL). An MRL is the highest level of a substance that is legally tolerated in or on food or feed when substances are applied correctly. *Filter samples* exceeding the concentration limits filter out all samples where one of the substances measured is exceeding the *MRL*.

*Substance conversions* rules may be used to *convert* food concentration data at the level of measured substances to food concentration data at the level of potentially active substances. These rules (provided as data) may be applicable, for example, when a measured substance represents multiple substances and these measurements should be converted into measurement values for these substances. This conversion may depend on *substance authorisations* which provides information on the likelihood of certain translations to occur. *points of departure* or *relative potency factors* might be needed when the substance conversion should select the most toxic candidate in case a measured substance translates to multiple active substances.

If there are only a few measurements in the food concentration data, then *extrapolation of concentration data* may be desired. In that case, *food extrapolation rules* may be provided to specify per food the alternative foods from which extrapolation is allowed. The extrapolation of food concentrations will then be performed within this module and the results are included in the resulting active substance concentrations data. *Substance authorisations* and/or *concentration limits* may be used to further restrict the to-food/from-food combinations per substance for which extrapolation is possible.

Concentration data for water are often not available in the food concentration data, but it may be desirable to include them in the assessments. For this, *imputation* of low-tier, deterministic estimates of water concentrations of the most toxic substances may be used to include (typically conservative) estimates in the calculations.

In some scenarios it may be desired to perform a prospective analysis in which anticipated (or foreground) *focal commodity concentration data* for a particular focal commodity food (and substance) is added to, or replaces part of the background concentration data that is used for the null-scenario. The food concentrations module offers various options to perform such *focal commodity scenario analyses*.

It is also possible to *filter (or subset) samples by specific sample properties* (e.g., year, location). This can be done by checking the option to *filter samples by specific property values (subset selection)*.

#### Filter samples exceeding the concentration limits

If the option **Filter samples exceeding the concentration limits** is checked, all samples with one or more substance concentrations exceeding the *MRL* are filtered out. Then a **concentration limit filter exceedance factor** ($factor$) is specified, which filters out samples with at least one substance concentration higher than $factor \cdot MRL$.

If the option **Filter samples exceeding the concentration limits** remains unchecked all samples are retained in the analysis.

### Substance conversion

When concentration data at the level of measured substances have to be converted into concentration data at the level of *active substances* (or perhaps also inactive substances), then *substance conversion rules* are specified to provide the rules, the so-called residue definitions. This section describes the basic substance conversion, and then the refinements using available *substance authorisations*.

For each measured substance in the concentration data, there may be zero or more conversion rules, each one linking to an active or inactive substance. Each rule is represented by a record in the substance conversion data source. Substance conversion rules may specify a link to an exclusive substance or not. For an exclusive conversion it is assumed that only one substance is present in the sample, therefore the measured substance is considered to be just one of the linked substances. Another possibility is that measured substances link to one or more exclusive substances, plus one (non-exclusive) substance that is considered a metabolite of the other exclusive substances. The metabolite can occur together with any of the exclusive substances. It is assumed that either all conversion rules linked to a measured substance are marked as exclusive (case 1), or exactly one rule is marked as exclusive and the others are marked as not exclusive (case 2). If this does not apply for any set of rules linked to a measured substance, data are regarded as erroneous.

Four methods for substance conversion are implemented:

**1. Allocate most potent:** for each measured substance, the linked substances are restricted to the active substances of interest. The concentration of the measured substance is assigned to the most potent active substance in this set. Potency is specified by the *relative potency factors*. All other candidate active substances are assigned a zero concentration. I.e., the measured substance concentration is allocated for 100% to the most potent substance specified by the conversion rules and for this allocation, the concentration or LOQ/LOD is multiplied by the molecular weight correction factor.

**2. Random allocation:** one of the conversion rules is drawn randomly (with equal probability), including the rules of both active and other substances. Then, the rule is used as follows to generate active substance concentrations:

- **If the conversion rule is marked as exclusive**, the concentration or LOQ/LOD is allocated to the linked substance.
- **If the conversion rule is marked as not exclusive**, a proportion *p*, as specified by the rule, of the concentration or LOQ/LOD is allocated to the linked substance. The remaining proportion *(1-p)* is allocated to the substance that is linked to the measured substance in a conversion rule marked as exclusive (in this case it is assumed that exactly one record per measured substance is marked as exclusive).

All assigned concentrations are multiplied by the molecular weight correction factor. All unselected candidate substances are assigned a zero concentration.

**3. Allocate least potent:** optimistic counterpart of *allocate most potent*. For each measured substance, the linked substances are restricted to the active substances of interest. The concentration of the measured substance is assigned to the least potent active substance in this set. Potency is specified by the *relative potency factors*. All other candidate active substances are assigned a zero concentration. I.e., the measured substance concentration is allocated for 100% to the least potent substance specified by the conversion rules and for this allocation, the concentration or LOQ/LOD is multiplied by the molecular weight correction factor.

**4. Nominal estimate:** the substances specified through the conversion rules are allocated with a nominal value based on all possible conversion rules. This may be regarded as the nominal or average allocation value of the random sampling method.

- **All conversion rules are marked as exclusive:** the measured substance concentration is allocated over all *n* active substances specified with equal proportions *1/n*, accounting for the molecular weight correction factor for all substances.
- **Precisely one conversion rule is marked exclusive and n conversion rules are marked as not exclusive:** the measured substance concentration is allocated over all active substances specified, with a proportion *1/2 + 1/n* for the substance belonging to the exclusive conversion rule, and equal proportions *1/n* for the other substances, accounting for the molecular weight correction factor for all substances.

**5. Allocate all:** the concentration of a measured substance is allocated to each active substance associated with the measured substance as if it were the most potent substance. I.e., the same measured substance is allocated to all

associated active substances simultaneously. This method is not sensible when using it in a cumulative assessment, but it is of use in substance screening assessments, where in a combined analysis of multiple substances all active substances are considered independently.

### Use of substance authorisations in substance conversion

When *substance authorisations* are available, these can be used to exclude conversions of measured substances to unauthorised substances on a given food. The information is used as follows in the substance conversion procedures:

**1. Allocate most potent:** the set of candidate active substances from which the most potent active substance is to be drawn is reduced to only the substances with authorised uses. However, if none of the candidate active substances is authorised, then the most potent of the unauthorised substances is selected for active substance allocation.

Table 3.94: Most potent allocation of a measured substance to active substances based on RPFs and authorised use.

| Active substance | RPF | Authorised use | Active substance | RPF | Authorised use | Measured substance allocated to |
|---|---|---|---|---|---|---|
| AS1 | 2 | true | AS2 | 1 | true | AS1 |
| AS1 | 2 | false | AS2 | 1 | true | AS2 |
| AS1 | 2 | true | AS2 | 1 | false | AS1 |
| AS1 | 2 | false | AS2 | 1 | false | AS1 |

In Table 3.94, results of most potent allocation.

**2. Random allocation:** the set of conversion rules from which to draw is reduced to the rules linking to authorised substances or the non-exclusive substance (thus allowing the selection of a possibly unauthorised metabolite of an authorised substance). If none of the conversion rules links to an authorised substance, then one rule is drawn from the full set of all (unauthorised) conversion rules.

Table 3.95: Random allocation of a measured substance to active substances based on authorised use.

| Active substance | RPF | Authorised use | Active substance | RPF | Authorised use | Measured substance allocated to |
|---|---|---|---|---|---|---|
| AS1 | 2 | true | AS2 | 1 | true | AS1 or AS2 |
| AS1 | 2 | false | AS2 | 1 | true | AS2 |
| AS1 | 2 | true | AS2 | 1 | false | AS1 |
| AS1 | 2 | false | AS2 | 1 | false | AS1 or AS2 |

In Table 3.95, results of random allocation.

**3. Allocate least potent:** the set of candidate active substances from which the least potent active substance is to be drawn is reduced to only the substances with authorised uses. However, if none of the candidate active substances is authorised, then the least potent of the unauthorised substances is selected for active substance allocation.

Table 3.96: Least potent allocation of a measured substance to active substances based on RPFs and authorised use.

| Active substance | RPF | Authorised use | Active substance | RPF | Authorised use | Measured substance allocated to |
|---|---|---|---|---|---|---|
| AS1 | 2 | true | AS2 | 1 | true | AS2 |
| AS1 | 2 | false | AS2 | 1 | true | AS2 |
| AS1 | 2 | true | AS2 | 1 | false | AS1 |
| AS1 | 2 | false | AS2 | 1 | false | AS2 |

In Table 3.96, results of least potent allocation.

**4. Nominal estimate:** the set of conversion rules is reduced in the same way as for random active substance allocation. Nominal calculation is performed on the resulting set of conversion rules.

**5. Allocate all:** For this method, the same rules apply as for *allocate most potent*. The set of candidate active substances that are to be allocated is reduced to only the substances with authorised uses. Hence, a substance is not allocated when it is not authorised and there is at least one other candidate active substance that is authorised. However, if none of the candidate active substances is authorised, then the most potent of the unauthorised substances is selected for active substance allocation.

### Multiple allocations of the same active substance in one sample

In some datasets substance conversion can cause the same active substance to be allocated multiple times in one sample. For example, when an active substance is measured directly, but also a measurement is recorded for a (measured) substance that converts to the active substance. By default, MCRA does not accept such cases, because often it is associated with errors in the data. Therefore, an error will be reported with a message

*"Unexpected substance translation in sample xxx: substance X is translated from multiple measured substances."*

However, if such cases are known to exist and accepted in the data, then a method is available to *fix duplicate substance allocation inconsistencies*. If active substance allocation leads to multiple allocated measurements then the following procedure is implemented for resolving these inconsistencies:

- If any measurement is positive or zero then: clone one of these records to create the "aggregate measurement record"; to make this selection deterministic, prefer records that have measured-substance equal to active-substance over other records, and take the record with the highest residue. Update the measured value of the clone with the mean of all positive/zero measurements.
- If all allocated active substance measurements are censored, then clone one of the censored values. Here also, records that have measured-substance equal to active-substance are preferred over other records, and then the measurement with the smallest LOQ/LOD is used.

Note that these rules are quite generic. They work quite well even when there are many measurements for the same active substance. In practice, only a few (two) are expected.

### Food extrapolation

If the *food extrapolation* setting has been checked, extrapolation of concentrations is performed for all food/*active substance* combinations for which:

1. the number of measurements in the analytical scope is smaller than a given threshold for extrapolation (default 10), and
2. there is an *extrapolation rule* allowing extrapolation of concentrations from one or more other foods (the from-food(s)) to the given food (the to-food), and
3. (optional criterion:) the substance is associated with *authorised use* for both foods, and
4. (optional criterion:) *concentration limits (e.g. MRLs)* on the from-food and to-food exist and are equal. Note: if the **active substance** is not a **measured substance**, then the MRL check has to be made per measurement at the level of the measured substance which provided the concentrations assigned to the active substance.

Food extrapolation is performed by one of the following procedures: 1) Substance-specific imputation of missing values by extrapolated measurements, or 2) Extrapolation of complete samples for multiple substances.

### 1. Substance-specific imputation of missing values by extrapolated measurements

The missing values in the active substance concentrations of the to-food are imputed in a random order by active substance concentrations (positive, censored or zero) from a randomised list obtained from the fromfood(s). By matching the randomised lists, each from-food measurement is assigned at most once, so after extrapolation there may still be missing values left, or not all measurements of the from-food(s) may have been used for extrapolation.

Note: In this method, it is assumed that the to-food has a sufficient number of samples. No extrapolation is applied for foods with no samples at all, and data gaps will also remain for foods with fewer than *n* samples, because no new samples are added.

Note: the resulting *occurrence patterns* will be random with respect to the extrapolated substances, i.e., observed occurrence patterns for the from-food are not extrapolated to the to-food.

#### 1. Extrapolation of complete samples for multiple substances

(not yet implemented)

All samples of the from-food(s), i.e., complete samples with data for all active substances, are copied as samples for the to-food and added to the existing to-food samples. For example, extrapolate all apple sample records to the available pear sample records. However, measurements for substances that do not fulfil the (optional) criteria 3 and 4 above are non-valid extrapolations and are replaced by missing values. The status of the extrapolated samples is stored to distinguish between extrapolated and non-extrapolated sample records. Note that this method maintains correlations in the occurrence patterns and postpones imputation of MVs until the concentration models step.

### Imputation of water concentrations

If water has been selected as an additional source of exposure, but concentration data is missing, then, fixed concentration values can be assigned to water for the five most toxic *active substances*, with the toxicity ranking being based on the *relative potency factors*. For all other substances, zero concentrations are imputed. The default imputation value is 0.05 µg/L, but this value can be chosen as a setting. If specified, *substance authorisations* may be used to restrict to the set of active substances for which water concentrations are imputed to only those for which concentrations may be expected from *authorised use*.

### Focal commodity scenario analysis

There are different *methods* for modifying the (background) concentration data for specific (prospective) focal commodity scenario analyses. In the frontend these methods are accessible through the option *include focal commodity concentrations* (see Figure 3.25). Checking this option will open the focal commodity scenario analysis form (see Figure 3.26) where the method and the focal food/substance can be selected, and associated other settings can be configured, see also *focal food concentrations*.

The following *focal commodity replacement methods* are available:

- **Replace samples with focal commodity samples:** This method will replace all samples for the selected focal commodity food by samples from the *focal commodity concentration data*. Food sample replacement is substance independent, therefore all substance concentrations of the focal commodity food in the background concentration data are replaced.
- **Append focal commodity samples:** This method adds the *focal commodity samples* of the selected focal commodity food to the background concentration data. This method is independent of the substance and may be a useful approach when the substances measured in the field trial do not overlap with the substances of the (background) concentration data. In this case, the focal commodity substance concentrations will be missing for the background concentration data and (also the other way around) the substance concentrations of all other substances will be considered missing for the focal commodity samples. These missing values may be imputed at a later stage according to the standard procedures.
- **Replace by focal commodity samples:** The focal food/substance measurements are obtained from *focal commodity samples*. Here, substance measurements of the focal commodity food in the background concentration data are replaced by randomly assigned substance measurements of the focal commodity samples.
- **Replace by concentration limits from data:** The focal food/substance measurements are obtained from *focal commodity samples*. Here, substance measurements of the focal commodity food in the background concentration data are replaced by the concentration limit value (e.g., *MRL* s) obtained from the provided *concentration limits data*.
- **Replace by proposed concentration limits:** Here, substance measurements of the focal commodity food in the background concentration data set are replaced by the proposed concentration limit values (e.g., MRLs in mg/kg) specified in the interface.

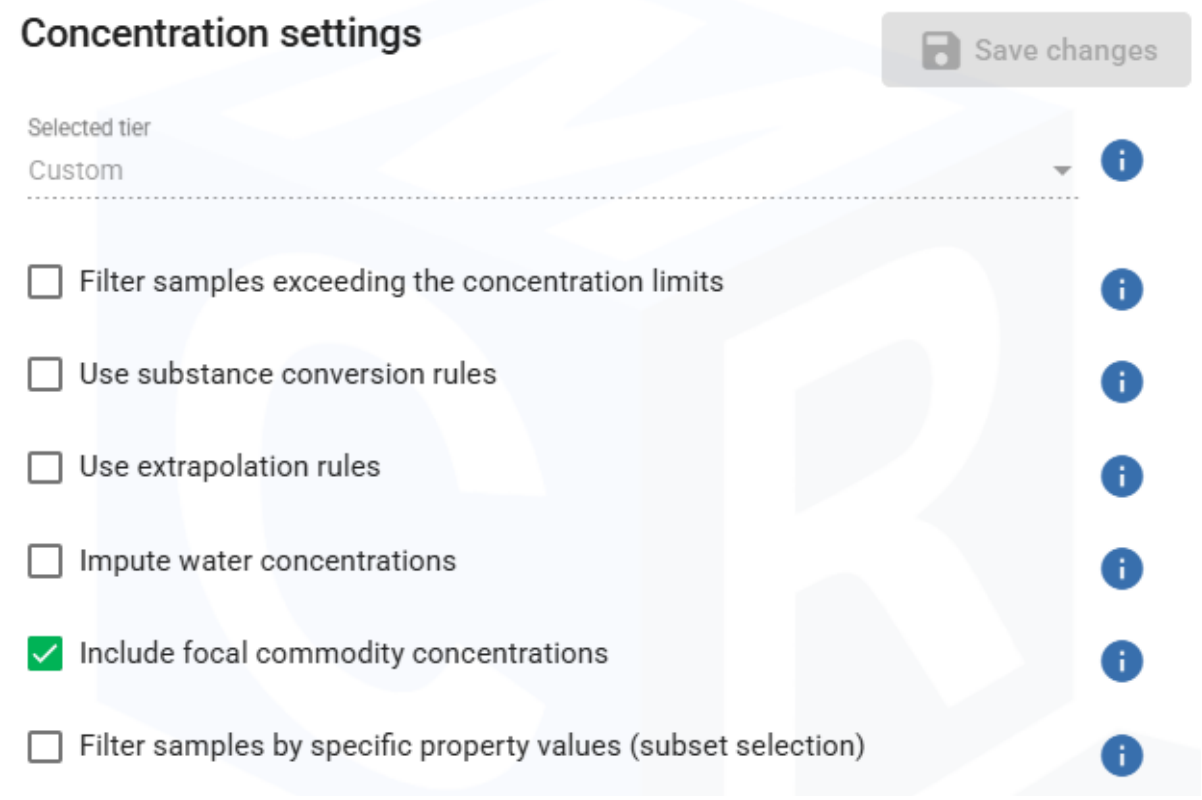


Figure 3.25: Concentration settings: include focal commodity concentrations.

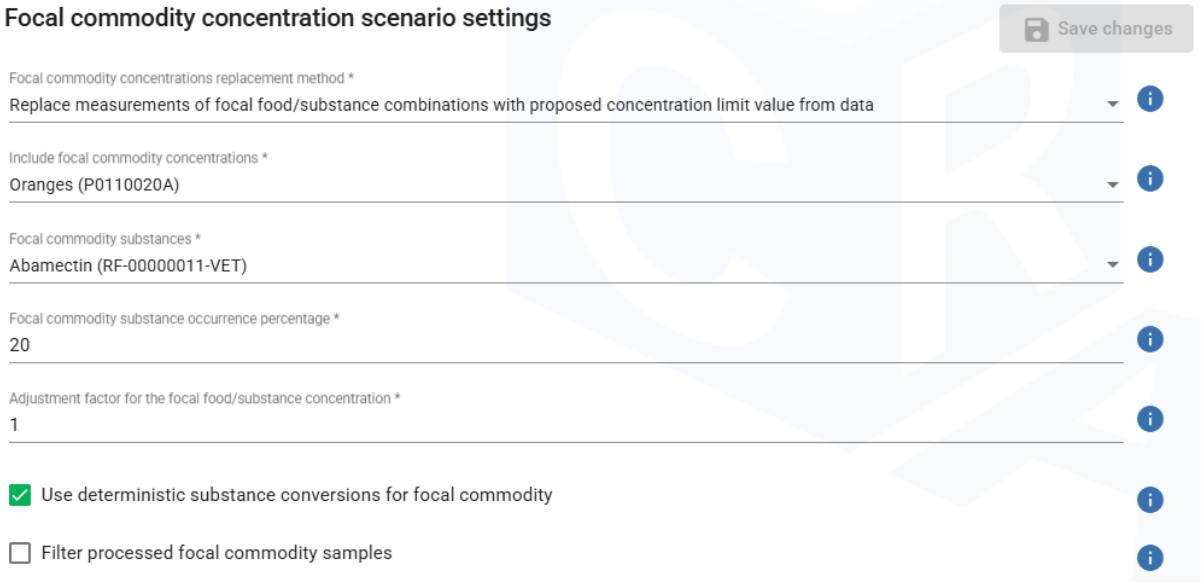


Figure 3.26: Focal commodity concentration scenario settings form. This form is a sub-form of the concentrations module panel.

- **Remove measurements of focal food/substance combinations:** Simply remove all background concentrations for the selected focal commodity food and substance combination, values are not replaced. This method is useful when a separate analysis is desired for the background and foreground concentrations.

Depending on the selected *replacement method*, different additional modelling options become available.

Use the *focal commodity substance occurrence percentage* to specify an occurrence percentage for the combination of focal food and substance. For percentages less than 100%, a part of concentrations of the focal commodity food and substance is replaced with the focal concentrations, the remaining part of the concentrations is replaced with zero concentrations. E.g., when background concentrations of the substance Abamectine on oranges are replaced with an MRL value, then a specified occurrence percentage of 40% will replace 40% of the measurements with the MRL, and 60% of the measurements with a zero concentration. Note that the replacement is random, i.e., each substance measurement has a probability of being assigned to a focal concentration (>0) or a zero. So, the actual replacement percentage may differ from the specified percentage. This option is, for example, used to simulate a percentage of agricultural use.

Use the *adjustment factor for the focal food/substance concentration* to adjust the (positive) concentrations of the focal food and substance measurements. This factor is used when the focal commodity concentrations (e.g., from field trials) are assumed to be higher than what is expected in practice. In this case, this factor could be set for instance, to the expected ratio of mean monitoring concentration and mean field trial concentration. Note that for replacement by focal commodity measurements, this factor will only adjust the positive concentrations and not the LORs.

By default, the focal commodity substance measurements are replaced before the optional step of *converting the concentrations from measured to active substance concentrations*. This means that the same substance conversion rules apply for the background and foreground concentrations when converting measured substance concentrations to active substance measurements. Alternatively, substance measurements can also be replaced after allocation of the active substance. This can be done using the option to *use deterministic substance conversion factors*. When this option is checked, *deterministic substance conversion factors* are used for the focal commodity food and substance to convert measurements to the level of *active substances* and replacement of background concentrations by foreground concentrations is done after active substance allocation. Figure Figure 3.27 illustrates how active substance allocation is done for the foreground and background concentration data with and without this option.

When the occurrence data includes samples for processed derivatives of the selected focal food(s) (e.g., orange juice samples for focal food oranges), the substance measurements of the focal substance for the samples of the processed food can also be replaced. Checking the option *include processed derivatives of the focal food* replaces focal substance measurements of the processed derivatives of the focal food. If there is a specific processing factor available for the focal food, focal substance, and processing type of the derivative, then this processing factor is used to first correct the focal concentrations for processing. Alternatively, it is also possible to just exclude the samples of the focal commodity, which can be done using the option to *filter processed focal commodity samples*.

Note that when also using using *substance authorisations*, the focal food and substance combination will be treated as authorised, even if there is no authorisation supplied for the combination. The approved authorisation status is considered to be part of this scenario analysis.

### Filter samples by specific sample properties

When the option to *filter samples by specific property values (subset selection)* is checked in the *main panel of the concentrations module*, a new form will appear in which various sample property subsets can be specified (see Figure 3.28). The visibility/availability of the sample property filters depends on the availability of these properties in the data. The following filters are available:

- The options to *filter samples by year* and *filter samples by month* allow the user to filter the samples by sampling date. The additional option to *include samples with missing sampling date* determines whether samples for which the sampling date is unknown/missing should be included or not.
- The options to *filter samples by location* and *filter samples by region* allow for subsets by location (country) and/or region within a location. Also for these options there is the possibility to include/exclude samples for which the location/region is unknown/missing.
- The option to *filter samples by production method* allows for subset selection on production method of the sampled product (e.g., organic or conventional).
- The option to filter samples by additional sample properties available in the data (see *data format*).

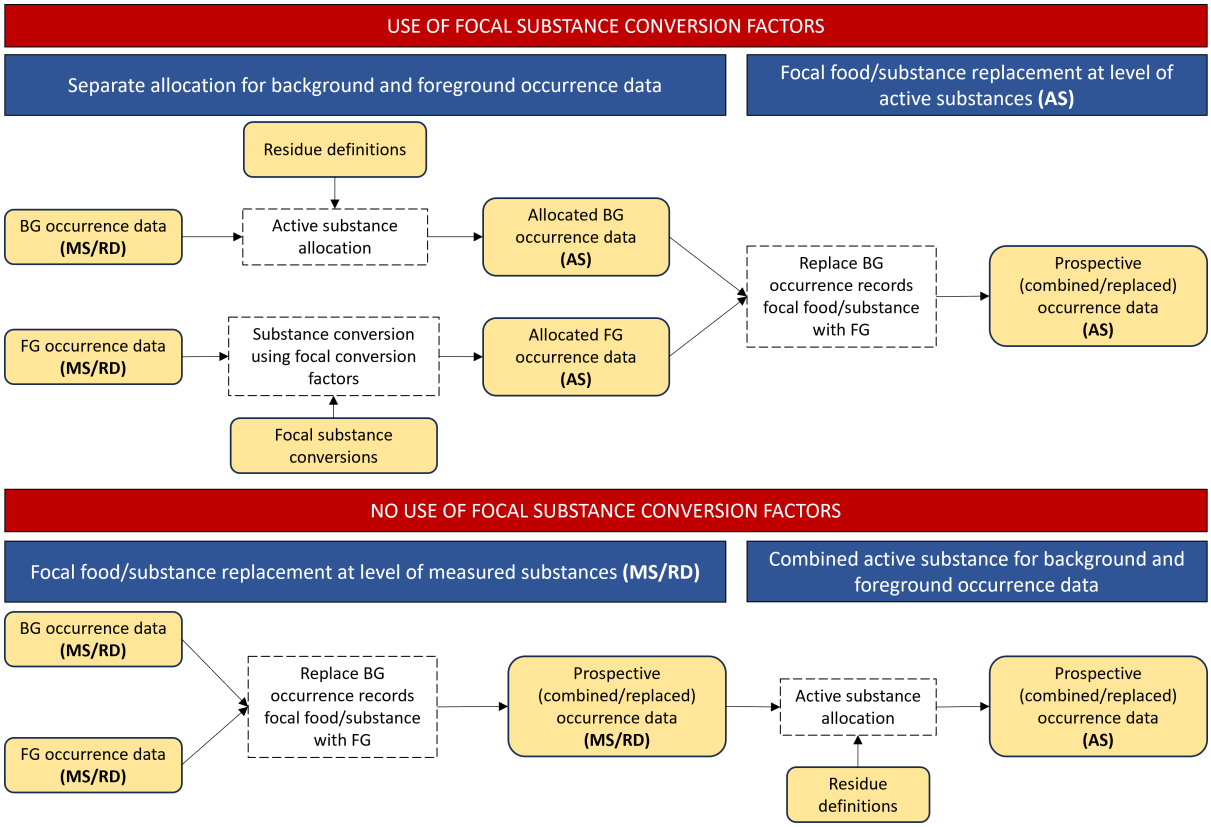


Figure 3.27: Active substance allocation of the background and foreground concentration data with and without the use of deterministic substance conversion factors.

### Food concentrations data formats

Food concentrations data are analytical measurements of chemical substances occurring in food samples. The following data formats are supported/available for providing food concentration data in MCRA:

1. **Relational concentration data format:** Concentration data is provided using a number of relational tables describing *(food) samples* (e.g., sampling date and location), the *analytical methods*, with their properties for substances (e.g., LOQ and LOD), *sample analyses*, describing the analyses performed on the samples (e.g., analysis date and the used analytical method), and *concentration measurements* (e.g., the measurement type and value). This relational table structure is also used internally by MCRA.
2. **EFSA Standard Sample Description (SSD) format:** Concentration data according to the EFSA Standard Sample Description (SSD) format. During upload, *SSD data* are converted automatically to the relational data format used internally by MCRA.
3. **Tabulated data scheme:** This is a simplified data format where samples and analytical methods are not explicitly specified. *Tabulated concentration data* are converted automatically to the MCRA relational data format.

### Relational concentration data format

The relational data format is the data format that is used internally in MCRA.

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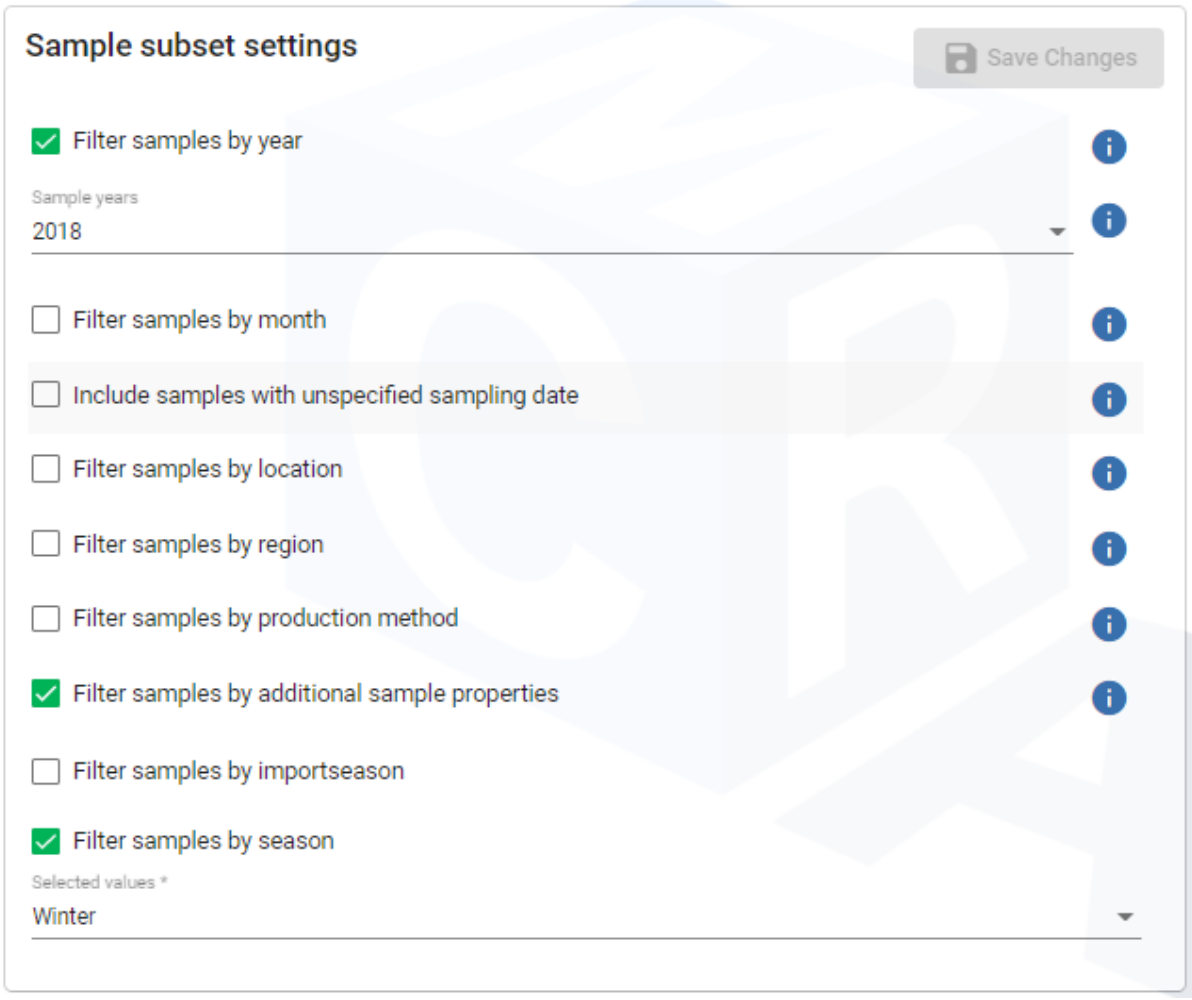


Figure 3.28: Sample subset selection form of the front end. This form is a sub-form of the concentrations module panel.

### Analytical methods

The analytical methods used for analysing the samples are recorded in the analytical methods table. Each analytical method should have a unique identification code (idAnalyticalMethod). The description field may be used for a more detailed description of the analytical method. The records of this table should be linked to one or more analytical method substance properties table, which record the substances that are measured by this method (and their limits of reporting).

Table 3.97: Table definition for Analytical methods.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idAnalytical-Method | AlphaNumeric (50) | The code for the method of analysis. | idAnalytical-Method, Analytical-MethodId, Analytical-MethodName, Id | Yes |
| Name | AlphaNumeric (100) | Name of the analytical method. | Name | No |
| Description | AlphaNumeric (255) | Additional description of method of analysis. | Description | No |

Accepted table names: AnalyticalMethod, AnalyticalMethods.

### Analytical method properties for substances

This table describes the substances analysed by an analytical method. For each substance analysed by an analytical method a record should be included that describes the unit of measurement and the reporting limits (LOQ/LOD).

Table 3.98: Table definition for Analytical method properties for substances.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idAnalytical-Method | AlphaNumeric (50) | The code of method of analysis. | idAnalytical-Method, Analytical-MethodName, Analytical-MethodId | Yes |
| idSubstance | AlphaNumeric (50) | The substance code. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| LOD | Numeric | The limit of detection (LOD) is the lowest concentration of an substance in a sample that can be consistently detected. | LOD | No |
| LOQ | Numeric | The limit of quantification (LOQ) is the lowest concentration of a substance that can be quantified. The LOQ should be larger than the LOD. | LOQ, LOR | No |
| Concentration-Unit | *ConcentrationUnit* | The unit used for reporting the LOD, LOQ, and the substance concentrations. When not specified, then a default unit of mg/kg is assumed. | Concentration-Unit, Units, Unit | No |

Accepted table names: AnalyticalMethodSubstances, AnalyticalMethodSubstance, AnalyticalMethodCompounds, AnalyticalMethodCompound.

### Food samples

Food sample for analysis of concentrations. May be characterised by location and/or date of sampling. A sample can be analysed multiple times, the results per analysis are stored as analysis samples.

Table 3.99: Table definition for Food samples.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFoodSample | AlphaNumeric (50) | The identification number of the food sample. | idFoodSample, idSample, SampleId, Id | Yes |
| idFood | AlphaNumeric (50) | The food code. | idFood, FoodId, Food, FoodCode | Yes |
| Location | AlphaNumeric (50) | The location or country code, sampling location. | Location, Location-Sampling, Sampling-Location, Country | No |
| Region | AlphaNumeric (50) | The area or region within the sampling location. | Region, Area, Sampling-Region, SamplingArea | No |
| DateSampling | DateTime | The date of sampling. | DateSampling, SamplingDate | No |
| Production-Method | AlphaNumeric (50) | Additional information on the type/method of production of the sampled food. | Production-Method, ProductionType | No |
| Name | AlphaNumeric (100) | Name of the food sample. | Name | No |
| Description | AlphaNumeric (200) | Additional description of the food sample. | Description | No |

Accepted table names: FoodSamples, FoodSample, Samples, Sample, PrimarySample, PrimarySamples.

### Sample properties

Food sample properties, additional columns that can also be specified as additional columns in the food samples table

Table 3.100: Table definition for Sample properties.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| Name | AlphaNumeric (50) | The name of the property. | Id | Yes |
| Description | AlphaNumeric (200) | Additional description of the sample property. | Description | No |

Accepted table names: SampleProperties, SampleProperty.

### Sample property values

Food sample property values, additional columns that can also be specified as additional columns in the food samples table

Table 3.101: Table definition for Sample property values.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSample | AlphaNumeric (50) | The identification number of the food sample. | Id, IdFoodSample | Yes |
| PropertyName | AlphaNumeric (50) | The name of the property. | IdProperty, Name | Yes |
| TextValue | AlphaNumeric (50) | The value of the property as text value. | | No |
| DoubleValue | Numeric | The value of the property as number. | | No |

Accepted table names: SamplePropertyValues, SamplePropertyValue.

### Sample Analyses

An analysis sample specifies the analysis of a sample by an analytical method. A sample can be analysed multiple times, the results per analysis are stored as analysis samples.

Table 3.102: Table definition for Sample Analyses.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSample-Analysis | AlphaNumeric (50) | The identification number of the analysed sample. | id, idSample-Analysis, SampleAnalysis, idAnalysis-Sample, AnalysisSample-Id | Yes |
| idFoodSample | AlphaNumeric (50) | The identification number of the food sample. | idFoodSample, idSample, SampleId, Sample | Yes |
| idAnalytical-Method | AlphaNumeric (50) | The code of method of analysis. | idAnalytical-Method, Analytical-MethodId | Yes |
| DateAnalysis | DateTime | The date of the analysis. | DateAnalysis, AnalysisDate, Date | No |
| Name | AlphaNumeric (100) | Name of the analysis sample. | Name | No |
| Description | AlphaNumeric (200) | Additional description of the the analysis sample. | Description | No |

Accepted table names: AnalysisSamples, AnalysisSample, SampleAnalysis, SampleAnalyses.

### Sample concentrations

This table contains substance concentration values specified in the unit defined by the analytical method. The analytical method contains the list of all substances which have been analyzed in the analysis sample. This ConcentrationsPerSample table contains the analysis results where substances with positive concentrations are included. Censored values (i.e. results 'less than LOQ or LOD') are reported as follows: 1) Substances for which an LOD (Limit of detection) is reported are included with ResType 'LOD', without a concentration value. 2) Substances for which only an LOQ (Limit of quantification) is reported are EXCLUDED, because the LOQ value from the ana-

lytical method substances table (AnalyticalMethodCompounds) is used by default. Explicitly missing concentration values are specified with ResType 'MV' (obligatory).

Table 3.103: Table definition for Sample concentrations.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSample-Analysis | AlphaNumeric (50) | The identification number of the analysed sample. | idSample-Analysis, SampleAnalysis, idAnalysis-Sample, AnalysisSample-Id | Yes |
| idSubstance | AlphaNumeric (50) | The substance code. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Concentration | Numeric | The measured concentration. | Concentration | No |
| ResType | *ResType* | The type of residue. Should be VAL (= default), LOQ, LOD or MV. | ResType | No |

Accepted table names: SampleConcentrations, ConcentrationsPerSample, ConcentrationPerSample.

### SSD concentration data format

The Standard Sample Description (SSD) concentration is the standard data format proposed by EFSA. Optionally, additional sample properties may be specified of fields that are not part of the SSD format (e.g., season of sampling). For this, the sample properties table and the sample property values table can be used.

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### SSD concentrations

MCRA uses the concept of samples analysed by analytical methods, where the analytical method contains the substances analysed and the LOQs and LODs for these substances. However, the SSD data do not provide information on the analytical methods at this level of detail. Therefore, the provided SSD sample records are used to generate analytical methods which are linked to the samples. All SSD records with the same labSampCode and labSubSampCode compose one MCRA analysis sample. All SSD samples that contain the same substance, LOQ/LOD values and resUnit combinations are linked to the corresponding generated analytical method. If both LOQ and LOD are provided, the LOQ is used as the LOR of the generated analytical method. It is highly recommended to supply LOQ/LOD values, even for positive measurements, because this reduces the number of gererated analytical methods.

Table 3.104: Table definition for SSD concentrations.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| labSampCode | AlphaNumeric (40) | Code of the laboratory sample. MCRA will use the combination of labSampCode and labSubSampCode as unique code for a sample. | labSampCode, sampId | Yes |
| labSubSamp-Code | AlphaNumeric (4) | Code of the laboratory sub-sample. MCRA will use the combination of labSampCode and labSubSampCode as unique code for a sample. | labSubSamp-Code | No |
| sampCountry | AlphaNumeric (2) | Two-letter code to identify the country of sampling. | sampCountry | No |
| sampArea | AlphaNumeric (5) | Area where the sample was collected. | sampArea | No |
| prodCode | AlphaNumeric (50) | Code identifying the modelled food. Should be equal to a code idFood in the Foods table. | prodCode, sampMatCode | Yes |
| prodProdMeth | AlphaNumeric (50) | Code providing additional information on the type of production for the food under analysis. | prodProdMeth | No |
| sampStrategy | AlphaNumeric (5) | Sampling strategy code. | sampStrategy, progSamp-Strategy, sampling-Strategy | No |
| fieldTrialType | AlphaNumeric (50) | Field trial type code. | fieldTrialType | No |
| sampAnId | AlphaNumeric (50) | Sample analysed identification code. | sampAnId | No |
| anPortSeq | AlphaNumeric (50) | Sample analysedportion sequence. | anPortSeq | No |
| sampY | Integer (4) | Year of sampling. | sampY | No |
| sampM | Integer (2) | Month of sampling. | sampM | No |
| sampD | Integer (2) | Day of sampling. | sampD | No |
| analysisY | Integer (4) | Year of analysis. | analysisY | No |
| analysisM | Integer (2) | Month of analysis. | analysisM | No |
| analysisD | Integer (2) | Day of analysis. | analysisD | No |
| paramCode | AlphaNumeric (50) | Code identifying the substance. | paramCode | Yes |
| resUnit | *ConcentrationUnit* | Unit of residue measurement. | resUnit | Yes |
| resLOD | Numeric | Residue Limit Of Detection. Required if resType is LOD. MCRA will use resLOD as LOR if resLOQ is not provided. | resLOD | No |
| resLOQ | Numeric | Residue Limit Of Quantification. Required if resType is LOQ. MCRA will use resLOQ as LOR if provided. | resLOQ | No |
| resVal | Numeric | Required if resType is VAL. | resVal | No |
| resType | *ResType* | Type of residue data. Should be VAL, LOQ, LOD or MV. | resType | Yes |

Accepted table names: ConcentrationsSSD, SSDConcentrations.

### Sample properties

Food sample properties, additional columns that can also be specified as additional columns in the food samples table

Table 3.105: Table definition for Sample properties.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| Name | AlphaNumeric (50) | The name of the property. | Id | Yes |
| Description | AlphaNumeric (200) | Additional description of the sample property. | Description | No |

Accepted table names: SampleProperties, SampleProperty.

### Sample property values

Food sample property values, additional columns that can also be specified as additional columns in the food samples table

Table 3.106: Table definition for Sample property values.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSample | AlphaNumeric (50) | The identification number of the food sample. | Id, IdFoodSample | Yes |
| PropertyName | AlphaNumeric (50) | The name of the property. | IdProperty, Name | Yes |
| TextValue | AlphaNumeric (50) | The value of the property as text value. | | No |
| DoubleValue | Numeric | The value of the property as number. | | No |

Accepted table names: SamplePropertyValues, SamplePropertyValue.

### Tabulated concentration data format

The tabulated concentration data format is an old data format for entering concentration data.

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### Tabulated concentrations

In the tabulated concentrations data table, each record represents one or multiple samples, and each sample contains a concentration value for a food/substance combination. Censored values (i.e. concentrations less than LOR) are specified as negative values, i.e. 'less than LOR' should be specified as minus the LOR value. MCRA uses the concept of samples analysed by analytical methods, where the analytical method is characterised by the substances analysed and the LORs for these substances. However, the tabulated data do not provide this information explicitly. Samples are reconstructed from the tabulated records using the NumberOfSamples field to create that number of single substance samples. Analytical methods are reconstructed from the data, with each analytical method having only one analysed substance with a LOR and concentration unit. When a negative concentration value is given (i.e., it is a censored measurement), this value is recorded as the LOR (negated). All censored measurements of the same substance with the same LOR and concentration unit are linked to the same analytical method. When a positive concentration value is given, this value is recorded as the measured concentration of the sample. All positive measurements of the same substance are linked to the same analytical method that has an artificial LOR that is smaller

than the lowest positive concentration. When a concentration of 0 (zero) is given, the measurement is considered to be a censored measurement and the LOR is set to the default value 1E-08.

Table 3.107: Table definition for Tabulated concentrations.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| GUID | AlphaNumeric (50) | Unique identifier of the analysis sample of this tabulated concentration record. | idAnalysis-Sample, SampleId, SampleCode, Code, Id | No |
| idSubstance | AlphaNumeric (50) | The code of the substance of this concentration value. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| idFood | AlphaNumeric (50) | The food code. | idFood, FoodId, FoodMeasured, Food | Yes |
| DateSampling | AlphaNumeric (10) | The date of sampling. | DateSampling | No |
| SamplingType | AlphaNumeric (50) | The type of sampling (monitoring). | SamplingType | No |
| Location | AlphaNumeric (50) | The location or country of sampling. | Location, Country | No |
| NumberOf-Samples | Integer | The count of the number of times the specified concentration or limit of reporting (LOR) occurs. | NumberOf-Samples | Yes |
| Concentration | Numeric | The concentration or LOR. LORs are specified using a minus (-) sign. | Concentration, Value | Yes |
| Concentration-Unit | *ConcentrationUnit* | The unit of the specified concentrations/LORs (default mg/kg). | Concentration-Unit, Unit | No |

Accepted table names: ConcentrationTabulated, ConcentrationValues, TabulatedConcentrations, TabulatedConcentration.

### Food concentrations settings

### Selection settings

Table 3.108: Selection settings for module Food concentrations.

| Name | Type | Description |
|---|---|---|
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |
| Selected tier | SettingsTemplateType | Specifies all module settings should be set according to a pre-defined tier or using custom settings. |
| Filter samples exceeding the concentration limits | Boolean | If checked, samples with at least one substance concentration higher than some factor (concentration limit filter exceedance factor) times the MRL are filtered out. |
| Concentration limit filter exceedance factor | Numeric | The multiplication factor for the concentration limit exceedance filter. |
| Use substance conversion rules | Boolean | If checked, concentrations are modelled in terms of active substances (using substance conversion). |

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Table 3.108 – continued from previous page

| Name | Type | Description |
|---|---|---|
| Substance conversion method | *SubstanceTranslationAllocationMethod* | Allocation method for assigning active substance concentrations from measured substance concentrations based on substance translations. |
| Retain all allocated substances after active substance allocation | Boolean | If checked, all allocated substances kept after substance conversion. Otherwise, the concentration data is restricted to th active substances of the assessment group. |
| Account for substance authorisations in substance conversions | Boolean | Account for substance authorisations when allocating measured substances to active substance using substance conversions. |
| Fix duplicate substance allocation inconsistencies | Boolean | Resolve inconsistencies when active substance allocation leads t multiple concentration value estimates for the same active substance. This method uses the mean of the positives or zero concentrations when available, or else the lowest of the censore values. |
| Use extrapolation rules | Boolean | Use extrapolation rules to extrapolate food samples for foods w a limited amount of samples (data poor foods) from other foods (data rich foods). |
| Threshold for extrapolation | Numeric | Threshold for extrapolation. |
| Restrict extrapolations to equal MRLs | Boolean | Restrict extrapolations to equal MRLs. |
| Restrict extrapolations to authorised uses | Boolean | Only extrapolate if substance use is authorised. |
| Impute water concentrations | Boolean | Impute constant concentration values on the selected (water) commodity. |
| Water commodity | AlphaNumeric | The commodity for which constant concentration values should added. |
| Water concentration value (µg/kg) | Numeric | Constant concentration value that should be used for water (in µg/kg). |
| Restrict water imputation to the five most toxic substances | Boolean | Restrict water imputation to the five most toxic substances. |
| Restrict water imputation to authorised uses | Boolean | Restrict water imputation to authorised uses. |
| Restrict water imputation to approved substances | Boolean | Specifies whether imputation of water should be limited to approved substances only. |
| Include focal commodity concentrations | Boolean | Specifies whether there is monitoring data that should replace p of the consumption data for the specified focal commodities. |
| Focal commodity food / substance combinations | FocalFood | The foods / substances for which background concentration dat are to be replaced by focal commodity concentrations. |
| Focal commodity substances | AlphaNumeric | The substances for which background concentration data are to replaced by focal commodity concentrations. |
| Focal commodity concentrations replacement method | *FocalCommodityReplacementMethod* | Replacement method to be used for replacing base concentratio data with concentration data of the focal commodity/commodit concentrations. |
| Focal commodity substance occurrence percentage | Numeric | Anticipated occurrence percentage / agricultural use percentage of the focal commodity. |
| Adjustment factor for the focal food/substance concentration | Numeric | Optional adjustment factor for the focal food/substance concentration. E.g., the expected ratio of mean monitoring concentration and mean field trial concentration. |
| Use deterministic substance conversions for focal commodity | Boolean | Convert measured substance concentrations of focal commodity to active substance concentrations using deterministic substance conversion factors. |
| Filter samples by specific property values (subset selection) | Boolean | Specifies whether a subset selection on specific sample properti should be made (e.g., by country or by year). |

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Table 3.108 – continued from previous page

| Name | Type | Description |
|---|---|---|
| Restrict to specific modelled foods (modelled foods subset) | Boolean | If checked, then the assessment is restricted to the specified modelled foods. |
| Align sampling location subset with population | Boolean | If checked, the samples are filtered based on the location of the selected population. |
| Include samples with unspecified location | Boolean | If checked, then samples for which the sample location is not specified are also included by the sample location filter. |
| Align sample date subset with population | Boolean | If checked, the samples are filtered based on the period of the selected population. |
| Align sampling month subset with population | Boolean | If checked, the samples are filtered based on the month/period the selected population. |
| Include samples with unspecified sampling date | Boolean | If checked, then samples for which the sample date is not specified are also included by the sample date filter. |
| Filter samples by location | Boolean | If checked, samples are filtered based on the selected locations. |
| Filter samples by year | Boolean | If checked, samples are filtered based on the selected years. |
| Filter samples by month | Boolean | If checked, samples are filtered based on the specified sampling month. |
| Samples subset definitions | SamplesSubsetDefinition | Samples subset definitions filter the concentration samples on custom properties using a set of keywords. |
| Samples by location subset definition | LocationSubsetDefinition | The subset definition to filter samples by location. |
| Samples by time period subset definition | PeriodSubsetDefinition | The subset definition to filter samples by time period. |
| Filter processed focal commodity samples | Boolean | Filter (exclude) concentration data at the level of raw primary commodity (RPC) derivatives (processed RPC) for the focal fo |
| Focal commodity proposed concentration limit (mg/kg) | Numeric | Proposed concentration value that should be used for the focal commodity substance combination (in mg/kg). |
| Include processed derivatives of the focal food in measurement replacement | Boolean | If checked, measurement replacement is also performed for processed derivatives of the focal food (e.g. for juiced oranges) |

### Output settings

Table 3.109: Output settings for module Food concentrations.

| Name | Type | Description |
|---|---|---|
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |

### Uncertainty settings

Table 3.110: Uncertainty settings for module Food concentrations.

| Name | Type | Description |
|---|---|---|
| Resample concentrations | Boolean | Specifies whether concentrations are resampled by empirical bootstrap or using a parametric uncertainty model. |

### Food concentrations tiers

In addition to the possibility for users to work with their own choices for all settings, MCRA implements Tier 1 and 2 from the European Commission working document SANTE-2015-10216 rev. 7 (2018) on risk management aspects related to the assessment of cumulative exposure.

### Overview

Table 3.111: Tier overview for module Food concentrations.

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Acute Pes-simistic | EFSA 2012 Chronic Pes-simistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFS 202 Chr Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| F te sa pl ex ce in th ce ce tr ti li it | false | false | false | false | false | false | false | false | false | false |
| U su st ce ve si ru | true | true | true | true | | | true | true | true | true |
| S st ce ve si m | UseMost-Toxic | UseMost-Toxic | DrawRan-dom | DrawRan-dom | | | UseMost-Toxic | UseMost-Toxic | DrawRan-dom | Draw dom |
| R ta al al lo ca su st af te ac ti su st al lo ca ti | true | true | true | true | | | true | true | true | true |
| A co fo su sp at th ri sa | false | false | true | true | | | false | false | true | true |

### Retrospective dietary CRA (EC 2018) - Acute / Tier I

Table 3.112: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier I.

| Name | Setting |
|---|---|
| Filter samples exceeding the concentration limits | false |
| Use substance conversion rules | true |
| Substance conversion method | UseMostToxic |
| Retain all allocated substances after active substance allocation | true |
| Account for substance authorisations in substance conversions | false |
| Fix duplicate substance allocation inconsistencies | false |
| Use extrapolation rules | true |
| Threshold for extrapolation | 10 |
| Restrict extrapolations to equal MRLs | true |
| Restrict extrapolations to authorised uses | true |
| Impute water concentrations | true |
| Water concentration value (µg/kg) | 0.1 |
| Restrict water imputation to the five most toxic substances | true |
| Restrict water imputation to authorised uses | false |
| Restrict water imputation to approved substances | false |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier I

Table 3.113: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier I.

| Name | Setting |
|---|---|
| Filter samples exceeding the concentration limits | false |
| Use substance conversion rules | true |
| Substance conversion method | UseMostToxic |
| Retain all allocated substances after active substance allocation | true |
| Account for substance authorisations in substance conversions | false |
| Fix duplicate substance allocation inconsistencies | false |
| Use extrapolation rules | true |
| Threshold for extrapolation | 10 |
| Restrict extrapolations to equal MRLs | true |
| Restrict extrapolations to authorised uses | true |
| Impute water concentrations | true |
| Water concentration value (µg/kg) | 0.1 |
| Restrict water imputation to the five most toxic substances | true |
| Restrict water imputation to authorised uses | false |
| Restrict water imputation to approved substances | false |

### Retrospective dietary CRA (EC 2018) - Acute / Tier II

Table 3.114: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier II.

| Name | Setting |
|---|---|
| Filter samples exceeding the concentration limits | false |
| Use substance conversion rules | true |
| Substance conversion method | DrawRandom |
| Retain all allocated substances after active substance allocation | true |
| Account for substance authorisations in substance conversions | true |
| Fix duplicate substance allocation inconsistencies | false |
| Use extrapolation rules | true |
| Threshold for extrapolation | 10 |
| Restrict extrapolations to equal MRLs | true |
| Restrict extrapolations to authorised uses | true |
| Impute water concentrations | true |
| Water concentration value (µg/kg) | 0.05 |
| Restrict water imputation to the five most toxic substances | true |
| Restrict water imputation to authorised uses | false |
| Restrict water imputation to approved substances | false |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier II

Table 3.115: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Filter samples exceeding the concentration limits | false |
| Use substance conversion rules | true |
| Substance conversion method | DrawRandom |
| Retain all allocated substances after active substance allocation | true |
| Account for substance authorisations in substance conversions | true |
| Fix duplicate substance allocation inconsistencies | false |
| Use extrapolation rules | true |
| Threshold for extrapolation | 10 |
| Restrict extrapolations to equal MRLs | true |
| Restrict extrapolations to authorised uses | true |
| Impute water concentrations | true |
| Water concentration value (µg/kg) | 0.05 |
| Restrict water imputation to the five most toxic substances | true |
| Restrict water imputation to authorised uses | false |
| Restrict water imputation to approved substances | false |

### Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic

Acute probabilistic exposure assessment using the pessimistic model settings according to the EFSA Guidance 2012. Only processing factors > 1 are applied. For unit variability, the Beta distribution is applied.

Table 3.116: Tier definition for Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic.

| Name | Setting |
|---|---|
| Filter samples exceeding the concentration limits | false |

### Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic

Chronic probabilistic exposure assessment using the pessimistic model settings according to the EFSA Guidance 2012. Only processing factors > 1 are applied.

Table 3.117: Tier definition for Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic.

| Name | Setting |
|---|---|
| Filter samples exceeding the concentration limits | false |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier I

Table 3.118: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier I.

| Name | Setting |
|---|---|
| Filter samples exceeding the concentration limits | false |
| Use substance conversion rules | true |
| Substance conversion method | UseMostToxic |
| Retain all allocated substances after active substance allocation | true |
| Account for substance authorisations in substance conversions | false |
| Fix duplicate substance allocation inconsistencies | false |
| Use extrapolation rules | false |
| Impute water concentrations | true |
| Water concentration value (µg/kg) | 0.1 |
| Restrict water imputation to the five most toxic substances | true |
| Restrict water imputation to authorised uses | false |
| Restrict water imputation to approved substances | true |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I

Table 3.119: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I.

| Name | Setting |
|---|---|
| Filter samples exceeding the concentration limits | false |
| Use substance conversion rules | true |
| Substance conversion method | UseMostToxic |
| Retain all allocated substances after active substance allocation | true |
| Account for substance authorisations in substance conversions | false |
| Fix duplicate substance allocation inconsistencies | false |
| Use extrapolation rules | false |
| Impute water concentrations | true |
| Water concentration value (µg/kg) | 0.1 |
| Restrict water imputation to the five most toxic substances | true |
| Restrict water imputation to authorised uses | false |
| Restrict water imputation to approved substances | true |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier II

Table 3.120: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier II.

| Name | Setting |
|---|---|
| Filter samples exceeding the concentration limits | false |
| Use substance conversion rules | true |
| Substance conversion method | DrawRandom |
| Retain all allocated substances after active substance allocation | true |
| Account for substance authorisations in substance conversions | true |
| Fix duplicate substance allocation inconsistencies | false |
| Use extrapolation rules | false |
| Impute water concentrations | true |
| Water concentration value (µg/kg) | 0.05 |
| Restrict water imputation to the five most toxic substances | true |
| Restrict water imputation to authorised uses | false |
| Restrict water imputation to approved substances | true |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II

Table 3.121: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Filter samples exceeding the concentration limits | false |
| Use substance conversion rules | true |
| Substance conversion method | DrawRandom |
| Retain all allocated substances after active substance allocation | true |
| Account for substance authorisations in substance conversions | true |
| Fix duplicate substance allocation inconsistencies | false |
| Use extrapolation rules | false |
| Impute water concentrations | true |
| Water concentration value (µg/kg) | 0.05 |
| Restrict water imputation to the five most toxic substances | true |
| Restrict water imputation to authorised uses | false |
| Restrict water imputation to approved substances | true |

### Prospective dietary CRA (EFSA 2023) - Acute / Tier II

Table 3.122: Tier definition for Prospective dietary CRA (EFSA 2023) - Acute / Tier II.

| Name | Setting |
|---|---|
| Filter samples exceeding the concentration limits | true |
| Concentration limit filter exceedance factor | 2 |
| Use substance conversion rules | true |
| Substance conversion method | DrawRandom |
| Retain all allocated substances after active substance allocation | true |
| Account for substance authorisations in substance conversions | true |
| Fix duplicate substance allocation inconsistencies | false |
| Use extrapolation rules | false |
| Impute water concentrations | true |
| Water concentration value (µg/kg) | 0.05 |
| Restrict water imputation to the five most toxic substances | true |
| Restrict water imputation to authorised uses | false |
| Restrict water imputation to approved substances | true |
| Include focal commodity concentrations | true |
| Focal commodity substance occurrence percentage | 20 |
| Adjustment factor for the focal food/substance concentration | 1 |
| Use deterministic substance conversions for focal commodity | true |

### Prospective dietary CRA (EFSA 2023) - Chronic / Tier II

Table 3.123: Tier definition for Prospective dietary CRA (EFSA 2023) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Filter samples exceeding the concentration limits | true |
| Concentration limit filter exceedance factor | 2 |
| Use substance conversion rules | true |
| Substance conversion method | DrawRandom |
| Retain all allocated substances after active substance allocation | true |
| Account for substance authorisations in substance conversions | true |
| Fix duplicate substance allocation inconsistencies | false |
| Use extrapolation rules | false |
| Impute water concentrations | true |
| Water concentration value (µg/kg) | 0.05 |
| Restrict water imputation to the five most toxic substances | true |
| Restrict water imputation to authorised uses | false |
| Restrict water imputation to approved substances | true |
| Include focal commodity concentrations | true |
| Focal commodity substance occurrence percentage | 20 |
| Adjustment factor for the focal food/substance concentration | 1 |
| Use deterministic substance conversions for focal commodity | true |

### Prospective dietary CRA (EFSA 2024) - Acute / Tier II

Table 3.124: Tier definition for Prospective dietary CRA (EFSA 2024) - Acute / Tier II.

| Name | Setting |
|---|---|
| Filter samples exceeding the concentration limits | true |
| Concentration limit filter exceedance factor | 2 |
| Use substance conversion rules | true |
| Substance conversion method | DrawRandom |
| Retain all allocated substances after active substance allocation | true |
| Account for substance authorisations in substance conversions | true |
| Fix duplicate substance allocation inconsistencies | false |
| Use extrapolation rules | false |
| Impute water concentrations | true |
| Water concentration value (µg/kg) | 0.05 |
| Restrict water imputation to the five most toxic substances | true |
| Restrict water imputation to authorised uses | false |
| Restrict water imputation to approved substances | true |
| Include focal commodity concentrations | true |
| Focal commodity substance occurrence percentage | 20 |
| Adjustment factor for the focal food/substance concentration | 1 |
| Use deterministic substance conversions for focal commodity | true |
| Include processed derivatives of the focal food in measurement replacement | true |

### Prospective dietary CRA (EFSA 2024) - Chronic / Tier II

Table 3.125: Tier definition for Prospective dietary CRA (EFSA 2024) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Filter samples exceeding the concentration limits | true |
| Concentration limit filter exceedance factor | 2 |
| Use substance conversion rules | true |
| Substance conversion method | DrawRandom |
| Retain all allocated substances after active substance allocation | true |
| Account for substance authorisations in substance conversions | true |
| Fix duplicate substance allocation inconsistencies | false |
| Use extrapolation rules | false |
| Impute water concentrations | true |
| Water concentration value (µg/kg) | 0.05 |
| Restrict water imputation to the five most toxic substances | true |
| Restrict water imputation to authorised uses | false |
| Restrict water imputation to approved substances | true |
| Include focal commodity concentrations | true |
| Focal commodity substance occurrence percentage | 20 |
| Adjustment factor for the focal food/substance concentration | 1 |
| Use deterministic substance conversions for focal commodity | true |
| Include processed derivatives of the focal food in measurement replacement | true |

#### Food concentrations uncertainty

Uncertainty due to a limited number of samples can be accounted for by resampling/bootstrapping. Resampling is done on a sample-based basis preserving co-occurrence of substance residue values on the same sample for multiple-substance analyses.

#### Food concentrations as data

Food concentration data can be entered using the internal, relational data format or using the EFSA SSD format. Depending on the settings, the entered food concentration data can be pre-processed for conversion to active substances, extrapolation to other foods, and/or default values can be added for water.

- *Food concentrations data formats*
- *Food concentrations from data*
- *Food concentrations calculation*

Inputs used: *Focal food concentrations Food extrapolations Substance conversions Deterministic substance conversion factors Relative potency factors Substance authorisations Active substances Concentration limits Substance approvals Processing factors*

### 3.3.5 Deterministic substance conversion factors

Deterministic substance conversion factors are (possibly food specific) conversion factors for converting measured substance concentrations to equivalent active substance concentrations. They are used in the *concentrations module* for translation of foreground/focal commodity substance concentrations to active substance concentrations (see option *use deterministic substance conversions for focal commodity* and the section on *focal commodity scenario analyses*).

Data module for deterministic substance conversion factors. These are (possibly food specific) conversion factors for expressing measured substance concentrations to equivalent active substance concentrations.

This module has as primary entities: *Substances Foods*

Output of this module is used by: *Food concentrations Single value concentrations*

#### Deterministic substance conversion factors from data

#### Deterministic substance conversion factors data formats

Deterministic substance conversion factors are (possibly food specific) conversion factors for expressing measured substance concentrations to equivalent active substance concentrations.

Download empty dataset template: Zipped CSV Excel

#### Deterministic substance conversion factors

Deterministic substance conversion factors for translating measured substance concentrations to active substance concentrations.

Table 3.126: Table definition for Deterministic substance conversion factors.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idMeasured-Substance | AlphaNumeric (50) | Substance code of the measured substance. | idMeasured-Substance, idResidue-Definition, Residue-Definition, Measured-Substance, ParamCode-Measured-Substance | Yes |
| idActive-Substance | AlphaNumeric (50) | Substance code of the active substance. | idActive-Substance, idSubstance, Active-Substance, Substance, ParamCode-ActiveSubstance | Yes |
| idFood | AlphaNumeric (50) | The unique identification code of the food. | idFood, Code, FoodId, FoodCode, Food | No |
| Conversion-Factor | Numeric | Specifies the conversion factor to translate concentrations of the measured substance to (equivalent) concentrations of the active substance according to e.g. the system used in PRIMo. | Factor, Conversion-Factor | Yes |
| Reference | AlphaNumeric (200) | Reference to the source from which this value is obtained. | Reference, References, Source, Sources | No |

Accepted table names: SingleValueSubstanceConversionFactors, SingleValueConversionFactors, SingleValueConversions, SubstanceConversionsFixed, DeterministicSubstanceConversionFactors, DeterministicConversionFactors.

#### Deterministic substance conversion factors as data

Deterministic substance conversion factors are (possibly food specific) conversion factors for expressing measured substance concentrations to equivalent active substance concentrations.

- *Deterministic substance conversion factors data formats*
- *Deterministic substance conversion factors from data*

### 3.3.6 Dust concentrations

Dust concentrations are analytical measurements of chemical substances occurring in dust samples. In their simplest form, concentration data can just be used as provided by datasets.

This module has as primary entities: *Substances*

Output of this module is used by: *Dust concentration distributions*

### Dust concentrations from data

### Dust concentrations data formats

Substance concentrations in dust.

Download empty dataset template: Zipped CSV Excel

### Dust concentrations

Substance concentrations in dust. Censored values, i.e., concentrations less than LOR, can be specified as negative values (minus the LOR value).

Table 3.127: Table definition for Dust concentrations.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSample | AlphaNumeric (50) | The identification number of the dust sample. | id, SampleId, idDustSample | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Concentration | Numeric | The substance concentration value or LOR of the dust sample. LORs are specified using a minus (-) sign. | Concentration, Value | Yes |
| Concentration-Unit | *ConcentrationUnit* | The unit for the substance concentrations. When not specified, then a default unit of ug/g is assumed. | Unit, Concentration-Unit | No |

Accepted table names: DustConcentrations, ConcentrationsDust.

### Dust concentrations settings

### Output settings

Table 3.128: Output settings for module Dust concentrations.

| Name | Type | Description |
|---|---|---|
| Show percentiles for | Numeric | Give specific percentiles of exposure distribution (%), e.g. 50 9 95 97.5 99 (space separated). |

### Uncertainty settings

Table 3.129: Uncertainty settings for module Dust concentrations.

| Name | Type | Description |
|---|---|---|
| Resample dust concentrations | Boolean | Dust concentration data are resampled from the original databa using the bootstrap methodology (Efron 1979, Efron & Tibshir 1993). |

#### Dust concentrations as data

Dust concentration data can be entered using the internal, relational data format.

- *Dust concentrations data formats*
- *Dust concentrations from data*

### 3.3.7 Dust concentration distributions

Dust concentration distributions are specified by a mean, cv and distribution type (lognormal). Specify the occurrence percentage as the percentage of samples that has positive concentrations.

This module has as primary entities: *Substances*

Output of this module is used by: *Dust exposures*

#### Dust concentration distributions from data

#### Dust concentration distributions calculation

This module calculates dust concentration models based on *concentrations* (option *Compute*), see also *concentration models* or uses data as input, see *dust concentration distributions* (option *Use Data*).

Currently, only a chronic exposure assessment is implemented. For option *Compute*, the mean value of all empirical concentration values is calculated. No correction for the occurrence fraction is applied i.c. the occurrence fraction is assumed equal to 1. Add zero concentrations where the occurrence is lower than 100%. In the data variant, the data format allows specification of an occurrence percentage (default value: 100%).

For more information, see *concentration model calculation* and *concentration model types*.

#### Dust concentration distributions data formats

Substance concentration distributions in dust.

Download empty dataset template: Zipped CSV Excel

#### Dust concentration distributions

Dust concentration distributions specified in the form of summary statistics: mean and a coefficient of variation, and a occurrence percentage.

Table 3.130: Table definition for Dust concentration distributions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Mean | Numeric | The mean of the concentration distribution. | Mean, Value, Concentration | Yes |
| Unit | *ConcentrationUnit* | The unit for the substance concentrations. When not specified, then a default unit of ug/kg is assumed. | Unit, Concentration-Unit | No |
| Distribution-Type | *DustConcentration-DistributionType* | Type of the distribution. | Distribution-Type, Distribution | Yes |
| CvVariability | Numeric | Coefficient of variation. | CvVariability, CV | No |
| Occurrence-Percentage | Numeric | Percentage (%) of the dust with substance (default 100%). | Occurrence-Percentage, Percentage | No |

Accepted table names: DustConcentrationDistributions, ConcentrationDistributionsDust.

#### Dust concentration distributions as data

Dust concentration distributions data can be entered using the internal, relational data format.

- *Dust concentration distributions data formats*
- *Dust concentration distributions from data*

#### Calculation of dust concentration distributions

Dust concentration distributions are computed from dust concentrations data.

- *Dust concentration distributions calculation*

Inputs used: *Dust concentrations*

### 3.3.8 Soil concentrations

Soil concentrations data are analytical measurements of chemical substances occurring in soil samples. In their simplest form, concentration data can just be used as provided by datasets.

This module has as primary entities: *Substances*

Output of this module is used by: *Soil concentration distributions*

#### Soil concentrations from data

#### Soil concentrations data formats

Substance concentrations in soil.

Download empty dataset template: Zipped CSV Excel

### Soil concentrations

Substance concentrations in soil.

Table 3.131: Table definition for Soil concentrations.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSample | AlphaNumeric (50) | The identification number of the soil sample. | idSample, SampleId, idSoilSample | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Concentration | Numeric | The substance concentration value of the soil sample. | Concentration, Value | Yes |
| Concentration-Unit | *ConcentrationUnit* | The unit for the substance concentrations. When not specified, then a default unit of ug/g is assumed. | Unit, Concentration-Unit | No |

Accepted table names: SoilConcentrations, ConcentrationsSoil.

### Soil concentrations settings

### Output settings

Table 3.132: Output settings for module Soil concentrations.

| Name | Type | Description |
|---|---|---|
| Show percentiles for | Numeric | Give specific percentiles of exposure distribution (%), e.g. 50 9 95 97.5 99 (space separated). |

### Uncertainty settings

Table 3.133: Uncertainty settings for module Soil concentrations.

| Name | Type | Description |
|---|---|---|
| Resample soil concentrations | Boolean | Soil concentration data are resampled from the original databas using the bootstrap methodology (Efron 1979, Efron & Tibshir 1993). |

### Soil concentrations as data

Soil concentrations data can be entered using the internal, relational data format.

- *Soil concentrations data formats*
- *Soil concentrations from data*

## 3.3.9 Soil concentration distributions

Soil concentration distributions are specified by a mean, cv and distribution type (lognormal). Specify the occurrence percentage as the percentage of samples that has positive concentrations.

This module has as primary entities: *Substances*

Output of this module is used by: *Soil exposures*

### Soil concentration distributions from data

### Soil concentration distributions calculation

This module calculates soil concentration models based on *concentrations* (option *Compute*), see also *concentration models* or uses data as input, see *soil concentration distributions* (option *Use Data*).

Currently, only a chronic exposure assessment is implemented. For option *Compute*, the mean value of all empirical concentration values is calculated. No correction for the occurrence fraction is applied i.c. the occurrence fraction is assumed equal to 1. Add zero concentrations where the occurrence is lower than 100%. In the data variant, the data format allows specification of an occurrence percentage (default value: 100%).

For more information, see *concentration model calculation* and *concentration model types*.

### Soil concentration distributions data formats

Substance concentration distributions in soil.

Download empty dataset template: Zipped CSV Excel

### Soil concentration distributions

Soil concentration distributions specified in the form of summary statistics: mean and a coefficient of variation, and a occurrence percentage.

Table 3.134: Table definition for Soil concentration distributions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Mean | Numeric | The mean of the concentration distribution. | Mean, Value, Concentration | Yes |
| Unit | *ConcentrationUnit* | The unit for the substance concentrations. When not specified, then a default unit of ug/kg is assumed. | Unit, Concentration-Unit | No |
| Distribution-Type | *SoilConcentration-DistributionType* | Type of the distribution. | Distribution-Type, Distribution | Yes |
| CvVariability | Numeric | Coefficient of variation. | CvVariability, CV | No |
| Occurrence-Percentage | Numeric | Percentage (%) of the Soil with substance (default 100%). | Occurrence-Percentage, Percentage | No |

Accepted table names: SoilConcentrationDistributions, ConcentrationDistributionsSoil.

#### Soil concentration distributions as data

Soil concentration distributions data can be entered using the internal, relational data format.

- *Soil concentration distributions data formats*
- *Soil concentration distributions from data*

#### Calculation of soil concentration distributions

Soil concentration distributions are computed from soil concentrations data.

- *Soil concentration distributions calculation*

Inputs used: *Soil concentrations*

### 3.3.10 Consumer product concentrations

Consumer product concentration (distributions) data are analytical measurements of chemical substances occurring in PCPs. In their simplest form, concentration data can just be used as provided by datasets.

This module has as primary entities: *Substances Consumer products*

Output of this module is used by: *Consumer product concentration distributions*

#### Consumer product concentrations from data

#### Consumer product concentrations data formats

Consumer product concentrations.

Download empty dataset template: Zipped CSV Excel

#### Consumer product concentrations

Consumer product concentrations. Censored values, i.e., concentrations less than LOR, can be specified as negative values (minus the LOR value).

Table 3.135: Table definition for Consumer product concentrations.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idProduct | AlphaNumeric (50) | The consumer product. | idProduct, ProductId | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Concentration | Numeric | The substance concentration value or LOR of the consumer product. LORs are specified using a minus (-) sign. | Concentration, Value | Yes |
| Unit | *ConsumerProduct-ConcentrationUnit* | The unit for the substance concentrations. When not specified, then a default unit of mg/kg is assumed or mg when the concentration is expressed per unit or item. | Unit, Concentration-Unit | No |
| Sampling-Weight | Numeric | The sampling weight for a concentration (default = 1). | SamplingWeight | No |

Accepted table names: ConsumerProductConcentrations, CPConcentrations.

### Consumer product concentrations settings

### Output settings

Table 3.136: Output settings for module Consumer product concentrations.

| Name | Type | Description |
|---|---|---|
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |

### Uncertainty settings

Table 3.137: Uncertainty settings for module Consumer product concentrations.

| Name | Type | Description |
|---|---|---|
| Resample consumer product concentrations | Boolean | Consumer product concentration data are resampled from the original database using the bootstrap methodology (Efron 1979 Efron & Tibshirani 1993). |

### Consumer product concentrations as data

Consumer product concentration (distributions) data can be entered using the internal, relational data format.

- *Consumer product concentrations data formats*
- *Consumer product concentrations from data*

### 3.3.11 Consumer product concentration distributions

Consumer product concentration distributions are specified by a mean, cv and distribution type (lognormal). Specify the occurrence percentage i.c. the percentage of the consumer product with positive concentrations.

This module has as primary entities: *Substances Consumer products*

Output of this module is used by: *Consumer product exposures*

#### Consumer product concentration distributions from data

#### Consumer product concentration distributions calculation

This module calculates consumer product concentration models based on *concentrations* (option *Compute*), see also *concentration models* or uses data as input, see *consumer product concentration distributions* (option *Use Data*).

Currently, only a chronic exposure assessment is implemented. For option *Compute*, the mean value of all empirical concentration values is calculated. No correction for the occurrence fraction is applied i.c. the occurrence fraction is assumed equal to 1. Add zero concentrations for consumer products where the occurrence is lower than 100%. In the data variant, the data format allows specification of an occurrence percentage (default value: 100%).

For more information, see *concentration model calculation* and *concentration model types*.

#### Consumer product concentration distributions data formats

Consumer product concentration distributions.

Download empty dataset template: Zipped CSV Excel

#### Consumer product concentration distributions

Consumer product concentration distributions specified in the form of summary statistics: mean and a coefficient of variation, and a occurrence percentage.

Table 3.138: Table definition for Consumer product concentration distributions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idProduct | AlphaNumeric (50) | The consumer product. | idProduct, ProductId | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Mean | Numeric | The substance mean value of the consumer product. | Concentration, Value | Yes |
| Unit | *ConcentrationUnit* | The unit for the substance concentrations. When not specified, then a default unit of ug/kg is assumed. | Unit, Concentration-Unit | No |
| Distribution-Type | *ConsumerProduct-Concentration-DistributionType* | Distribution type (LogNormal). If not specified, the concentration is assumed to be a constant factor. | Distribution-Type, Distribution | No |
| CvVariability | Numeric | Coefficient of variation. | CvVariability, CV | No |
| Occurrence-Percentage | Numeric | Percentage (%) of the consumer product with substance (default 100%). | Occurrence-Percentage, Percentage | No |

Accepted table names: ConsumerProductConcentrationDistributions, CPConcentrationDistributions.

### Consumer product concentration distributions settings

### Uncertainty settings

Table 3.139: Uncertainty settings for module Consumer product concentration distributions.

| Name | Type | Description |
|---|---|---|
| Resample consumer product concentrations | Boolean | Consumer product concentration data are resampled from the original database using the bootstrap methodology (Efron 1979 Efron & Tibshirani 1993). |

### Consumer product concentration distributions as data

Data are provided in the form of summary statistics for a specific consumer product and substance.

- *Consumer product concentration distributions data formats*
- *Consumer product concentration distributions from data*

### Calculation of consumer product concentration distributions

Consumer product concentration distributions are computed from consumer product concentrations.

- *Consumer product concentration distributions calculation*

Inputs used: *Consumer product concentrations*

### 3.3.12 Air concentration distributions

Air (indoor, outdoor) concentration distributions are specified by a mean, cv and distribution type (lognormal). Specify the occurrence percentage as the percentage of samples that has positive concentrations.

This module has as primary entities: *Substances*

Output of this module is used by: *Air exposures*

#### Air concentration distributions from data

#### Air concentration distributions calculation

This module calculates indoor and outdoor air concentration models based on *indoor air* and *outdoor air* concentrations (option *Compute*), see also *concentration models* or uses data as input, see *indoor air concentration distributions* and *outdoor air concentration distributions* (option *Use Data*).

Currently, only a chronic exposure assessment is implemented. For option *Compute*, the mean value of all empirical concentration values is calculated. No correction for the occurrence fraction is applied i.c. the occurrence fraction is assumed equal to 1. Add zero concentrations where the occurrence is lower than 100%. In the data variant, the data format allows specification of an occurrence percentage (default value: 100%).

For more information, see *concentration model calculation* and *concentration model types*.

#### Air concentration distributions data formats

Substance concentration distributions in air (indoor, outdoor).

Download empty dataset template: Zipped CSV Excel

#### Indoor air concentration distributions

Indoor air concentration distributions specified in the form of summary statistics: mean and a coefficient of variation, and a occurrence percentage.

Table 3.140: Table definition for Indoor air concentration distributions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Mean | Numeric | The mean of the concentration distribution. | Mean, Value, Concentration | Yes |
| Unit | *ConcentrationUnit* | The unit for the substance concentrations. When not specified, then a default unit of ug/m3 is assumed. | Unit, Concentration-Unit | No |
| Distribution-Type | *AirConcentration-DistributionType* | Type of the distribution. | Distribution-Type, Distribution | Yes |
| CvVariability | Numeric | Coefficient of variation. | CvVariability, CV | No |
| Occurrence-Percentage | Numeric | Percentage (%) of the indoor air samples with substance (default 100%). | Occurrence-Percentage, Percentage | No |

Accepted table names: IndoorAirDistributions, DistributionsIndoorAir.

### Outdoor air concentration distributions

Outdoor air concentration distributions specified in the form of summary statistics: mean and a coefficient of variation, and a occurrence percentage.

Table 3.141: Table definition for Outdoor air concentration distributions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Mean | Numeric | The mean of the concentration distribution. | Mean, Value, Concentration | Yes |
| Unit | *ConcentrationUnit* | The unit for the substance concentrations. When not specified, then a default unit of ug/m3 is assumed. | Unit, Concentration-Unit | No |
| Distribution-Type | *AirConcentration-DistributionType* | Type of the distribution. | Distribution-Type, Distribution | Yes |
| CvVariability | Numeric | Coefficient of variation. | CvVariability, CV | No |
| Occurrence-Percentage | Numeric | Percentage (%) of the OutdoorAir with substance (default 100%). | Occurrence-Percentage, Percentage | No |

Accepted table names: OutdoorAirDistributions, DistributionsOutdoorAir.

### Air concentration distributions as data

Air concentration distributions data can be entered using the internal, relational data format.

- *Air concentration distributions data formats*
- *Air concentration distributions from data*

### Calculation of air concentration distributions

Air concentration distributions are computed from air (indoor, outdoor) concentrations data.

- *Air concentration distributions calculation*

Inputs used: *Indoor air concentrations Outdoor air concentrations*

## 3.3.13 Indoor air concentrations

Indoor air concentrations data are analytical measurements of chemical substances occurring in indoor air samples. In their simplest form, concentration data can just be used as provided by datasets.

This module has as primary entities: *Substances*

Output of this module is used by: *Air concentration distributions*

### Indoor air concentrations from data

### Indoor air concentrations data formats

Substance concentration in indoor air.

Download empty dataset template: Zipped CSV Excel

### Indoor air concentrations

Substance concentrations in indoor air.

Table 3.142: Table definition for Indoor air concentrations.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSample | AlphaNumeric (50) | The identification number of the indoor air sample. | idSample, SampleId, idAirSample | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Location | AlphaNumeric (50) | The location or country code. | Country, Location | No |
| Concentration | Numeric | The substance concentration value of the indoor air sample. | Concentration, Value | Yes |
| Unit | *AirConcentration-Unit* | The unit for the substance concentrations. When not specified, then a default unit of ug/m3 is assumed. | Unit, Concentration-Unit, Air-Concentration-Unit | No |

Accepted table names: IndoorAirConcentrations, IndoorConcentrationsAir.

### Indoor air concentrations settings

### Output settings

Table 3.143: Output settings for module Indoor air concentrations.

| Name | Type | Description |
|---|---|---|
| Show percentiles for | Numeric | Give specific percentiles of exposure distribution (%), e.g. 50 9 95 97.5 99 (space separated). |

### Uncertainty settings

Table 3.144: Uncertainty settings for module Indoor air concentrations.

| Name | Type | Description |
|---|---|---|
| Resample indoor/outdoor air concentrations | Boolean | Air concentration data (indoor and outdoor) are resampled fron the original database using the bootstrap methodology (Efron 1979, Efron & Tibshirani 1993). |

#### Indoor air concentrations as data

Indoor air concentrations data can be entered using the internal, relational data format.

- *Indoor air concentrations data formats*
- *Indoor air concentrations from data*

### 3.3.14 Outdoor air concentrations

Outdoor air concentrations data are analytical measurements of chemical substances occurring in outdoor air samples. In their simplest form, concentration data can just be used as provided by datasets.

This module has as primary entities: *Substances*

Output of this module is used by: *Air concentration distributions*

#### Outdoor air concentrations from data

#### Outdoor air concentrations data formats

Substance concentration in outdoor air.

Download empty dataset template: Zipped CSV Excel

#### Outdoor air concentrations

Substance concentrations in outdoor air.

Table 3.145: Table definition for Outdoor air concentrations.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSample | AlphaNumeric (50) | The identification number of the outdoor air sample. | idSample, SampleId, idAirSample | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Location | AlphaNumeric (50) | The location or country code. | Country, Location | No |
| Concentration | Numeric | The substance concentration value of the outdoor air sample. | Concentration, Value | Yes |
| Unit | *AirConcentration-Unit* | The unit for the substance concentrations. When not specified, then a default unit of ug/m3 is assumed. | Unit, Concentration-Unit, Air-Concentration-Unit | No |

Accepted table names: OutdoorAirConcentrations, OutdoorConcentrationsAir.

#### Outdoor air concentrations settings

#### Output settings

Table 3.146: Output settings for module Outdoor air concentrations.

| Name | Type | Description |
|---|---|---|
| Show percentiles for | Numeric | Give specific percentiles of exposure distribution (%), e.g. 50 9 95 97.5 99 (space separated). |

#### Uncertainty settings

Table 3.147: Uncertainty settings for module Outdoor air concentrations.

| Name | Type | Description |
|---|---|---|
| Resample indoor/outdoor air concentrations | Boolean | Air concentration data (indoor and outdoor) are resampled fron the original database using the bootstrap methodology (Efron 1979, Efron & Tibshirani 1993). |

#### Outdoor air concentrations as data

Outdoor air concentrations data can be entered using the internal, relational data format.

- *Outdoor air concentrations data formats*
- *Outdoor air concentrations from data*

### 3.3.15 Focal food concentrations

In some cases the attention in an assessment is to evaluate concentrations (e.g., from specific field trials) for a specific food (and substance), in combination with a background of concentration data for other foods. Focal food concentrations can be included to provide these separate (foreground) concentration data for one or more focal food commodities that should replace measurements in the (background) *concentration data* in *focal commodity scenario analyses*.

This module has as primary entities: *Foods Substances*

Output of this module is used by: *Food concentrations*

#### Focal food concentrations from data

#### Focal food concentrations data formats

#### Focal food concentrations settings

#### Selection settings

Table 3.148: Selection settings for module Focal food concentrations.

| Name | Type | Description |
|---|---|---|
| Focal commodity food / substance combinations | FocalFood | The foods / substances for which background concentration dat are to be replaced by focal commodity concentrations. |

### Calculation settings

Table 3.149: Calculation settings for module Focal food concentrations.

| Name | Type | Description |
|---|---|---|
| Focal commodity concentrations replacement method | *FocalCommodityReplacementMethod* | Replacement method to be used for replacing base concentratio data with concentration data of the focal commodity/commodit concentrations. |
| Focal commodity substances | AlphaNumeric | The substances for which background concentration data are to replaced by focal commodity concentrations. |
| Filter samples by specific property values (subset selection) | Boolean | Specifies whether a subset selection on specific sample properti should be made (e.g., by country or by year). |
| Samples subset definitions | SamplesSubsetDefinition | Samples subset definitions filter the concentration samples on custom properties using a set of keywords. |

### Output settings

Table 3.150: Output settings for module Focal food concentrations.

| Name | Type | Description |
|---|---|---|
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |

### Focal food concentrations as data

Focal food concentrations are concentration data and specified in the exact same manner. The difference is that this data will be used to replace part of the concentration data in order to combine specific concentration data with a background of ordinary concentration data.

- *Focal food concentrations data formats*
- *Focal food concentrations from data*

Settings used

- *Calculation Settings*

## 3.3.16 Food extrapolations

Food extrapolations data specify which foods (data rich foods) can be used to impute concentration data for other foods with insufficient data (data poor foods).

This module has as primary entities: *Foods*

Output of this module is used by: *Food concentrations Food conversions*

### Food extrapolations from data

### Food extrapolations data formats

Food extrapolations (or read-across food translations) can be used to specify whether data (e.g, occurrence data) on a food for which this is missing (a data poor food) may be extrapolated from another food for which data is available (read-across food).

Download empty dataset template: Zipped CSV Excel

### Food extrapolations

Food extrapolations are simply specified as combinations of two food codes. One code for the food for the data poor food, and one for the data rich food (or read-across food).

Table 3.151: Table definition for Food extrapolations.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| DataPoorFood | AlphaNumeric (50) | The code of the data poor food. I.e., the food for which missing data is allowed to be extrapolated. | IdFoodDataPoor, FoodDataPoor, idFromFood, FromFoodId, FromFood, FoodFrom, Food, IdFood | Yes |
| CodeDataRichFood | AlphaNumeric (50) | The code of the read-across food (or data rich food). I.e., the food from which data is used for extrapolation. | IdFoodDataRich, FoodDataRich, IdFoodReadAcross, FoodReadAcross, IdReadAcrossFood, ReadAcrossFood, idToFood, ToFoodId, ToFood, FoodTo | Yes |

Accepted table names: ReadAcrossFoodTranslations, ReadAcrossFoodTranslation, ReadAcrossTranslations, ReadAcrossTranslation, FoodExtrapolations, FoodExtrapolation.

### Food extrapolations as data

Food extrapolations are specified as data in the form of simple tuples of data rich food and data poor food for which extrapolation is allowed/reasonable.

- *Food extrapolations data formats*
- *Food extrapolations from data*

## 3.3.17 Modelled foods

Modelled foods are foods within the foods scope for which concentration data or MRLs of substances are available (or expected).

This module has as primary entities: *Foods Substances*

Output of this module is used by: *Food concentration models Food conversions*

### Modelled foods calculation

Modelled foods are the foods within the foods scope for which concentration data or MRLs of substances are available (or expected). Modelled foods are derived primarily from *concentration data*. That is, all foods for which food samples are available in the concentration data or MRL data are considered to be modelled foods. In addition, this set may be extended when *concentration limits* such as MRLs are available (see *calculation settings*) and/or when *food*

*extrapolation rules* are used. Foods for which such data is available are considered to be modelled foods. The set of foods can also be restricted by omitting foods with only censored measurements (see *calculation settings*).

#### Modelled foods settings

#### Calculation settings

Table 3.152: Calculation settings for module Modelled foods.

| Name | Type | Description |
|---|---|---|
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Restrict to specific modelled foods (modelled foods subset) | Boolean | If checked, then the assessment is restricted to the specified modelled foods. |
| Selected modelled foods | AlphaNumeric | Set of modelled foods that are of particular interest. |
| Derive modelled foods from concentrations | Boolean | Derive modelled foods from sample based concentration data. |
| Derive modelled foods from single value concentrations | Boolean | Derive modelled foods from single value concentrations. |
| Derive modelled foods from concentration limits | Boolean | Derive modelled foods from concentration limits. |
| Include foods with only censored value measurements | Boolean | Specifies whether foods with only censored value measurements are part of the exposure assessment (default yes). |
| Include substances with only censored value measurements | Boolean | Specifies whether substances with only censored value measurements are part of the exposure assessment (default yes) |
| Include substances without measurements | Boolean | Specifies whether substances without any measurements should included. |

#### Calculation of modelled foods

Modelled foods are computed from concentration data (which may also be in the form of single-value concentrations) and/or derived from available maximum residue limits.

- *Modelled foods calculation*

Inputs used: *Food concentrations Single value concentrations Concentration limits*

Settings used

- *Calculation Settings*

### 3.3.18 Occurrence frequencies

Occurrence frequencies specify how often substances occur on foods. Frequencies are expressed as percentages.

This module has as primary entities: *Foods Substances*

Output of this module is used by: *Food concentration models Single value dietary exposures*

#### Occurrence frequencies from data

#### Occurrence frequencies calculation

Occurrence frequencies can be provided as data or computed from *occurrence patterns*. For a food and substance, they are computed by collecting all occurrence patterns of this food and summing up the frequencies of the occurrence patterns containing the substance. In the unlikely case that the total frequency of the occurrence patterns of a food exceeds 100%, then a rescaling is applied first. If the sum of the frequencies does not sum up to 100%, the interpretation of the remaining unspecified percentage can be designated as either “no use” or “all use”. In the the first case it is assumed that none of the substances occur on this remaining percentage. In the latter it is assumed that all

of the substances occur on this remaining percentage. This choice is available as the setting *associate the unspecified percentage with no-occurrence for foods with at least one specified occurrence pattern*.

Depending on the setting *apply occurrence pattern percentages*, occurrence frequencies can be computed in a crisp form in which the occurrence frequency is either 0% or 100% or as percentages ranging from 0% to 100%.

### Occurrence frequencies data formats

Occurrence frequencies are described by one simple table, specifying for pairs of food and substance, the associated occurrence frequencies as percentages.

Download empty dataset template: Zipped CSV Excel

### Occurrence frequencies

Occurrence frequencies are specified as percentages for pairs of food and substance. Optionally, a reference can be included in each record to specify the source (e.g., from literature) from which the percentage was obtained.

Table 3.153: Table definition for Occurrence frequencies.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFood | AlphaNumeric (50) | The food code. | idFood, CodeFood, FoodId, FoodCode, Food | Yes |
| idSubstance | AlphaNumeric (50) | Code of the substance. | idSubstance, CodeSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Percentage | Numeric | The occurrence frequency percentage. | Percentage, Frequency-Percentage | Yes |
| Reference | AlphaNumeric (200) | Reference to the source from which this use frequency value is obtained. | Reference, References, Source, Sources | No |

Accepted table names: OccurrenceFrequencies.

### Occurrence frequencies settings

### Selection settings

Table 3.154: Selection settings for module Occurrence frequencies.

| Name | Type | Description |
|---|---|---|
| Associate the unspecified percentage with no-occurrence for foods with at least one specified occurrence pattern | Boolean | If checked, for foods with at least one specified occurrence pattern, unspecified occurrence patterns for the same food are assumed to be associated with no use. If unchecked, all substances are considered to be authorised (potentially present i samples). Note that this setting cannot be used for foods that ha no specified AUs. These foods have 100% potential presence o all substances. To declare all AUs on such a food un-authorised include an empty AU with percentage 100% in the AU data tab (i.e., use an AU for this food, without specifying substances in t AU Substances table) |
| Apply occurrence pattern percentages | Boolean | If checked, use the percentages of potential presence as specifie by the occurrence patterns. If unchecked, 100% potential presence in samples is assumed for all substances identified by t occurrence patterns. |
| Selected tier | SettingsTemplateType | Specifies all module settings should be set according to a pre-defined tier or using custom settings. |

### Calculation settings

Table 3.155: Calculation settings for module Occurrence frequencies.

| Name | Type | Description |
|---|---|---|
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |

### Uncertainty settings

Table 3.156: Uncertainty settings for module Occurrence frequencies.

| Name | Type | Description |
|---|---|---|
| Recompute occurrence patterns | Boolean | Specifies whether occurrence patterns should be recomputed in the uncertainty runs. |

### Occurrence frequencies as data

Occurrence frequencies are described by one table, specifying for a food and substance the associated occurrence frequency as percentage.

- *Occurrence frequencies data formats*
- *Occurrence frequencies from data*

Inputs used: *Active substances*

Settings used

- *Calculation Settings*

### Calculation of occurrence frequencies

Occurrence frequencies for a food and substance are computed according to the model that is part of the EC 2018 Tier II definition (see van Klaveren et al. 2019)

- *Occurrence frequencies calculation*

Inputs used: *Occurrence patterns*

Settings used

- *Calculation Settings*

### 3.3.19 Occurrence patterns

Occurrence patterns (OPs) are the combinations (or mixtures) of substances that occur together on foods and the frequencies of these mixtures occurring per food, expressed in percentages. In the context of pesticides, occurrence patterns are associated with agricultural use percentages. Occurrence patterns are relevant to account for co-occurrence of active substances in exposed individuals. Occurrence patterns may be specified as data or modelled based on observed patterns of positive concentrations.

This module has as primary entities: *Foods Substances*

Output of this module is used by: *Occurrence frequencies Dietary exposures*

#### Occurrence patterns from data

#### Occurrence patterns calculation

Assumptions can be made for each food on the basis of findings in concentration data.

> **Tier 1:** 0% occurrence is assumed for all substances with no positive concentrations at all; 100% occurrence is assumed for all substances with at least one positive concentration;
>
> **Tier 2:** 0% occurrence is assumed for all substances with no positive concentrations at all; for substance-food combinations with at least one positive (finding), use findings patterns to implement a specific interpretation of Option 5 in the SANTE document, as described below.

Therefore in both tiers, substance-food combinations without any positive finding are handled in the optimistic way by assuming absolute zeroes for any censored observation.

If Tier 2 is selected, then for each of the modelled foods a tabulation is made of the observed frequencies of positives for all substance combinations (including the empty set), based on the *active substance concentrations*. For an OP consisting of just one substance, the basic frequency is the number of samples with a positive concentration divided by the number of samples where the substance has been measured (i.e., is not a MV). For an OP consisting of multiple substances, the basic frequency is the number of samples with all concentrations positive for the members divided by the number of samples where all members of the set have been measured.

After calculation of the basic frequencies for all occurrence patterns, these frequencies are rescaled such that the overall sum of frequencies is 100%. When *substance authorisations* are available, then patterns involving unauthorised substances are not rescaled and only those patterns for which all substances are authorised are rescaled such that the sum of all frequencies is 100%.

Note: the Tier 2 procedure is not what is literally written in the SANTE document, but is an interpretation agreed upon by EFSA and RIVM. An alternative model, not yet implemented, but perhaps more in line with the text of the SANTE document, would be to double the basic frequencies to modelled occurrence pattern frequencies. Only if the sum of all frequencies becomes larger than 100%, the set of frequencies would be normalised to 100% sum.

#### Occurrence patterns data formats

Agricultural use percentages for plant protection products (PPPs) may be of use for concentration modelling, as they provide information about what substance mixtures are expected to be present simultaneously on food samples. Especially for censored concentration measurements, this information may aid to determine whether the censored measurement originated from a true zero or may be a positive measurement below the limit of detection. Agricultural use percentages are specified using the agricultural uses and agricultural use substances table. This data format expects agricultural use percentages to be specified for mixtures of substances. Each mixture has an id (idAgriculturalUse) and a list of substances that are part of this mixture (agricultural use substances). These agricultural uses are assumed

to be exclusive (i.e., only one mixture or PPP is used per sample). Hence, the sum of the agricultural uses for one food should not exceed 100%.

Download empty dataset template: Zipped CSV Excel

### Agricultural uses

The AgriculturalUses contains the definitions of the agricultural use mixtures, or PPPs and the specification of the percentage of the products treated with this mixture. Optionally also the time period of the use percentage may be specified.

Table 3.157: Table definition for Agricultural uses.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idAgricultural-Use | AlphaNumeric (50) | The unique identification code of the agricultural use group / plant protection product (PPP). | idAgricultural-Use, AgriculturalUse-Id, Id | Yes |
| idFood | AlphaNumeric (50) | The food code. | idFood, FoodId, Food | Yes |
| Location | AlphaNumeric (50) | The location or country code, agricultural use location. | Country, Location | No |
| StartDate | DateTime | | StartDate | No |
| EndDate | DateTime | | EndDate | No |
| Percentage-CropTreated | Numeric | The percentage agricultural use (%). | PercentageCrop-Treated, Percentage, PercCrop-Treated, PercentageUse | Yes |
| Name | AlphaNumeric (100) | Name of the agricultural use. | Name | No |
| Description | AlphaNumeric (200) | Additional description of the agricultural use. | Description | No |

Accepted table names: AgriculturalUses, AgriculturalUse.

### Agricultural use substances

The agricultural use substances table records the substances that are part of the agricultural use mixtures (PPPs).

Table 3.158: Table definition for Agricultural use substances.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idAgricultural-Use | AlphaNumeric (50) | The agricultural use code, normally a code for a combination of authorised substances. | idAgricultural-Use, AgriculturalUse-Id | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |

Accepted table names: AgriculturalUseHasSubstances, AgriculturalUsesHasSubstances, AgriculturalUseSubstances, AgriculturalUseGroups, AgriculturalUseGroup.

### Occurrence patterns settings

### Selection settings

Table 3.159: Selection settings for module Occurrence patterns.

| Name | Type | Description |
|---|---|---|
| Selected tier | SettingsTemplateType | Specifies all module settings should be set according to a pre-defined tier or using custom settings. |
| Associate the unspecified percentage with no-occurrence for foods with at least one specified occurrence pattern | Boolean | If checked, for foods with at least one specified occurrence pattern, unspecified occurrence patterns for the same food are assumed to be associated with no use. If unchecked, all substances are considered to be authorised (potentially present i samples). Note that this setting cannot be used for foods that ha no specified AUs. These foods have 100% potential presence o all substances. To declare all AUs on such a food un-authorised include an empty AU with percentage 100% in the AU data tab (i.e., use an AU for this food, without specifying substances in t AU Substances table) |
| Apply occurrence pattern percentages | Boolean | If checked, use the percentages of potential presence as specifie by the occurrence patterns. If unchecked, 100% potential presence in samples is assumed for all substances identified by t occurrence patterns. |
| Scale up use frequency to 100% | Boolean | Scale up use frequency to 100%. |
| Restrict use percentage up-scaling to authorised uses | Boolean | Restrict use percentage up-scaling to authorised uses. |

### Calculation settings

Table 3.160: Calculation settings for module Occurrence patterns.

| Name | Type | Description |
|---|---|---|
| Compute cumulative exposures | Boolean | Specifies whether the assessment involves multiple substances a results should be cumulated over all substances. |
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |

### Uncertainty settings

Table 3.161: Uncertainty settings for module Occurrence patterns.

| Name | Type | Description |
|---|---|---|
| Recompute occurrence patterns | Boolean | Specifies whether occurrence patterns should be recomputed in the uncertainty runs. |

### Occurrence patterns tiers

## Overview

Table 3.162: Tier overview for module Occurrence patterns.

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec-tive Tier II | EFS 202 Chr Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| A pl oc cu re pa te pe ce ag | false | false | true | true | false | false | true | true | true | true |
| F te sa pl ex ce in th ce ce tr ti li it | false | false | false | false | false | false | false | false | true | true |
| U su st co ve si ru | true | true | true | true | true | true | true | true | true | true |
| S st co ve si m | UseMost-Toxic | UseMost-Toxic | DrawRan-dom | DrawRan-dom | UseMost-Toxic | UseMost-Toxic | DrawRan-dom | DrawRan-dom | DrawRan-dom | Draw dom |
| R ta al al lo ca su st af te ac ti | true | true | true | true | true | true | true | true | true | true |
| st al lo ca | | | | | | | | | | |

### Retrospective dietary CRA (EC 2018) - Acute / Tier I

Table 3.163: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | false | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier I

Table 3.164: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | false | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |

### Retrospective dietary CRA (EC 2018) - Acute / Tier II

Table 3.165: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | true | | |
| Scale up use frequency to 100% | true | | |
| Restrict use percentage up-scaling to authorised uses | true | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC* | *Food concentrations* |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier II

Table 3.166: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | true | | |
| Scale up use frequency to 100% | true | | |
| Restrict use percentage up-scaling to authorised uses | true | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC* | *Food concentrations* |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier I

Table 3.167: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | false | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I

Table 3.168: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | false | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier II

Table 3.169: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | true | | |
| Scale up use frequency to 100% | true | | |
| Restrict use percentage up-scaling to authorised uses | true | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA* | *Food concentrations* |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II

Table 3.170: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | true | | |
| Scale up use frequency to 100% | true | | |
| Restrict use percentage up-scaling to authorised uses | true | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA* | *Food concentrations* |

### Prospective dietary CRA (EFSA 2023) - Acute / Tier II

Table 3.171: Tier definition for Prospective dietary CRA (EFSA 2023) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | true | | |
| Scale up use frequency to 100% | true | | |
| Restrict use percentage up-scaling to authorised uses | true | | |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA* | *Food concentrations* |

### Prospective dietary CRA (EFSA 2023) - Chronic / Tier II

Table 3.172: Tier definition for Prospective dietary CRA (EFSA 2023) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | true | | |
| Scale up use frequency to 100% | true | | |
| Restrict use percentage up-scaling to authorised uses | true | | |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA* | *Food concentrations* |

### Prospective dietary CRA (EFSA 2024) - Acute / Tier II

Table 3.173: Tier definition for Prospective dietary CRA (EFSA 2024) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | true | | |
| Scale up use frequency to 100% | true | | |
| Restrict use percentage up-scaling to authorised uses | true | | |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA* | *Food concentrations* |

### Prospective dietary CRA (EFSA 2024) - Chronic / Tier II

Table 3.174: Tier definition for Prospective dietary CRA (EFSA 2024) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | true | | |
| Scale up use frequency to 100% | true | | |
| Restrict use percentage up-scaling to authorised uses | true | | |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA* | *Food concentrations* |

#### Occurrence patterns as data

Occurrence patterns are provided as data by specification of the occurrence mixtures and their associated occurrence/agricultural use percentages.

- *Occurrence patterns data formats*
- *Occurrence patterns from data*

Inputs used: *Substance authorisations Active substances*

Settings used

- *Calculation Settings*

#### Calculation of occurrence patterns

Occurrence patterns are computed from the observed patterns of positive concentrations in the concentration data.

- *Occurrence patterns calculation*

Inputs used: *Food concentrations*

Settings used

- *Calculation Settings*

### 3.3.20 Processing factors

Processing factors are multiplication factors to derive the concentration in a processed food from the concentration in an unprocessed food and can be specified for identified processing types (e.g., cooking, washing, drying). Processing factors are primarily used in dietary exposure assessments to correct for the effect of processing on substance concentrations in dietary exposure calculations.

This module has as primary entities: *Foods Substances*

Output of this module is used by: *Food concentrations Food conversions Dietary exposures Single value dietary exposures*

#### Processing factors from data

#### Processing factors calculation

#### Processing factors fixed or distribution based

Processing factors can be specified as fixed factors (nominal) or as statistical distributions for the variability across samples.

- The distribution is either *the logistic-normal distribution* for processing types with factors restricted between 0 and 1 (e.g. washing),
- or the lognormal distribution *the lognormal distribution* for processing types with non-negative factors (e.g. drying).

Variability distribution parameters are specified indirectly via the 50th and 95th percentile. Uncertainty for processing factors can be specified using uncertainty distributions of the same form as for variability. Uncertainty distribution parameters are specified indirectly via the 95th uncertainty percentiles on the 50th and 95th variability distribution percentiles.

For distribution based processing factors specify $f_{k,nominal}$ and $f_{k,upper}$ (*Nominal* and *Upper* in table *Processing factors*). Two situations are distinguished depending on the type of transformation.

### Nonnegative processing factors

Equate the logarithms of $f_{k,nominal}$ and $f_{k,upper}$ to the mean and the 95% one-sided upper confidence limit of a normal distribution. This normal distribution is specified by a mean

$$ln(f_{k,nominal})$$

and a standard deviation

$$ln(f_{k,upper})–ln(f_{k,nominal})/1.645$$

### Processing factors between 0 and 1

Equate the logits of $f_{k,nominal}$ and $f_{k,upper}$ to the mean and the 95% one-sided upper confidence limit of a normal distribution. This normal distribution is specified by a mean

$$logit(f_{k,nominal})$$

and a standard deviation

$$logit(f_{k,upper})–logit(f_{k,nominal})/1.645.$$

See also *processing correction*

### Processing factors data formats

Processing factors connect to a food id and a processing type or (food) facet (FoodEx 2). The specification of a substance (id) is optional. Specify the unprocessed food code and the processing type or facet. The combination of idFood-idProcessingType represents a processed food.

Processing factors are defined for triplets of processing type, food, and substance. The processing types are defined in the processing types table and the processing factors are defined in the processing factors table.

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### Processing factors

Processing factor records should be linked to processing types (or facets) using the processing type (or facet) code (idProcessingType) and for the foods and substances. The codes of the processing factor records should match the codes of the foods, substances, and processing type (of facets) definitions.

Table 3.175: Table definition for Processing factors.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idProcessing-Type | AlphaNumeric (50) | The code of the processing type. | idProcessing-Type, ProcessingType-Id, ProcessingType, ProcType, facet, idFacet, codeFacet | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | No |
| idFood-Unprocessed | AlphaNumeric (50) | The code of the unprocessed food. | idFood-Unprocessed, Food-UnprocessedId, idFood, FoodId, Food-Unprocessed | Yes |
| Nominal | Numeric | The nominal value (best estimate of 50th percentile) of processing factor (defines median processing factor). | Nominal, ProcNom | Yes |
| Upper | Numeric | The upper value (estimate of 95th percentile or “worst case” estimate) of processing factor due to variability. | Upper, ProcUpp | No |
| Nominal-Uncertainty-Upper | Numeric | The upper 95th percentile of nominal value (Nominal) due to uncertainty. A standard deviation for uncertainty of the nominal value (Nominal) is derived using the nominal value (Nominal) and upper 95th percentile (NominalUncertaintyUpper). | Nominal-Uncertainty-Upper, ProcNomUnc-Upp | No |
| Upper-Uncertainty-Upper | Numeric | The upper 95th percentile of upper value (Upper) due to uncertainty. From the nominal value (Nominal), upper value (Upper) and the specified uncertainties of these values (NominalUncertaintyUpper and UpperUncertaintyUpper, respectively) the degrees of freedom of a chi-square distribution describing the uncertainty of the standard deviation for variability is derived. | Upper-Uncertainty-Upper, ProcUppUnc-Upp | No |

Accepted table names: ProcessingFactors, ProcessingFactor, Processing.

### Processing factors settings

### Calculation settings

Table 3.176: Calculation settings for module Processing factors.

| Name | Type | Description |
|---|---|---|
| Selected tier | SettingsTemplateType | Specifies all module settings should be set according to a pre-defined tier or using custom settings. |
| Apply processing factors | Boolean | Specified in table ProcessingFactor. If checked, processing fact are applied. Concentrations in the consumed food may be different from concentrations in the modelled food in monitorin programs (typically raw food) due to processing, such as peelin washing, cooking etc. If unchecked, no processing information used. This is in most (though not all) cases a worst-case assumption |
| Use distribution | Boolean | Probabilistic specifications of processing factors will be used |
| Ignore processing factors less than 1 | Boolean | This setting will suppress the use of processing factors lower th 1 (it is used in the EFSA 2012 Pessimistic tier). |
| Use default processing factor for missing processing types | Boolean | Use default processing factor for missing processing types |
| Default processing factor for missing processing types (except foods with processing type equal to 'Unspecified' (default = 1)) | Numeric | Specify a processing factor for missing processing types. When the processing type is 'Unspecified', the default processing facto is equal to 1. |

### Uncertainty settings

Table 3.177: Uncertainty settings for module Processing factors.

| Name | Type | Description |
|---|---|---|
| Resample processing factors | Boolean | Specifies whether processing factors are resampled from a parametric uncertainty distribution. |

### Processing factors tiers

### Overview

Table 3.178: Tier overview for module Processing factors.

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| A pl pr ce in fa to | true | true | true | true | true | true | true | true | true | true |
| U di tr bu ti | false | false | false | false | false | false | false | false | false | false |
| Ig no pr ce in fa to le th 1 | false | false | false | false | false | true | true | false | false | false |

### Retrospective dietary CRA (EC 2018) - Acute / Tier I

Table 3.179: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier I.

| Name | Setting |
|---|---|
| Apply processing factors | true |
| Use distribution | false |
| Ignore processing factors less than 1 | false |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier I

Table 3.180: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier I.

| Name | Setting |
|---|---|
| Apply processing factors | true |
| Use distribution | false |
| Ignore processing factors less than 1 | false |

### Retrospective dietary CRA (EC 2018) - Acute / Tier II

Table 3.181: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier II.

| Name | Setting |
|---|---|
| Apply processing factors | true |
| Use distribution | false |
| Ignore processing factors less than 1 | false |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier II

Table 3.182: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Apply processing factors | true |
| Use distribution | false |
| Ignore processing factors less than 1 | false |

### Retrospective dietary CRA (EFSA 2012) - Optimistic

Use the optimistic model settings according to the EFSA Guidance 2012. Concentration values are sampled using a sample-based empirical distribution. Available processing factors are applied. No unit variability model should be applied.

Table 3.183: Tier definition for Retrospective dietary CRA (EFSA 2012) - Optimistic.

| Name | Setting |
|---|---|
| Apply processing factors | true |
| Use distribution | false |
| Ignore processing factors less than 1 | false |

### Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic

Acute probabilistic exposure assessment using the pessimistic model settings according to the EFSA Guidance 2012. Only processing factors > 1 are applied. For unit variability, the Beta distribution is applied.

Table 3.184: Tier definition for Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic.

| Name | Setting |
|---|---|
| Apply processing factors | true |
| Use distribution | false |
| Ignore processing factors less than 1 | true |

### Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic

Chronic probabilistic exposure assessment using the pessimistic model settings according to the EFSA Guidance 2012. Only processing factors > 1 are applied.

Table 3.185: Tier definition for Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic.

| Name | Setting |
|---|---|
| Apply processing factors | true |
| Use distribution | false |
| Ignore processing factors less than 1 | true |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier I

Table 3.186: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier I.

| Name | Setting |
|---|---|
| Apply processing factors | true |
| Use distribution | false |
| Ignore processing factors less than 1 | false |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I

Table 3.187: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I.

| Name | Setting |
|---|---|
| Apply processing factors | true |
| Use distribution | false |
| Ignore processing factors less than 1 | false |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier II

Table 3.188: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier II.

| Name | Setting |
|---|---|
| Apply processing factors | true |
| Use distribution | false |
| Ignore processing factors less than 1 | false |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II

Table 3.189: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Apply processing factors | true |
| Use distribution | false |
| Ignore processing factors less than 1 | false |

### Prospective dietary CRA (EFSA 2023) - Acute / Tier II

Table 3.190: Tier definition for Prospective dietary CRA (EFSA 2023) - Acute / Tier II.

| Name | Setting |
|---|---|
| Apply processing factors | true |
| Use distribution | false |
| Ignore processing factors less than 1 | false |

### Prospective dietary CRA (EFSA 2023) - Chronic / Tier II

Table 3.191: Tier definition for Prospective dietary CRA (EFSA 2023) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Apply processing factors | true |
| Use distribution | false |
| Ignore processing factors less than 1 | false |

### Prospective dietary CRA (EFSA 2024) - Acute / Tier II

Table 3.192: Tier definition for Prospective dietary CRA (EFSA 2024) - Acute / Tier II.

| Name | Setting |
|---|---|
| Apply processing factors | true |
| Use distribution | false |
| Ignore processing factors less than 1 | false |

### Prospective dietary CRA (EFSA 2024) - Chronic / Tier II

Table 3.193: Tier definition for Prospective dietary CRA (EFSA 2024) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Apply processing factors | true |
| Use distribution | false |
| Ignore processing factors less than 1 | false |

### Processing factors uncertainty

Processing effects are modelled either by a fixed processing factor, or by a lognormal or logistic-normal distribution (depending on the distribution type of the *processing type*). In case of a fixed factor, the uncertainty distribution is lognormal or logistic-normal with the same mean $\mu$ as the fixed value, and with a standard deviation $\sigma_{unc}$ which is calculated from the specified central value $\mu$ (or nominal) and an estimate of the p95 of the *uncertainty distribution* (set *NominalUncertaintyUpper* in the *table for Processing factors*).

The calculation is:

$$\sigma_{unc} = \frac{f(\mathit{NominalUncertaintyUpper}) - f(\mu)}{1.645}$$

with $f() = logit$ for the logistic-normal distribution (distribution type 1) and $f() = ln$ for the lognormal distribution (distribution type 2). Values lower than 0.01 or higher than 0.99 (distribution type 1 only) are replaced by default

values (0.01 and 0.99); this is useful computationally to avoid problems. In each iteration of the uncertainty analysis a new value is drawn from this distribution to be used as a fixed factor in the Monte Carlo calculation. In case of distribution based processing factors (describing the variability of processing factors) two uncertainties can be specified. For $\sigma_{unc}$, specification and calculation is as before (set *NominalUncertaintyUpper* in the *table for Processing factors*).

The uncertainty about the variability standard deviation

$$\sigma_{var} = \frac{f(Upper) - f(\mu)}{1.645}$$

can be specified by the *UpperUncertaintyUpper* value. This value is specified as the p95 upper limit on *Upper*. The specified value is used to derive in a iterative search the number of degrees of freedom *df* (van der Voet et al. (2009)). In the uncertainty analysis, a modified chi-square distribution with *df* degrees of freedom is used to generate new values of $\sigma_{var}$. A very high value of *df* means little uncertainty and $\sigma_{var}$ will be almost equal in all iterations of the uncertainty analysis. A *df* close to 0 means a large uncertainty and very different values of $\sigma_{var}$ will be obtained in the iterations of the uncertainty analysis. The p95 upper limit on Upper is set through parameter *UpperUncertaintyUpper*.

#### Processing factors as data

Specify for a combination of processing type, food and substance the processing factor (nominal, upper).

- *Processing factors data formats*
- *Processing factors from data*
- *Processing factors calculation*

Settings used

- *Calculation Settings*

### 3.3.21 Single value concentrations

Single value concentrations data are the single value estimates (High Residue, Maximum Residue Limit, Supervised Trials Median Residue) of residue concentrations on modelled foods.

This module has as primary entities: *Foods Substances*

Output of this module is used by: *Modelled foods Single value dietary exposures*

#### Single value concentrations from data

#### Single value concentrations calculation

Single value concentrations as data are supplied as mean concentrations, median concentrations, highest residues, percentiles, LOQs or maximum residue limits. Specify the 'Use data' option in the interface. In a retrospective context, the single values are computed based on the concentration distributions available for the modelled food as supplied in the *Concentrations module*. Specify option 'Compute' in the Single value concentrations action.

#### Single value concentrations data formats

Single value concentrations data provides a single value concentration for a substance.

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#### Concentration single values

The food codes (idFood) and substance codes (idSubstance) should match the codes of the foods and substances table respectively.

Table 3.194: Table definition for Concentration single values.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFood | AlphaNumeric (50) | Code of the food of this concentration single value. | idFood, FoodId, Food | Yes |
| idSubstance | AlphaNumeric (50) | Code of the substance of this concentration single value. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Value | Numeric | Concentration single value. | Value, Concentration, Concentration-Value | Yes |
| ValueType | *ConcentrationLimit-ValueType* | Value type of the concentration value. | Concentration-SingleValue-Type, Concentration-ValueType, SingleValue-Type, Concentration-Type, ValueType, Type | Yes |
| Percentile | Numeric | Percentile. | Percentile | No |
| Concentration-Unit | *ConcentrationUnit* | The unit of the concentration single value (default mg/kg). | Concentration-Unit, Unit | No |
| Reference | AlphaNumeric (200) | Reference to the source from which this concentration single value is obtained. | Reference, References, Source, Sources | No |

Accepted table names: ConcentrationSingleValues, SingleValueConcentrations.

### Single value concentrations settings

### Selection settings

Table 3.195: Selection settings for module Single value concentrations.

| Name | Type | Description |
|---|---|---|
| Use substance conversion factors | Boolean | Specifies whether to use substance conversion factors to convert measured substance concentrations to active substance concentrations. |

### Single value concentrations as data

Single value concentrations data are the single value concentrations of residues on modelled foods.

- *Single value concentrations data formats*
- *Single value concentrations from data*

Inputs used: *Active substances*

#### Calculation of single value concentrations

Single value concentrations are calculated as a percentile (p50, p97.5 or maximum residue limit) of the modelled food concentration distribution.

- *Single value concentrations calculation*

Inputs used: *Food concentrations Concentration limits Deterministic substance conversion factors*

### 3.3.22 Substance authorisations

Substance authorisations specify which food/substance combinations are authorised for (agricultural) use. If substance authorisations are used, then only the food/substance combinations that are specified in the data are assumed to be authorised and all other combinations are assumed to be not authorised. This information may, for instance, be used to determine whether concentration measurements below the LOQ or LOD could be assumed true zeros. I.e., if a food/substance combinations is assumed to be unauthorised, then the LOQ, LOD may be assumed to be a zero.

This module has as primary entities: *Foods Substances*

Output of this module is used by: *Food concentrations Occurrence patterns Food concentration models*

#### Substance authorisations from data

#### Substance authorisations data formats

Authorised uses data provides information about whether substance use is allowed for specified foods. For cumulative exposure assessments, this information is used for imputation of censored values/missing values.

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#### Authorised uses

The authorised uses table

Table 3.196: Table definition for Authorised uses.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFood | AlphaNumeric (50) | The food code. | idFood, FoodId, Food | Yes |
| idSubstance | AlphaNumeric (50) | The substance code. | idSubstance, Substance, SubstanceId | Yes |
| Reference | AlphaNumeric (200) | External reference(s) to sources containing more information about the effect (key event) relationships. | Reference, References | No |

Accepted table names: AuthorisedUses, AuthorisedUse.

#### Substance authorisations as data

Substance authorisations are specified as data in the form of a list of authorised food/substance combinations, with combinations not on the list associated with no authorised use.

- *Substance authorisations data formats*

- *Substance authorisations from data*

## 3.3.23 Substance approvals

Substance approvals specify which substances are approved within the definition under regulation (EC) No 1107/2009. This information may, for instance, be used to to restrict water imputation to approved substances only.

This module has as primary entities: *Substances*

Output of this module is used by: *Food concentrations*

### Substance approvals from data

### Substance approvals data formats

Substance approvals specify which substances are approved within the definition under regulation (EC) No 1107/2009. This information may, for instance, be used to restrict water imputation to approved substances only.

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### Substance approvals

Substance approval records are tuples consisting of an identifier of the substance and a boolean value specifying the approval status of the substance. Substances that are not included in the table are assumed to be NOT approved.

Table 3.197: Table definition for Substance approvals.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubstance | AlphaNumeric (50) | The substance code. | idSubstance, Substance, SubstanceId | Yes |
| IsApproved | Boolean | Specifies whether the substance is approved or not. Substances not included in the table are assumed to be NOT approved. | IsApproved, Approved | Yes |

Accepted table names: SubstanceApprovals, ApprovedSubstances.

### Substance approvals as data

Substance approvals are specified as data in the form of a list of approved substances. Substances not on the list are assumed to be not approved.

- *Substance approvals data formats*
- *Substance approvals from data*

## 3.3.24 Substance conversions

Substance conversions specify how measured substances are converted into active substances, which are the substances assumed to cause health effects. In pesticide legislation such measured substances and the substance conversion rules are known as residue definitions.

This module has as primary entities: *Substances*

Output of this module is used by: *Food concentrations*

### Substance conversions from data

### Substance conversions data formats

Two types of substance conversions are implemented, with two subtypes for the first type:

> 1a) The measured substance is one or more of a set of possible substances (e.g. isomers or metabolites), and the toxicity of all substances in this set is assumed to be the same and is expressed in one active substance. Example: The measured substance Parathion-methyl(RD) is either Parathion-methyl or paraoxon-methyl, but both are expressed as the active substance Parathion-methyl.
>
> 1b) The measured substance is one or more of a set of possible substances (e.g. isomers or metabolites), and the toxicity of all substances in this set is assumed to relate with equal probability to one of a subset of active substances. Example: The measured substance Dithiocarbamates includes the active substances maneb, mancozeb, metiram, propineb, thiram and ziram, one of which will be assumed to be the active substance present with equal probability.
>
> 2) If $n$ *active substances* all metabolise to the same active substance (the metabolite), it is assumed that all $n+1$ substances have equal probability of being the source of the measured concentration. The measured substance then is either one active substance (the metabolite) or a mixture of two active substances, one being the metabolite and the other one of the possible parent substances. Example: the measured substance Carbofuran(RD) is either the active substance Carbufuran or a mixture of Carbofuran and one of the possible active parent substances Benfuracarb or Carbosulfan.

Note, it is not allowed to have conversion factors equal to 0.

Substance conversions are described by a single substance conversions table.

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### Substance conversion rules

The records of the substance translations definitions table specify which active substances (idActiveSubstance) link to a measured substance (idMeasuredSubstance). Each record contains a conversion factor that specifies how a concentration of the measured substance translates to a concentration of the active substance, a flag that states whether the residue definition should be assumed to translate exclusively to one of its active substances, and a proportion. The proportion specifies the proportion of the samples that should translate to this specific active substance in case the translation is exclusive, otherwise it specifies the proportion of the concentration that is assumed to be attributed to the active substance.

Table 3.198: Table definition for Substance conversion rules.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idMeasured-Substance | AlphaNumeric (50) | Substance code of the measured substance. | idResidue-Definition, Residue-Definition, Measured-Substance | Yes |
| idActive-Substance | AlphaNumeric (50) | Substance code of the active substance. | idActive-Substance, idSubstance, Active-Substance, Substance | Yes |
| Conversion-Factor | Numeric | Specifies the (molecular weight) conversion factor to translate the concentration of the residue definition to a concentration of the active substance | Conversion-Factor | Yes |
| IsExclusive | Boolean | Specifies whether a measurement of the residue substance should be translated exclusively to this active substance, or if the residue definition represents/breaks down to a mixture of active substances. | IsExclusive | Yes |
| Proportion | Numeric | Only applicable for non-exclusive conversions. The proportion of the concentration that is assumed to be attributed to the active substance. | Proportion | No |

Accepted table names: ResidueDefinitions, ResidueDefinition.

#### Substance conversions as data

Substance conversions are provided as data.

- *Substance conversions data formats*
- *Substance conversions from data*

Inputs used: *Active substances*

### 3.3.25 Total diet study sample compositions

Total diet study sample compositions specify the composition of mixed food samples, such as used in a total diet study (TDS), in terms of their constituting foods.

This module has as primary entities: *Foods*

Output of this module is used by: *Food concentration models Food conversions*

#### Total diet study sample compositions from data

#### Total diet study sample compositions data formats

Total diet studies (TDS) complement traditional monitoring of substance concentrations on raw commodities by measuring substance occurrence in main foods prepared as consumed and pooled into representative food groups. To include occurrence data from TDS for exposure assessment, the composition of the TDS samples is needed in order to link the composite samples to the consumed foods (either directly or indirectly). TDS composition data describes the composition of TDS samples by specifying the foods (and the amounts) of TDS samples.

Download empty dataset template: Zipped CSV Excel

#### TDS food sample compositions

The TDS food sample compositions table contains the descriptions of the TDS samples and specifications of the foods (with amounts) included in the TDS samples.

Table 3.199: Table definition for TDS food sample compositions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idTDSFood | AlphaNumeric (50) | The code of the TDS food. | idTDSFood | Yes |
| idFood | AlphaNumeric (50) | Sub-food of the TDS food. | idFood | Yes |
| PooledAmount | Numeric | Total weight (in g) or volume (in ml) of the food. | PooledAmount, Weight | Yes |
| Description | AlphaNumeric (200) | Additional description of the TDS sample (e.g. number of subsamples). | Description | No |
| Regionality | AlphaNumeric (250) | Regionality information. | Regionality | No |
| Seasonality | AlphaNumeric (250) | Seasonality information. | Seasonality | No |

Accepted table names: TDSFoodSampleCompositions, TDSFoodSampleComposition, CompositionTDSFoodSamples, CompositionTDSFoodSample.

#### Total diet study sample compositions as data

Total diet study sample compositions are provided as data.

- *Total diet study sample compositions data formats*
- *Total diet study sample compositions from data*

### 3.3.26 Unit variability factors

Unit variability factors specify the variation in concentrations between single units of the same food, which have been put together in a mixture sample on which the concentration measurements have been made. Unit variability factors are used for *modelling unit variability* in acute *(individual) dietary exposures calculations* to account for the fact that concentration data often relate to composite samples, whereas an acute risk may result from consumption of single food units. For the same purpose, they are also used in the *IESTI model* for *single value dietary exposures calculations*.

This module has as primary entities: *Foods Substances*

Output of this module is used by: *Dietary exposures Single value dietary exposures*

#### Unit variability factors from data

#### Unit variability factors data formats

Unit variability factors specify the unit-to-unit variation of substance concentrations on foods. Unit variability factors are described by a single unit variability factors table.

Download empty dataset template: Zipped CSV Excel

### Unit variability factors

Unit variability factors are defined for a food, and may possibly also be specified for a specific substance and/or processing type. The unit variability factors are linked to the foods by means of the food code (idFood). Unit variability factors can be specified as unit variability factors (P97.5/mean) or as coefficients of variation of a statistical distribution.

Table 3.200: Table definition for Unit variability factors.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFood | AlphaNumeric (50) | The food code. | idFood, FoodId, Food | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | No |
| idProcessing-Type | AlphaNumeric (50) | The processing type code. | idProcessing-Type, ProcessingType-Id, ProcessingType, ProcType | No |
| Factor | Numeric | The variability factor. | Factor, VarFac, VariabilityFactor | No |
| UnitsIn-Composite-Sample | Numeric | The number of units in the composite sample. | UnitsIn-Composite-Sample, NoUnitComp | Yes |
| Coefficient | Numeric | The coefficient of variation. | Coefficient, Variability-Coefficient, CoefVar, VarCoef | No |

Accepted table names: UnitVariabilityFactors, UnitVariabilityFactor, VariabilityFactor, VariabilityFactors, VariabilityProcCompProd, UnitVariability.

### IESTI special cases

IESTI special cases for specified combinations of food, substance. The application type (post-harvest or pre-harvest) determines whether Case 1 or Case 3 should be used.

Table 3.201: Table definition for IESTI special cases.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idFood | AlphaNumeric (50) | The unique identification code of the food. | idFood, Code, FoodId, FoodCode, Food, Id | Yes |
| idSubstance | AlphaNumeric (50) | The unique identification code of the substance. This code may be from an existing coding system, such as CAS-codes or Param codes of EFSA, or it may be a used-defined code. | idSubstance, SubstanceId, Substance, Code, Id | Yes |
| Application-Type | *HarvestApplication-Type* | Harvest application type (pre-harvest or post-harvest). | Application-Type, Harvest-ApplicationType | Yes |
| Reference | AlphaNumeric (200) | External reference(s) to pre-harvest use. | Reference | No |

Accepted table names: IestiSpecialCases.

### Unit variability factors

### Calculation settings

Table 3.202: Calculation settings for module Unit variability factors.

| Name | Type | Description |
|---|---|---|
| Selected tier | SettingsTemplateType | Specifies all module settings should be set according to a pre-defined tier or using custom settings. |
| Unit variability model | *UnitVariabilityModelType* | Describes variation between single units when concentration da are from composite samples. |
| Estimates nature | *EstimatesNature* | Simulated unit concentrations can be higher or lower than composite value (realistic) or only equal or higher (conservative |
| Unit variability parameter | *UnitVariabilityType* | Use Coefficient of variation or Variability factor, specified in VariabilityFactor table. |
| Mean of LogNormal simulated values (biasing) | *MeanValueCorrectionType* | Unbiased: correct unit simulations for difference between medi and mean. |
| Default variability factor for unit weight <= 25g | Numeric | Default variability factor 1 (unit weight <= 25 g, small crops). S requires specification of unit weight (FoodProperties table) and case of beta model, also the Number of units in a composite sample (UnitVariability table). |
| Correlation between substances on the same units | *UnitVariabilityCorrelationType* | Specifies the type of correlation between substances on the sam units; no correlation or full correlation. |
| Default variability factor for unit weight > 25g | Numeric | Default variability factor 5 (unit weight > 25 g, medium/large crops). Still requires specification of unit weight (FoodPropertie table) and, in case of beta model, also the Number of units in a composite sample (UnitVariability table). |

### Unit variability factors tiers

### Overview

Table 3.203: Tier overview for module Unit variability factors.

| N | EC 2018 Acute Tier I | EC 2018 Acute Tier II | EFSA 2012 Acute Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Acute Tier II | EFSA 2023 Acute Prospective Tier II | EFSA 2024 Acute Prospective Tier II |
|---|---|---|---|---|---|---|---|
| U va al it m | BetaDistribution | BetaDistribution | BetaDistribution | BetaDistribution | BetaDistribution | BetaDistribution | BetaDistribution |
| E ti m na tu | Realistic | Realistic | Realistic | Realistic | Realistic | Realistic | Realistic |
| U va al it pa ra e- te | VariabilityFactor | VariabilityFactor | VariabilityFactor | VariabilityFactor | VariabilityFactor | VariabilityFactor | VariabilityFactor |

### Retrospective dietary CRA (EC 2018) - Acute / Tier I

Table 3.204: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier I.

| Name | Setting |
|---|---|
| Unit variability model | BetaDistribution |
| Estimates nature | Realistic |
| Unit variability parameter | VariabilityFactor |

### Retrospective dietary CRA (EC 2018) - Acute / Tier II

Table 3.205: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier II.

| Name | Setting |
|---|---|
| Unit variability model | BetaDistribution |
| Estimates nature | Realistic |
| Unit variability parameter | VariabilityFactor |

### Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic

Acute probabilistic exposure assessment using the pessimistic model settings according to the EFSA Guidance 2012. Only processing factors > 1 are applied. For unit variability, the Beta distribution is applied.

Table 3.206: Tier definition for Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic.

| Name | Setting |
|---|---|
| Unit variability model | BetaDistribution |
| Estimates nature | Realistic |
| Unit variability parameter | VariabilityFactor |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier I

Table 3.207: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier I.

| Name | Setting |
|---|---|
| Unit variability model | BetaDistribution |
| Estimates nature | Realistic |
| Unit variability parameter | VariabilityFactor |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier II

Table 3.208: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier II.

| Name | Setting |
|---|---|
| Unit variability model | BetaDistribution |
| Estimates nature | Realistic |
| Unit variability parameter | VariabilityFactor |

### Prospective dietary CRA (EFSA 2023) - Acute / Tier II

Table 3.209: Tier definition for Prospective dietary CRA (EFSA 2023) - Acute / Tier II.

| Name | Setting |
|---|---|
| Unit variability model | BetaDistribution |
| Estimates nature | Realistic |
| Unit variability parameter | VariabilityFactor |

### Prospective dietary CRA (EFSA 2024) - Acute / Tier II

Table 3.210: Tier definition for Prospective dietary CRA (EFSA 2024) - Acute / Tier II.

| Name | Setting |
|---|---|
| Unit variability model | BetaDistribution |
| Estimates nature | Realistic |
| Unit variability parameter | VariabilityFactor |

#### Unit variability factors as data

Unit variability factors are provided as data.

- *Unit variability factors data formats*
- *Unit variability factors from data*

Settings used

- *Calculation Settings*

## 3.4 Exposure modules

*Exposures* are, in the simplest applications, *dietary exposures*, which combine consumption and occurrence data, either for single or for multiple *substances* causing the same adverse *effect*. Links between the foods-as-eaten and the *modelled foods* are made using *food conversions*, and the consumptions are expressed as *consumptions per modelled food*. For large assessment groups, the use of *dietary exposures screening* may be used to reduce the complexity of the calculations and only focus calculations on the risk drivers.

In aggregate exposure assessments, *exposures* combine *dietary exposures* with *non-dietary exposures*, which have to be entered as pre-calculated data.

*Human monitoring data* can be compared to *exposures* using *human monitoring analysis*.

In cumulative assessments, important mixtures of *substances* can be identified using *exposure mixtures*.

### 3.4.1 Consumptions by modelled food

Consumptions by modelled food are consumptions of individuals expressed on the level of the foods for which concentration data are available (i.e., the modelled-foods). These are calculated from consumptions of foods-as-eaten and food conversions that link the foods-as-eaten amounts to modelled-foods amounts.

This module has as primary entities: *Populations Foods Substances*

Output of this module is used by: *Single value consumptions High exposure food-substance combinations Dietary exposures*

#### Consumptions by modelled food calculation

Consumptions by modelled food are calculated from *consumptions* of *modelled foods* and *food conversions* that link the foods-as-eaten amounts to modelled-foods amounts. Given that the food conversion is already available, the procedure for computing the consumptions by modelled-food is straightforward. For each consumption of each individual, a modelled-food consumption record is created for each modelled-food that is linked to the consumed foods through the food conversion, with the amount being the total consumption amount multiplied by the proportion indicated by the food conversion. Also, if in the *food conversion algorithm* one or more *processing types* are found, then these types are recorded in the consumption by modelled food record.

#### Consumptions by modelled food settings

### Calculation settings

Table 3.211: Calculation settings for module Consumptions by modelled food.

| Name | Type | Description |
|---|---|---|
| Restrict population to consumers or consumer days only (food-as-measured) | Boolean | Specifies whether the population should be restricted to the individuals (chronic) or individual days (acute) with consumptio containing any of the modelled foods. |
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Restrict population to consumers or consumer days with consumptions of specified modelled foods only | Boolean | Specifies whether the population should be restricted to the individuals (chronic) or individual days (acute) with consumptio containing any of the specified modelled food subset. |
| Selected modelled foods | AlphaNumeric | Set of consumed modelled foods that are of particular interest f restricting the consumers / consumption days. |
| Apply processing factors | Boolean | Specified in table ProcessingFactor. If checked, processing fact are applied. Concentrations in the consumed food may be different from concentrations in the modelled food in monitorin programs (typically raw food) due to processing, such as peelin washing, cooking etc. If unchecked, no processing information used. This is in most (though not all) cases a worst-case assumption |

### Output settings

Table 3.212: Output settings for module Consumptions by modelled food.

| Name | Type | Description |
|---|---|---|
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |

### Calculation of consumptions by modelled food

Consumptions by modelled food are calculated from consumptions of foods-as-eaten and food conversions that link the foods-as-eaten amounts to modelled-foods amounts.

- *Consumptions by modelled food calculation*

Inputs used: *Consumptions Food conversions*

Settings used

- *Calculation Settings*

## 3.4.2 Dietary exposures

Dietary exposures are the amounts of substances, expressed per kg bodyweight or per individual, to which individuals in a population are exposed from their diet per day. Depending on the exposure type, dietary exposures can be short-term/acute exposures and then contain exposures for individual-days, or they can be long-term/chronic exposures, in which case they represent the average exposure per day over an unspecified longer time period.

This module has as primary entities: *Populations Foods Substances Effects*

Output of this module is used by: *Internal exposures Exposure mixtures Dust exposures Soil exposures Air exposures Risks Environmental burden of disease*

### Dietary exposures calculation

In probabilistic exposure assessment we consider a population of individuals. Exposure assessment with MCRA can address *acute exposure* or *chronic exposure*. Acute exposure is relevant when the short-term effect on individuals is relevant, chronic exposure when the long-term effects on the individuals matter. In MCRA short-term is operationalised as one day, so effectively acute exposure assessment is concerned with a population of person-days, whereas chronic exposure assessment is concerned with a population of persons.

The basic operation in exposure assessment is integrating consumptions and concentrations per food. With multiple foods, consumptions are typically correlated, therefore MCRA works with the multivariate distribution of a consumption vector, as represented by the consumption data of individuals in a consumption survey. In contrast, the distributions of concentration for each food are typically considered to be independent between foods. E.g., eating an apple with an accidentally high residue concentration does not predict that another food eaten on the same day will also have a high residue concentration. As a consequence of this assumption, concentrations of substances are modelled for each food independently.

For large assessment groups, the use of *dietary exposures screening* may be used to reduce the complexity of dietary exposures calculations and only focus calculations on the risk drivers. In this case, only detailed information is recorded for the risk drivers. With or without screening MCRA produces the same estimated cumulative exposure distribution summarized by percentiles and exceedance percentages, the same contributions of all substances and all modelled foods. After screening, contributions related to food-as-eaten are available for the risk drivers only.

In cumulative exposure calculations two simple approaches are used to identify and select mixtures contributing to the exposure of a target population:

1. qualitative approach: *counting of co-exposure*. To which combinations of substances are individuals exposed?

   Co-exposure of substances is a qualitative approach where the number of combinations of substances to which an individual is exposed is recorded. There is no cut-off level, the only criterion is the presence of a substance in the simulated daily diet or not. For an *acute* or short term exposure assessment, a simulated individual day is the smallest entity to determine co-exposure. For a *chronic* or long term exposure assessment, co-exposures are summarized at the individual level, e.g. co-exposure is determined combining all consumption days of an individual. For more information see *co-exposure of substances*.

2. quantitative approach: *maximum cumulative ratio (MCR)*. To what degree are mixtures more important than single substances?

For a quantitative approach, see also the *exposure mixtures module*.

### Acute exposure assessment

In an acute exposure assessment, the short term exposure to a substance or group of substances is estimated. The interest is in the distribution of individual day exposures and derived statistics like the fraction of days that exceed an intake limit or point of departure (*PoD*). The PoD is calculated as the acute reference dose (ARfD) * safety factor (SF). The basic model for the exposure to a substance in an acute exposure assessment is:

$$y_{ij} = \frac{\sum_{k=1}^{p} x_{ijk} c_{ijk}}{bw_i}$$

where $y_{ij}$ is the intake by individual $i$ on day $j$ (in microgram substance per kg body weight), $x_{ijk}$ is the consumption by individual $i$ on day $j$ of food $k$ (in g), $c_{ijk}$ is the *(simulated) concentration* of that substance in food $k$ eaten by individual $i$ on day $j$ (in mg/kg), and $bw_i$ is the body weight of individual $i$ (in kg). Finally, $p$ is the number of foods accounted for in the model. Within parenthesis, the default unit definitions are assumed, but decimal multiples or submultiples of units are easily specified using the relevant tables.

In the exposure assessment, individual days enter the Monte Carlo sample using the inverse of the sampling weights $w_i$ when the number of MC iterations is > 0 (see *table for Individuals*, field *SamplingWeight*).

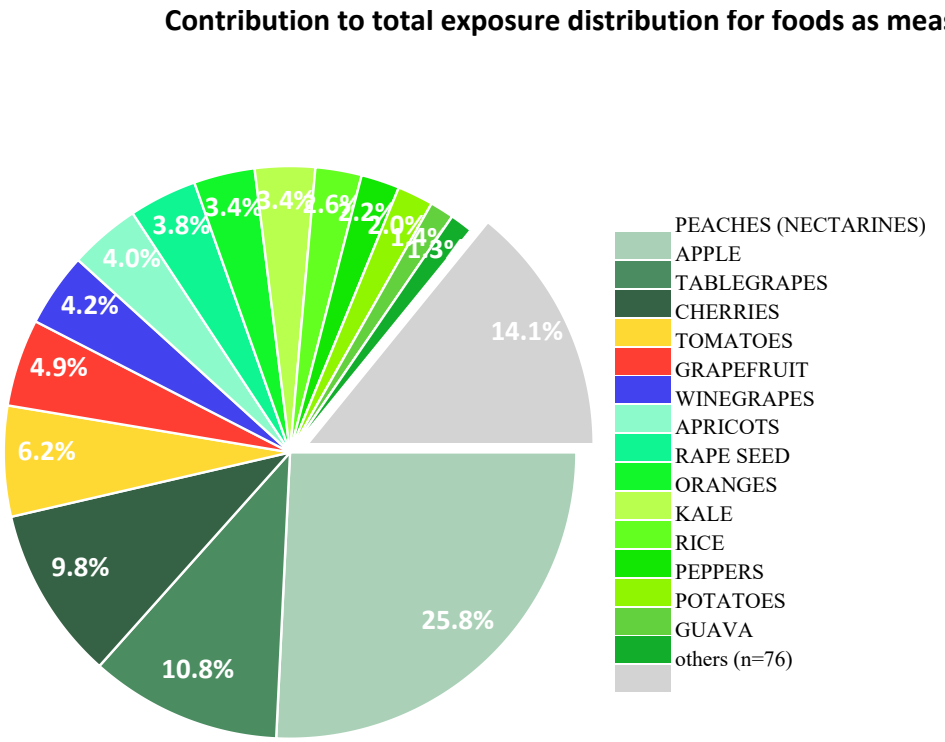


Figure 3.29: Example MCRA dietary exposure contributions modelled foods.

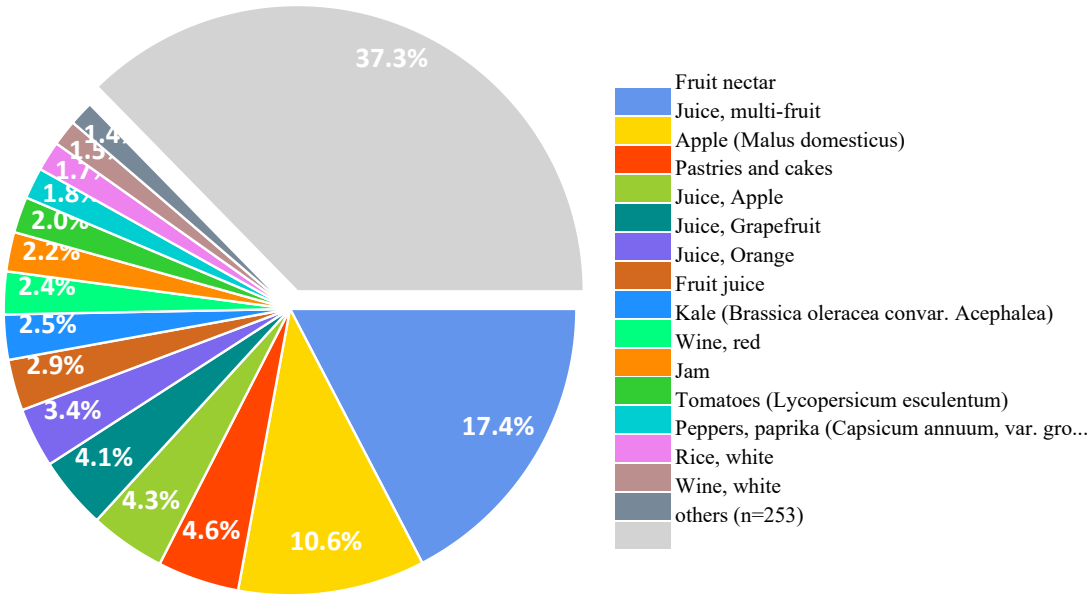


Figure 3.30: Example MCRA dietary exposure contributions foods as eaten

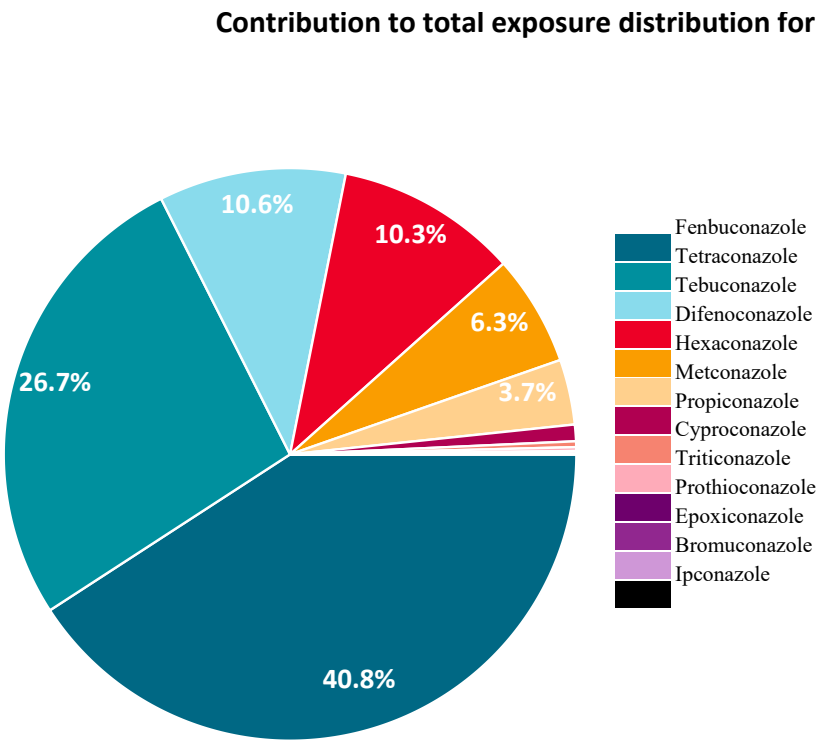


Figure 3.31: Example MCRA dietary exposure contributions substances

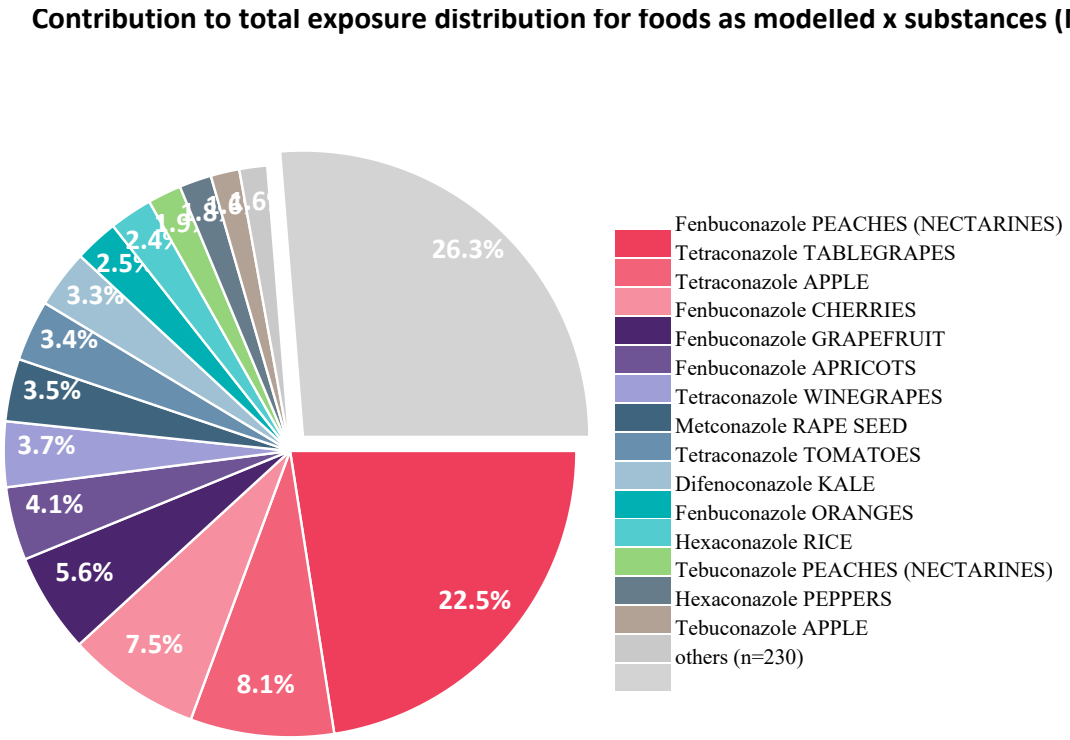


Figure 3.32: Example MCRA dietary exposure contributions modelled foods x substances

### Modelling unit-to-unit variation

The basic model for an acute exposure assessment assumes that the concentration of the substance displays the variation of residues between units in the marketplace. In general, both monitoring data and controlled field trial data are obtained using composite samples. As a result some of the unit-to-unit variation is averaged out. The model for unit variability aims to adjust the composite sample mean such that sampled concentrations represent the originally unit-to-unit variation of the units in the composite sample.

MCRA offers three distributions to sample from:

1. the *beta distribution*,
2. the *lognormal distribution*,
3. and the *bernoulli distribution*.

The beta distribution simulates values for a unit in the composite sample. It requires knowledge of the number of units in a composite sample and of the variability between units.

The lognormal distribution simulates values for a new unit in the batch. It requires only knowledge of the variability between units.

The bernoulli distribution is considered as a limiting case of the beta distribution when knowledge of the variability between units is lacking and only the number of units in the composite sample is known. For the beta and lognormal distribution, estimates of unit variability are either realistic (no censoring at the value of the monitoring residue) or conservative (unit values are left-censored at the value of the monitoring residue). For the lognormal distribution sampled concentrations have no upper limit. Whereas for the beta distribution, sampled concentration values for a unit are never higher than the monitoring residue times the number of units in the composite sample.

Variability between units is specified using a variability factor $v$ (defined as 97.5th percentile divided by mean) or a coefficient of variation $c_v$ (standard deviation divided by mean). Following FAO/WHO recommendations, the default variability factor $v$ = 1 for small crops (unit weight < 25 g). For large crops (unit weight ≥ 25 g) $v$ = 5. For foods which are processed in large batches, e.g. *juicing, marmalade/jam, sauce/puree, bulking/blending* the variability factor $v$ = 1 is proposed.

### Estimation of intake values using the concept of unit variability

A composite sample for food $k$ is composed of $nu_k$ units with *nominal (whole food/RAC) unit weight* $wu_k$. The weight of a composite sample is $wm_k = nu_k \cdot wu_k$ with mean residue value $cm_k$.

- For each iteration $i$ in the MC-simulation, obtain for each food k a simulated intake $x_{ik}$, and a simulated composite sample concentration $cm_{ik}$.
- Calculate the number of unit intakes $nux_{ik}$ in $x_{ik}$ (round upwards) and set weights $w_{ikl}$ equal to unit weight $wu_k$, except for the last partial intake, which has weight $w_{ikl} = x_{ik} - (nux_{ik} - 1)wu_k$ .
- For the beta or bernoulli distribution: draw $nux_{ik}$ simulated values $bc_{ikl}$ from a beta or bernoulli distribution. Calculate concentration values as $c_{ikl} = bc_{ikl} \cdot cm_{ik,max} = bc_{ikl} \cdot cm_{ik} \cdot nu_k = svf_{ikl} \cdot cm_{ik}$, where $nu_k$ is the number of units in a composite sample of food $k$, and $svf_{ikl}$ is the stochastic variability factor for this simulated unit, i.e. the ratio between simulated concentration $c_{ikl}$ and the simulated composite sample concentration $cm_{ik}$. Sum to obtain the simulated concentration in the consumed portion:

$$c_{ik} = \sum_{l=1}^{nux_{ik}} w_{ikl} c_{ikl} / x_{ik}$$

- For the lognormal distribution: draw $nux_{ik}$ simulated logconcentration values $lc_{ikl}$ from a normal distribution with (optional) a biased mean $\mu = ln(cm_{ik})$ or (default) unbiased mean $\mu = ln(cm_{ik}) - 1/2\sigma^2$ and standard deviation $\sigma$. Calculate concentration values as

$$c_{ikl} = \exp(lc_{ikl}) = svf_{ikl} * cm_{ik}$$

where $svf_{ikl}$ is the stochastic variability factor for this simulated unit, i.e. the ratio between simulated concentration $c_{ikl}$ and the simulated composite sample concentration $cm_{ik}$. Back transform and sum to obtain the simulated

concentration in the consumed portion:

$$c_{ik} = \sum_{l=1}^{nux_{ik}} w_{ikl} c_{ikl} / x_{ik}$$

For cumulative exposure assessments, a sensitivity analysis may be performed by specifying a full correlation between concentrations from different substances on the same unit. As a result, high (or low) concentrations from different substances occur together on the same unit. In MCRA, for each unit the random sequence is repeatedly used to generate concentration values for all substances.

### Beta distribution

Under the beta model simulated unit values are drawn from a bounded distribution on the interval (0, $c_{max}$) with $c_{max} = nu_k \cdot cm_k$. The standard beta distribution is defined on the interval (0, 1) and is usually characterised by two parameters $a$ and $b$, with $a > 0$, $b > 0$ (see e.g. Mood et al. (1974)). Alternatively, it can be parameterised by the mean

$$\mu = a/(a+b)$$

and the variance

$$\sigma^2 = ab/(a+b+1)^{-1}(a+b)^{-2}$$

or, as applied in MCRA, by the mean $\mu$ and the squared coefficient of variation

$$c_v^2 = ba^{-1}(a+b+1)^{-1}$$

For the simulated unit values in *each iteration of the program* we require an expected value $cm_k$. This scales down to a mean value $\mu = cm_k/c_{max} = 1/nu_k$ in the (standard) beta distribution. From this value for $\mu$ and an externally specified value for $cv_k$ the parameters $a$ and $b$ of the beta distribution are calculated as:

$$a = b(nu_k - 1)^{-1}$$

and

$$b = \frac{(nu_k - 1)(nu_k - 1 - cv_k^2)}{nu_k cv_k^2}$$

From the second formula it can be seen that $cv_k$ should not be larger than $\sqrt{nu_k - 1}$ in order to avoid negative values for $b$. When the unit variability is specified by a variability factor

$$v_k = \frac{p97.5_k}{cm_k}$$

instead of a coefficient of variation $cv_k$ then MCRA applies a bisection algorithm to find a such that the cumulative probability

$$P[Beta(a,b)] = 0.975$$

for $b = a(nu_k - 1)$.

Sampled values from the beta distribution are rescaled by multiplication with $cm_{max}$ to unit concentrations $c_{ijk}$ on the interval $(0, cm_{max})$.

### Lognormal distribution

The lognormal distribution is characterised by $\mu$ and $\sigma$, which are the mean and standard deviation of the log-transformed concentrations. The unit log-concentrations are drawn from a normal distribution with mean $\mu = ln(cm_{ik}) - 1/2\sigma^2$. The coefficient of variation $cv$ is turned into the standard deviation $\sigma$ on the log-transformed scale with:

$$\sigma = \sqrt{ln(cv^2 + 1)}$$

The variability factor is defined as the 97.5th percentile of the concentration in the individual measurements divided by the corresponding mean concentration seen in the composite sample. A variability factor $v$ is converted into the standard deviation $\sigma$ as follows:

$$v = \frac{p97.5}{mean} = \frac{e^{\mu+1.96\sigma}}{e^{\mu+1/2\sigma^2}} = e^{1.96\sigma-1/2\sigma^2}$$

with $\mu$ and $\sigma$ representing the mean and standard deviation of the log-transformed concentrations. So

$$ln(v) = 1.96\sigma–1/2\sigma^2$$

Solving for $\sigma$ gives:

$$\sigma^2–2 \cdot 1.96\sigma + 2log(v) = 0$$

with roots for $\sigma$ according to:

$$\sigma = 1.96 \pm \sqrt{(1.96^2–2log(v))}$$

The smallest positive root is taken as an estimate for $\sigma$.

### Bernoulli distribution

The bernoulli model is a limiting case of the beta model, which can be used if no information on unit variability is available, but only the number of units in a composite sample is known (see van der Voet et al. 2001). As a worst case approach we may take the coefficient of variation $cv$ as large as possible. When $cv$ is equal to the maximum possible value $\sqrt{nu_k - 1}$, the (unstandardised) beta distribution simplifies to a bernoulli distribution with probability

$$(nu_k–1)\,/nu_k$$

or

$$(v_k - 1)/v_k$$

for the value 0 and probability

$$1/nu_k$$

or

$$1/v_k$$

for the value $c_{max} = nu_k \cdot cm_k$.

In MCRA values 0 are actually replaced by $cm_k$, to keep all values on the conservative side. For example, with $nu_k$ = 5, there will be 80% probability at $c_{ijk} = cm_k$ and 20% probability at $c_{ijk} = c_{max}$. When the number of units $nu_k$ in the composite sample is missing, the nominal unit weight $wu_k$ is used to calculate the parameter for unit variability.

### Chronic exposure assessment

In a chronic exposure assessment, usual exposure is defined as the long-run average of daily exposure to a substance or group of substances by an individual. The interest is in the distribution of individual exposures and derived statistics like the fraction of individuals that exceed an intake limit or point of departure *PoD*). The PoD is calculated as the average daily intake (ADI) * safety factor (SF). Usually, for an individual, dietary recall data are available on 2 (or more) consecutive days. We assume an equal number of days for each individual, unless specified differently in *table for Individuals*.

For a chronic exposure assessment the available data are used to calculate exposures per person-day (daily exposure):

$$y_{ij} = \frac{\sum_{k=1}^{p} x_{ijk} c_{ijk}}{bw_i}$$

where $y_{ij}$, $x_{ijk}$ and $bw_i$ are defined as before but now concentrations of the substance found in food $k$ enter the model as the *estimated mean substance concentration value* $c_k$. Using the person-day exposures MCRA, provides a number of *exposure models* to calculate the distribution of usual exposure at the person level.

### Chronic exposure models

Using the person-day exposures MCRA uses one of the following models to calculate the distribution of usual exposure at the person level:

1. The observed individual means *observed individual means* (OIM) model;
2. The *logisticnormal-normal (LNN) model*, in a full version that includes the estimation of correlation between exposure frequency and amount, and in a simpler version without this estimation;
3. The *betabinomial-normal* (BBN) model;
4. The *discrete/semi-parametric* model known as the Iowa State University Foods (ISUF) model. For this model, an equal number of days per individual is assumed.

In modelling usual exposure, two situations can be distinguished. Foods are consumed on a *daily basis* or foods are *episodically consumed*. For the logisticnormal-normal model and the betabinomial-normal model, the latter requires fitting of a two-part model,

1. a model for the frequency of consumption, and
2. a model for the exposure amount on consumption days.

In the final step, both models are integrated in order to obtain the usual exposure distribution. For daily consumed foods, fitting of the frequency of consumption is skipped and modelling resorts to fitting the model to daily exposure amounts only. Note that the distinction between BNN and LNN disappears and modelling will give equivalent results.

### Observed individual means (OIM)

The usual exposure distribution for a population is estimated with the empirical distribution of individual means. Each mean is the average of all single-day exposures for an individual. The mean value for an individual still contains a considerable amount of within-individual variation. As a consequence, the distribution of within-individual means has larger variance than the true usual exposure distribution and estimates using the OIM-method are biased, leading to a too high estimate of the fraction of the population with a usual exposure above some standard. Despite its known tendency to over-estimate high-tail exposures, the OIM method is the method to be used in EFSA (2012) basic assessments.

### Model based and model assisted

Following Kipnis et al. (2009), some of the models available in MCRA are extended to predict individual usual exposures. This model assisted approach has been added to BBN and LNN when used without correlation) and may be a useful extension in evaluating the relationship between health outcomes and individual usual exposures of foods. In contrast, the estimation of the usual exposure distribution in the general population is called the model based approach. Summarizing, we get Table 3.213:

Table 3.213: Model based and assisted approach available for chronic exposure models

| Model based approach | Model assisted approach |
|---|---|
| | observed individual means (OIM) |
| betabinomial-normal (BBN) | betabinomial-normal (BBN) |
| logisticnormal-normal (LNN) without correlation | logisticnormal-normal (LNN) without correlation |
| logisticnormal-normal (LNN) with correlation | |
| Iowa State University Foods (ISUF) | |

The model assisted approach builds on the proposal of Kipnis et al. (2009), but is modified to ensure that the population mean and variance are better represented. The method is based on shrinkage of the observed individual means (modified BLUP estimates) and shrinkage of the observed exposure frequencies. The model-assisted usual exposure distribution applies to the population for which the consumption data are representative, and automatically integrates over any covariates present in the model. Model-assisted exposures are not yet available for LNN, and when a covariable is modelled by a spline function of degree higher than 1. In case of a model with covariates the usual exposure is presented in graphs and tables as a *function of the covariates* (conditional usual exposure distributions).

### Betabinomial-Normal model (BBN)

The *Betabinomial-Normal (BBN)* model for chronic risk assessment is described in de Boer et al. (2009), including its near-identity to the STEM-II model presented in Slob (2006). The BBN model combines a betabinomial model for the exposure frequencies with a normal model for transformed positive exposures.

### Logisticnormal-Normal model (LNN with and without correlation)

In the logisticnormal-normal (LNN) model, exposure frequencies are modelled by a logistic normal distribution. In notation, for probability $p$:

$$\text{logit}(p) = \log(p/1-p) = \mu_i + \underline{c}_i$$

where $\mu_i$ represents the person specific fixed effect model and $\underline{c}_i$ represent person specific random effects with estimated variance component $\sigma^2_{between}$. Similarly as in the BBN model, the positive exposure amounts are modelled, after transformation (logarithmic or *Box-Cox* ), with a normal distribution. This model is referred to as the *LogisticNormal-Normal (LNN)* model. The full *LNN model* model includes the estimation of a correlation between exposure frequency and exposure amount. This is similar to the NCI model described in Tooze et al. (2006). A simple and computationally less demanding version of the LNN method does not estimate the correlation between frequency and amount. The models are fitted by maximum likelihood, employing *Gauss-Hermite integration*.

For chronic models amounts are usually transformed before the statistical model is fit. The power transformation, given by $y^p$, has been replaced by the equivalent Box-Cox transformation. The Box-Cox transformation is a linear function of the power transformation, given by $(y^p - 1)/p$, and has a better numerical stability. *Gauss-Hermite integration* is used for back-transformation (see also *Box Cox power transformation*).

### Discrete/semi-parametric model (ISUF)

Nusser et al. (1996) described how to assess chronic risks for data sets with positive exposures (a small fraction of zero exposures was allowed, but then replaced by a small positive value). The modelling allowed for heterogeneity of variance, e.g. the concept that some people are more variable than others with respect to their consumption habits. However, a disadvantage of the method was the restricted use to contaminated foods which were consumed on an almost daily basis, e.g. dioxin in fish, meat or diary products. The estimation of usual exposure from data sets with a substantial amount of zero exposures became feasible by modelling separately zero exposure on part or all of the days via the estimation of exposure probabilities as detailed in Nusser et al. (1997) and Dodd (1996). In MCRA, a discrete/semi-parametric model is implemented allowing for zero exposure and heterogeneity of variance following the basic ideas of Nusser et al. (1996), Nusser et al. (1997) and Dodd (1996). This implementation of the ISUF model for chronic risk assessment is fully described in de Boer et al. (2009).

### Model-Then-Add

The traditional approach can be termed the Add-Then-Model approach, because adding over foods precedes the statistical modelling of usual exposure. MCRA offers, as an advanced option, an alternative approach termed Model-Then-Add (van der Voet et al. (2014)). In this approach the statistical model is applied to subsets of the diet (single foods or food groups), and then the resulting usual exposure distributions are added to obtain an overall usual exposure distribution. The advantage of such an approach is that separate foods or food groups may show a better fit to the normal distribution model as assumed in all common models for usual exposure (including MCRA's *betabinomial-normal* (BBN) model and *logisticnormal-normal* model (LNN)). That this principle can work in practice was shown in previous work (de Boer et al. (2009), Slob et al. (2010), Goedhart et al. (2012)) and a simulation model was developed and implemented in MCRA 7.1 to show how multimodal distributions can arise from adding unimodal distributions of foods that are not always consumed (Slob et al. (2010), de Boer and van der Voet (2011)). For specific cases involving separate modelling of dietary supplements and the rest of the diet, proposals have been made (Verkaik-Kloosterman et al. (2011)). However, a practical approach to apply the Model-Then-Add approach to general cases of usual exposure estimation was still missing. Therefore a module in MCRA was developed to implement such an approach based on a visual inspection of a preliminary estimate of the usual exposure distribution using the *Observed Individual Means* (OIM) method.

### The Model step

At this stage of development the division of foods into a number of food groups is performed in an interactive process, where the MCRA user is presented with a visual display (see example in Figure 3.33) which shows:

1. The OIM distribution represented as a histogram, where each bar shows the frequency of exposures (summed over foods) of individuals in a certain exposure interval; each bar is subdivided according to the contributions of the individual foods contributing to those exposures (left panel Figure 3.33).
2. The contributions graph, where each of the bars in the OIM histogram is expanded to 100%. This graph allows a better view of the lower bars in the OIM histogram.

The visual display identifies the nine foods that contribute most to the total exposure; the remaining foods are grouped in a rest category to avoid identification problems because of too many colours (right panel Figure 3.33).

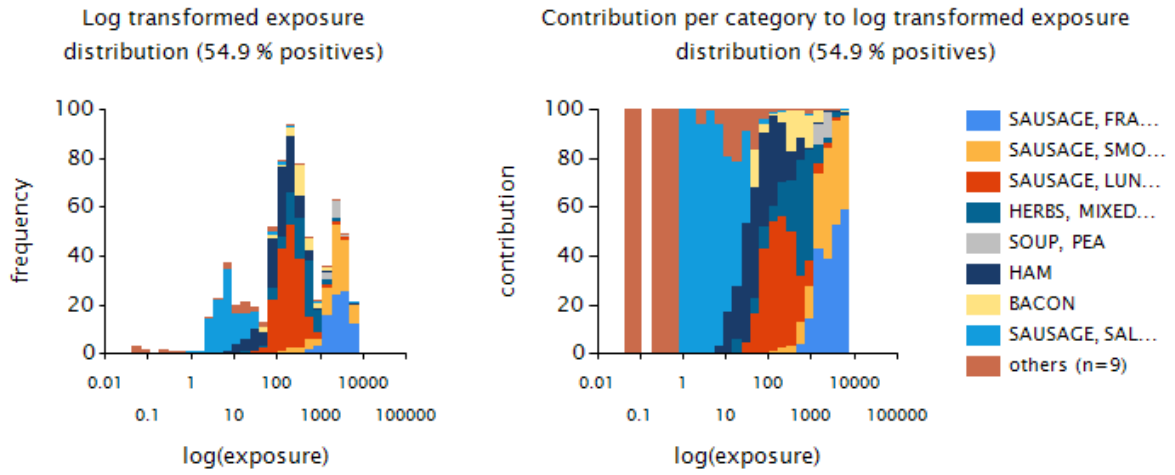


Figure 3.33: Left panel: OIM usual exposure distribution to smoke flavours via the different foods (excluding the zero exposures) in young children; right panel: Contribution of foods to exposures within each bar of the OIM distribution histogram.

The user has now the possibility to select one or more foods and to split these from the main exposure histogram. A separate graph shows the OIM distribution for the split-off food or food group. The graphs for the main group (now called the rest group) are adapted to show the OIM distribution and the contributions for the remaining foods only (see Figure 3.34 upper two panels). This splitting-off can be repeated several times for other foods or food groups. In this way the user can try to obtain foods or food groups that show unimodal OIM distributions. If the result is not what is intended, a food or food group can be added again to the rest group. Per split-off food or food group the usual exposure can be modelled using either BBN or LNN, with a logarithmic or power transformation. The rest group will always be modelled as OIM. It is possible that the rest group is empty, when the total exposure via the different split-off foods and /or food groups is modelled with BBN or LNN.

After a split-off selection has been made, the OIM distribution is summarised in terms of the defined grouping (Figure 3.35), and the usual exposure distribution per split-off food or food group is fitted according to the chosen modelling settings.

### The Add step

Consumptions of foods may be correlated. In the traditional Add-Then-Model approach the Add step automatically reflects any correlations that are apparent in the consumptions at the individual-day or individual level. In the Model-Then-Add approach the estimated usual exposure distributions for different foods or food groups have to be combined to assess the total usual exposure. Two approaches are available for this:

1. *Model-based approach*: adds independent samples from the usual exposure distribution per food or food group, ignoring any correlations in consumption;
2. *Model-assisted approach*: adds the model-assisted, person-specific usual exposure estimates per food or food group, taking correlations in consumptions into account.

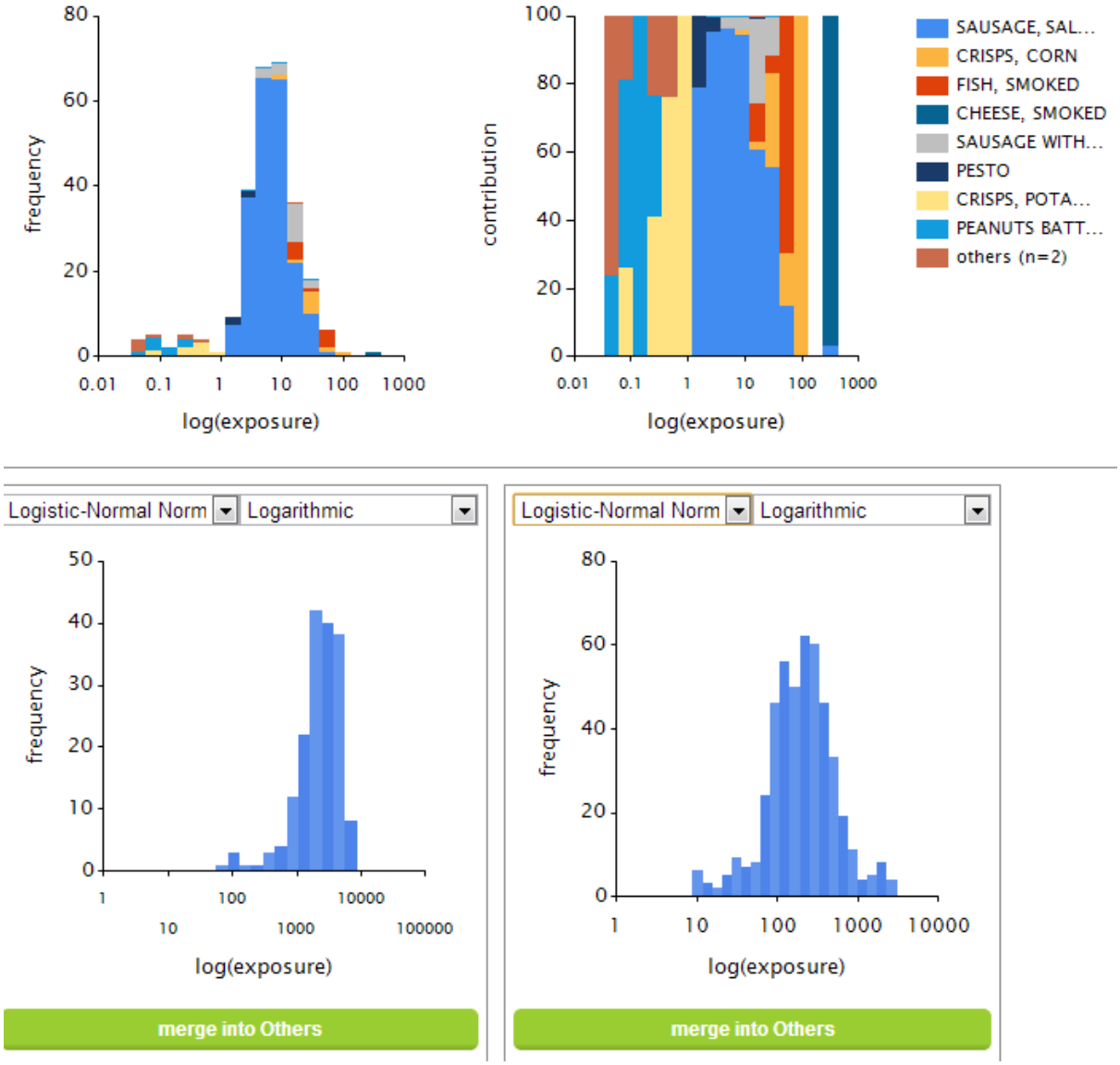


Figure 3.34: Result of a selection into two split-off groups and a rest group. The graph bottom left represents the exposure via a food group containing *'Sausage, frankfurter'* and *'Sausage, smoked cooked'*. The graph bottom right represents the exposure via a food group containing *'Sausage, luncheon meat', Herbs, mixed, main brands, not prepared', 'Soup, pea', 'Ham', and 'Bacon'*. The top graph represents the exposure via the rest group.

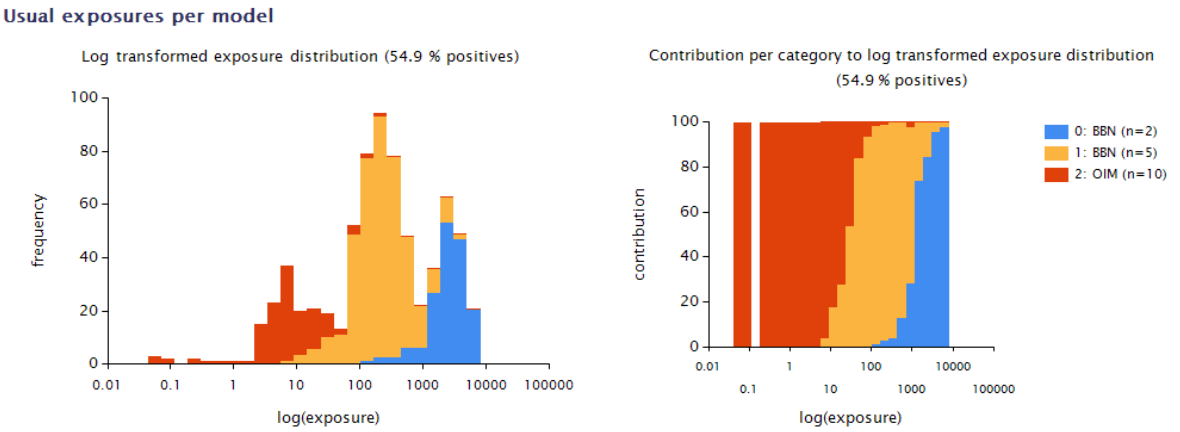


Figure 3.35: OIM usual exposure distribution showing the contributions from the three food groups as constructed in Figure 3.34.

See also, *episodically consumed foods, model-based, model-assisted*.

Before the addition is made, in the model-based approach, model-based estimates of the usual exposure amounts distribution per food or food group are back-transformed values from the normal distribution assumed for transformed amounts per food or food group, and the *model-based frequency* distribution is sampled to decide if a simulated individual has exposure via the food or food group or not. Model-assisted estimates of the usual exposure distribution are back-transformed values from a shrunken version of the transformed OIM distribution, also done per food or food group, where the shrinkage factor is based on the variance components estimated using the linear mixed model for amounts at the transformed scale (van Klaveren et al. (2012)). For individuals with no observed exposure (OIM=0) no model-assisted estimate of usual exposure can be made and a model-based replacement is used.

The model-based approach was investigated in Slob et al. (2010) and performed surprisingly well, even if correlations in consumptions of foods were present. The model-assisted approach adds exposures at the individual level, and therefore retains effects of correlations between foods in the usual exposure distribution.

MCRA calculates both the model-based and model-assisted usual intake distributions.

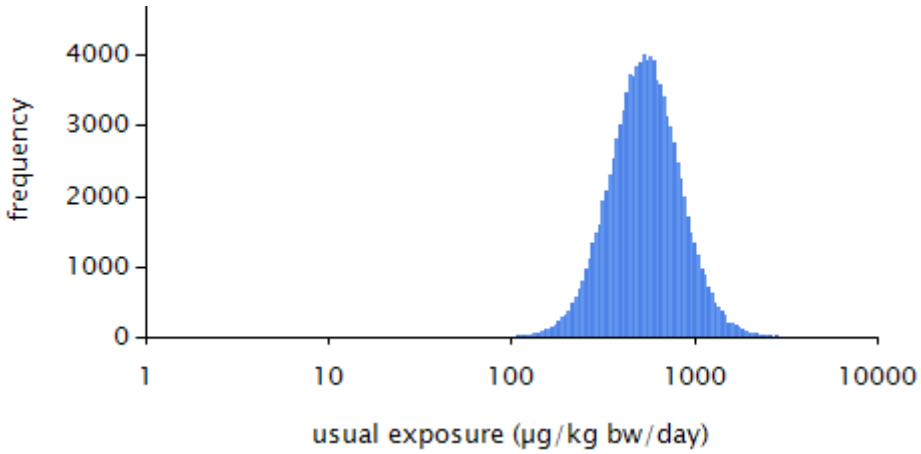


Figure 3.36: Model-assisted estimated usual exposure distributions (excluding the zero exposures).

### Chronic exposure as a function of covariates

The intake frequency and transformed intake amounts may be modelled as a function of covariates. MCRA allows one covariable and/or one cofactor.

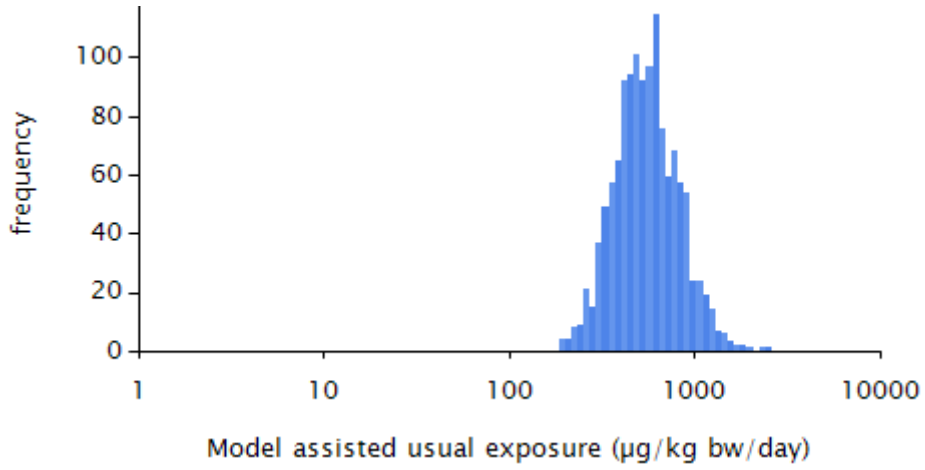


Figure 3.37: Model-based estimated usual exposure distributions (excluding the zero exposures).

Table 3.214: Intake frequencies and amounts, modelled as a function of covariates.

| | Frequencies | Amounts |
|---|---|---|
| cofactor | $logit(\pi) = \beta_{0l}$ | $transf(y_{ij}) = \beta_{0l} + c_i + u_{ij}$ |
| covariable | $logit(\pi) = \beta_0 + \beta_1 f(x_1; df)$ | $transf(y_{ij}) = \beta_0 + \beta_l f(x_1; df) + c_i + u_{ij}$ |
| both | $logit(\pi) = \beta_{0l} + \beta_1 f(x_1; df)$ | $transf(y_{ij}) = \beta_{0l} + \beta_l f(x_1; df) + c_i + u_{ij}$ |
| interaction | $logit(\pi) = \beta_{0l} + \beta_{1l} f(x_1; df)$ | $transf(y_{ij}) = \beta_{0l} + \beta_{1l} f(x_1; df) + c_i + u_{ij}$ |

Here $l = 1 \cdots L$ and $L$ is the number of levels of the cofactor, $y_{ij}$ , the intake amount, $x_1$ is the covariable, $f$ is a polynomial function with the degrees of freedom $df$, $c_i$ and $u_{ij}$ are the individual effect and interaction effect, respectively. These effects are assumed to be normally distributed $N(0, \sigma^2_{between})$ resp. $N(0, \sigma^2_{within})$. The degree of the function is determined by backward or forward selection. In the output, the usual intake is displayed for a specified number of values of the covariable and/or the levels of the cofactor.

### Total Diet Study

In Total Diet Studies (TDS), substance occurrence data is obtained from measuring food products as consumed. TDS offers a more direct measure of substance concentrations compared to traditional monitoring and surveillance programs that are concerned with contamination of raw agricultural commodities. In a TDS, food selection is based on national consumption data in such a way that 90 to 95% of the usual diet is represented by the samples. Selected foods are collected, prepared as consumed and related foods are pooled prior to analysis. The compositions these TDS food samples are described by the *TDS food sample compositions* data module.

In MCRA, TDS concentration data can also be used in *dietary exposure assessments*, using it as an alternative type of concentration data where the modelled foods are not the raw primary commodities (RACs), but these are TDS food compositions. To link the concentration data to the consumed foods, the *TDS food sample composition information* is used in the *food conversion algorithm* in a manner analogous to the use of *food recipes* describing the composition of a composite food. The main difference is that the translation proportion is always 100% (default). Take, as an example, a TDS food *FruitMix* that is composed of *apple, orange* and *pear*, then a consumed food (food-as-eaten) *apple-pie* is converted to *apple*, *wheat* and *butter* (in some specific proportions) and subsequently, *apple* is converted to modelled food *FruitMix* (100%). Not necessarily all foods as consumed are represented in a TDS food sample. In addition to the TDS food sample compositions, there may be additional foods that are not officially part of a TDS food, but which can be extrapolated to a TDS food sample. Through the use of *food extrapolations* (read across translations), these foods may be directly linked to a TDS food sample, e.g., by specifying that *pineapple* is translated to *FruitMix*, *pineapple* or foods containing *pineapple* will also be matched to a *FruitMix* concentration.

Because TDS samples only contain one single, average measurement, TDS occurrence data can currently only be used for only applicable for chronic exposures assessments. However, when variability information is available for

the raw primary foods in the TDS food samples (e.g., from monitoring), this information may be used *to approximate the variance of TDS samples*.

For more information about Total Diet Studies, visit the TDS-Exposure website http://www.tds-exposure.eu.

### TDS reduction to limit scenario analysis

The outcome of a MCRA risk assessment may be that some foods dominate the right upper tail of the exposure distribution. A scenario analysis answers the question to what extent the risk of foods with a high exposure would have been diminished by an intervention or by taking any precautions. To be able to do so, some information is needed about the concentration distributions of the raw agricultural commodities (RACs) that make up the TDS food sample. The decision to intervene or not can be based on comparison between the p95 percentile point of the concentration distribution and a concentration limit value that associated with a high risk.

- For p95 ≤ limit, most concentration values are below the value that is considered as a potential risk, so there is no urgency to take any precautions.
- When the opposite is true, i.c. p95 > limit, there may be an argument to intervene for this specific food.

In MCRA, limits and p95's are supplied by the *concentration distributions module*. In the MCRA interface, a scenario analysis can be checked and the scroll down list allows to select the foods that should be included in the scenario analysis. For the selected foods, concentration reduction factors are computed based on the p95 percentile and the limit value:

$$f_{\texttt{reduction}} = limit/p95$$

These reduction factors (computed for the RACs) are applied to the simulated concentrations on the level of the TDS composite foods of which the conversion paths contain the RACs included in the scenario analysis.

$$f_{\texttt{reduction}} \cdot c_{TDS}$$

Here, $c_{TDS}$ is the concentration value of the TDS food.

### Substance concentrations generation

Both *chronic* and *acute* dietary exposure assessments rely on assigning substance concentrations to consumed modelled foods. For chronic exposure assessments, this concentration should be the mean concentration of the food x substance combination, as obtained from the concentration models. For acute, these concentrations are obtained through random sampling. For acute, two approaches are available: sample-based and substance-based.

### Sample-based concentrations generation

This approach is based on the analytical samples behind the concentration data. For each modelled food, substance concentration values are generated by taking a random sample from the set of analytical samples. For each analytical sample, the corresponding substance concentration values are kept together, maintaining the correlations between the substance concentrations.

Occasionally, one or more substances have censored or missing concentration values. Then, apply imputation first.

For imputation of missing values there are two methods:

1. **Imputation by zero:** all missing values are assumed zero.
2. **Imputation using substance-based concentration models:** all missing values are imputed by drawing a concentration value from the substance-based concentration models.

For imputation of censored values, three methods exist:

1. **Replace by zero:** Censored values are imputated by a zero concentration value. This is an optimistic approach.
2. **Replace by factor times LOR:** Each censored value is replaced by a factor f (e.g., 1 or 1/2) times its LOR.
3. **Replace by factor times LOD LOQ system:** Non-detects are replaced by f * LOD; non-quantifications are replaced by LOD + f * (LOQ - LOD) and factor f is e.g., 1 or 1/2. For f = 0, non-detects are replaced by zero, non-quantifications are replaced by LOD; for f = 1, non-detects are replaced by LOD, non-quantifications are replaced by LOQ.

### Substance-based concentrations generation

In this approach, substance concentrations for a given food are drawn independently per substance from the food/substance concentration models.

### Processing correction

Concentrations in the consumed food (food as eaten) may be different from concentrations in the modelled food in monitoring programs (typically raw food) due to processing, such as peeling, washing, cooking etc. Concentrations are therefore corrected according to

$$c'_{jhk} = pf_{jhk} \cdot c_{jhk} = \left(\frac{PF_k}{cf_k}\right) \cdot c_{jhk}$$

where $c_{jhk}$ is the concentration of substance $k$ in the food $j$ with processing type $h$, and where $pf_{jhk} = \frac{PF_{jhk}}{cf_{jhk}}$ is a factor indicating the mass change for a specific combination $k$ of modelled food and processing. The processing correction factor $cf_{jhk}$ is used to correct for the fact that the processing factors $PF_{jhk}$ as commonly available from the input data describe both the effects of chemical alteration and weight change. E.g. for a dried food with a consumption of 100 gram which is translated to 300 gram raw agricultural commodity, the correction factor is 3. Note that the weight change is already included when calculating the consumption amounts of the modelled foods.

### Chronic exposure assessment, daily consumed foods

### Model based usual intake

Foods are consumed on a daily basis.

For individual $i$ on day $j$ let $Y_{ij}$ denote the 24 hour recall of a food $(i = 1...n; j = 1...n_i)$. In most cases within-individual random variation is dependent on the individual mean and has a skewed distribution. It is therefore customary to define a one-way random effects model for $Y_{ij}$ on some transformed scale

$$Y^*_{ij} = g(Y_{ij}) = \mu_i + b_i + w_{ij}$$

with $b_i \sim N(0, \sigma^2_b)$ and $w_{ij} \sim N(0, \sigma^2_w)$

Note that $b_i$ represents variation between individuals and $w_{ij}$ represents variation within individuals between days.

The mean $\mu_i$ may depend on a set of covariate $Z_i = (Z_{i1}, ..., Z_{ip})$:

$$\mu_i = \beta_0 + \beta^t_1 Z_i$$

where $\beta_0$ and $\beta_1$ are regression coefficients.

The usual intake $T_i$ for an individual $i$ is defined as the mean consumption over many many days. This assumes that the untransformed intakes $Y_{ij}$ are unbiased for true usual intake rather than the transformed intakes $Y^*_{ij}$. In mathematical terms $T_i$ is the expectation of the intake for this individual where the expectation is taken over the random day effect:

$$T_i = E_w[g^{-1}(\mu_i + b_i + w_{ij})|b_i] = F(b_i)$$

### Model based usual intake on the transformed scale

For the model based usual intake first note that the conditional distribution

$$(\mu_i + b_i + w_{ij}|b_i) \sim N(\mu_i + b_i, \sigma^2_w)$$

It follows that the usual intake $T_i$ is given by

$$T_i = E_w[g^{-1}(\mu_i + b_i + w_{ij}|b_i)] = \int_{-\infty}^{\infty} g^{-1}(\mu_i + b_i + w_{ij}) \frac{1}{\sqrt{2\pi\sigma^2_w}} \exp\left(-\frac{w^2}{2\sigma^2_w}\right) \mathrm{d}w$$

### Model based using a logarithmic transformation

For the logarithmic transform the usual intake $T_i$ can be written in closed form using the formula for the mean of the lognormal distribution:

$$T_i = \exp(\mu_i + b_i + \sigma_w^2/2)$$

In this case $T_i$ follows a log-normal distribution with mean $\mu_i + \sigma_w^2/2$ and variance $\sigma_b^2$. This fully specifies the usual intake distribution, e.g. the mean and variance of the usual intake are given by

$$\mu_{iT} = E[T_i] = \exp(\mu_i + \sigma_w^2/2 + \sigma_b^2/2)$$

$$\sigma_{iT}^2 = Var[T_i] = [\exp(\sigma_b^2) - 1]\exp(2\mu_i + \sigma_w^2 + \sigma_b^2)$$

### Model based using a power transformation

For the *power transformation* the integral can be approximated by means of N-point Gauss-Hermite integration. This results in the following usual intake

$$T_i \approx \frac{1}{\sqrt{\pi}} \sum_{j=1}^{N} w_j (\mu_i + b_i + \sqrt{2}\sigma_w x_j)^p$$

with $p$ the inverse of the power transformation. A similar approximation can be used for the Box-Cox transformation. There can be a small problem with Gauss-Hermite integration. The summation term $(\mu_i + b_i + \sqrt{2}\sigma_w x_j)^p$ can not be calculated when the factor between round brackets is negative and the power $p$ is not an integer. This can happen when $(\mu_i + b_i)$ is small relative to the between day standard error $\sigma_w$. In that case the corresponding term is set to zero. This is not a flaw in the numerical method but in the statistical model since the model allows negative intakes on the transformed scale which cannot be transformed back to the natural scale. The mean and variance of $T_i$ can be approximated again by using Gauss-Hermite integration:

$$\mu_{iT} = E[T_i] = \frac{1}{\sqrt{\pi}} \sum_{k=1}^{N} w_k \frac{1}{\sqrt{\pi}} \sum_{j=1}^{N} w_j (\mu_i + \sqrt{2}\sigma_w x_j + \sqrt{2}\sigma_b x_k)$$

$$\sigma_{iT} = Var[T_i] = \frac{1}{\sqrt{\pi}} \sum_{k=1}^{N} w_k \left[ \frac{1}{\sqrt{\pi}} \sum_{j=1}^{N} w_j (\mu_i + \sqrt{2}\sigma_w x_j + \sqrt{2}\sigma_b x_k) \right]^2 - \mu_T^2$$

An alternative method for obtaining model based usual intakes for the power transformation employs a Taylor series expansion for the power, see e.g. Kipnis et al. (2009). This is however less accurate than Gauss-Hermite integration. For the power transformation simulation is required to derive the usual intake distribution: simulate a random effect $b_i$ for many individuals and then approximate $T_i$ for these individuals. The $T_i$ values then form a sample form the usual intake distribution.

### Model assisted usual intake on the transformed scale

The model assisted approach employs a prediction for the usual intakes of every individual in the study. This requires a prediction of the individual random effect $b_i$ for every individual.

In the one-way random effects model the Best Linear Unbiased Prediction for $(\mu_i + b_i)$ is given by

$$BLUP_i = \mu_i + (\bar{Y}_i^* - \mu_i)\left(\frac{\sigma_b^2}{\sigma_b^2 + \sigma_w^2/n_i}\right)$$

in which $\bar{Y}_i^*$ is the mean of the transformed intakes for individual $i$. BLUPs have optimal properties for some purposes, but not for the purpose of representing the variation $\sigma_b^2$ between individuals. This can be seen by noting that

$$Var(\bar{Y}_i^*) = \sigma_b^2 + \sigma_w^2/n_i$$

and thus

$$\mathit{Var}(\mathit{BLUP}_i) = \left(\frac{\sigma_b^4}{\sigma_b^2 + \sigma_w^2/n_i}\right)$$

which is smaller than the between individual variance $\sigma_b^2$. As an alternative a modified BLUP can be defined by means of

$$\mathit{modifiedBLUP}_i = \mu_i + (\bar{Y}_i^* - \mu_i)\sqrt{\left(\frac{\sigma_b^2}{\sigma_b^2 + \sigma_w^2/n_i}\right)}$$

which has the correct variance $\sigma_b^2$ and also the correct mean $\mu_i$. However these optimal properties disappear when modified BLUPs are directly backtransformed to the original scale.

### Model assisted using a logarithmic transformation

For the logarithmic transformation the usual intake $T_i$ follows a log-normal distribution with mean $\mu_i + \sigma_w^2/2$ and variance $\sigma_b^2$. If we can construct a BLUP like stochastic variable with the same mean and variance, then this variable be an unbiased predictor with the correct variance. It is easy to see that the following variable has the same distribution as $T_i$

$$\mathit{modelassistedBLUP}_i = \mu_i + \frac{\sigma_w^2}{2} + (\bar{Y}_i^* - \mu_i)\sqrt{\left(\frac{\sigma_b^2}{\sigma_b^2 + \sigma_w^2/n_i}\right)}$$

So the model assisted individual intake $\exp(\mathit{modelassistedBLUP}_i)$ has the same distribution as the usual intake and is thus the best predictor for usual intake.

Kipnis et al. (2009) employs the conditional distribution of $b_i$ given the observations $Y_{i1}, \cdots, Y_{in_i}$ to obtain a prediction. First note that

$$(b_i | Y_{i1}, \cdots, Y_{in_i}) = (b_i | Y_{i1}^*, \cdots, Y_{in_i}^*) = (b_i | \bar{Y}_i^*)$$

Since all distributions in the one-way random effects model are normal it follows that:

$$(b_i, \bar{Y}_i^*) \sim \mathit{BivariateNormal}(0, \mu_i, \sigma_b^2, \sigma_b^2 + \sigma_w^2/n_i, \sigma_b^2)$$

where the last parameter represents the covariance between $b_i$ and $\bar{Y}_i^*$. It follows that the conditional distribution

$$(b_i | \bar{Y}_i^*) \sim N(\mu_c, \sigma_c^2)$$

with

$$\mu_c = \frac{\sigma_b^2}{\sigma_b^2 + \sigma_w^2/n_i}(\bar{Y}_i^* - \mu_i)$$

and

$$\sigma_c^2 = \frac{\sigma_b^2 \sigma_w^2/n_i}{\sigma_b^2 + \sigma_w^2/n_i}$$

A prediction for the usual intake $T_i = F(b_i)$ is then obtained by the expectation

$$E[F(b_i)|\bar{Y}_i^*] = \int F(b)\phi(b; \mu_c, \sigma_c^2)\mathrm{d}b$$

For the logarithmic transform $F(b_i) = \exp(\mu_i + b_i + \sigma_w^2/2)$ and the expectation reduces to

$$E[F(b_i)|\bar{Y}_i^*] = \exp(\mu_i + \mu_c + \sigma_c^2/2 + \sigma_w^2/2)$$

which is a function of $\bar{Y}_i^*$ through $\mu_c$. To obtain the mean and variance of the prediction note that

$$\mu_i + \mu_c + \sigma_c^2/2 + \sigma_w^2/2 \sim N\left(\mu_i + \frac{\sigma_b^2 \sigma_w^2/n_i}{2(\sigma_b^2 + \sigma_w^2/n_i)} + \frac{\sigma_w^2}{2}, \frac{\sigma_b^4}{\sigma_b^2 + \sigma_w^2/n_i}\right)$$

It follows that the expectation of the prediction equals

$$E[E[F(b_i)|\bar{Y}_i^*]] = \exp\left(\mu_i + \frac{\sigma_b^2\sigma_w^2/n_i}{2(\sigma_b^2+\sigma_w^2/n_i)} + \frac{\sigma_w^2}{2} + \frac{\sigma_b^4}{2(\sigma_b^2+\sigma_w^2/n_i)}\right)$$
$$= \exp\left(\mu_i + \frac{\sigma_b^2}{2} + \frac{\sigma_w^2}{2}\right)$$

which equals the mean of the usual intake. However the variance of the prediction equals

$$Var[E[F(b_i|\bar{Y}_i^*]] = \left[\exp\left(\frac{\sigma_b^4}{(\sigma_b^2+\sigma_w^2/n_i)}\right) - 1\right]\exp(2\mu_i + \sigma_b^2 + \sigma_w^2)$$

Which is less than the variance of the usual intake. The approach of Kipnis et al. (2009) will therefor result in too much shrinkage of the model assisted usual intake.

### Model assisted using a power transformation

For the *power transformation* a model assisted BLUP with optimal properties, as derived above, cannot be constructed. The approach of Kipnis et al. (2009) can however be used to obtain a prediction in the following way. First approximate $T_i = F(b_i)$ by *Gauss-Hermite integration*:

$$F(b_i) = T_i \approx \frac{1}{\sqrt{\pi}}\sum_{j=1}^{N} w_i(\mu_i + b_i + \sqrt{2}\sigma_w x_i)^p$$

Secondly again use Gauss-Hermite to approximate the expectation of the conditional distribution giving the prediction $P_i$.

$$P_i = E[F(b_i)|\bar{Y}_i^*] = \int F(b_i)\phi(b;\mu_c,\sigma_c^2)\mathrm{d}b \approx \frac{1}{\pi}\sum_{k=1}^{N} w_k \sum_{j=1}^{N} w_j(\mu_i + \mu_c + \sqrt{2}\sigma_w x_j + \sqrt{2}\sigma_c x_k)^p$$

which is a function of $\bar{Y}_i^*$ through $\mu_c$. It is likely that the thus obtained predictions $P_i$ have a variance that is too small. If we would know the mean $\mu_{iP}$ and variance $\sigma_{iP}^2$ of the predictions, the predictions could be linearly rescaled to have the correct mean $\mu_{iT}$ and variance $^2_{iT}$. The mean and variance of the prediction can be calculated using *Gauss-Hermite integration*.

$$\mu_{iP} = \frac{1}{\sqrt{\pi}}\sum_{l=1}^{N} w_l \frac{1}{\pi}\sum_{k=1}^{N} w_k \sum_{j=1}^{N} w_j(\mu_i + \sqrt{2}\frac{\sigma_b^2}{\sigma_b^2+\sigma_w^2/n_i}x_l + \sqrt{2}\sigma_w x_j + \sqrt{2}\sigma_c x_k)^p$$

$$\sigma_{iP}^2 = \frac{1}{\sqrt{\pi}}\sum_{l=1}^{N} w_l \left[\frac{1}{\pi}\sum_{k=1}^{N} w_k \sum_{j=1}^{N} w_j(\mu_i + \sqrt{2}\frac{\sigma_b^2}{\sigma_b^2+\sigma_w^2/n_i}x_l + \sqrt{2}\sigma_w x_j + \sqrt{2}\sigma_c x_k)^p\right]^2 - \mu_{iP}^2$$

The proposed prediction then equals

$$P_i^* = \mu_{iT} + \frac{\sigma_{iT}}{\sigma_{iP}}(P_i - \mu_{iP})$$

### Chronic exposure assessment, episodically consumed foods

For episodically consumed foods we need to take the probability of consumption into account. Define $p_i$ as the probability that individual $i$ consumes the food on any given day. The usual intake for this individual is then given by the product of $p_i$ and $T_i$ which is now defined as the usual amount on consumption days. Since individuals will vary in their probability pi, besides modelling the amounts as for daily consumed foods, it is also necessary to model the frequency of consumption. A three stage analysis of 24-hour recall data is the necessary:

1. A model for the frequency of consumption
2. A model for the intakes on consumption days
3. Integration of both models in order to obtain a usual intake distribution.

Step 2 uses the analysis outlined in the previous section for the positive intakes only. For step 1 two popular models which describe between-individual variation for the probability of consumption are the beta-binomial model and the logistic-normal model.

### Beta-Binomial model for frequencies (BBN)

Let $n_i$ be the total number of recall days for individual $i$ and $X_i$ the number of days with a positive intake. The distribution of $X_i$, with $p_i$ the probability of consumption for individual $i$, is given by

$$X_i = \textit{Binomial}(n_i, p_i)$$

In this model the probability $p_i$ varies among individuals according to the Beta distribution:

$$f(p) = B^{-1}(\alpha, \beta) p^{\alpha-1}(1-p)^{\beta-1}$$

with

$$B(\alpha, \beta) = \frac{\Gamma(\alpha)\Gamma(\beta)}{\Gamma(\alpha+\beta)}$$

Combining the binomial and the Beta distribution results in the betabinomial distribution:

$$P(X_i = x) = \left( \begin{array}{c} n_i \\ r \end{array} \right) \frac{B(\alpha + x, n_i + \beta - x)}{B(\alpha, \beta)}$$

The mean and variance of the betabinomial distribution are given by

$$E[X_i] = n_i \frac{\alpha}{\alpha + \beta}$$

and

$$\textit{Var}[X_i] = n_i \frac{\alpha\beta(\alpha + \beta + n_i)}{(\alpha + \beta)^2(\alpha + \beta + 1)}$$

Using the reparameterization $\pi = \alpha/(\alpha + \beta)$ and $\phi = 1/(\alpha + \beta + 1)$, it follows that

$$E[X_i] = n_i \pi$$

and

$$\textit{Var}[X_i] = n_i \pi(1-\pi)[1 + (n_i - 1)\phi]$$

This reparameterization enables to model the probability $\pi_i$ of consumption for individual $i$ directly as a logistic regression:

$$\textit{logit}(\pi_i) = \gamma_0 + \gamma_1^t Z_i$$

Note that the dispersion parameter $\phi$: is assumed to be equal for all individuals. The betabinomial logistic regression model can be fitted by means of maximum likelihood.

### Model based frequencies for usual intake

For the model based usual intake distribution the estimated parameters $\pi_i$ and $\phi$ are backtransformed using $\alpha_i = \pi_i\phi/(1-\phi)$ and $\beta_i = (1-\pi_i)\phi/(1-\phi)$. These can then be used to draw from the Beta distribution.

### Model assisted frequencies for usual intake

For the model assisted usual intake distribution a prediction of the consumption probability is required for every individual. Simple predictions are

1. the observed frequencies for every individual or
2. the fitted probability for every individual. When there are no covariables the fitted probability is the same for every individual.
3. Alternatively one can use the approach outlined in Kipnis et al (2009) employing the conditional expectation of the probability given the observed frequency:

$$E(p_i|X_i = x) = \int_p pf(p|X_i = x)\mathrm{d}p$$

$$= \int_p p\frac{f(X_i = x|p)f(p)}{\int f(X_i = x|p)f(p)dp}\mathrm{d}p$$

$$= \frac{1}{P(x_i = x)}\int_p p\begin{pmatrix} n_i \\ r \end{pmatrix} p^x(1-p)^{n_i-x}B^{-1}(\alpha_i, \beta_i)p^{\alpha_i-1}(1-p)^{\beta_i-1}\mathrm{d}p$$

$$= \frac{B^{-1}(\alpha_i, \beta_i)}{P(x_i = x)}\begin{pmatrix} n_i \\ r \end{pmatrix}\int_p p^{\alpha_i+x}(1-p)^{n_i+\beta_i-x-1}\mathrm{d}p$$

$$= \frac{B(\alpha_i + x + 1, n_i + \beta_i - x)}{B(\alpha_i + x, n_i + \beta_i - x)}$$

$$= \frac{\alpha_i + x}{\alpha_i + \beta_i - x}$$

For individual with zero intakes on all recall days a prediction for the random individual amount effect $b_i$ is not available. There seem to be two option for predicting the usual intake for such individuals:

- Set the individual intake to zero
- Simulate a model based prediction for the amount and combine this with the conditional expected probability given above to obtain an individual usual intake.

### Logistic-Normal model for frequencies (LNN0)

In this model the distribution of $X_i$ is again binomial:

$$X_i = \mathit{Binomial}(n_i, p_i)$$

The probability $p_i$ is now given by a logistic regression with a random effect in the linear predictor which represents the between-individual variation in the probability $p_i$

$\mathit{logit}(p_i) = \lambda_i + v_i$ with $v_i \sim N(0, \sigma_v^2)$ and the regression equation $\lambda_i = \gamma_0 + \gamma_1^t Z_i$

The marginal probability $\pi_i$ is obtained by integrating over the random effect $v_i$, i.e. using *Gauss-Hermite integration*

$$\pi_i = \int H(\lambda_i + v)f(v)dv \approx \frac{1}{\sqrt{\pi}}\sum_{j=1}^{N} w_j H(\lambda_i + \sqrt{2}\sigma_v x_j)$$

in which $H()$ is the inverse of the logit transformation. Note that this is different from $\mathit{logit}^{-1}(\lambda_i)$ which is the median probability. The model can be fitted by maximum likelihood using Gauss-Hermite integration. An (approximate) maximum likelihood procedure is implemented in routine glmer of the lme4 package in R. For a new vector of covariates $Z_i^*$ the linear predictor $\lambda_i^*$ can be calculated along with its standard error $\mathit{Se}(\lambda_i^*)$. The marginal predicted probability $\pi_i^*$ can be calculated by means of Gauss-Hermite integration and the standard error of the predicted probability can be calculated by means of the usual Taylor series expansion:

$$\mathit{Se}(\pi_i^*) \approx \frac{\mathit{Se}(\lambda_i^*)}{\sqrt{\pi}}\sum_{j=1}^{N} w_j \frac{d}{d\lambda_i^*}H(\lambda_i^* + \sqrt{2}\sigma_v x_j)$$

$$= \frac{\mathit{Se}(\lambda_i^*)}{\sqrt{\pi}}\sum_{j=1}^{N} w_j H(\lambda_i^* + \sqrt{2}\sigma_v x_j)[1 - H(\lambda_i^* + \sqrt{2}\sigma_v x_j)]$$

### Model based frequencies for usual intake

For the model based usual intake distribution the estimated parameters $\lambda_i$ and $\sigma_v^2$ can be used to generate individual probabilities.

### Model assisted frequencies for usual intake

For the model assisted usual intake distribution simple predictors are (a) the observed frequencies and (b) the marginal probability $\pi_i$. The conditional expectation (c) is given by

$$E(p_i|X_i = x) = \int_v H(\lambda_i + v) f(v|X_i = x) \mathrm{d}v$$

$$= \int_v H(\lambda_i + v) \frac{f(X_i = x_i|v) f(v)}{\int f(X_i = x_i|v) f(v) \mathrm{d}v} \mathrm{d}v$$

$$= \frac{\int_v H(\lambda_i + v)[H(\lambda_i + v)]^{x_i}[1 - H(\lambda_i + v)]^{n_i - x_i} f(v) \mathrm{d}v}{\int_v [H(\lambda_i + v)]^{x_i}[1 - H(\lambda_i + v)]^{n_i - x_i} f(v) \mathrm{d}v}$$

and both nominator and denominator can be approximated by means of the *Gauss-Hermite integration*. For individual with zero intakes on all recall days see above for the two options.

### Logistic-Normal model for frequencies correlated with amounts (LNN)

This model is extends the LNN0 model with a correlation between the individual random effect $b_i$ for amounts and the individual random effect $v_i$ for frequencies. This model is also known as the NCI model and is introduced by Tooze et al. (2006) with further mathematical details in Kipnis et al. (2009). The model can be written as

$$\mathit{logit}(P(Y_{ij} > 0)) = \lambda_i + v_i$$

$$g(Y_{ij}) = \mu_i + b_i + w_{ij}$$

and $(v_i, b_i) \sim \mathit{BivariateNormal}(0, 0, \sigma_v^2, \sigma_b^2, \rho)$ and $w_{ij} \sim N(0, \sigma_w^2)$

The model can be fitted by maximum likelihood employing *two-dimensional Gauss-Hermite integration*.

### Model based usual intake

Model based usual intake requires generation of the pair $(v_i, b_i)$ for many hypothetical individual. The usual intake $U_i$ for such a hypothetical individual is then given by

$$U_i = H(\lambda_i + \nu_i) T_i$$

$$= H(\lambda_i + \nu_i) E_w[g^{-1}(\mu_i + b_i + w_{ij})|b_i]$$

$$= H(\lambda_i + \nu_i) F(b_i)$$

The second term can be calculated using the method outlined for daily intakes.

### Model assisted usual intake

This requires simultaneous prediction of the random effect for frequency and for amount as outlined in Kipnis et al. (2009). We have for individual $i$ in the study $(U_i|Y_{i1}, \cdots, Y_{in_i}) = (U_i|Y^*_{i1}, \cdots, Y^*_{in_i}) = (U_i|x_i, \bar{Y}^*_i)$ where $x_i$ is the number of positive intakes and $\bar{Y}^*_i$ is the mean of the transformed **positive** intakes. It follows that the required conditional expectation $P_i$ equals

$$P_i = E[U_i|x_i, \bar{Y}^*_i]$$

$$= E_{v_i, b_i}[H(\lambda_i + v_i) F(b_i)|x_i, \bar{Y}^*_i]$$

$$= \frac{\int\int H(\lambda_i + v_i) F(b_i) f(x_i, \bar{Y}^*_i|v_i, b_i) \phi(v_i, b_i) dv_i db_i}{\int\int f(x_i, \bar{Y}^*_i|v_i, b_i) \phi(v_i, b_i) dv_i db_i}$$

where

$$f(x_i, \bar{Y}^*_i|v_i, b_i) = [H(\lambda_i + v_i)]^{x_i}[1 - H(\lambda_i + v_i)]^{n_i - x_i} \phi(\bar{Y}^*_i - \mu_i - b_i; 0, \sigma_w^2/x_i)$$

Both nominator and denominator can be approximated by a *two-dimensional Gauss-Hermite integration*. Note that for the log-transform $F(b_i) = T_i = \exp(\mu_i + b_i + \sigma_w^2)/2)$ can be calculated exactly; for the *power transformation* an approximation must be used. It can be expected that the predicted usual intake will not have the correct variance. This can possibly be remedied by equating the mean and variance of $U_i$ and $P_i$. These are however rather involved to calculate.

For individual with zero intakes on all recall days the model assisted usual intake can be set to zero, or can be simulated as follows

1. Calculate the Model assisted frequency $P_0$ for usual intake (see LNN0)
2. Transform $P_0$ back to the logistic scale, i.e. $L_0 = \mathit{logit}(P_0)$ . Get the conditional distribution of

$$(b|v = L_0 - \lambda_i) \sim N\left(\frac{\sigma_b}{\sigma_v}\rho(L_0 - \lambda_i), (1-\rho^2)\sigma_b^2\right)$$

3. Simulate a draw $b_0$ from this conditional distribution and obtain the usual intake as $P_0 \exp(\mu_i + b_0 + \sigma_w^2)$

Note that the backtransformation from $P_0$ to $L_0$ is according to the median of the distribution rather than the mean.

### Dietary exposures settings

### Selection settings

Table 3.215: Selection settings for module Dietary exposures.

| Name | Type | Description |
|---|---|---|
| Scenario analysis foods | AlphaNumeric | The foods of interest for the scenario analysis. |

### Calculation settings

Table 3.216: Calculation settings for module Dietary exposures.

| Name | Type | Description |
|---|---|---|
| Selected tier | SettingsTemplateType | Specifies all module settings should be set according to a pre-defined tier or using custom settings. |
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Compute shorter than lifetime exposures | Boolean | Compute shorter than lifetime exposures. |
| Shorter than lifetime number of days | Numeric | Number of days considered for shorter than lifetime exposure assessment. |
| Total diet study concentration data | Boolean | Specifies whether exposure is based on sampling data from tota diet studies. |
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Compute cumulative exposures | Boolean | Specifies whether the assessment involves multiple substances a results should be cumulated over all substances. |
| Residue generation method for shorter than lifetime | *ShorterThanLifetimeResidue-GenerationMethod* | The method for generating residues for shorter than lifetime exposure assesment. |
| Sample based | Boolean | Include co-occurrence of substances in samples in simulations. checked, substance residue concentrations are sampled using th correlations between values on the same sample. If unchecked, any correlation between substances is ignored, substance residu concentrations are sampled ignoring the correlations between values on the same sample. |

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Table 3.216 – continued from previous page

| Name | Type | Description |
|---|---|---|
| Consumptions on the same day come from the same sample | Boolean | If checked, in procedure of EFSA Guidance 2012, section 4.1. all consumptions of a raw commodity of an individual on the same day are assumed to come from the same sample. If unchecked, all consumptions of a raw commodity of an individ on the same day are assumed to come from different samples. |
| Maximise co-occurrence of high values in simulated samples | Boolean | Within each pattern of substance presence. If checked, substan residue concentrations are sorted within co-occurrence patterns substances on the same samples. After sorting, high residue val occur more frequently on the same sample. This choice is conservative. If unchecked, substance residue concentrations ar sampled at random, ignoring any co-occurrence patterns of substances on the same samples. This choice is less conservativ |
| Apply processing factors | Boolean | Specified in table ProcessingFactor. If checked, processing fact are applied. Concentrations in the consumed food may be different from concentrations in the modelled food in monitorin programs (typically raw food) due to processing, such as peelin washing, cooking etc. If unchecked, no processing information used. This is in most (though not all) cases a worst-case assumption |
| Use distribution | Boolean | Probabilistic specifications of processing factors will be used |
| Ignore processing factors less than 1 | Boolean | This setting will suppress the use of processing factors lower th 1 (it is used in the EFSA 2012 Pessimistic tier). |
| Default processing factor for missing processing types (except foods with processing type equal to 'Unspecified' (default = 1)) | Numeric | Specify a processing factor for missing processing types. When the processing type is 'Unspecified', the default processing facto is equal to 1. |
| Use default processing factor for missing processing types | Boolean | Use default processing factor for missing processing types |
| Perform MCR analysis | Boolean | Perform a Maximum Cumulative Ratio (MCR) analysis to determine co-exposure between substances. |
| Substance weighting in mixtures | *ExposureApproachType* | Risk based: exposures in equivalents of the reference substance standardised: standardised exposures per substance have varian 1; or unweighted exposures: RPFs are equal to 1. |
| Use unit variability | Boolean | Controls whether to use unit variability. |
| Unit variability model | *UnitVariabilityModelType* | Describes variation between single units when concentration da are from composite samples. |
| Estimates nature | *EstimatesNature* | Simulated unit concentrations can be higher or lower than composite value (realistic) or only equal or higher (conservative |
| Unit variability parameter | *UnitVariabilityType* | Use Coefficient of variation or Variability factor, specified in VariabilityFactor table. |
| Mean of LogNormal simulated values (biasing) | *MeanValueCorrectionType* | Unbiased: correct unit simulations for difference between medi and mean. |
| Default variability factor for unit weight <= 25g | Numeric | Default variability factor 1 (unit weight <= 25 g, small crops). S requires specification of unit weight (FoodProperties table) and case of beta model, also the Number of units in a composite sample (UnitVariability table). |
| Correlation between substances on the same units | *UnitVariabilityCorrelationType* | Specifies the type of correlation between substances on the sam units; no correlation or full correlation. |
| Default variability factor for unit weight > 25g | Numeric | Default variability factor 5 (unit weight > 25 g, medium/large crops). Still requires specification of unit weight (FoodPropertie table) and, in case of beta model, also the Number of units in a composite sample (UnitVariability table). |
| Model type | *IntakeModelType* | The parametric model for between-and within-individual variation, and possibly covariates. |

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Table 3.216 – continued from previous page

| Name | Type | Description |
|---|---|---|
| Model-then-add | Boolean | Specifies whether to create separate exposure models for specif groups of modelled foods (model-then-add). |
| Covariate modelling | Boolean | Specifies whether to model exposures as a function of covariate at individual level. |
| Model-then-add sub-category models | IntakeModelPerCategory | Sub-model specifications for foods groups that should be model separately. |
| Grid precision frequency model | Numeric | The discrete frequency distribution (ISUF) is approximated via number of classes. |
| Number of iterations (x 1000) | Numeric | The number of iterations that is used to estimate the discrete frequency distribution for the ISUF model. |
| Spline-fit | Boolean | To achieve a better normality, a second transformation is performed: a spline function is fitted to the logarithmically or power transformed data as a function of the normal Blom score |
| Amount model covariate model | *CovariateModelType* | Specifies whether, and how to model exposures amounts as function of covariates. |
| Function | *FunctionType* | Functional relation between exposure and covariable. |
| Transformation | *TransformType* | The data transformation used to approximate normality for amounts. |
| Testing level | Numeric | Significance level for testing the degree of the function. e.g., 0.( |
| Testing method | *TestingMethodType* | Starting from a full model (backward) or empty model (forward |
| Maximum degrees of freedom | Numeric | Order of function. Determines the maximum degree of complexity of the function. |
| Minimum degrees of freedom | Numeric | Order of function. Determines the minimum degree of complexity of the function. |
| Amounts model: variance ratio (between/within) | Numeric | Estimate of the ratio of the variance components of the amount model (only relevant for data with only 1 day per individual) |
| Frequency model covariates model | *CovariateModelType* | Specifies whether, and how to model exposure frequency as function of covariates. |
| Function | *FunctionType* | Functional relation between exposure and covariable. |
| Testing level | Numeric | Significance level for testing the degree of the function. e.g., 0.( |
| Testing method | *TestingMethodType* | Starting from a full model (backward) or empty model (forward |
| Minimum degrees of freedom | Numeric | Order of function. Determines the minimum degree of complexity of the function. |
| Maximum degrees of freedom | Numeric | Order of function. Determines the maximum degree of complexity of the function. |
| Frequency model dispersion | Numeric | Frequency model dispersion estimate for (only relevant for data with only 1 day per individual). |
| Use occurrence patterns for generating simulated samples | Boolean | When selected, this simulated samples will be based on occurrence patterns. |
| Associate the unspecified percentage with no-occurrence for foods with at least one specified occurrence pattern | Boolean | If checked, for foods with at least one specified occurrence pattern, unspecified occurrence patterns for the same food are assumed to be associated with no use. If unchecked, all substances are considered to be authorised (potentially present i samples). Note that this setting cannot be used for foods that ha no specified AUs. These foods have 100% potential presence o all substances. To declare all AUs on such a food un-authorised include an empty AU with percentage 100% in the AU data tab (i.e., use an AU for this food, without specifying substances in t AU Substances table) |
| Details level dietary exposures | *DietaryExposuresDetailsLevel* | Level of detail for summarizing dietary exposure/intakes. |
| Iterate survey | Boolean | Instead of (re-)sampling the individual days, loop over the entir survey (= 1 iteration). The number of iterations for a survey is calculated as round (number of Monte Carlo iterations /(numbe of individuals * surveys days)). |

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Table 3.216 – continued from previous page

| Name | Type | Description |
|---|---|---|
| Monte Carlo iterations | Numeric | The number of iterations for Monte Carlo simulations, e.g. 100,000 (maximum is 100,000). |
| Impute exposure distributions | Boolean | Impute exposure distributions for substances with missing concentrations. |
| Include diagnostics analysis for variability | Boolean | For each percentile the variability (standard deviation) of the estimated percentiles versus sample size are plotted. |
| Cofactor name | AlphaNumeric | Specify the name of the cofactor. |
| Covariable name | AlphaNumeric | Specify the name of the covariable. |
| Allow conversion using food extrapolations | Boolean | Try to find read across codes. If unchecked, read across table is ignored, default is 'Use read across info'. E.g. for pineapple no measurements are found but by specifying that pineapple is converted to FruitMix (with a default proportion of 100%), the TDS sample concentration value of FruitMix will be used for pineapple (as-eaten or as ingredient). |
| Censored values replacement | *NonDetectsHandlingMethod* | How to replace censored values (when not co-modelled, as in censored models). |
| Default concentration model | *ConcentrationModelType* | The concentration model type that will be used as default for al food/substance combinations. If this model type cannot be fitte e.g., due to a lack of data, a simpler model will be chosen automatically as a fall-back. |
| Apply reduction-to-limit scenario | Boolean | Total diet study: specify reduction-to-limit scenario. If unchecked, all residue values are taken as such (base scenario: apply no reduction factors). If checked, reduction factors are applied for selected foods. Select foods where a reduction is assumed (only foods with Percentile > Limit are shown). Only foods with reduction factors > 1 (percentile / limit) are shown. |
| Cutoff MCR | Numeric | For selection of individual(day) exposures with maximum cumulative ratio (MCR = total exposure/maximum) above the cutoff. |
| Cutoff percentage in population ranked on total exposure | Numeric | For selection of individual(day) exposures above the cutoff percentage in the set of individual(day)s ranked on total exposu |
| Display ratio total exposure/ maximum (in MCR plot) | Numeric | For MCR plot: specify ratio total exposure/ maximum for individual(day) exposures . |
| Show tail percentiles (MCR plot) for: | Numeric | Give specific percentiles of exposure distribution (%), e.g. 97.5 99 (space separated). |
| Set minimum percentage contribution per substance to the tail exposure (MCR plot) | Numeric | Set minimum percentage contribution per substance to the tail exposure. |
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |
| DIET: Population alignment method diet exposures | *PopulationAlignmentMethod* | Population aligment methods for dietary exposure sources. |

### Output settings

Table 3.217: Output settings for module Dietary exposures.

| Name | Type | Description |
|---|---|---|
| Exclude privacy sensitive data from outputs | Boolean | Use this setting to not report the parts of the results (i.e., figures tables, or sections) that are marked as (potentially) privacy sensitive. |
| Include drill-down on 9 individuals around specified percentile | Boolean | Specifies whether drilldown on 9 individuals is to be included in the output. |
| Show percentiles for | Numeric | Give specific percentiles of exposure distribution (%), e.g. 50 9 95 97.5 99 (space separated). |
| Percentage for drilldown | Numeric | Gives detailed output for nine individuals near this percentile of the exposure distribution. |
| Percentage for upper tail | Numeric | Gives detailed output for this upper percentage of the exposure distribution. |
| Show % of population below level(s) | *ExposureMethod* | This setting is used for reporting the percentages of individuals (chronic) or individual days (acute) exceeding certain exposure levels. These exposure levels can be generated automatically based on the observed exposures (Automatic, default) or specifi explicitly (Manual). |
| Exposure levels | Numeric | Specify exposure levels for which to give the percentage of exposure below these levels, e.g. 1 10 50 100 200 500. |
| Number of levels of covariable to predict exposure | Numeric | Specify the number of levels, e.g. 20. The range of the covariat is divided by the number of levels: range = (max - min)/levels. For these covariable levels exposures are predicted. |
| Predict exposure at extra covariable levels | Numeric | Specify specific prediction levels in addition to the automaticall generated prediction levels (space separated). |
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |
| Report consumptions and exposures per individual instead of per kg body weight | Boolean | Specifies whether body weights should be ignored and consumptions and exposures should be expressed per individual Otherwise, the consumptions and exposures are per kg body weight. |
| Show co-exposure | Boolean | Show co-exposure in output. |

### Uncertainty settings

Table 3.218: Uncertainty settings for module Dietary exposures.

| Name | Type | Description |
|---|---|---|
| Resample imputation exposure distributions | Boolean | Specifies whether to resample the imputated exposure distributions. |
| Resample portion sizes | Boolean | Specifies whether portion sizes should be resampled based on food consumption quantification data, see (Souverein et al. 201 |
| Perform uncertainty analysis | Boolean | In probabilistic risk assessment of dietary exposure, distributior describe the variability in consumption within a given populatio of individuals and the variability of the occurrence and level of substances in the consumed foods. However, these calculations not consider the amount of uncertainty that is due to the limited size of the underlying datasets. |
| Iterations uncertainty analysis | Numeric | Specifies the number of uncertainty cycles (default 100). |
| Monte Carlo iterations per uncertainty run | Numeric | Specifies the number of Monte Carlo iterations in each uncertainty cycle (default 10,000). |
| Lower uncertainty limit (%) | Numeric | Percentage lower bound, e.g. 2.5%. |
| Upper uncertainty limit (%) | Numeric | Percentage upper bound, e.g. 97.5%. |

### Dietary exposures tiers

#### Overview

Table 3.219: Tier overview for module Dietary exposures

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| C su ti or th sa da co fr th sa sa pl | false | false | false | false | false | true | true | false | false | false |
| U ur va al it | true | | true | | false | true | | true | | true |
| M th ac | false | false | false | false | false | | false | false | false | false |

Table 3.219 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| C va at m el | false | false | false | false | false | false | false | false | false | false |
| It er at su ve | false | false | false | false | false | false | false | false | false | false |
| R po co su ti ar ex po su po in di vi ua in st of po kg bo w | false | false | false | false | false | false | false | false | false | false |
| Ig no sa pl w | true | true | true | true | | | | true | true | true |
| E cl in di vi u- al w le th N da | false | true | false | true | | | | false | true | false |

Table 3.219 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| T ta di st co ce tr ti da | false | false | false | false | false | | false | false | false | false |
| F te sa pl ex co in th co ce tr ti li it | false | false | false | false | | false | false | false | false | false |
| U su st co ve si ru | true | true | true | true | | | | true | true | true |
| S st co ve si m | UseMost-Toxic | UseMost-Toxic | DrawRandom | DrawRandom | | | | UseMost-Toxic | UseMost-Toxic | Draw dom |

Table 3.219 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| R ta al al lc ca su st af te ac ti su st al lc ca ti | true | true | true | true | | | | true | true | true |
| A co fo su st au th ri sa ti in su st co ve si | false | false | true | true | | | | false | false | true |
| F du pl ca su st al lc ca ti in co si te ci | false | false | false | false | | | | false | false | false |

Table 3.219 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| U ex tr o- la ti ru | true | true | true | true | | | | false | false | false |
| T ol fc ex tr o- la ti | 10 | 10 | 10 | 10 | | | | | | |
| R st ex tr o- la ti tc ec M | true | true | true | true | | | | | | |
| R st ex tr o- la ti tc au th ri us | true | true | true | true | | | | | | |
| Ir pr w te co co tr ti | true | true | true | true | | | | true | true | true |

Table 3.219 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| W te co ce tr ti va (μ | 0.1 | 0.1 | 0.05 | 0.05 | | | | 0.1 | 0.1 | 0.05 |
| R st w te ir pr ta ti to th fi m to su st | true | true | true | true | | | | true | true | true |
| R st w te ir pr ta ti to au th ri us | false | false | false | false | | | | false | false | false |
| R st w te ir pr ta ti to ap pr su st | false | false | false | false | | | | true | true | true |

Table 3.219 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| A pl pr ce in fa to | true | true | true | true | true | true | true | true | true | true |
| U di tr bu ti | false | false | false | false | false | false | false | false | false | false |
| Ig ne pr ce in fa to le th 1 | false | false | false | false | false | true | true | false | false | false |
| D fa co ce tr ti m | Empirical | Empirical | Empirical | Empirical | Empirical | NonDetect-SpikeLog-Normal | NonDetect-SpikeLog-Normal | Empirical | Empirical | Emp |
| In cl M fa ba m | false | false | false | false | false | true | true | false | false | false |
| R st L in pu ta ti to au th ri us | false | false | false | false | | false | false | false | false | false |

Table 3.219 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| C sc va ue re pl m | Replace-ByLOR | Replace-ByLOR | Replace-ByLOR | Replace-ByLOR | Replace-ByZero | Replace-ByLOR | Replace-ByLOR | Replace-ByLOR | Replace-ByLOR | Repl ByL |
| F to f (f x L or f x L or L + f x (I - L | 0.5 | 0.5 | 0.5 | 0.5 | | 1 | 1 | 0.5 | 0.5 | 0.5 |
| S pl ba | true | true | true | true | true | true | true | true | true | true |

Table 3.219 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| In p m in va uc fr av al va uc (i u m in va uc ar in p w 0 | true | true | true | true | false | true | true | true | true | true |
| C re la in p va uc w sa pl pc te | true | true | false | false | false | true | true | true | true | false |
| U oc cu re fr qu ci fc in pu ta ti | true | true | true | true | false | | | true | true | true |

Table 3.219 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| P m ri u c ta | false | false | false | false | false | true | false | false | false | false |
| A pl oc cu re pa te pe ce ag | false | false | true | true | | | | false | false | true |
| T ge le | External | External | External | External | External | External | External | External | External | Exte |
| U va al it m | BetaDistribution | | BetaDistribution | | | BetaDistribution | | BetaDistribution | | Beta tribu |
| E ti m na tu | Realistic | | Realistic | | | Realistic | | Realistic | | Real |
| U va al it pa ra e- te | VariabilityFactor | | VariabilityFactor | | | VariabilityFactor | | VariabilityFactor | | Vari tyFa |
| C pu sh th li ti ex pe su | | false | | false | false | | false | | false | |
| M ty | | OIM | | OIM | OIM | | OIM | | OIM | |

Table 3.219 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| N (r bo of da in su ve | | 2 | | 2 | | | | | 2 | |
| S up us fr qu to 1( | | | true | true | | | | | | true |
| R st us pe ce ag up sc to au th ri us | | | true | true | | | | | | true |
| M Fa to (f x M | | | | | | 1 | 1 | | | |
| C ce tr ti li fi te ex ce fa to | | | | | | | | | | |

Table 3.219 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| In cl fo ca co m it co ce tr ti | | | | | | | | | | |
| F ca co m it su st oc cu re p ce ag | | | | | | | | | | |
| A ju m fa to fo th fo ca fo co ce tr ti | | | | | | | | | | |

Table 3.219 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| U de te m is ti su st co ve si fo fo ca co m it | | | | | | | | | | |
| In cl pr ce de ti of th fo ca fo in m su m re pl m | | | | | | | | | | |

### Retrospective dietary CRA (EC 2018) - Acute / Tier I

Table 3.220: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Consumptions on the same day come from the same sample | false | | |
| Use unit variability | true | | |
| Model-then-add | false | | |
| Covariate modelling | false | | |

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Table 3.220 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Iterate survey | false | | |
| Report consumptions and exposures per individual instead of per kg body weight | false | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |

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Table 3.220 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Restrict extrapolations to equal MRLs | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Restrict extrapolations to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |

continues on next page

Table 3.220 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Water concentration value (µg/kg) | 0.1 | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to approved substances | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Processing factors* |

continues on next page

Table 3.220 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |

continues on next page

Table 3.220 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Correlate imputed values with sample potency | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Apply occurrence pattern percentages | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Hazard characterisations* |
| Unit variability model | BetaDistribution | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Unit variability factors* |
| Estimates nature | Realistic | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Unit variability factors* |

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Table 3.220 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Unit variability parameter | VariabilityFactor | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Unit variability factors* |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier I

Table 3.221: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute shorter than lifetime exposures | false | | |
| Consumptions on the same day come from the same sample | false | | |
| Model type | OIM | | |
| Model-then-add | false | | |
| Covariate modelling | false | | |
| Iterate survey | false | | |
| Report consumptions and exposures per individual instead of per kg body weight | false | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Consumptions* |
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Consumptions* |

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Table 3.221 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |

continues on next page

Table 3.221 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Restrict extrapolations to equal MRLs | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Restrict extrapolations to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.1 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |

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Table 3.221 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to approved substances | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Processing factors* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |

continues on next page

Table 3.221 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Correlate imputed values with sample potency | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |

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Table 3.221 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Parametric uncertainty | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Apply occurrence pattern percentages | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Hazard characterisations* |

### Retrospective dietary CRA (EC 2018) - Acute / Tier II

Table 3.222: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Consumptions on the same day come from the same sample | false | | |
| Use unit variability | true | | |
| Model-then-add | false | | |
| Covariate modelling | false | | |
| Iterate survey | false | | |
| Report consumptions and exposures per individual instead of per kg body weight | false | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Consumptions* |

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Table 3.222 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |

continues on next page

Table 3.222 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Restrict extrapolations to equal MRLs | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Restrict extrapolations to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |

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Table 3.222 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Processing factors* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |

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Table 3.222 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |

continues on next page

Table 3.222 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Parametric uncertainty | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Apply occurrence pattern percentages | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Hazard characterisations* |
| Unit variability model | BetaDistribution | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Unit variability factors* |
| Estimates nature | Realistic | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Unit variability factors* |

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Table 3.222 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Unit variability parameter | VariabilityFactor | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Unit variability factors* |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier II

Table 3.223: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute shorter than lifetime exposures | false | | |
| Consumptions on the same day come from the same sample | false | | |
| Model type | OIM | | |
| Model-then-add | false | | |
| Covariate modelling | false | | |
| Iterate survey | false | | |
| Report consumptions and exposures per individual instead of per kg body weight | false | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Consumptions* |
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Consumptions* |

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Table 3.223 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |

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Table 3.223 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Restrict extrapolations to equal MRLs | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Restrict extrapolations to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |

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Table 3.223 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Processing factors* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |

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Table 3.223 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |

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Table 3.223 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Parametric uncertainty | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Apply occurrence pattern percentages | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Hazard characterisations* |

### Retrospective dietary CRA (EFSA 2012) - Optimistic

Use the optimistic model settings according to the EFSA Guidance 2012. Concentration values are sampled using a sample-based empirical distribution. Available processing factors are applied. No unit variability model should be applied.

Table 3.224: Tier definition for Retrospective dietary CRA (EFSA 2012) - Optimistic.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute shorter than lifetime exposures | false | | |
| Consumptions on the same day come from the same sample | false | | |
| Use unit variability | false | | |
| Model type | OIM | | |
| Model-then-add | false | | |
| Covariate modelling | false | | |
| Iterate survey | false | | |
| Report consumptions and exposures per individual instead of per kg body weight | false | | |
| Total diet study concentration data | false | *Retrospective dietary CRA (EFSA 2012) - Optimistic* | *Food conversions* |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2012) - Optimistic* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2012) - Optimistic* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EFSA 2012) - Optimistic* | *Processing factors* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EFSA 2012) - Optimistic* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EFSA 2012) - Optimistic* | *Food concentration models* |
| Censored values replacement | ReplaceByZero | *Retrospective dietary CRA (EFSA* | *Food concentration models* |

### Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic

Acute probabilistic exposure assessment using the pessimistic model settings according to the EFSA Guidance 2012. Only processing factors > 1 are applied. For unit variability, the Beta distribution is applied.

Table 3.225: Tier definition for Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Consumptions on the same day come from the same sample | true | | |
| Use unit variability | true | | |
| Covariate modelling | false | | |
| Iterate survey | false | | |
| Report consumptions and exposures per individual instead of per kg body weight | false | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Processing factors* |
| Ignore processing factors less than 1 | true | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Processing factors* |
| Default concentration model | NonDetect-SpikeLogNormal | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Food concentration models* |
| Include MRL fallback model | true | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary* | *Food concentration models* |

### Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic

Chronic probabilistic exposure assessment using the pessimistic model settings according to the EFSA Guidance 2012. Only processing factors > 1 are applied.

Table 3.226: Tier definition for Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute shorter than lifetime exposures | false | | |
| Consumptions on the same day come from the same sample | true | | |
| Model type | OIM | | |
| Model-then-add | false | | |
| Covariate modelling | false | | |
| Iterate survey | false | | |
| Report consumptions and exposures per individual instead of per kg body weight | false | | |
| Total diet study concentration data | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Processing factors* |
| Ignore processing factors less than 1 | true | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Processing factors* |
| Default concentration model | NonDetectSpikeLogNormal | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food concentration models* |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier I

Table 3.227: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Consumptions on the same day come from the same sample | false | | |
| Use unit variability | true | | |
| Model-then-add | false | | |
| Covariate modelling | false | | |
| Iterate survey | false | | |
| Report consumptions and exposures per individual instead of per kg body weight | false | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |

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Table 3.227 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |

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Table 3.227 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Water concentration value (µg/kg) | 0.1 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Processing factors* |

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Table 3.227 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Processing factors* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |

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Table 3.227 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Sample based | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Correlate imputed values with sample potency | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Apply occurrence pattern percentages | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Occurrence patterns* |

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Table 3.227 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Target level | External | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Hazard characterisations* |
| Unit variability model | BetaDistribution | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Unit variability factors* |
| Estimates nature | Realistic | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Unit variability factors* |
| Unit variability parameter | VariabilityFactor | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Unit variability factors* |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I

Table 3.228: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute shorter than lifetime exposures | false | | |
| Consumptions on the same day come from the same sample | false | | |
| Model type | OIM | | |
| Model-then-add | false | | |
| Covariate modelling | false | | |
| Iterate survey | false | | |
| Report consumptions and exposures per individual instead of per kg body weight | false | | |

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Table 3.228 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Consumptions* |
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |

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Table 3.228 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |

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Table 3.228 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Water concentration value (µg/kg) | 0.1 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Processing factors* |

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Table 3.228 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Processing factors* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |

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Table 3.228 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Sample based | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Correlate imputed values with sample potency | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Apply occurrence pattern percentages | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Occurrence patterns* |

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Table 3.228 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Target level | External | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Hazard characterisations* |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier II

Table 3.229: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Consumptions on the same day come from the same sample | false | | |
| Use unit variability | true | | |
| Model-then-add | false | | |
| Covariate modelling | false | | |
| Iterate survey | false | | |
| Report consumptions and exposures per individual instead of per kg body weight | false | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food conversions* |

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Table 3.229 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |

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Table 3.229 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |

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Table 3.229 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Processing factors* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |

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Table 3.229 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |

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Table 3.229 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Parametric uncertainty | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Apply occurrence pattern percentages | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Hazard characterisations* |
| Unit variability model | BetaDistribution | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Unit variability factors* |

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Table 3.229 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Estimates nature | Realistic | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Unit variability factors* |
| Unit variability parameter | VariabilityFactor | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Unit variability factors* |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II

Table 3.230: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute shorter than lifetime exposures | false | | |
| Consumptions on the same day come from the same sample | false | | |
| Model type | OIM | | |
| Model-then-add | false | | |
| Covariate modelling | false | | |
| Iterate survey | false | | |
| Report consumptions and exposures per individual instead of per kg body weight | false | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Consumptions* |

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Table 3.230 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |

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Table 3.230 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |

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Table 3.230 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Processing factors* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |

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Table 3.230 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Include MRL fallback model | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |

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Table 3.230 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Correlate imputed values with sample potency | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Apply occurrence pattern percentages | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Occurrence patterns* |

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Table 3.230 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Target level | External | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Hazard characterisations* |

### Prospective dietary CRA (EFSA 2023) - Acute / Tier II

Table 3.231: Tier definition for Prospective dietary CRA (EFSA 2023) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Consumptions on the same day come from the same sample | false | | |
| Use unit variability | true | | |
| Model-then-add | false | | |
| Covariate modelling | false | | |
| Iterate survey | false | | |
| Report consumptions and exposures per individual instead of per kg body weight | false | | |
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food conversions* |

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Table 3.231 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |

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Table 3.231 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |

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Table 3.231 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Processing factors* |

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Table 3.231 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use distribution | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Processing factors* |
| Default concentration model | Empirical | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |

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Table 3.231 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Sample based | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |

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Table 3.231 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Occurrence patterns* |
| Target level | External | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Hazard characterisations* |
| Unit variability model | BetaDistribution | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Unit variability factors* |
| Estimates nature | Realistic | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Unit variability factors* |

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Table 3.231 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Unit variability parameter | VariabilityFactor | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Unit variability factors* |

### Prospective dietary CRA (EFSA 2023) - Chronic / Tier II

Table 3.232: Tier definition for Prospective dietary CRA (EFSA 2023) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute shorter than lifetime exposures | false | | |
| Consumptions on the same day come from the same sample | false | | |
| Model type | OIM | | |
| Model-then-add | false | | |
| Covariate modelling | false | | |
| Iterate survey | false | | |
| Report consumptions and exposures per individual instead of per kg body weight | false | | |
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Consumptions* |
| N (number of days in survey) | 2 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Consumptions* |

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Table 3.232 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |

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Table 3.232 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |

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Table 3.232 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |

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Table 3.232 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply processing factors | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Processing factors* |
| Use distribution | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Processing factors* |
| Default concentration model | Empirical | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |

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Table 3.232 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Censored values replacement | ReplaceByLOR | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Sample based | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |

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Table 3.232 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Parametric uncertainty | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Occurrence patterns* |
| Target level | External | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Hazard characterisations* |

### Prospective dietary CRA (EFSA 2024) - Acute / Tier II

Table 3.233: Tier definition for Prospective dietary CRA (EFSA 2024) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Consumptions on the same day come from the same sample | false | | |
| Use unit variability | true | | |
| Model-then-add | false | | |

continues on next page

Table 3.233 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Covariate modelling | false | | |
| Iterate survey | false | | |
| Report consumptions and exposures per individual instead of per kg body weight | false | | |
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |

continues on next page

Table 3.233 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |

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Table 3.233 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |

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Table 3.233 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Include processed derivatives of the focal food in measurement replacement | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Processing factors* |
| Use distribution | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Processing factors* |

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Table 3.233 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Sample based | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |

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Table 3.233 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Occurrence patterns* |

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Table 3.233 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Occurrence patterns* |
| Target level | External | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Hazard characterisations* |
| Unit variability model | BetaDistribution | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Unit variability factors* |
| Estimates nature | Realistic | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Unit variability factors* |
| Unit variability parameter | VariabilityFactor | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Unit variability factors* |

### Prospective dietary CRA (EFSA 2024) - Chronic / Tier II

Table 3.234: Tier definition for Prospective dietary CRA (EFSA 2024) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute shorter than lifetime exposures | false | | |
| Consumptions on the same day come from the same sample | false | | |

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Table 3.234 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Model type | OIM | | |
| Model-then-add | false | | |
| Covariate modelling | false | | |
| Iterate survey | false | | |
| Report consumptions and exposures per individual instead of per kg body weight | false | | |
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Consumptions* |
| N (number of days in survey) | 2 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |

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Table 3.234 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |

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Table 3.234 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |

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Table 3.234 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Include processed derivatives of the focal food in measurement replacement | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Processing factors* |

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Table 3.234 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use distribution | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Processing factors* |
| Default concentration model | Empirical | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |

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Table 3.234 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Sample based | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |

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Table 3.234 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Occurrence patterns* |
| Target level | External | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Hazard characterisations* |

#### Calculation of dietary exposures

Dietary exposures are calculated from consumptions per modelled food and concentration models. Optionally, also processing factors and unit variability models are applied.

- *Dietary exposures calculation*

Inputs used: *Consumptions by modelled food Food concentration models Processing factors Unit variability factors High exposure food-substance combinations Active substances Occurrence patterns Relative potency factors Food conversions Food concentration distributions*

Settings used

- *Calculation Settings*

### 3.4.3 Dust exposures

Dust exposures are the amounts of substances, expressed per kg bodyweight, to which individuals in a population are exposed from dust per day. Dust exposures are long-term/chronic exposures, they represent the average exposure per day over an unspecified longer time period.

This module has as primary entities: *Populations Substances*

Output of this module is used by: *Internal exposures*

### Dust exposures calculation

Long-term (chronic) exposure to substances via dust can be estimated as a single value calculated from single value inputs. MCRA implements the calculation method that is also available in the *RSExpo* tool. The long term (chronic) dust exposure assessment can be split in dermal and oral exposure related to exposure to substances in dust.

Dust exposures are generated using properties age, sex and *BSA* of a *simulated set of individuals* or, as an alternative, an existing set of individuals from another module (e.g., the *dietary exposures module*). Specify the reference population with option *Specify individuals for generating dust exposures* with settings *Simulate individuals* or *Use dietary individuals*.

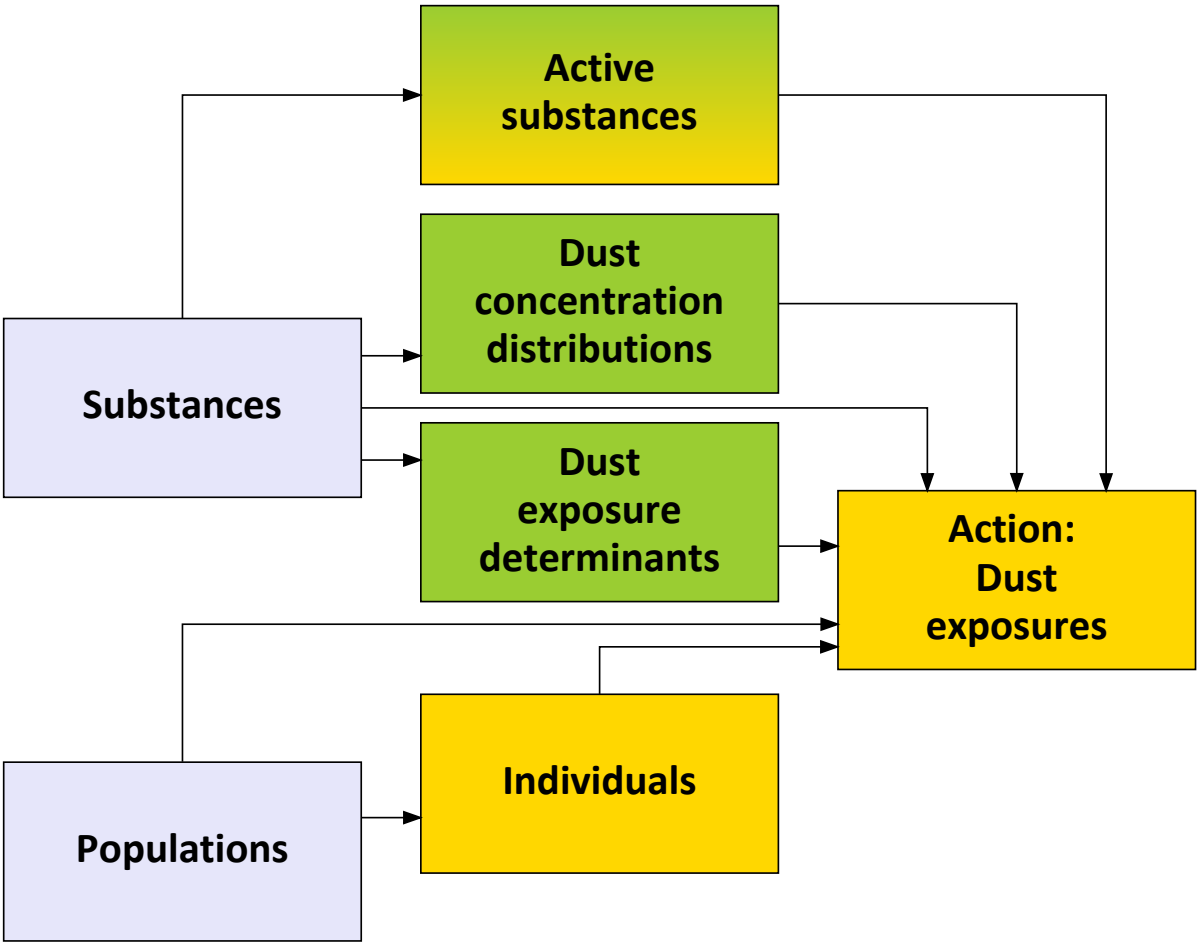


Figure 3.38: Modular design for dust exposures module when simulated individuals are used to generate exposures for source dust

### Dermal exposure

The calculation for dermal exposure is:

$$\mathrm{E}_{\mathrm{dust-derm}} = \frac{1}{\mathrm{BW}} \cdot \mathrm{f}_{\mathrm{d}} \cdot \mathrm{M}_{\mathrm{adh,d}} \cdot \frac{\mathrm{t}_{\mathrm{dust}}}{24} \cdot \mathrm{S} \cdot \mathrm{f}_{\mathrm{s,d}} \cdot \mathrm{c}_{\mathrm{d}}$$

Parameters used in the equation

$\mathrm{E}_{\mathrm{dust-derm}}$ : average daily external exposure of an individual to substances by dust dermal contact ($\mu g/kg\,bw/day$)

$BW$: body weight of the individual (default in $kg$)

$f_d$: fraction of substance in dust available for dermal contact ($\%$)

$M_{adh,d}$: amount of dust adhering to the skin (default in $g/m^2/day$)

$t_{dust}$: time of home dust exposure (in $h$)

$S$: body surface (default in $m^2$)

$f_{s,d}$: fraction of the body surface exposed to dust ($\%$)

$c_d$: substance concentration in dust (default in $\mu g/g$)

### Oral exposure

The calculation for exposure through oral ingestion is:

$$E_{dust-ing} = \frac{1}{BW} \cdot q_d \cdot c_d$$

Parameters used in the equation

$E_{dust-ing}$ : average daily external exposure of an individual to substances by dust ingestion ($\mu g/kg\,bw/day$)

$BW$: body weight of the individual (default in $kg$)

$q_d$: average daily amount of dust ingested by the individual (default in $g/day$)

$c_d$: substance concentration in dust (default in $\mu g/g$)

### Dust exposures settings

### Calculation settings

Table 3.235: Calculation settings for module Dust exposures.

| Name | Type | Description |
|---|---|---|
| Method for generating individual set for dust exposures | *DustExposuresIndividualGenerationMethod* | Method for generating individual set for generation of dust exposures. |
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |
| Selected exposure routes | *SelectedExposureRoutes* | Exposure routes included in exposure computation. |
| Time exposed to home dust | Numeric | Hours per day exposed to dust. |
| DUST: Population alignment method (RSExpo) dust exposures | *PopulationAlignmentMethod* | Population aligment methods for (RSExpo) dust exposure sourc |

### Output settings

Table 3.236: Output settings for module Dust exposures.

| Name | Type | Description |
|---|---|---|
| Show percentiles for | Numeric | Give specific percentiles of exposure distribution (%), e.g. 50 9 95 97.5 99 (space separated). |
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |
| Report consumptions and exposures per individual instead of per kg body weight | Boolean | Specifies whether body weights should be ignored and consumptions and exposures should be expressed per individual Otherwise, the consumptions and exposures are per kg body weight. |

### Uncertainty settings

Table 3.237: Uncertainty settings for module Dust exposures.

| Name | Type | Description |
|---|---|---|
| Resample dust concentrations | Boolean | Dust concentration data are resampled from the original databa using the bootstrap methodology (Efron 1979, Efron & Tibshir 1993). |
| Lower uncertainty limit (%) | Numeric | Percentage lower bound, e.g. 2.5%. |
| Upper uncertainty limit (%) | Numeric | Percentage upper bound, e.g. 97.5%. |

### Calculation of dust exposures

Dust exposures are calculated from dust concentration models.

- *Dust exposures calculation*

Inputs used: *Dietary exposures Dust concentration distributions Dust exposure determinants Individuals*

Settings used

- *Calculation Settings*

## 3.4.4 Soil exposures

Soil exposures are the amounts of substances, expressed per kg bodyweight, to which individuals in a population are exposed from soil per day. Soil exposures are long-term/chronic exposures, they represent the average exposure per day over an unspecified longer time period.

This module has as primary entities: *Populations Substances*

Output of this module is used by: *Internal exposures*

### Soil exposures calculation

Long-term (chronic) exposure to substances via dust can be estimated as a single value calculated from single value inputs. MCRA implements the calculation method that is also available in the *RSExpo* tool.

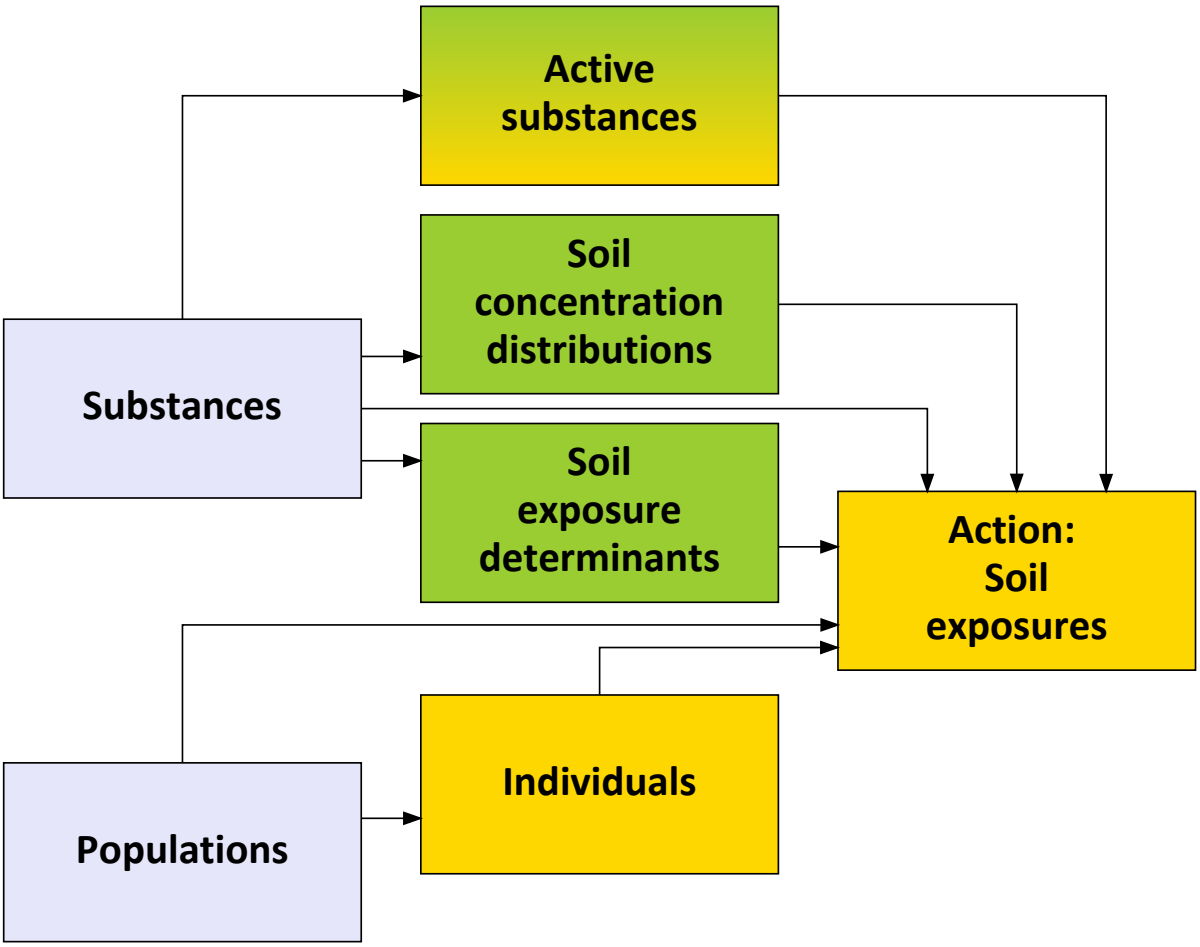


Figure 3.39: Modular design for soil exposures module when simulated individuals are used to generate exposures for source soil

### Soil exposures calculation details

The long term (chronic) soil exposure assessment is assessed as oral exposure related to exposure to substances in soil. MCRA applies in principle the equations as used in *RSExpo*.

Soil exposures are generated using properties age and sex of a *simulated set of individuals* or, as an alternative, an existing set of individuals (currently, the dietary individual population, see *module dietary exposures*). Specify the reference population with option *Specify individuals for generating soil exposures* with settings *Simulate individuals* or *Use dietary individuals*.

### Oral exposure

The calculation for oral exposure is:

$$\mathrm{E}_{\mathrm{soil-ing}} = \frac{1}{\mathrm{BW}} \cdot \mathrm{q}_{\mathrm{s}} \cdot \mathrm{c}_{\mathrm{s}}$$

Parameters used in the equation

$\mathrm{E}_{\mathrm{soil-ing}}$ : average daily external exposure of an individual to substances by soil ingestion ($\mu g/kg\, bw/day$)

$\mathrm{BW}$: body weight of the individual (default in $kg$)

$\mathrm{q}_{\mathrm{s}}$: average daily amount of soil ingested by the individual (default in $g/day$)

$\mathrm{c}_{\mathrm{s}}$: substance concentration in soil (default in $\mu g/g$)

### Soil exposures settings

### Calculation settings

Table 3.238: Calculation settings for module Soil exposures.

| Name | Type | Description |
|---|---|---|
| Method for generating individual set for soil exposures | *SoilExposuresIndividualGenerationMethod* | Method for generating individual set for generation of soil exposures. |
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |
| SOIL: Population alignment method (RSExpo) soil exposures | *PopulationAlignmentMethod* | Population aligment methods for (RSExpo) soil exposure sourc |

### Output settings

Table 3.239: Output settings for module Soil exposures.

| Name | Type | Description |
|---|---|---|
| Show percentiles for | Numeric | Give specific percentiles of exposure distribution (%), e.g. 50 9 95 97.5 99 (space separated). |
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |
| Report consumptions and exposures per individual instead of per kg body weight | Boolean | Specifies whether body weights should be ignored and consumptions and exposures should be expressed per individual Otherwise, the consumptions and exposures are per kg body weight. |

### Uncertainty settings

Table 3.240: Uncertainty settings for module Soil exposures.

| Name | Type | Description |
|---|---|---|
| Resample soil concentrations | Boolean | Soil concentration data are resampled from the original databas using the bootstrap methodology (Efron 1979, Efron & Tibshir 1993). |
| Lower uncertainty limit (%) | Numeric | Percentage lower bound, e.g. 2.5%. |
| Upper uncertainty limit (%) | Numeric | Percentage upper bound, e.g. 97.5%. |

### Calculation of soil exposures

Soil exposures are calculated from soil concentration models.

- *Soil exposures calculation*

Inputs used: *Dietary exposures Soil concentration distributions Soil exposure determinants Individuals*

Settings used

- *Calculation Settings*

## 3.4.5 Air exposures

Air exposures are the amounts of substances, expressed per kg bodyweight, to which individuals in a population are exposed from air per m3. Air exposures are long-term/chronic exposures, they represent the average exposure per m3 over an unspecified longer time period.

This module has as primary entities: *Populations Substances*

Output of this module is used by: *Internal exposures*

### Air exposures calculation

Long-term chronic exposure to airborne substances is estimated via single-value inputs. The MCRA uses the calculation methodology established in the *RSExpo* tool for inhalation and dermal exposure.

### Air exposures calculation details

Long-term (chronic) inhalation or dermal exposure can be estimated using a single value derived from single-value inputs. MCRA implements the same calculation method as the *RSExpo* tool for inhalation and dermal contact.

Air exposures are generated using properties age and sex of a *simulated set of individuals* or, as an alternative, an existing set of individuals (currently, the dietary individual population, see *module dietary exposures*). Specify the reference population with option *Specify individuals for generating air exposures* with settings *Simulate individuals* or *Use dietary individuals*.

### Inhalation exposure

The calculation for inhalation exposure is:

$$\mathrm{E}_{\mathrm{air-inhal}} = \frac{1}{\mathrm{BW}} \cdot \mathrm{F}_{\mathrm{a}} \cdot \left[\mathrm{c}_{\mathrm{in,a}} \cdot \mathrm{t}_{\mathrm{in}} + \mathrm{c}_{\mathrm{out,a}} \cdot (1 - \mathrm{t}_{\mathrm{in}})\right]$$

Parameters used in the equation

$\mathrm{E}_{\mathrm{air-inhal}}$: average daily external exposure of an individual to substances by air inhalation (default in $\mu g/kg\,bw/day$)

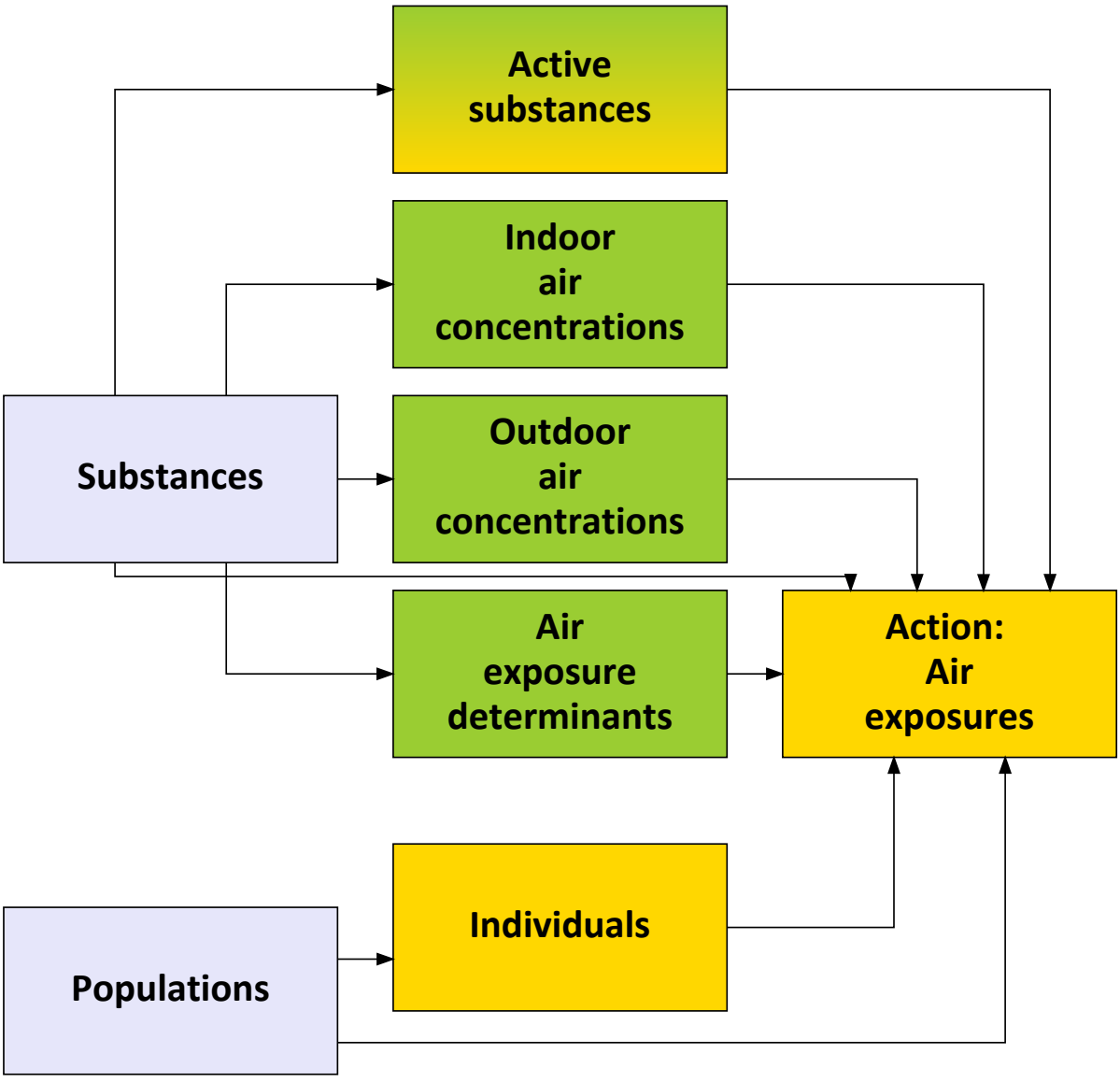


Figure 3.40: Modular design for air exposures module when simulated individuals are used to generate exposures for source air

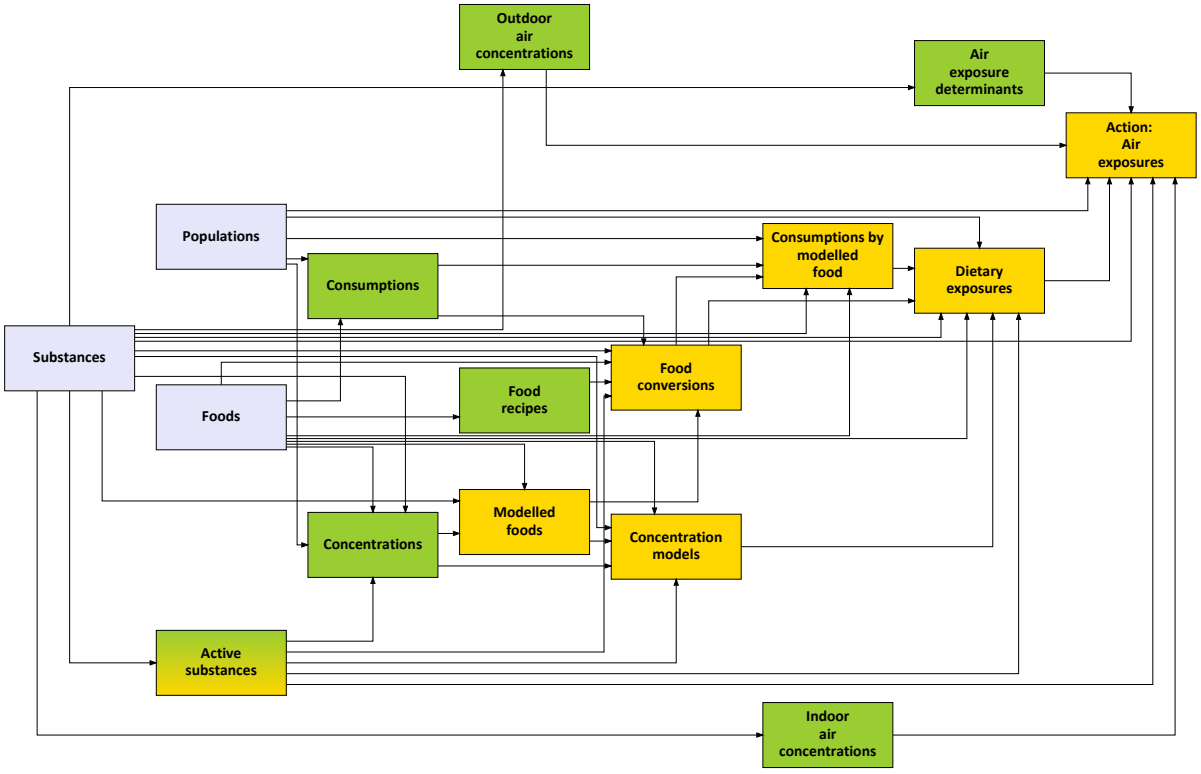


Figure 3.41: Modular design for air exposures module when dietary individuals are used to generate exposures for source air

$\mathtt{BW}$: body weight of the individual (default in $kg$)

$\mathtt{F}_{\mathtt{a}}$: daily ventilatory flow ($m^3/day$)

$\mathtt{t}_{\mathtt{in}}$: fraction of daily time spend indoors ($/1$)

$\mathtt{c}_{\mathtt{in,a}}$: substance concentration in indoor air (default in $\mu g/m^3$)

$\mathtt{c}_{\mathtt{out,a}}$: substance concentration in outdoor air (default in $\mu g/m^3$)

## Dermal exposure

The calculation for dermal exposure is:

$$\mathtt{E}_{\mathtt{air-derm}} = \frac{1}{\mathtt{BW}} \cdot \mathtt{S} \cdot \mathtt{F}_{\mathtt{s,a}} \cdot \mathtt{v}_{\mathtt{p}} \cdot \left[\mathtt{c}_{\mathtt{in,a}} \cdot \mathtt{t}_{\mathtt{in}} + \mathtt{c}_{\mathtt{out,a}} \cdot (1 - \mathtt{t}_{\mathtt{in}})\right]$$

Parameters used in the equation

$\mathtt{E}_{\mathtt{air-derm}}$: average daily external exposure of an individual to substances by air dermal contact (default in $\mu g/kg\, bw/day$)

$\mathtt{BW}$: body weight of the individual (default in $kg$)

$\mathtt{S}$: body surface ($m^2$)

$\mathtt{F}_{\mathtt{s,a}}$: fraction of the body surface exposed to air ($/1$), default = 0.15

$\mathtt{v}_{\mathtt{p}}$: deposition velocity of airborne particles onto the skin's surface ($m/day$), default = 2.15

$\mathtt{t}_{\mathtt{in}}$: fraction of daily time spend indoors ($/1$)

$\mathtt{c}_{\mathtt{in,a}}$: substance concentration in indoor air (default in $\mu g/m^3$)

$\mathtt{c}_{\mathtt{out,a}}$: substance concentration in outdoor air (default in $\mu g/m^3$)

### Air exposures settings

### Calculation settings

Table 3.241: Calculation settings for module Air exposures.

| Name | Type | Description |
|---|---|---|
| Method for generating individual set for air exposures | *AirExposuresIndividualGenerationMethod* | Method for generating individual set for generation of air exposures. |
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |
| Selected exposure routes | *SelectedExposureRoutes* | Exposure routes included in exposure computation. |
| Deposition velocity | Numeric | Deposition velocity of airborne particles onto the skin's surface (m/h). |
| Default air body exposure fraction | Numeric | Default fraction of total body surface area exposed to air. Used when no distributions (for specific sub-groups) are found in the data. |

### Output settings

Table 3.242: Output settings for module Air exposures.

| Name | Type | Description |
|---|---|---|
| Show percentiles for | Numeric | Give specific percentiles of exposure distribution (%), e.g. 50 9 95 97.5 99 (space separated). |
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |
| Report consumptions and exposures per individual instead of per kg body weight | Boolean | Specifies whether body weights should be ignored and consumptions and exposures should be expressed per individual Otherwise, the consumptions and exposures are per kg body weight. |

### Uncertainty settings

Table 3.243: Uncertainty settings for module Air exposures.

| Name | Type | Description |
|---|---|---|
| Resample indoor/outdoor air concentrations | Boolean | Air concentration data (indoor and outdoor) are resampled fron the original database using the bootstrap methodology (Efron 1979, Efron & Tibshirani 1993). |
| Lower uncertainty limit (%) | Numeric | Percentage lower bound, e.g. 2.5%. |
| Upper uncertainty limit (%) | Numeric | Percentage upper bound, e.g. 97.5%. |

### Calculation of air exposures

Air exposures are calculated from air concentration models.

- *Air exposures calculation*

Inputs used: *Dietary exposures Air concentration distributions Air exposure determinants Individuals*

Settings used

- *Calculation Settings*

### 3.4.6 Occupational exposures

Occupational exposures are the amounts of substances to which individuals are exposed while performing job tasks. Occupational exposures are long-term/chronic exposures, they represent the average exposure per day over an unspecified longer time period.

This module has as primary entities: *Substances*

Output of this module is used by: *Internal exposures*

#### Occupational exposures calculation

Long-term (chronic) occupational exposure to substances refers to contact with chemical, physical, or biological agents that occurs while performing job-related activities. Respiratory Protective Equipment (*RPE*) is a particular type of Personal Protective Equipment (*PPE*), used to protect the individual wearer against the inhalation of hazardous substances in the workplace air.

#### Occupational exposures settings

#### Calculation settings

Table 3.244: Calculation settings for module Occupational exposures.

| Name | Type | Description |
|---|---|---|
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Selected exposure routes | *SelectedExposureRoutes* | Exposure routes included in exposure computation. |
| Method for generating occupational exposures | *ExposureApproachMethod* | Method for generating occupational exposures (modelled or measured). |
| Method for generating occupational exposures | *OccupationalExposureModelType* | Method for generating occupational exposures (based on a specified percentile or distribution). |
| Select a percentage (with corresponding percentile) | Numeric | Select a percentage (with corresponding percentile). Note, percentages may very within occupational task exposures. A warning is thrown when the selected percentage is not available for a specific the task exposure. |
| Compute external doses | Boolean | Compute external occupational doses for the exposure scenario |
| Calculation method | *OccupationalExposuresCalculationMethod* | Method for calculating occupational exposures. |
| Ventilatory flow rate (m3/day) | Numeric | Ventilatory flow rate for occupational inhalation exposures (in m3/day). |
| Nominal body surface area (cm2) | Numeric | Nominal body surface area (in cm2). |
| Fraction skin exposed | Numeric | Fraction skin exposed for occupational dermal exposures. |

#### Output settings

Table 3.245: Output settings for module Occupational exposures.

| Name | Type | Description |
|---|---|---|
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |

### Calculation of occupational exposures

Occupational exposures are calculated from job task exposures data.

- *Occupational exposures calculation*

Inputs used: *Occupational task exposures Occupational scenarios*

Settings used

- *Calculation Settings*

## 3.4.7 Occupational scenarios

Occupational scenarios are scenarios, tasks and scenario tasks associated with specific job tasks performed by workers.

Output of this module is used by: *Occupational task exposures Internal exposures HBM analysis Occupational exposures*

### Occupational scenarios from data

### Occupational scenarios data formats

Occupational scenarios.

Download empty dataset template: Zipped CSV Excel

### Occupational scenarios

Definitions of occupational exposure scenarios, described as combinations of different tasks/activities and task determinants (e.g., use of RPE).

Table 3.246: Table definition for Occupational scenarios.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| id | AlphaNumeric (50) | Identifier of specific scenario. | id, idScenario, idOccupational-Scenario | Yes |
| Name | AlphaNumeric (100) | The name of the scenario. | Name | No |
| Description | AlphaNumeric (200) | Description of the scenario. | Description | No |
| CaseControl | *CaseControlType* | Scenario is case or control. | CaseControl | No |

Accepted table names: OccupationalScenarios.

### Occupational tasks

Definitions of occupational tasks.

Table 3.247: Table definition for Occupational tasks.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| id | AlphaNumeric (50) | Identifier of specific task. | id, idTask, idOccupational-Task | Yes |
| Name | AlphaNumeric (100) | The name of the occupational task. | Name | No |
| Description | AlphaNumeric (200) | Description of the occupational task. | Description | No |

Accepted table names: OccupationalTasks.

### Occupational scenario tasks

Table linking occupational tasks/activities to scenarios. I.e., describing what activities are part of a scenario, including details on task duration and other determinants (e.g., use of RPE), described via the contributing tasks relationship.

Table 3.248: Table definition for Occupational scenario tasks.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idOccupational-Scenario | AlphaNumeric (50) | Reference to the scenario. | idOccupational-Scenario, idScenario | Yes |
| idOccupational-Task | AlphaNumeric (50) | Reference to the task that is part of the scenario. | idOccupational-Task, idTask | Yes |
| Duration | Numeric | Duration of performing the task within this scenario. | Duration | Yes |
| Frequency | Numeric | Frequency with which the task is executed within this scenario, specified in number of times per day/week/etc. The resolution of the frequency is specified by the frequency resolution field. | Frequency | Yes |
| Frequency-Resolution | *Frequency-ResolutionType* | Resolution of the specific task frequency (e.g. per day, per week, etc.). | Frequency-Resolution | Yes |
| RPE type | *RPEType* | Type of RPE (e.g., None, RPE). If not specified then considered to be undefined. | RPEType, RPE | No |
| Hand protection type | *RPEType* | Type of hand protection (e.g., None, Gloves). If not specified then considered to be undefined. | HandProtection-Type, HandProtection, Gloves | No |
| Protective clothing type | *ProtectiveClothing-Type* | Type of protective clothing (e.g., None, ProtectiveClothing). If not specified then considered to be undefined. | Protective-ClothingType, Protective-Clothing, Clothing | No |

Accepted table names: OccupationalScenarioTasks, ScenarioTasks, ContributingScenarios.

#### Occupational scenarios as data

Occupational scenarios can be entered using the internal, relational data format.

- *Occupational scenarios data formats*
- *Occupational scenarios from data*

### 3.4.8 Occupational task exposures

Occupational task exposures are exposures associated with specific job tasks performed by workers.

This module has as primary entities: *Substances*

Output of this module is used by: *Occupational exposures*

#### Occupational task exposures from data

#### Occupational task exposures data formats

Occupational task exposures.

Download empty dataset template: Zipped CSV Excel

#### Occupational task exposures

Exposure (percentile) estimates of the occupational tasks.

Table 3.249: Table definition for Occupational task exposures.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idOccupational-Task | AlphaNumeric (50) | Activity for which the estimate applies. | idTask, idOccupational-Task | Yes |
| ExposureRoute | *ExposureRoute* | The exposure route. | ExposureRoute, Route | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| RPE type | *RPEType* | Type of RPE considered for this activity exposure estimate. If not specified, then considered to be undefined. | RPEType, RPE | No |
| Hand protection type | *HandProtectionType* | Type of protective hand protection considered for this activity exposure estimate. If not specified, then considered to be undefined. | HandProtection-Type, HandProtection, Gloves | No |
| Protective clothing type | *RPEType* | Type of protective clothing considered for this activity exposure estimate. If not specified, then considered to be undefined. | Protective-ClothingType, Protective-Clothing, Clothing | No |
| Unit | *JobTaskExposure-Unit* | Unit of the estimate. | Unit, JobTask-ExposureUnit | Yes |
| ExposureType | *JobTaskExposure-EstimateType* | Type of the exposure estimate. | ExposureType, EstimateType | No |
| Percentage | Numeric | The percentage to which the percentile value belongs. | Percentage, Percentile | Yes |
| Value | Numeric | The percentile value. I.e., the exposure value belonging to the specified percentage. | Value, Exposure | Yes |
| Reference | AlphaNumeric (200) | Reference to the source from which this exposure value is obtained. | Reference, References, Source, Sources | No |

Accepted table names: OccupationalTaskExposures, TaskExposures.

### Occupational task exposures as data

Occupational task exposures can be entered using the internal, relational data format.

- *Occupational task exposures data formats*
- *Occupational task exposures from data*

Inputs used: *Occupational scenarios*

## 3.4.9 Consumer product exposures

Consumer product exposures are the amounts of substances, expressed per kg bodyweight, to which individuals in a population are exposed from average consumer product usage per individual. Consumer product exposures are long-term/chronic exposures, they represent the average exposure per day over an unspecified longer time period.

This module has as primary entities: *Populations Substances Consumer products*

Output of this module is used by: *Internal exposures*

### Consumer product exposures calculation

Long-term (chronic) exposure to substances via consumer products is based on:

1. realistic product usage information obtained from surveys. Currently, information on the usage (frequency and amount) of personal care products and household cleaning products in various European countries is included. The methods implemented are following the approach in *PACEM* and *RSExpo*.
2. simulated exposure percentiles, preferably covering percentages from p = 0 to p = 100. Available as download from PACEMweb.

See also, PACEM website.

### Consumer product exposures calculation details

The long term (chronic) consumer product exposure assessment through oral ingestion, dermal contact and inhalation via personal care products, household cleaning products and do-it-yourself products is following the methodology as developed in *PACEM* and *RSExpo*. MCRA applies in principle the equations as used in PACEM and RSExpo.

Consumer product exposures are generated using an existing set of individuals, see *module consumer product use frequencies*. Together with information on the application amounts the exposure of personal care products, household cleaning products and do-it-yourself products in various European countries is estimated.

Two approaches are available, depending on the *Consumer product exposure calculation method* setting:

- **Use concentration models and survey**
- **Use percentiles**

### Use consumer product concentration models and survey

The calculation for exposure to consumer products is:

$$\mathtt{E}_{\mathtt{consumer-product}} = \mathtt{frequency} \cdot \mathtt{amount} \cdot \mathtt{concentration} \cdot \frac{\sum_{route=1}^{p} EF_{route}}{BW} \cdot \mathtt{occurrence}\% / 100$$

Parameters used in the equation

$\mathtt{E}_{\mathtt{consumer-product}}$: average daily external exposure of an individual to substances in consumer products (default in $\mu g / kg\, bw / day$)

$\mathtt{BW}$: body weight of the individual (default in $kg$)

$\mathtt{amount}$: application amount ($mg$)

$\mathtt{concentration}$: substance concentration in consumer product ($mg/kg$)

$\mathtt{frequency}$: use frequency of een individual

$\mathtt{occurrence}\%$: occurence percentage, % of products with substance (default 100%)

$\mathtt{EF}_{\mathtt{route}}$: exposure fraction of a specific route (substance specific)

### Use consumer product percentiles

For each exposure set a lognormal distribution is fitted to the percentile data using R package rriskDistributions. Parameters $\mu$ and $\sigma$, which represent the mean and standard deviation on log scale, are used to simulate the exposure for each individual. Note that the total exposure is the sum of all exposures of the underlying products as defined for the exposure set.

Select a *Consumer product filter method* to match individual properties, such as gender and age, with the the population characterists describing an assessment.

- **Filter by gender and age** option is the most restrictive,

- **No filtering** selects any assessments regardsless of its specified population.
- **Filter by age**, this option matches the individual's age with the population criteria of the assessments, selecting any assessment that fits the age group regardless of gender.
- **Filter by gender**, this option matches the individual's gender with the population criteria of the assessments, selecting any assessment that fits the gender regardless of age.

Individuals are generated based on the primary entity settings in module *populations*. The **Compute** option generates individuals with gender categories "male" and "female" and ages between 0 and 100 year. For a specific population, such as females between 18 and 65 years old, select **Use data** and specify the population characterics in a file.

### Consumer product exposures settings

### Calculation settings

Table 3.250: Calculation settings for module Consumer product exposures.

| Name | Type | Description |
|---|---|---|
| Selected exposure routes | *SelectedExposureRoutes* | Exposure routes included in exposure computation. |
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |
| Consumer product exposure calculation method | *ConsumerProductExposureCalculationMethod* | Method types for consumer product exposure calculation. |
| Consumer product assessment filter method | *ConsumerProductAssessmentMatchingMethod* | Method types for consumer product assessment filtering based gender and age ranges. |

### Output settings

Table 3.251: Output settings for module Consumer product exposures.

| Name | Type | Description |
|---|---|---|
| Show percentiles for | Numeric | Give specific percentiles of exposure distribution (%), e.g. 50 9 95 97.5 99 (space separated). |
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |
| Report consumptions and exposures per individual instead of per kg body weight | Boolean | Specifies whether body weights should be ignored and consumptions and exposures should be expressed per individual Otherwise, the consumptions and exposures are per kg body weight. |

### Uncertainty settings

Table 3.252: Uncertainty settings for module Consumer product exposures.

| Name | Type | Description |
|---|---|---|
| Lower uncertainty limit (%) | Numeric | Percentage lower bound, e.g. 2.5%. |
| Upper uncertainty limit (%) | Numeric | Percentage upper bound, e.g. 97.5%. |

### Calculation of consumer product exposures

Consumer product exposures are calculated from consumer product concentration, use frequencies and amount models.

- *Consumer product exposures calculation*

Inputs used: *Consumer product concentration distributions Consumer product use frequencies Consumer product exposure determinants Individuals Consumer product exposure estimates*

Settings used

- *Calculation Settings*

## 3.4.10 Consumer product exposure estimates

Consumer product exposure estimates describing metadata and the distribution of chemical substances in consumer products for exposure assessments from the Probabilistic Aggregate Consumer Exposure Model (PACEM).

This module has as primary entities: *Substances Consumer products*

Output of this module is used by: *Consumer product exposures*

### Consumer product exposure estimates from data

### Consumer product exposure estimates data formats

The Probabilistic Aggregate Consumer Exposure Model (*PACEM*), see also PACEM website, estimates long-term exposure to chemical substances found in numerous consumer products. Examples include personal care products (such as shampoo, body lotion, and soap), household cleaning products, and do-it-yourself products. The exposure results are provided as percentiles, preferably covering percentages from p = 0 to p = 100.

A PACEM assessment is defined by an assessment ID, name, and description. In addition to general population characteristics such as gender and age, the exposure type (acute or chronic) must be specified.

An assessment can contain multiple exposure sets. Typically, an exposure set outlines metadata such as the targeted substance, a specific selection of consumer products, exposure routes and the designated endpoints:

- Systemic dose: the amount of substance absorbed into the body per kilogram of body weight of the exposed individual.
- Dermal load: the amount of substance per square centimeter of exposed skin. Dermal load is specifically used to evaluate the risk of sensitization from sensitizing substances.

Currently, only

1. systemic endpoints are implemented,
2. exposure sets with one exposure route are allowed.

Consumer product exposure data.

Download empty dataset template: Zipped CSV Excel

### Consumer product exposure percentiles

Describes the exposure percentiles in the study.

Table 3.253: Table definition for Consumer product exposure percentiles.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExposureSet | AlphaNumeric (50) | Exposure set identification code. | idExposureSet, ExposureSet | Yes |
| Percentage | Numeric | Percentage value of the exposure percentile. | Percentage | Yes |
| Value | Numeric | Value of the exposure percentile. | Value | Yes |

Accepted table names: ConsumerProductExposurePercentiles, CPExposurePercentiles.

### Consumer product exposure assessments

Describes the exposure assessments in the study.

Table 3.254: Table definition for Consumer product exposure assessments.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idAssessment | AlphaNumeric (50) | Exposure assessment identification code. | id, idAssessment, Assessment | Yes |
| Name | AlphaNumeric (100) | Name of the exposure assessment. | name | No |
| Description | AlphaNumeric (200) | Exposure assessment description. | Description | No |
| ExposureType | *ExposureType* | The exposure type associated with the assessment (i.e., chronic or acute). | ExposureType | Yes |
| Location | AlphaNumeric (50) | The location or country where survey is held. It is recommended to use ISO Alpha-2 country codes. | Location, Country | No |
| AgeMin | Numeric (50) | Specifies the minimum age (in years) of the assessment group. | AgeMin, MinAge | No |
| AgeMax | Numeric (50) | Specifies the maximum age (in years) of the assessment group. | AgeMax, MaxAge | No |
| Gender | *GenderType* | The gender of the assessment group. | Gender | No |
| Reference | AlphaNumeric (200) | Reference(s) to PACEM assessments. | References | No |

Accepted table names: ConsumerProductExposureAssessments, CPExposureAssessments.

### Consumer product exposure sets

Describes the exposure sets in the study.

Table 3.255: Table definition for Consumer product exposure sets.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExposureSet | AlphaNumeric (50) | Exposure set identification code. | idExposureSet, Set | Yes |
| idAssessment | AlphaNumeric (50) | Name of the exposure assessment. | idAssessment, Assessment | Yes |
| idSubstance | AlphaNumeric (50) | The unique identification code of the substance. This code may be from an existing coding system, such as CAS-codes or Param codes of EFSA, or it may be a user-defined code. | idSubstance, Substance | Yes |
| idProducts | AlphaNumeric (200) | The consumer products associated with the assessment, separated by a pipe (\|) character. | idProducts, Products | Yes |
| EstimateType | *ConsumerProductExposureEstimateType* | The estimate type associated with the assessment. | EstimateType | No |
| ExposureRoutes | AlphaNumeric (200) | The exposure routes associated with the assessment, separated by a pipe (\|) character. | ExposureRoutes | Yes |
| PercentageZeros | Numeric | The percentage of zeros associated with the assessment. | PercentageZeros, PercentageZeroes | No |
| Unit | *ConsumerProductExposureEstimateUnit* | Unit for the exposure. This is typically a dose unit, such as mg/cm2/day (DermalLoad) or mg/kg bw/day (SystemicDose). | Unit | No |

Accepted table names: ConsumerProductExposureSets, CPExposureSets.

### Consumer product exposure estimates settings

### Output settings

Table 3.256: Output settings for module Consumer product exposure estimates.

| Name | Type | Description |
|---|---|---|
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |

### Consumer product exposure estimates as data

Consumer product exposure estimates from Probabilistic Aggregate Consumer Exposure Model (PACEM).

- *Consumer product exposure estimates data formats*
- *Consumer product exposure estimates from data*

### 3.4.11 Individuals

Simulates individuals with properties like age, body weight, sex, and body surface area.

This module has as primary entities: *Populations*

Output of this module is used by: *Occupational exposures Internal exposures Dust exposures Soil exposures Air exposures Consumer product exposures*

#### Individuals from data

#### Individuals calculation

This module is used to generate a set of simulated individuals with properties age, bodyweight, sex and body surface area (BSA). The simulated individuals are used for generating exposures in the modules for sources like dust, air and soil. After selecting *Simulate individuals* (see option 'Specify individuals for generating *dust*, *air* and *soil* exposures') in the *dust exposures*, *air exposures* and *soil exposures* modules the individuals module becomes visible. Also specify the number of individuals.

Ages are randomly drawn in a range from 0 to 100. For sex, available levels are *male* and *female*. Bodyweights are calculated as

$$\texttt{BW} = \texttt{BW}_{\texttt{birth}} + 4.47 \cdot \texttt{age} - 0.093 \cdot \texttt{age}^2 + 0.00061 \cdot \texttt{age}^3$$

(see https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2020.6223, appendix, sensitivity analysis)

$\texttt{BW}$: body weight of the individual (default in $kg$)

$\texttt{BW}_{\texttt{birth}}$: body weight at birth = 3.68 (in $kg$)

The *BSA* is based on an allometric scaling using a standard bodyweight of 70 $kg$ and standard BSA of 2.70 $m^2$. Then the applied scaling is:

$$\texttt{scaling} = \texttt{BW}_{\texttt{standard}} / \texttt{BW}^{(1-0.7)}$$

$$\texttt{BSA} = \texttt{BSA}_{\texttt{standard}} / \texttt{scaling}$$

See also *dust exposures*, *soil exposures* and *air exposures* module.

#### Individuals data formats

Simulates individuals with properties like age, body weight, sex, and body surface area.

Download empty dataset template: Zipped CSV Excel

#### Individual sets

Contains the definitions of individual sets.

Table 3.257: Table definition for Individual sets.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSet | AlphaNumeric (50) | Unique identification code of the individual set. | id, idSet, idIndividualSet, SetCode, Code | Yes |
| Name | AlphaNumeric (100) | Name of the individual set. | Name | No |
| Description | AlphaNumeric (200) | Description of the individual set. | Description | No |
| BodyWeight-Unit | AlphaNumeric (50) | The unit of bodyweight of the individuals of the set: kg (default) or g. | BodyWeight-Unit, UnitBody-Weight, WeightIn | No |
| AgeUnit | AlphaNumeric (50) | The unit of age, i.e., year or month. | UnitAge, agein, AgeUnit | No |
| StartDate | DateTime | The starting date of the set. | StartDate | No |
| EndDate | DateTime | The end date of the set. | EndDate | No |
| idPopulation | AlphaNumeric (50) | Unique identification code of the population. | IdPopulation, PopulationId | No |

Accepted table names: IndividualSets, IndividualSet.

### Individuals

The individuals of a survey are recorded in the Individuals table. Add additional properties like Region, Breastfeeding to further describe an individual. In table IndividualProperties, each property in the Individuals table is described (recommended way). Note that only those properties that are available in the Individuals table are used in module Populations, table Populations or PopulationIndividualPropertyValues to subset the individuals. This is only relevant when the UseData option in the population module is used.

Table 3.258: Table definition for Individuals.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual | AlphaNumeric (50) | Unique identification code of the individual. | idIndividual, IndividualId, Individual, Id | Yes |
| idFoodSurvey | AlphaNumeric (50) | The identification code / short name of survey. | idSurvey, idFoodSurvey, Survey, FoodSurvey, SurveyId, FoodSurveyId, SurveyCode, idSet, SetCode, Code | Yes |
| BodyWeight | Numeric | The body weight of the individual. | BodyWeight, Weight | No |
| Sampling-Weight | Numeric | The sampling weight for an individual (default = 1). | SamplingWeight | No |
| NumberOf-SurveyDays | Integer | The number of days the individual participated in the survey. | NumberOf-SurveyDays, NumberOfDays-InSurvey, DaysInSurvey, NDaysInSurvey | No |
| Name | AlphaNumeric (100) | Name or label of the individual. | Name | No |
| Description | AlphaNumeric (200) | Additional description of the individual. | Description | No |
| Individual properties | | Other individual properties can be added like the fields Age, Gender, Region etc. These properties are automatically parsed as co-factors or co-variables. | | No |

Accepted table names: Individuals, SurveyIndividuals, ConsumptionSurveyIndividuals, FoodConsumptionSurveyIndividuals.

### Individual properties

This table is used to describe the properties used in the Populations or PopulationIndividualPropertyValues table characterising the population (table Populations) and/or the properties used in the Individuals table characterising an individual. Properties like Age, Gender, Region are describing an individual (PropertyLevel = Individual). Properties like Period (for populations) or Month (sampling date for an individual day) are describing an individual day (PropertyLevel = IndividualDay).

Table 3.259: Table definition for Individual properties.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual-Property | AlphaNumeric (50) | The code of the property. | idIndividual-Property, Individual-PropertyId, Individual-Property | Yes |
| Name | AlphaNumeric (100) | The name of the property. | Name | No |
| PropertyLevel | *PropertyLevelType* | The level of the property. This type follows a controlled terminology, with possible values: Individual or IndividualDay. | PropertyLevel, LevelProperty | No |
| Description | AlphaNumeric (200) | Description of the property. | Description | No |
| Type | *IndividualProperty-Type* | This field specifies the type of the values of this individual property. This type follows a controlled terminology, with possible values: Boolean, Categorical (default), Numeric, Nonnegative, Integer, NonnegativeInteger, Month, Datetime, Gender. | Type | No |

Accepted table names: IndividualProperties, IndividualProperty.

### Individual property values

Not recommended. This table describes individual property values. Property values are describing an individual for properties like e.g. Region, Breastfeeding. The recommended way is to add these columns as additional columns in the Individuals table. In table IndividualProperties, each property in the IndividualPropertyValues table is described.

Table 3.260: Table definition for Individual property values.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual | AlphaNumeric (50) | The identification number of the Individual. | Id | Yes |
| PropertyName | AlphaNumeric (50) | The name of the property. | Name | Yes |
| TextValue | AlphaNumeric (50) | The value of the property as text value. | | No |
| DoubleValue | Numeric | The value of the property as number. | | No |

Accepted table names: IndividualPropertyValues, IndividualPropertyValue.

### Individuals settings

### Calculation settings

Table 3.261: Calculation settings for module Individuals.

| Name | Type | Description |
|---|---|---|
| Number of simulated individuals | Numeric | Number of individuals that is simulated for dust exposures. |
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |

### Uncertainty settings

Table 3.262: Uncertainty settings for module Individuals.

| Name | Type | Description |
|---|---|---|
| Resample simulated individuals | Boolean | Simulated individuals are resampled from the set of original simulated individuals (air, soil and dust modules) using the bootstrap methodology (Efron 1979, Efron & Tibshirani 1993) |

### Individuals as data

When provided as data, in the form of sets of individuals, each individual can be specified with additional properties.

- *Individuals data formats*
- *Individuals from data*

Settings used

- *Calculation Settings*

### Calculation of individuals

Simulates individuals.

- *Individuals calculation*

Settings used

- *Calculation Settings*

## 3.4.12 High exposure food substance combinations

Identification of food-as-eaten/modelled food/substance combinations that have the highest expected contribution to exposure based on a simple screening model.

This module has as primary entities: *Foods Substances Effects*

Output of this module is used by: *Dietary exposures*

### High exposure food substance combinations calculation

A full Monte Carlo analysis can be unwieldy for large cumulative assessment groups (CAGs) and/or large number of foods or concentration data. An algorithmic approach was developed to handle large CAGs. Two unique features of MCRA are:

- contributions to the exposure results can be seen both in terms of foods as eaten (e.g. white bread) and modelled foods (e.g. wheat), and

- a drill-down can be made into the exact foods and substances contributing for simulated individuals or individual-days in the upper tail.

The number of combinations of simulation, substance, modelled food and food as eaten can be very large. To avoid memory problems with very large datasets, an additional optional modelling step, named *screening*, was added to MCRA. *Screening* should be used if the data dimensions are too large for a direct analysis. Screening identifies risk drivers. A full analysis based on screened risk drivers will still retain all food/substance combinations in the exposure calculation, and will therefore produce exactly the same cumulative exposure distribution, and allow to see contributions of all substances and all modelled foods. Details with respect to foods as eaten are however restricted to the risk drivers selected in the screening step. For more details see *screening calculation for large Cumulative Assessment Groups*.

The two-step approach consists of:

- **Step 1: Data screening and selection of risk drivers**
  Run a simple analysis for each potential source/substance combination (SCC). Here source means the combination of food as eaten and modelled food, for example apple in apple pie. The screening is based on this combination, and not just modelled foods, to avoid problems with potentially multi-modal consumption distributions as much as possible (see van der Voet et al. 2014). SCCs are also referred to as risk driver components. The screening step in MCRA implements a simple model that is applied to each SCC. The model calculates a percentile of interest in a distribution, consisting of a spike of zeroes (non-consumptions), and a mixture of two lognormal distributions for the exposure related to censored and positive concentrations, respectively. SCCs (risk driver components) can be combined to measured source/substance combinations (MSCCs, risk drivers). For example APPLE/apple juice/captan and APPLE/apple pie/captan combine to APPLE/captan. MCRA has an interface which identifies the Top-$N$ SCCs (based on a chosen exposure percentile, e.g. p95) with an option to select $N$ based on cumulative importance according to some criterion. Remark: Screening is performed before concentration modelling. Therefore there is no correction for processing at the screening stage. Note, originally SCC stands for Source Compound Combination, MSCC for Measured Source Compound Combination.
- **Step 2: Full MC analysis**
  Perform the standard MC to all combinations of substances and foods, but restrict the stored information regarding foods as eaten to the SCCs selected in step 1.

The screening method requires to specify:

- Which percentile to consider for each single source/substance combination (SCC, potential risk driver component) (default p95)
- Which percentage of all exposures (according to the screening model) should be covered by the selected set of SCCs (default 95%)
- How to impute censored (non-detect or non-quantified) concentrations (c < LOR) in the screening step. The choice of a factor 0 (default) represents optimistic imputation, the choice of a factor 1 represents a pessimistic imputation. It may be noted that a factor 1 (pessimistic imputation) may select many SCCs (risk driver components) with relatively high LORs and high RPFs, but with only censored measurements. Choosing a lower fraction, e.g. 0.25 can be useful if a more realistic method is sought.

Based on limited experience with the EFSA test data, useful settings of these three screening parameters were found to be (95, 95, 0) in preparation for an EFSA optimistic run, and (50, 95, 0.25) in preparation for an EFSA pessimistic run. See also screening calculation *acute exposure* and *chronic exposure* .

### Screening calculation for large Cumulative Assessment Groups

### Statistical model for the screening step (acute exposure)

The screening step implements a simple model that is applied to each SCC. Assume independent *NonDetectSpike-LogNormal* (NDS-LN) models for both the consumptions of modelled food in source S and the concentrations of substance C in source S. A 'non-detect' consumption is assumed to be a zero consumption. A censored concentration will be imputed by a user-specified fraction f of the Limit of Reporting. Then the model for consumption has 3 parameters and the model for concentration has four parameters, as specified in Table 3.263. Note that the parameters of the consumption distribution are estimated from the consumption data using sampling weights if these have been provided in the consumption data set.

Table 3.263: Parameters for screening models (per source/substance)

| parameter | consumptions | concentrations |
|---|---|---|
| probability of a positive | $\pi_x$ | $\pi_c$ |
| mean positives (ln scale) | $\mu_x$ | $\mu_c$ |
| standard deviation positives (ln scale) | $\sigma_x$ | $\sigma_c$ |
| value to use for censored values (ln scale) | | $f \cdot L_c$ |

Exposure is consumption times concentration, so on logarithmic scale they can be added:

$$e = x + c.$$

The assessment will focus on a chosen percentile of exposure, e.g. p95. The relevant fraction will be denoted by $p$, for example $p = 0.95$ for the 95th percentile. The two NDS-LN models combine to three possibilities, depending on whether there is consumption and if so, whether the concentration is censored or positive. In the screening model the two possibilities that lead to potential exposure are modelled with a mixture of two lognormal distribution. For the censored case the positive exposure distribution equals the positive consumption distribution modified by the multiplication of a user-chosen factor times an estimate of the average worst-case limit value for concentration (LOR):

$$\pi_1 = \pi_x(1 - \pi_c); \mu_1 = \mu_x + f \cdot L_c; \sigma_1 = \sigma_x$$

where $L_c$ is the logarithm of the LOR, or, if there are multiple analytical methods with different LOR, a weighted average of these different LORs.

For the detect case the positive exposure distribution is easily combined from the positive consumption distribution and the positive concentration distribution:

$$\pi_2 = \pi_x\pi_c; \mu_2 = \mu_x + \mu_c; \sigma_{12} = \sqrt{\sigma_x^2 + \sigma_c^2}$$

$p$ can be corrected for the non-consumptions to the appropriate fraction needed in the mixture of the two positive distributions:

$$p' = \frac{p - (1 - \pi_x)}{\pi_x}$$

If $p' \leq 0$ then all positive exposures are beyond the requested fraction, and the estimated exposure is just 0.

If $p' > 0$ then the relevant log exposure $e_p$ satisfies

$$(1 - \pi_c) \cdot \Phi\left(\frac{e_p - \mu_1}{\sigma_1}\right) + \pi_c \cdot \Phi\left(\frac{e_p - \mu_{12}}{\sigma_2}\right) = p'$$

where $\Phi(\cdot)$ represents the cumulative standard normal distribution function. The value of $e_p$ can easily be found in a bisection search within the interval

$$[\mu_{min} - 4\sigma_{max}, \mu_{max} + max(0, z_{p'}\sigma_{max})].$$

The final exposure percentile estimate then is $\exp(e_p)$.

Denote by $e_{(p,max)}$ the highest estimate (for the SCC denoted by $SSC_{highest}$). Then evaluate for each SCC the probability to exceed $e_{(p,max)}$.

$$P_i = Pr(e > e_{p,max}) = \pi_x \cdot \left[(1 - \pi_c) * \Phi\left(\frac{e_{p,max} - \mu_1}{\sigma_1}\right) + \pi_c \cdot \Phi\left(\frac{e_{p,max} - \mu_2}{\sigma_1}\right)\right]$$

$P_i$ is a tentative measure for the 'probability of a high exposure'. For $SSC_{highest}$ $P_i = 1 - p$, for all other SCCs it will be lower. The sum of all these probabilities is not a meaningful probability in itself. However, this sum is used to scale the individual $P_i$ values to measures of relative importance for the SCCs

$$Imp_i = P_i / \sum P_i$$

Rank all SCCs according to $Imp_i$ and calculate cumulative importance. The relative importance of the two mixture components at $e_p$ can be estimated as

$$w_{1,2} = \frac{\pi_{1,2} \cdot \phi\left(\frac{e_p - \mu_{1,2}}{\sigma_{1,2}}\right) / \sigma_{1,2}}{\pi_1 \cdot \phi\left(\frac{e_p - \mu_1}{\sigma_1}\right) / \sigma_1 + \pi_2 \cdot \phi\left(\frac{e_p - \mu_2}{\sigma_2}\right) / \sigma_2}$$

where $\phi(.)$ represent the standard normal probability density function. The user interface should allow to select the top-$N$ SCCs from the list, based on a chosen percentage (e.g. 95%) of cumulative importance included. The full analysis will calculate exactly the same exposure distribution as a full analysis without screening. However, less information is retained in the output. This concerns tables with information on foods-as-eaten, which is only shown for the selected risk driver components (SCCs). Risk drivers are groupings of SCCs (risk driver components) at the level of measured-source-substance combinations (MSCCs). Note that output for an MSSC (e.g. APPLE/captan) only covers the selected SCCs (e.g. APPLE from apple juice/captan and APPLE from apple pie/captan), but not unselected SCCs (e.g. APPLE from fruit yoghurt/captan).

### Statistical model for the screening step (chronic exposure)

In chronic exposure assessments, the mean concentration of chemicals is calculated first, and combined with the consumption distribution. For this reason a chronic calculation uses less memory, and therefore larger datasets can be handled.

The model described under *acute exposure* can be simplified for a chronic screening. The concentration distribution is only used to estimate a mean exposure, incorporating any effect from the imputation of censored values. The exposure distribution is therefore only a scaled version of the consumption distribution.

$$\pi_2 = \pi_x \pi_c; \mu_2 = \mu_x + \mu_c; \sigma_2 = \sigma_x$$

The parameters of the consumption distribution $(\pi_x, \mu_x, \sigma_x)$ are calculated from the observed individual means (*OIM*), i.e. the mean daily consumptions over the survey days of each person in the data (allowing for sampling weights). The percentiles are calculated as $e_p = \mu_2 + z_p$ where $z$ is a percentile of the standard normal distribution. The exceedances of the maximum percentile are calculated as

$$P_i = Pr(e > e_{p,max}) = \pi_x \cdot \Phi\left(\frac{e_{p,max} - \mu_2}{\sigma_2}\right)$$

### High exposure food substance combinations settings

### Calculation settings

Table 3.264: Calculation settings for module High exposure food-substance combinations.

| Name | Type | Description |
|---|---|---|
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Compute cumulative exposures | Boolean | Specifies whether the assessment involves multiple substances a results should be cumulated over all substances. |
| Percentage defining the exposure percentile of interest per food-as-eaten/food-as-measured/substance combination | Numeric | Percentage defining the exposure percentile of interest per food-as-eaten/food-as-measured/substance combination. |
| Include risk drivers to include minimally a percentage | Numeric | The selection criterion for the risk drivers. The cumulative contribution percentage of the selected risk drivers will be this percentage. |
| Censored value replacement: factor x LOR | Numeric | A constant between 0 and 1. A value 0 can be used for an optimistic screening (LOR not used). Note that a factor 0.5 (pessimistic) may result in many and often high contributions from food-substance combinations with only censored values. |
| Report consumptions and exposures per individual instead of per kg body weight | Boolean | Specifies whether body weights should be ignored and consumptions and exposures should be expressed per individual Otherwise, the consumptions and exposures are per kg body weight. |

### Calculation of high exposure food-substance combinations

Screening results are computed for each combination of source (being a specific combination of food-as-eaten/modelled food) and substance by combining simple approximations of the consumption and the concentration distribution.

- *High exposure food-substance combinations calculation*

Inputs used: *Consumptions by modelled food Food concentration models Active substances Relative potency factors*

Settings used

- *Calculation Settings*

## 3.4.13 Internal exposures

Internal doses and concentrations are amounts of substances, typically expressed per mass unit and per day, to which individuals in a population are exposed at the chosen target level. This target level is an internal dose or an internal concentration (expressed per unit [organ] weight). Internal exposures may be aggregated from dietary and non-dietary exposures using either absorption factors for systemic doses or kinetic conversion factors or PBK models to translate the external exposures to internal concentrations at the specific target or tissue. Internal exposures can be short-term/acute exposures and then contain exposures for individual-days, or they can be long-term/chronic exposures, in which case they represent the average exposure per day over an unspecified longer time period.

This module has as primary entities: *Populations Substances*

Output of this module is used by: *Exposure mixtures Exposure comparisons Risks Environmental burden of disease*

### Internal exposures calculation

The main goal of the internal exposures module is to calculate the exposure as an internal concentration or internal dose. The internal concentration refers to the amount of chemical present in a specific target, tissue or (*biological matrix*) using kinetic conversion factors or PBK models. The internal dose is the amount of chemical that is systemically available using absorption factors and is the fraction of the external dose that is absorbed and enters the general circulation, see also WHO, Chapter 5 (2008). External exposures from dietary and non-dietary sources (including *dust*, *air*, *soil* and *consumer products*) are aggregated at a specified internal level in two steps:

1. Linking *dietary and/or non-dietary individual/individual-day exposures*.
2. Computing *the (aggregated) internal exposures at the specified internal level* concentration or dose.

*Absorption factors* are just simple multiplication factors and aggregate the exposure from multiple routes into an internal dose, see also *module kinetic conversion factors*. *Kinetic conversion factors* or more advanced *PBK models* aggregate the exposures from multiple routes into an internal concentration at a specified target (*biological matrix*). Currently, dietary exposures, dust, soil or air exposures or non-dietary exposures are aggregated to an internal level.

In cumulative internal exposure calculations two simple approaches are used to identify and select mixtures contributing to the exposure of a target population:

1. qualitative approach: *counting of co-exposure*. To which combinations of substances are individuals exposed? Just the co-occurence of substances is observed.
2. quantitative approach: *maximum cumulative ratio (MCR)*. To what degree are mixtures more important than single substances? The relative exposure levels of the substances present in a measurement, e.g. an individual (chronic) or individual day (acute) are taken into account.

In the *exposures mixtures module*, two more advanced approaches are available to analyse the co-occurence of substances, the *SNMU approach* and a *network analysis*.

Computation of internal exposures (e.g. an internal doses or internal concentrations) requires *absorption factors*, *kinetic conversion factors* or *PBK models* to translate external doses, possibly from multiple routes, to internal doses (absorption) or concentrations at the target matrix/organ of interest (kinetic conversion).

### Calculation of internal doses using absorption factors

In its simplest form, internal doses are derived from external doses using absorption factors specified for each substance and route combination. That is, for a given substance, the internal dose $dose_{\mathtt{int}}$ is calculated as

$$dose_{\mathtt{int}} = \sum_{r \in routes} f_{\mathtt{abs},r} \cdot exp_{\mathtt{ext},r}$$

Here, *routes* denotes the set of external exposure routes, $exp_{\mathtt{ext},r}$ represents the external exposure for route $r$ and $f_{\mathtt{abs},r}$ is the absorption factor of route $r$. Note that this model assumes that both external and internal doses refer to amounts or doses consistent with the *dietary exposures* setting. Specifically, external exposure is expressed as either substance amount per individual or substance amount divided by body weight, while internal exposure is expressed as substance amount per organ or substance amount divided by organ weight. Additionally, both external and internal doses are expressed on a per-day basis.

### Calculation of internal concentrations using kinetic conversion factors

Kinetic conversion factors are used to convert an external (administered) dose to a concentration in a target or *biological matrix*. For a given substance, the internal concentration $conc_{\mathtt{int}}$ is computed as

$$conc_{\mathtt{int}} = \sum_{r \in routes} f_{\mathtt{kc},r} \cdot exp_{\mathtt{ext},r}$$

Here, *routes* denotes the set of external exposure routes, $exp_{\mathtt{ext},r}$ denotes the external exposure for route $r$ and $f_{\mathtt{kc},r}$ denotes the kinetic conversion factor for route $r$.

When biological matrix urine is selected, concentrations are interpreted as such or interpreted as standardised by creatinine or normalised by specific gravity. Check option *Standardised (creatinine) or normalised (specific gravity) urine concentrations* and make a choice between expression type *creatinine* or *specific gravity*

When blood is selected as the biological matrix, concentrations are either expressed as such or standardised for lipid content. Check option *Standardised blood concentrations (lipids)*.

### Calculation of internal concentrations using PBK models

A more detailed alternative to using kinetic conversion factors is to use one of the *advanced kinetic models* available in MCRA. In this approach, for each substance independently, the external exposures of an individual (chronic) or individual-day (acute) are input into a PBK model of the individual for a number of simulated days. This yields a time course of the internal substance amount in the specified target or *biological matrix* from which a long-term average amount (chronic) or peak amount (acute) can be derived. Examples of such time courses are given in Figure 3.42 for acute exposure assessments, and in Figure 3.43 for chronic exposure assessments. By dividing this substance amount by the mass of the biological matrix, an internal concentration is obtained. Notice that this procedure also changes the exposure from a daily rate to a long-term exposure.

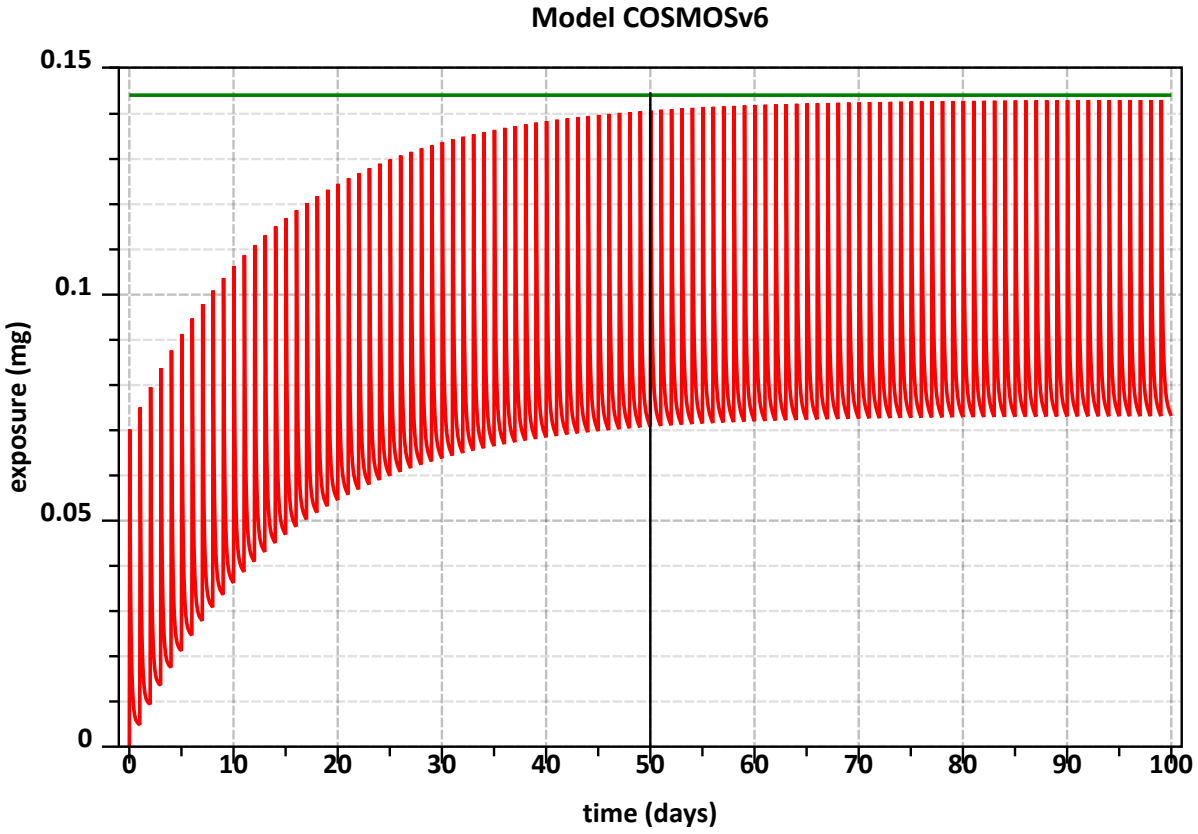


Figure 3.42: Time course of the internal substance amount when applying the same single dose on each day. The acute internal concentration is derived as the peak substance amount (the green line in the figure) divided by the weight of the biological matrix. The vertical line at 50 indicates the selected end of an assumed non-stationary period, defining a burn-in period that is to be ignored for computing the peak substance amount.

Mathematically, the calculation of the peak substance amount ($d_{\text{peak}}$) for deriving acute internal concentration is as follows:

$$d_{\text{peak}} = \max_{i=0,\ldots,n_{\text{stop}}} \{d(t_{\text{start}} + i\Delta t)\}\,.$$

Here, $d(t)$ denotes the substance amount at time $t$, $t_{\text{start}}$ denotes the starting time of the evaluation window (defined by the *non-stationary period*), $\Delta t$ denotes the time resolution of the kinetic model (e.g., hours or minutes), and $n_{\text{stop}}$ denotes the total number of time-points, marking the end of the evaluation window (defined by the specified number of simulation days), which is computed as

$$n_{\text{stop}} = \left\lfloor \frac{t_{\text{stop}} - t_{\text{start}}}{\Delta t} \right\rfloor .$$

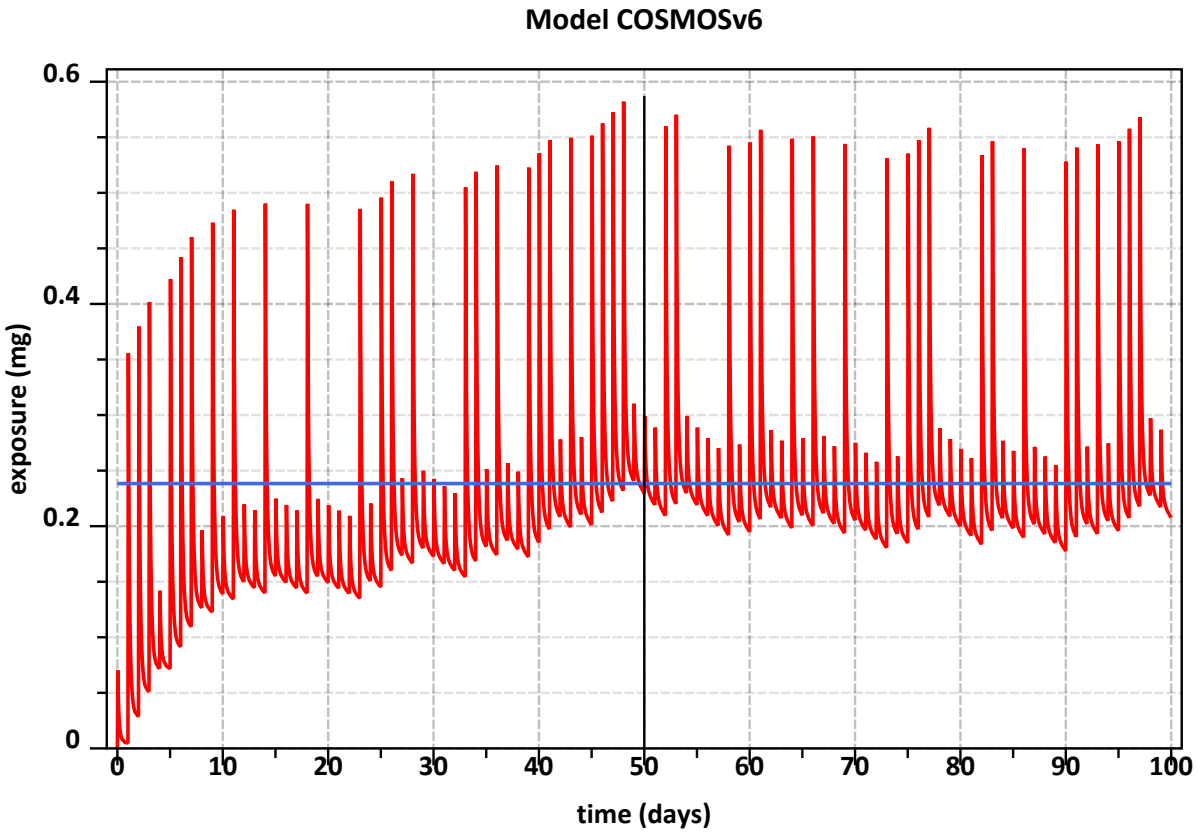


Figure 3.43: Time course of the internal substance amount when randomly applying one of the individual-day doses for a number days. The chronic internal concentration is derived as the average substance amount (the blue line in the figure), divided by the weight of the biological matrix. The vertical line at 50 indicates the selected end of an assumed non-stationary period, defining a burn-in period that is to be ignored for computing the average substance amount.

Likewise, chronic long term average substance amounts ($d_{\text{avg}}$) are computed as:

$$d_{\text{avg}} = \frac{\sum_{i=0}^{n_{\text{stop}}} d(t_{\text{start}} + i\Delta t)}{n_{\text{stop}}}.$$

### Dosing patterns

In MCRA, dietary and non-dietary exposures are computed as daily exposure levels. However, when applying advanced PBK models, dosing patterns may be specified at a much finer resolution (e.g., hours or minutes). This requires a method to translate daily external exposures into intra day dosing patterns. The simplest, though less realistic, approach is to apply the full daily exposure for each route as a single dose at the start of the day. Alternatively, MCRA allows users to specify the *number of exposure events per day* per route. When multiple doses are specified, the total daily substance amount is divided into equal portions which are then applied at regular time-intervals throughout the day.

### Non-stationary period

Especially in chronic exposure assessments, where a long-term average exposure is computed based on the simulated time-course, it is important to note that at time zero, the substance is typically assumed to be entirely absent from the simulated system. However, this is often an unrealistic assumption. In practice, it is more likely that the substance is already present at a level consistent with the chronic exposure pattern. Therefore, a burn-in period - specified as the *number of days skipped* is required to reach these steady-state initial concentrations. This period is not used to compute the long-term average or peak exposures, but serves solely to establish baseline levels.

### Combining exposure sources

Individuals in a population are exposed to substances in sources like *food (diet)*, *plant protection products (PPPs)* (in MCRA also referred as non-dietary exposures), *dust*, *air*, *soil* and/or *consumer products* exposures.

In a dietary exposure assessment, individuals generally have known values for properties such as age, sex, and body weight. The same applies to non-dietary exposures generated by *BROWSE* when individual IDs are linked to a known set of individuals—such as those from a dietary exposure assessment—or through the specification of *survey properties* related to age and/or sex. For exposures generated by the dust, air and soil modules, no explicit individuals or population are available. However, the exposure determinants used in these modules require information about age and/or sex. For example, dust exposure determinants such as *ingestions* rates, *body exposure fractions*, *adherence amounts* or *availibility fractions* are age- and/or sex specific. Therefore, in order to generate exposures, a population of individuals is required.

There are two options available for generating this set of individuals. Generate exposures based on:

- individuals of the dietary survey e.g. see option *Use dietary exposure*,
- a set of *Simulated individuals* (see e.g. *generation method individuals*).

Navigate to the air, dust and soil modules to specify which set of individuals for generating exposures should be used. This choice is independently for each exposure source.

Before aggregating exposures from different sources at the internal level, all exposures must first be combined at the external level for each individual. To begin, specify one exposure source, its corresponding set of individuals (simulated or dietary) will serve as the reference set. All other exposure sources will then be aligned with this reference.

It is clear that combining exposures at the external level becomes complex when different sets of individuals are used by the exposure generator in the air, dust and/or soil modules.

After specifying the reference source, there are three options available for matching an individual in the reference set with an individual from the other sources:

- completely at random,
- based on individual properties like age, sex (or other properties)
- based on their individual ID,

For the first option, no additional information is required. Option 3, on the other hand, is the most restrictive, see also *population alignment methods*. This option is only applicable when each exposure source uses the same set of individuals. If the assessment includes a dietary source, all exposures from other source modules should be generated based on dietary individuals. If no dietary source is present, the appropriate choice is to use simulated individuals.

For the second option, individuals are matched based on specific properties. You can choose whether to use age and/or sex (male, female) or both as stratifying covariate. For age, matching can be done by specifying bins (e.g. 18 - 45 years) or by selecting individuals whose ages are closest to the age of the individual in the reference set. From the resulting subset, one individual is randomly sampled.

### Non-dietary exposures

Originally, the *non-dietary exposure* module was developed to implement Bystanders, Residents, Operators and WorkerS Exposure models for plant protection products (*BROWSE*) software. Because this module has a different data format compared to the format of the *dust*, *air* and *soil* modules the method of matching individuals on the reference set is further explained.

In general, dietary and non-dietary surveys are independently taken (separated in space, location and time etc). Each survey contains a unique set of individuals and the only way to match individuals is *completely at random* or *use stratifying covariates* like age and or sex e.g. males, females between 18-45 years, children in the age of 0 to 5 years, etc.

### Matching completely at random

For each individual in the dietary survey a random nondietary individual(day) from the nondietary surveys is sampled or vice versa. This option is also possible when surveys are identical.

### Matching based on individual ID

When both dietary and non-dietary surveys contain identical individuals, individuals are matched based on their ID.

### Matching based on individual properties

When dietary and non-dietary surveys are identical or partly identical, dietary and non-dietary exposures of indiviuals are matched based on the individual ID, e.g. for all *Individuals* of the food survey also a nondietary exposure is available or vice versa (method 3: *individuals are matched based on the individual Id*). Any nondietary exposure that does not correspond to an individual in the food survey will be ignored and vice versa (see *Example 2*). Occasionally, this is too restrictive and the assumption can be relaxed by specifying the individual ID in the nondietary survey as *Id = General*. Then, individual properties of the dietary individual should match the non-dietary survey properties.

When multiple non-dietary surveys are available, option *Match individuals of multiple non-dietary surveys* is relevant. When *matching* (correlation) is chosen, the exposure contributions of non-dietary individuals with identical *Id* in different surveys are combined and allocated to a dietary individual. When no correlation is chosen, the non-dietary exposures of randomly selected individuals from different surveys are combined and allocated to a dietary individual.

The user may also define demographic criteria for the assignment (for each source of non-dietary exposure) to indicate that those exposures are relevant only to a defined sub-population. Only those individuals in the food survey who meet the criteria of the non-dietary survey will be assigned non-dietary exposures from that source e.g. only males aged 18 to 65 (see *Example 1*). The simplest assessment consists of a single (deterministic) non-dietary exposure estimate which is assigned to all individuals in the food survey (*Id = General*). This case, and more complex possibilities are illustrated below using hypothetical examples (method 2: *individuals are match based on individual properties*).

### Example 1

Deterministic cumulative (multi-substance) non-dietary exposure input, adult male sub-population. Unmatched case.

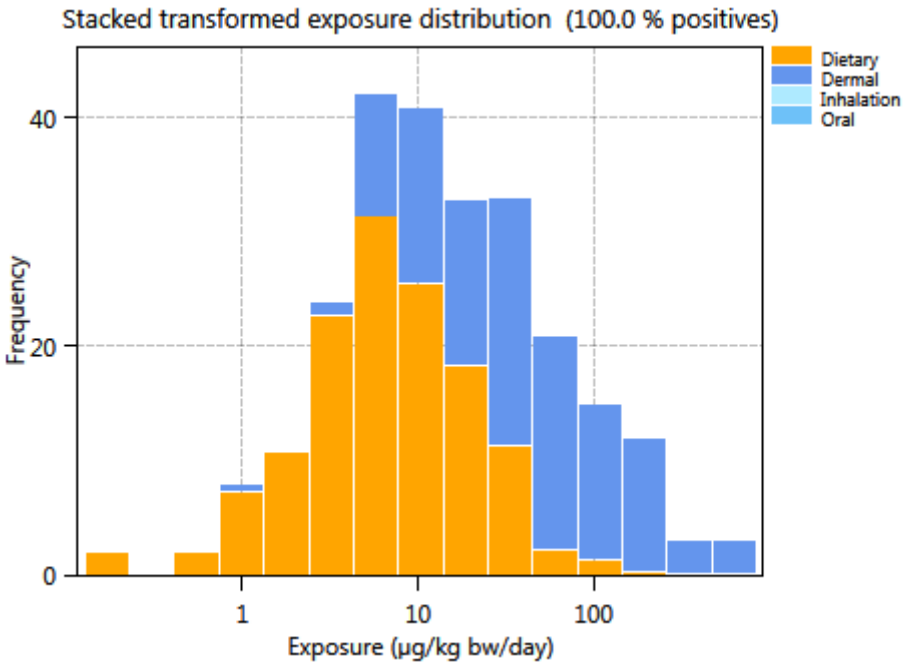


Figure 3.44: Exposure distributions for routes.

Table 3.265: NonDietaryExposures

| idIndividual | idNonDietarySurvey | idSubstance | Dermal | Oral | Inhalation |
|---|---|---|---|---|---|
| General | 1 | 011003001 | 10 | 5 | 17 |
| General | 1 | 011003002 | 34 | 20 | 18 |
| General | 1 | 011003003 | 56 | 43 | 19 |

Table 3.266: NonDietarySurveys

| idNonDietary-Survey | Description | Location | Date | NonDietary-IntakeUnit |
|---|---|---|---|---|
| 1 | BROWSE, acute, cumulative, operators | York | 09/10/2012 | $\mu g/day$ |

Table 3.267: NonDietarySurveyProperties

| idNonDietary-Survey | Property-IndividualName | Individual-PropertyText-Value | Individual-Property-DoubleMin-Value | Individual-Property-DoubleMax-Value |
|---|---|---|---|---|
| 1 | Age | | 18 | 65 |
| 1 | Gender | Male | | |

In this example, there are exposure values for multiple substances in Table 3.265 and the user has provided Table 3.267 which specifies that the non-dietary exposures given in survey number 1 relate to males aged 18 to 65.

When this assessment is performed, only those individuals whose property values fit the criteria in Table 3.267 will receive the non-dietary exposures in survey 1. The use of *idIndividual* = *General* indicates that this is the

default exposure. All individuals in the dietary survey meeting the criteria receive all exposures given in the 3 rows, corresponding to 3 substances. The following should be noted:

- Specify only one *General* entry in the non-dietary exposures table per substance x survey combination.
- Property names and text properties must precisely match the values in the **IndividualProperties** and **IndividualPropertyValues** tables.
- The minimum and maximum values for numeric properties are inclusive boundaries.

In the next example, all males aged 18 to 65 receive the given exposures of all three substances and the other members of the population receive no non-dietary exposure. Note that example 1 describes the unmatched case.

### Example 2

Variability (but no uncertainty) in cumulative non-dietary exposure input (matched to dietary survey individuals).

Table 3.268: NonDietaryExposures

| idIndividual | idNonDietarySurvey | idSubstance | Dermal | Oral |
|---|---|---|---|---|
| 5432 | 1 | 011003001 | 10 | 5 |
| 5432 | 1 | 011003002 | 33 | 22 |
| 5433 | 1 | 011003001 | 12 | 7 |
| 5433 | 1 | 011003002 | 34 | 23 |
| 5434 | 1 | 011003001 | 18 | 9 |
| 5434 | 1 | 011003002 | 35 | 25 |
| 5435 | 1 | 011003001 | 10 | 5 |
| 5435 | 1 | 011003002 | 33 | 21 |

Table 3.269: NonDietarySurveys

| idNonDietary-Survey | Description | Loca-tion | Date | NonDietaryIntakeU-nit |
|---|---|---|---|---|
| 1 | BROWSE, acute, cumulative, opera-tors | York | 09/10/2012 | $\mu g/day$ |

In this example, the non-dietary exposures are specified explicitly for individuals in the dietary population. Switch 'matching' on to allow exposure variability to be specified at the individual level. Only four individuals are used. The values in the *idIndividual* column of Table 3.268 match those in the *Individuals* table (dietary population).

It is not mandatory to specify exposures for every individual in the population. Those not included will simply receive a zero non-dietary exposure, unless there is also a default exposure value (*General* row(s) in Table 3.268) and the individual matches the specified demographic criteria for the survey, as specified in Table 3.267. (In this example, a default exposure would apply to all individuals not listed in Table 3.268 because Table 3.267 has not been used).

There is variability between individuals in this example, but no uncertainty in exposure. Note that these data could also be used with matching switched off. This would be the same as treating the *idIndividual* values as generic individuals, so that each pair of exposure lines would be assigned at random to individuals meeting the criteria.

### Example 3

Variability (no uncertainty) in cumulative non-dietary exposure input (unmatched individuals).

Table 3.270: NonDietaryExposures

| idIndividual | idNonDietarySurvey | idSubstance | Dermal | Oral | Inhalation |
|---|---|---|---|---|---|
| ND1 | 1 | 011003001 | 10 | 5 | 17 |
| ND1 | 1 | 011003002 | 33 | 22 | 45 |
| ND2 | 1 | 011003001 | 12 | 7 | 18 |
| ND2 | 1 | 011003002 | 34 | 23 | 47 |
| ND3 | 1 | 011003001 | 18 | 9 | 19 |
| ND3 | 1 | 011003002 | 35 | 25 | 49 |
| ND4 | 1 | 011003001 | 10 | 5 | 17 |
| ND4 | 1 | 011003002 | 33 | 21 | 45 |

Table 3.271: NonDietarySurveys

| idNonDietary-Survey | Description | Loca-tion | Date | NonDietaryIntakeU-nit |
|---|---|---|---|---|
| 1 | BROWSE, acute, cumulative, opera-tors | York | 09/10/2012 | $\mu g/day$ |

Table 3.272: NonDietarySurveyProperties

| idNonDi-etarySurvey | PropertyIndi-vidualName | IndividualProper-tyTextValue | IndividualProperty-DoubleMinValue | IndividualProperty-DoubleMaxValue |
|---|---|---|---|---|
| 1 | Age | | 50 | 65 |
| 1 | Gender | Female | | |

This example is similar to example 2, except that the values in the *idIndividual* column of Table 3.270 do not match those in the *Individuals* table. In this instance, 'matching' would not be an option, and the non-dietary exposures would be randomly assigned to individuals who meet the criteria in Table 3.272. (In fact for the same result rather than changing the values in the *idIndividual* column in Table 3.268 from the previous example may be used with matching switched off). Exposures in Table 3.270 will be recycled if the number of exposure rows is less than the number of dietary records with which to aggregate exposures.

Again, there is variability between individuals in this example, but no uncertainty in exposure.

By allowing generic *idIndividual* values in this way, correlations between different sources (within individual) can be accounted for even in the unmatched case. If the same *idIndividual* value is used in different surveys, then the corresponding exposure values will be kept together and assigned to an eligible individual as a combined exposure.

So for option matching switched of, it is relevant whether individuals are correlated or not. In the following example, two non-dietary surveys are available, per survey three individuals are specified.

Table 3.273: matching switched of, with correlation or without.

| idIndividual | idNonDietarySurvey | idSubstance | Dermal | Oral | Inhalation |
|---|---|---|---|---|---|
| ND0 | 1 | 011003001 | 10 | 5 | 17 |
| ND1 | 1 | 011003001 | 23 | 22 | 45 |
| ND2 | 1 | 011003001 | 12 | 7 | 18 |
| ND0 | 2 | 011003001 | 34 | 23 | 47 |
| ND3 | 2 | 011003001 | 18 | 9 | 19 |
| ND4 | 2 | 011003001 | 33 | 16 | 35 |

- When a correlation is applied, the non-dietary exposure for individual ND0 from survey 1 and 2 are combined and allocated to a dietary individual. For individual ND1, ND2, ND3 and ND4 just a single non-dietary exposure is found and allocated to a dietary individual.

- When no correlation is applied, the exposure for individual ND0 from survey 1 is combined with one of the exposures of ND0, ND3 or ND4 from survey 2; exposure of ND1 from survey 1 is combined with one of the exposures of ND0, ND3 or ND4 from survey 2, etc.

When the intention is to sample just one exposure for a dietary individual, specify per survey different codes, e.g. ND1, ND2, ND3 for survey 1, ND4, ND5, ND6 for survey 2 and apply correlation, or specify 6 different individual codes and just one *idNonDietarySurvey*. Then, options with or without correlation are irrelevant and sampling results are identical.

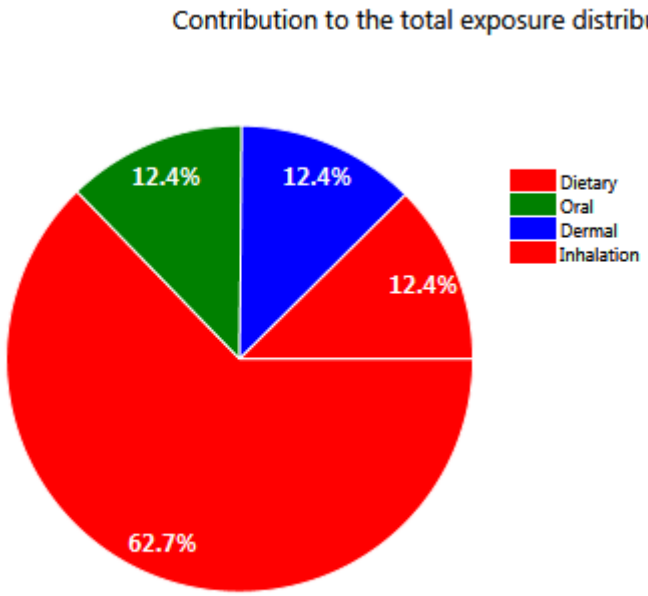


Figure 3.45: Contributions by route of the external exposure distributions.

See *non-dietary exposure settings*.

### Counting of co-exposure

In this qualitative approach, the number of combinations of substances to which an individual is exposed are recorded, see Table 3.274. There is no cut-off level, the only criterion is the presence of a substance in the simulated daily diet (eventually aggregated withe the exposure from non-dietary sources) or not. For an *acute* or short term exposure assessment, a simulated individual day is the smallest entity to determine co-exposure. For a *chronic* or long term exposure assessment, co-exposures are summarized at the individual level, e.g. co-exposure is determined combining all consumption days of an individual.

Table 3.274: Counting combinations of substances in the exposure matrix: for example, on day 1 there is coexposure to substances Tebuconazole, Bitertanol and Triadimefon

| Substance | day 1 | day 2 | day 3 | ... | day n |
|---|---|---|---|---|---|
| Tebuconazole | x | x | | … | |
| Bitertanol | x | | x | … | x |
| Triadimefon | x | | … | … | x |
| … | … | … | … | … | … |

In Table 3.275, the frequency and percentage for the number of substances occurring together are shown.

Table 3.275: Co-exposure of substances

| Number of substances | Frequency | Percentage |
|---|---|---|
| 0 | 337 | 3.4 |
| 1 | 959 | 9.6 |
| 2 | 1207 | 12.1 |
| 3 | 1275 | 12.8 |
| … | … | … |

In Table 3.276, the mixtures containing the substance(s) including all other combinations with the specified combination of substance(s), (a maximum number of 15 records is shown).

Table 3.276: Mixtures containing substances

| Number of substances | Percentage | Substances |
|---|---|---|
| 1 | 5.88 | Tebuconazole |
| 2 | 3.88 | Imazalil (aka enilconazole), Tebuconazole |
| 0 | 3.37 | |
| 3 | 2.20 | Difenoconazole, Imazalil (aka enilconazole), Tebuconazole |
| 1 | 1.78 | Imazalil (aka enilconazole) |
| 3 | 1.76 | Imazalil (aka enilconazole), Tebuconazole, Triadimenol |
| … | … | … |

### Maximum Cumulative Ratio

Price and Han (2011) propose the Maximum Cumulative Ratio (MCR) which is defined as the ratio of the cumulative exposure received by an individual on an intake day to the largest exposure received from a single substance:

$$\text{MCR} = \frac{\text{Cumulative exposure}}{\text{Maximum exposure}}$$

This MCR statistic is also picked up as a practical device in a recent JRC report, Bopp et al. (2015), to investigate cumulative exposure. If MCR is large, it is important to consider cumulative effects. If MCR is close to 1, the individual exposure does not differ significantly from a single-substance assessment. The MCR can therefore be interpreted as the degree to which the risk is underestimated when a cumulative risk assessment is not performed.

The MCR statistic is implemented in MCRA for both *acute* and *chronic* exposure assessment. In an acute exposure assessment, short-term (single-day) exposures are used. For the chronic case, long-term individual exposures — estimated by aggregating the available survey days for each individual — are used.".

### Exposure assessment

### Risk based, standardised or unweighted exposures

Before calculating the MCR statistics, three optional choices are available, *see settings, MCR exposure approach type*.

- Risk based exposures: exposures are multiplied by the *relative potency factor* (RPF) of each substance and thus exposures for different substances are on the same and comparable scale.
- Standardised exposures: all exposures are standardised to equal variance (unit variance).
- Unweighted exposures: exposures are taken as such, this is equivalent to RPF s equal to 1 for each substance.

Table 3.277 shows an artificial example how the MCR is calculated in an acute exposure assessment. First the cumulative exposure per day is calculated by cumulating the exposure of each substance multiplied by the RPF. Then, for each day, the cumulative exposure (in equivalents of the reference substance) is divided by the maximum exposure of a single substance on that day. The last column shows the MCR values, with the substance with the highest exposure in parenthesis. The MCR has a value of 1, or close to 1, for mixtures where the exposure is dominated by one substance (e.g. day 1, substance B). When all substances have approximately equal exposure (e.g. day 3) the MCR value is equal or close to the number of substances, here 4. Day 2 represents an intermediate case. The MCR

suggest that for exposure days (or persons) with MCR values close to 1, the need for a cumulative risk assessment is low.

Table 3.277: Maximum Cumulative Ratios

| | Substance A | Substance B | Substance C | Substance D | total exposure | ratio |
|---|---|---|---|---|---|---|
| day 1 | 0.01 | 0.99 | 0 | 0 | 1 | 1.01 (B) |
| day 2 | 0.1 | 0.2 | 0.3 | 0.4 | 1 | 2.50 (D) |
| day 3 | 0.25 | 0.25 | 0.24 | 0.26 | 1 | 3.99 (D) |

In this artificial example, all days have equal values for total exposure (= 1). “n real-world data, total exposure varies. It is therefore of interest to determine whether the MCR is high or low on days (or for individuals) where the total exposure is at its peak.

In Figure 3.46, French steatosis data (39 substances, 4079 persons) are used to calculate the chronic exposure matrix. For each individual MCR is calculated and plotted against the total exposure. Different colours are used to distinguish the substances with the highest exposures. From the 39 original substances, 10 were identified as the primary drivers. The black line segments indicate the $p_5$, $p_{50}$ and $p_{95}$ percentiles for both total exposure and MCR. The red line marks a ratio of 5, while the dashed green lines represent the $p_{95}$ percentiles for MCR across various total exposure ranges.

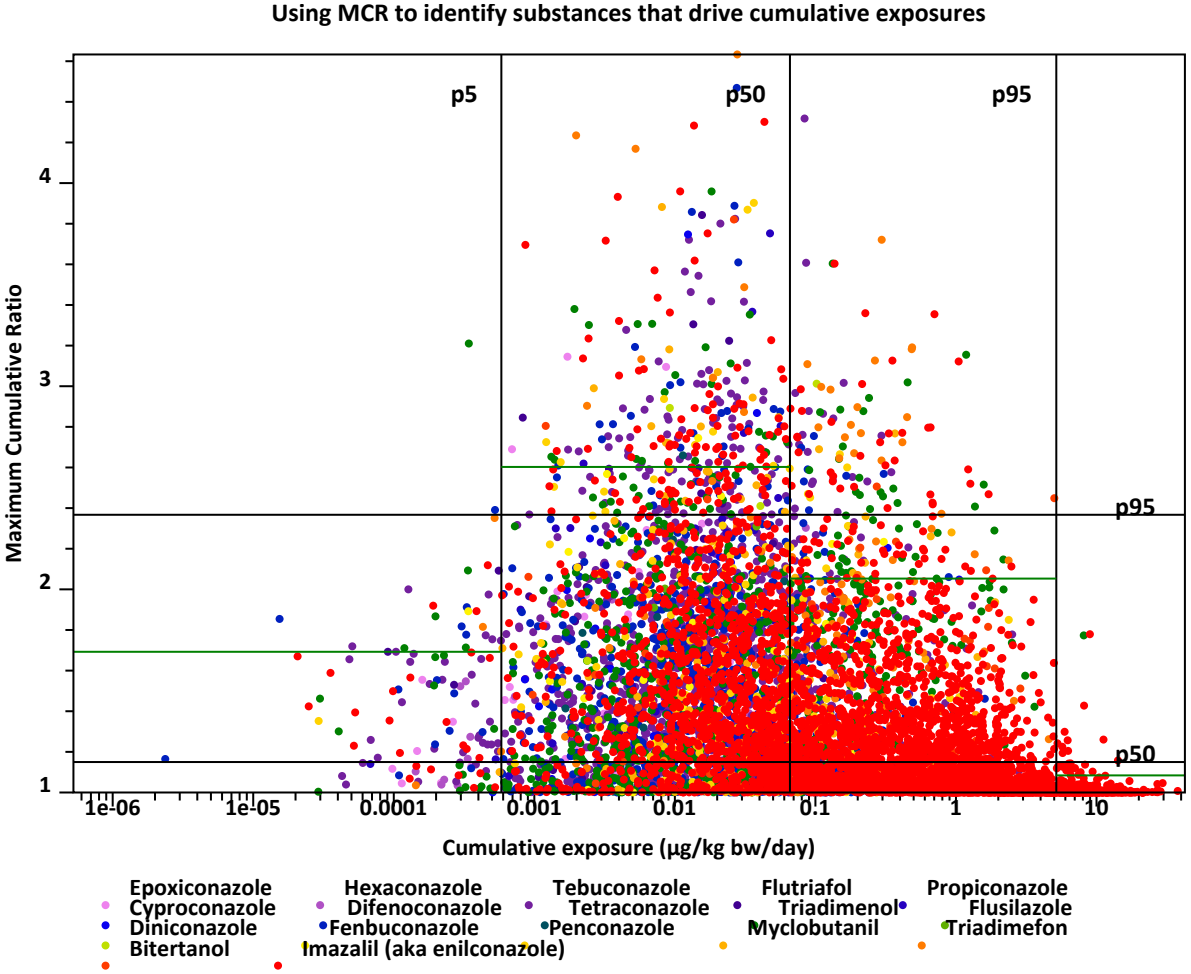


Figure 3.46: Maximum Cumulative Ratios vs total exposure

The plot shows that MCR values with Imazalil as risk-driving substance (purple) are predominantly found in the lower part of the plot at relatively high values of total exposure. Secondly, MCR values decline as total exposure increases. This implies that cumulative exposure for most individuals is driven by multiple substances. At the right site of the

plot, individuals with high exposure are found. Because MCR values tend to be lower in this region, higher exposures are driven by one predominant substance rather than by multiple substances being above the average level. For those individuals, a cumulative risk assessment has limited added value.

Because the Figure 3.46 plot can be very dense, in Figure 3.47, 95% confidence regions representing bivariate log-normal distributions of MCR and total exposure are plotted. The latter figure facilitates interpretation of the former. Note that substances with only one or two observations cannot be visualized in this display (substances with 2 observations are represented by a line).

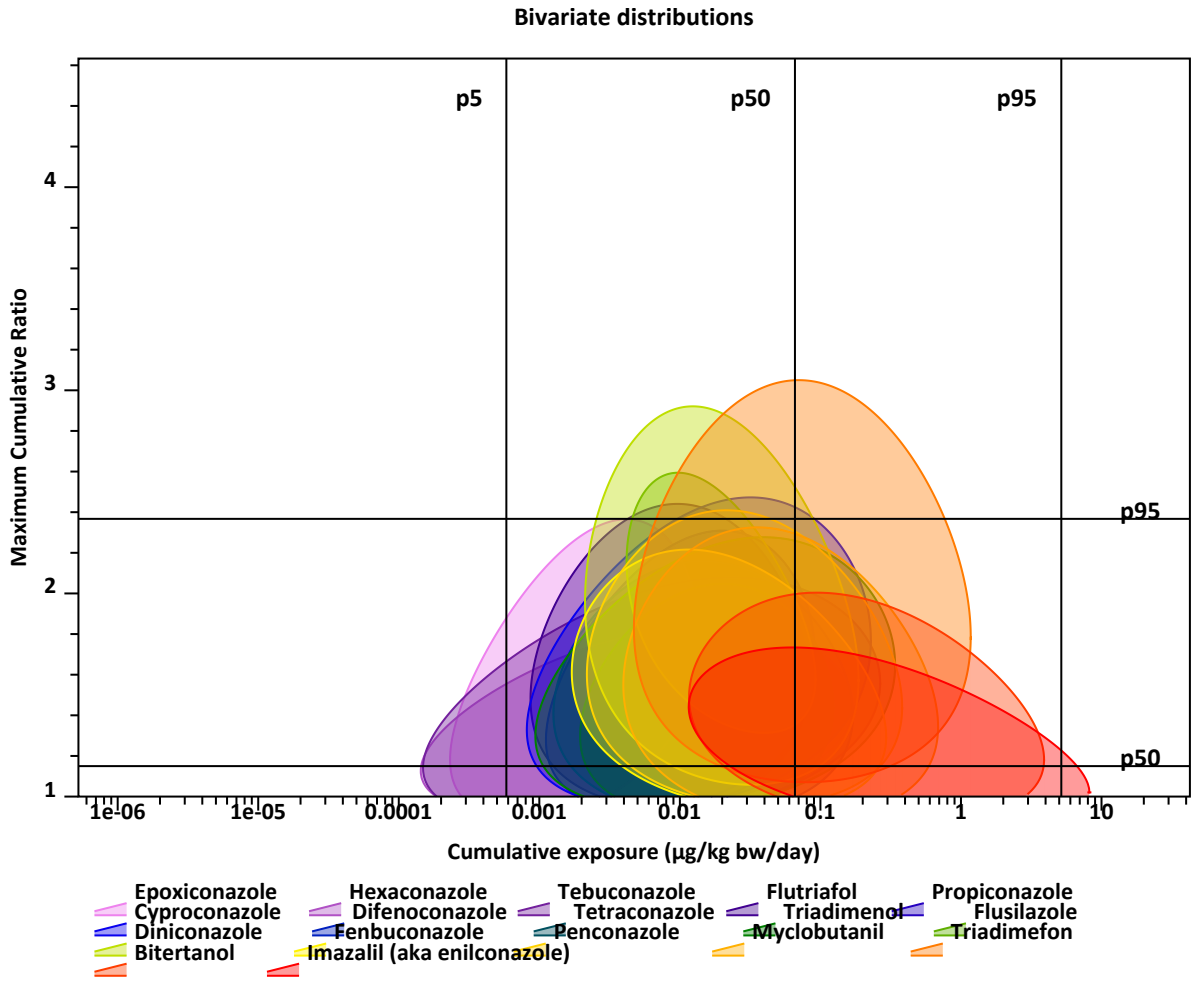


Figure 3.47: Bivariate distributions MCR vs total exposure

In Figure 3.48 and Figure 3.49 scattered MCR distributions for the total and upper tail (here 37%) that drive the cumulative exposure are shown. The red line indicates the MCR threshold, 1.5. The black lines represent the regression lines MCR vs ln(Cumulative exposure) for each tail. Substances with an exposure contribution less than 15% are not displayed.

In Table 3.278 contributions to tail exposures at various percentile are shown. Column MCR $= 1$ shows the percentage of tail exposure due to individual(day)s with a single substance. Column $1 <$ MCR $\leq 2$ shows the percentage of tail exposure due to individual(day)s with multiple substances, but the MCR $\leq 2$. Column MCR $> 2$ shows the percentage of tail exposure due to individual(day)s with multiple substances with MCR $> 2$.

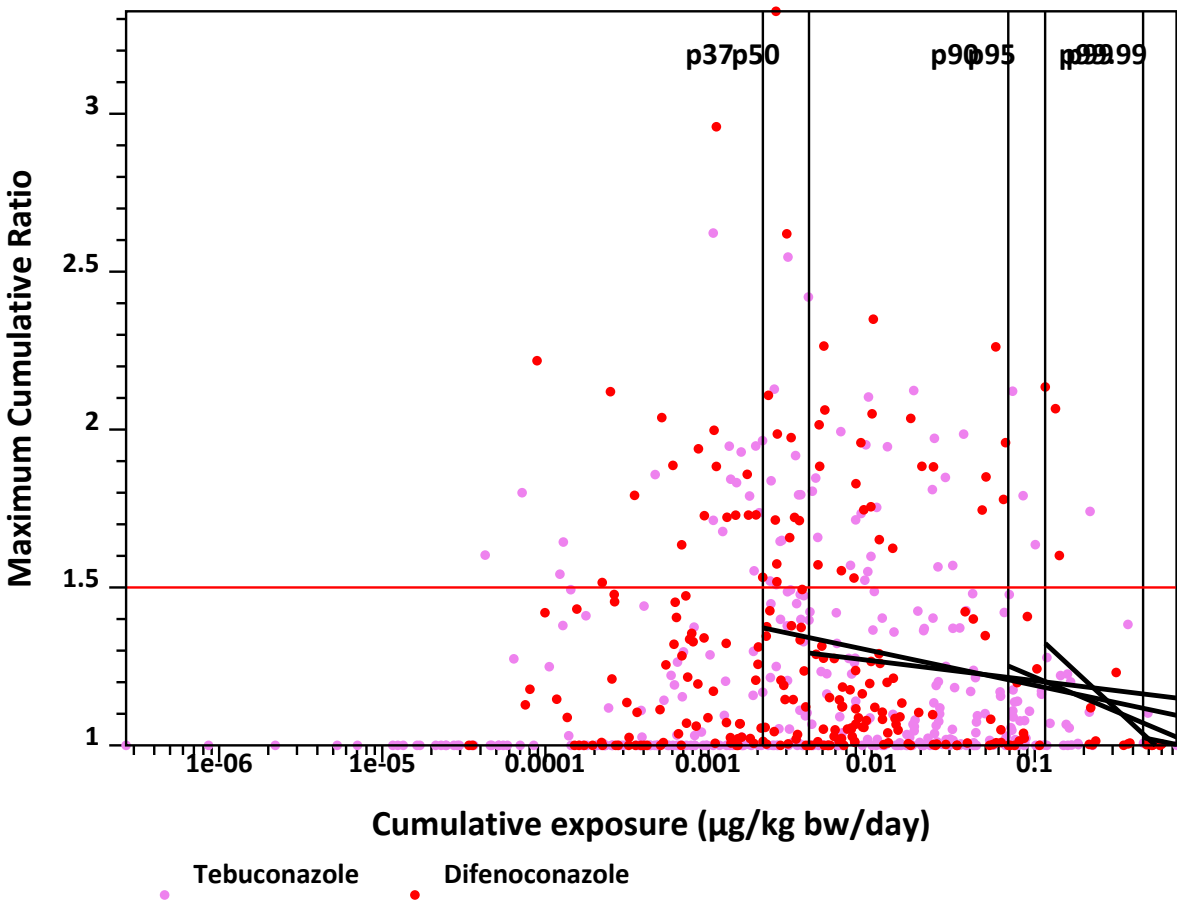


Figure 3.48: Using MCR to identify substances that drive cumulative exposures, scatter distributions (total).

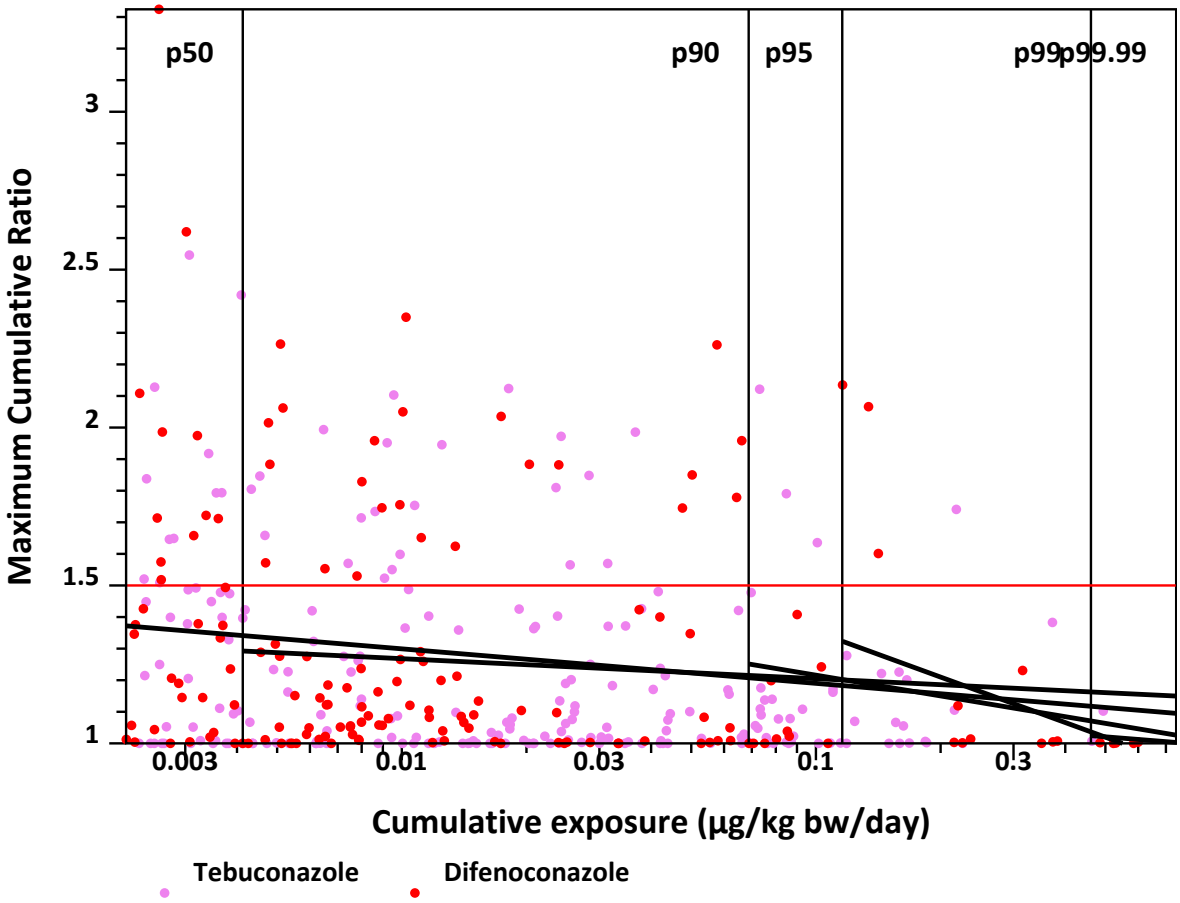


Figure 3.49: Using MCR to identify substances that drive cumulative exposures, scatter distributions (upper tail 37%).

Table 3.278: Maximum Cumulative Ratio summary

| Tail % | % with MCR = 1 | Sub-stances | % with 1 < MCR<=2 | Substances | % with MCR > 2 | Sub-stances |
|---|---|---|---|---|---|---|
| 37 | 20.6 | Difeno, Tebu | 73.7 | Difeno, Tebu | 5.7 | Difeno, Tebu |
| 50 | 19.2 | Difeno, Tebu | 75.6 | Difeno, Tebu | 5.2 | Difeno, Tebu |
| 90 | 16.3 | Difeno, Tebu | 78.8 | Difeno, Tebu | 5.0 | Difeno, Tebu |
| 95 | 15.0 | Difeno, Tebu | 82.5 | Difeno, Tebu | 2.5 | Difeno, Tebu |
| 99 | 25.0 | Difeno | 75.0 | Difeno, Tebu Propi | 0.0 | |

To configure the MCR plot, see *dietary exposures settings*, *human monitoring analysis settings* and *internal exposures settings* with options to display the ratio total exposure/ maximum for individual(day) exposures (MCR plot), to specify tail percentiles of the exposure distribution, e.g. 95, 97.5 and 99% (MCR plot) or to set the minimum percentage contribution per substance to the tail exposure (MCR plot).

### Risk assessment

Recently, a new plot was added that is especially useful for a risk assessment approach (Kortenkamp et al. (2022)). In Figure 3.50 each dot represents the MCR of an individual, the sum of risk characterisation ratios divided by the ratio of the highest contributing substance. The blue area, where $E/H < threshold$, marks combined exposures that do not present any concern. The white area - defined by the vertical red line for acceptable risks and the curved line depicting $E/H = threshold * MCR$ (with a default threshold of 1) - shows subjects with combined exposures above the threshold ($E/H > threshold$) but whose risk quotient for any single substance does not exceed the limit. The red area represents subjects where $E/H > threshold$ and where exposures produce risk quotients exceeding the threshold for at least one substance. Data points below the horizontal red line (corresponding to MCR = 2) indicate subjects where one substance contributes 50% ore more to the total risk (e.g. single substance issue). Above the line, subjects experience combined exposures from multiple substances (e.g. co-exposure).

## Internal exposures settings

### Calculation settings

Table 3.279: Calculation settings for module Internal exposures.

| Name | Type | Description |
|---|---|---|
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Target level | *TargetLevelType* | Select whether the assessment is at the level of external dose, internal (target) concentration or internal (systemic) dose. For a aggregate assessment, combining dietary and nondietary exposures, the target level is always internal concentration or internal (systemic) dose. When only dietary exposures are available, the target level is optional and may be an external (administered) dose, an internal (tissue) concentration or an internal (absorbed) dose. |
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Compute cumulative exposures | Boolean | Specifies whether the assessment involves multiple substances a results should be cumulated over all substances. |
| Specify the type of kinetic model | *InternalModelType* | Specify the type of model to convert external exposure to the internal level. |

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Table 3.279 – continued from previous page

| Name | Type | Description |
|---|---|---|
| Biological matrix | *BiologicalMatrix* | The target biological matrix (internal compartment) for which t results are computed. Biological matrices from kinetic conversions will become available after selecting a data source i the kinetic models module. |
| Exposure sources | *ExposureSource* | Specifies the exposure sources involved in the exposure assessment. |
| Exposure routes | ExposureRoutes | Exposure routes included in assessment. |
| Individual reference set | *ReferenceIndividualSet* | Specifies the exposure sources used as reference set for matchir individuals. |
| Match individuals of multiple non-dietary surveys | Boolean | If checked, then non-dietary exposures of individuals from different surveys with the same identifier (ID) are combined. |
| Substance weighting in mixtures | *ExposureApproachType* | Risk based: exposures in equivalents of the reference substance standardised: standardised exposures per substance have varian 1; or unweighted exposures: RPFs are equal to 1. |
| Perform MCR analysis | Boolean | Perform a Maximum Cumulative Ratio (MCR) analysis to determine co-exposure between substances. |
| Display ratio total exposure/ maximum (in MCR plot) | Numeric | For MCR plot: specify ratio total exposure/ maximum for individual(day) exposures . |
| Show tail percentiles (MCR plot) for: | Numeric | Give specific percentiles of exposure distribution (%), e.g. 97.5 99 (space separated). |
| Set minimum percentage contribution per substance to the tail exposure (MCR plot) | Numeric | Set minimum percentage contribution per substance to the tail exposure. |
| Cutoff MCR | Numeric | For selection of individual(day) exposures with maximum cumulative ratio (MCR = total exposure/maximum) above the cutoff. |
| Cutoff percentage in population ranked on total exposure | Numeric | For selection of individual(day) exposures above the cutoff percentage in the set of individual(day)s ranked on total exposu |
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |
| Standardised blood concentrations (lipids) | Boolean | Standardised blood concentrations (lipids). |
| Standardised (creatinine) or normalised (specific grafity) urine concentrations | Boolean | Standardised (creatinine) or normalised (specific grafity) urine concentrations. |
| Selected expression type | *ExpressionType* | Standardised urine (creatinine) or normalised urine (specific grafity). |
| Exposure events and dose generation method | *ExposureEventsGeneration-Method* | Generates doses and events for PBK model |
| Number of simulated days | Numeric | The total duration (in days) of the PBK model simulations. |
| Number of initial days skipped | Numeric | The initial period (or burn-in period, specified in days) that nee to be skipped when calculating the steady-state or peak internal exposures from the simulated time series. |
| Use PBK model parameter variability | Boolean | When specified, use parameter variability. |
| Number of events per day for the DERMAL dose | Numeric | The daily dose is administered in equal portions (dose / number events) per event. |
| Number of events per day for the INHALATION dose | Numeric | The daily dose is administered in equal portions (dose / number events) per event. |
| Number of events per day for the ORAL dose | Numeric | The daily dose is administered in equal portions (dose / number events) per event. |
| Specify the hours (events). | Numeric | Specify the hours on which exposure events are simulated. Allowed numbers are 1, 2, 3, 4,…, 24 separated by spaces. |

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Table 3.279 – continued from previous page

| Name | Type | Description |
|---|---|---|
| Specify event timings | Boolean | If checked, a specific sequence of hours on a day can be specifi on which exposure events are simulated. Otherwise the events a derived based on the number of exposure events per day. |
| PBK simulation method | *PbkSimulationMethod* | Specifies in which mode to run the PBK model |
| Allow use of other matrix as surrogate for target | Boolean | Specifies whether to use exposures from another matrix as surrogate for the specified biologial matrix in case the target its is not included in the PBK model. |
| Surrogate matrix | *BiologicalMatrix* | Biological matrix of the PBK model to use as surrogate for the target matrix. |
| Lifetime window size in years | Numeric | The size of the time window (in years) for the lifetime window simulation. |
| Lifetime start age in years | Numeric | The starting age (in years) for lifetime range simulation. |
| Lifetime end age in years | Numeric | The ending age (in years) for lifetime range simulation. |
| Use bodyweight adjusted exposures | Boolean | Use bodyweight adjusted exposures in PBK model simulations. |
| Allow fallback to systemic dosing for missing exposure routes | Boolean | If the PBK model misses specific compartments for certain exposure routes, this setting allows the model to fallback to systemic dosing for those route. |
| PBK output resolution time unit | *PbkModelOutputResolution-TimeUnit* | Time unit in which the output resolution of PBK model simulations is specified. |
| PBK output resolution step size | Numeric | PBK model simulation output step size/length, specifying the evaluation resolution in terms of the step length (period) betwe two evaluations. For example, a step length of 12 with a resolut time unit of hours is interpreted as every 12 hours. |
| DIET: Population alignment method diet exposures | *PopulationAlignmentMethod* | Population aligment methods for dietary exposure sources. |
| Diet: match at random based on sex | Boolean | Match at random based on stratifying cofactor sex. |
| Diet: match at random based on age | Boolean | Dietary exposures are randomly matched on stratifying covaria age. |
| Diet: matching method for age | *AgeAlignmentMethod* | Match at random based on age using user defined bins (in years or fit to closest available set of ages. |
| Diet: specify bins: | Numeric | Specify bins, e.g. 10 25 50 (space separated) in years. |
| AIR: Population alignment method (RSExpo) air exposures | *PopulationAlignmentMethod* | Population aligment methods for (RSExpo) air exposure source |
| Air: match at random based on sex | Boolean | Match at random based on stratifying cofactor sex. |
| Air: match at random based on age | Boolean | Air exposures are randomly matched on stratifying covariable a |
| Air: matching method for age | *AgeAlignmentMethod* | Match at random based on age using user defined bins (in years or fit to closest available set of ages. |
| Air: specify bins: | Numeric | Specify bins, e.g. 10 25 50 (space separated) in years. |
| SOIL: Population alignment method (RSExpo) soil exposures | *PopulationAlignmentMethod* | Population aligment methods for (RSExpo) soil exposure sourc |
| Soil: match at random based on sex | Boolean | Match at random based on stratifying cofactor sex. |
| Soil: match at random based on age | Boolean | Soil exposures are randomly matched on stratifying covariable age. |
| Soil: matching method for age | *AgeAlignmentMethod* | Match at random based on age using user defined bins (in years or fit to closest available set of ages. |
| Soil: specify bins: | Numeric | Specify bins, e.g. 10 25 50 (space separated) in years. |

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Table 3.279 – continued from previous page

| Name | Type | Description |
|---|---|---|
| DUST: Population alignment method (RSExpo) dust exposures | *PopulationAlignmentMethod* | Population aligment methods for (RSExpo) dust exposure sourc |
| Dust: match at random based on sex | Boolean | Match at random based on stratifying cofactor sex. |
| Dust: match at random based on age | Boolean | Dust exposures are randomly matched on stratifying covariable age. |
| Dust: matching method for age | *AgeAlignmentMethod* | Match at random based on age using user defined bins (in years or fit to closest available set of ages. |
| Dust: specify bins: | Numeric | Specify bins, e.g. 10 25 50 (space separated) in years. |
| NON-DIETARY: Population alignment method other non-dietary exposures | *PopulationAlignmentMethod* | Population aligment methods for nondietary exposure sources. |
| Nondietary: match at random based on sex | Boolean | Match at random based on stratifying cofactor sex. |
| Nondietary: match at random based on age | Boolean | Nondietary exposures are randomly matched on stratifying covariable age. |
| CONSUMER-PRODUCT: Population alignment method consumer product exposures | *PopulationAlignmentMethod* | Population aligment methods for consumer product exposure sources. |
| Consumer product: match at random based on sex | Boolean | Match at random based on stratifying cofactor sex. |
| ConsumerProduct: match at random based on age | Boolean | Consumer product exposures are randomly matched on stratifyi covariable age. |
| ConsumerProduct: matching method for age | *AgeAlignmentMethod* | Match at random based on age using user defined bins (in years or fit to closest available set of ages. |
| Consumer product: specify bins: | Numeric | Specify bins, e.g. 10 25 50 (space separated) in years. |

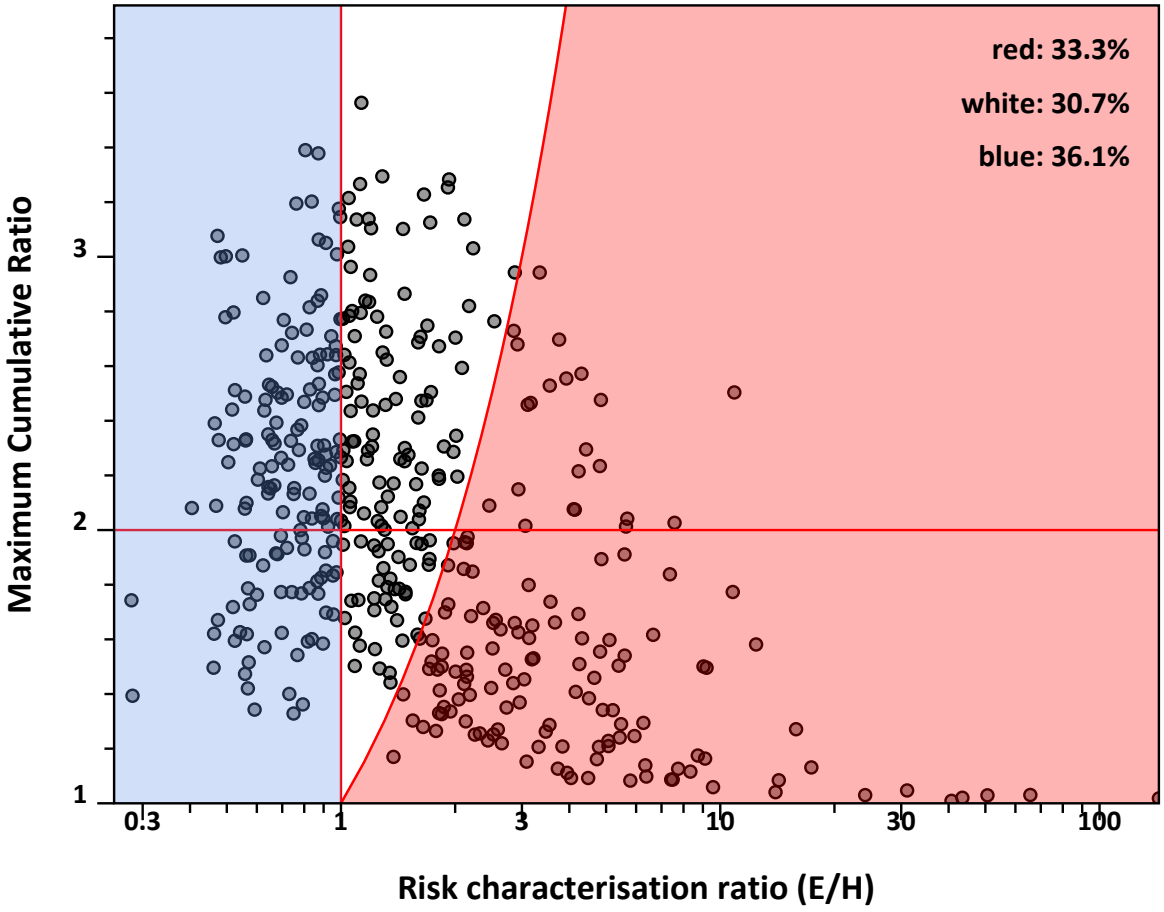



Figure 3.50: Using MCR to identify substances that drive cumulative risk, scatter distributions (total).

### Output settings

Table 3.280: Output settings for module Internal exposures.

| Name | Type | Description |
|---|---|---|
| Stratify outputs | Boolean | This setting is used to get more details e.g. how exposures are distributed among males or females. |
| Show co-exposure | Boolean | Show co-exposure in output. |
| Stratification variable | *OutputStratificationVariable* | The variable used to categorise individuals into distinct subgrou for presentation of stratified outputs. |
| Age stratification boundaries | Numeric | Give specific age boundaries (years), e.g. 18 40 65 (space separated). |
| Exclude privacy sensitive data from outputs | Boolean | Use this setting to not report the parts of the results (i.e., figure tables, or sections) that are marked as (potentially) privacy sensitive. |
| Include drill-down on 9 individuals around specified percentile | Boolean | Specifies whether drilldown on 9 individuals is to be included i the output. |
| Store simulated individual day exposures | Boolean | Store the simulated individual day exposures. If unchecked, no additional output will be generated. If checked, the output will contain an additional section with the simulated individual day exposures. |
| Show percentiles for | Numeric | Give specific percentiles of exposure distribution (%), e.g. 50 9 95 97.5 99 (space separated). |
| Percentage for drilldown | Numeric | Gives detailed output for nine individuals near this percentile of the exposure distribution. |
| Percentage for upper tail | Numeric | Gives detailed output for this upper percentage of the exposure distribution. |
| Show % of population below level(s) | *ExposureMethod* | This setting is used for reporting the percentages of individuals (chronic) or individual days (acute) exceeding certain exposure levels. These exposure levels can be generated automatically based on the observed exposures (Automatic, default) or specifi explicitly (Manual). |
| Exposure levels | Numeric | Specify exposure levels for which to give the percentage of exposure below these levels, e.g. 1 10 50 100 200 500. |
| Number of levels of covariable to predict exposure | Numeric | Specify the number of levels, e.g. 20. The range of the covaria is divided by the number of levels: range = (max - min)/levels. For these covariable levels exposures are predicted. |
| Predict exposure at extra covariable levels | Numeric | Specify specific prediction levels in addition to the automaticall generated prediction levels (space separated). |
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |
| Report consumptions and exposures per individual instead of per kg body weight | Boolean | Specifies whether body weights should be ignored and consumptions and exposures should be expressed per individual Otherwise, the consumptions and exposures are per kg body weight. |

### Uncertainty settings

Table 3.281: Uncertainty settings for module Internal exposures.

| Name | Type | Description |
|---|---|---|
| Resample kinetic conversion factors | Boolean | Specifies whether kinetic conversion factors are resampled. |
| Resample PBK model parameter values | Boolean | Specifies whether PBK model parameter values are resampled. |
| Lower uncertainty limit (%) | Numeric | Percentage lower bound, e.g. 2.5%. |
| Upper uncertainty limit (%) | Numeric | Percentage upper bound, e.g. 97.5%. |

### Calculation of internal exposures

Internal exposures are computed by linking dietary and (if available) non-dietary individual/individual-day exposures. The (aggregated) internal exposure is computed as an internal concentration at the specified target compartment using kinetic conversion factors or PBK models or as an internal dose that is systemically available in the general circulation using absorption factors.

- *Internal exposures calculation*

Inputs used: *Active substances Dietary exposures Consumer product exposures Air exposures Dust exposures Soil exposures Non-dietary exposures Occupational scenarios Occupational exposures Individuals Absorption factors Kinetic conversion factors PBK model parametrisations Relative potency factors*

Settings used

- *Calculation Settings*

## 3.4.14 Exposure mixtures

Exposure mixtures will select sets of co-occurring substances (one or more) that contribute most to the overall exposure patterns.

This module has as primary entities: *Substances Effects*

### Exposure mixtures calculation

The most common approach to cumulative risk assessment is to focus on substances belonging to the same common assessment groups (CAG). *Substances* within such a group often share a chemical family and may or may not exhibit a similar mode of action. In risk assessments, potential interactions between substances are frequently ignored; furthermore, limited information is available regarding synergistic effects at low doses. While more data on the combined effects of these substances is needed, investigating all possible mixtures is impractical. Therefore, prioritization tools are required to select the most relevant substances for further study. This selection should be based not only on the hazard (highest relative potencies) but also on the exposure of the population to these substances. The potential risk of mixture exposure depends on individual food *consumption* patterns of *individuals* in a population. ince a regular diet can contain hundreds of substances, the number of potential combinations is vast. The exposure mixtures module is used to identify the most relevant components and substance combinations to which a population is exposed.

### Risk based, standardised or unweighted exposures

Before performing the mixture exposure assessment, the data are preprocessed. Three optional choices are available, *see settings, exposure approach type*.

- Risk based exposures: exposures are multiplied by the *relative potency factor* (RPF) of each substance and thus exposures for different substances are on the same and comparable scale.
- Standardised exposures: all exposures are standardised to equal variance (unit variance).

- Unweighted exposures: exposures are taken as such, this is equivalent to RPF s equal to 1 for each substance.

Exposure mixtures are identified using a quantitative approach: *sparse non-negative matrix underapproximation (SNMU)* (Gillis and Plemmons (2013)) and answers the question what combination of substances predominantly determine the underlying patterns in the exposure matrix (substance x person (day)).

After identifying the components, a cluster analysis is applied to group individuals with similar profiles of exposure to the obtained component (Crépet et al. (2022)).

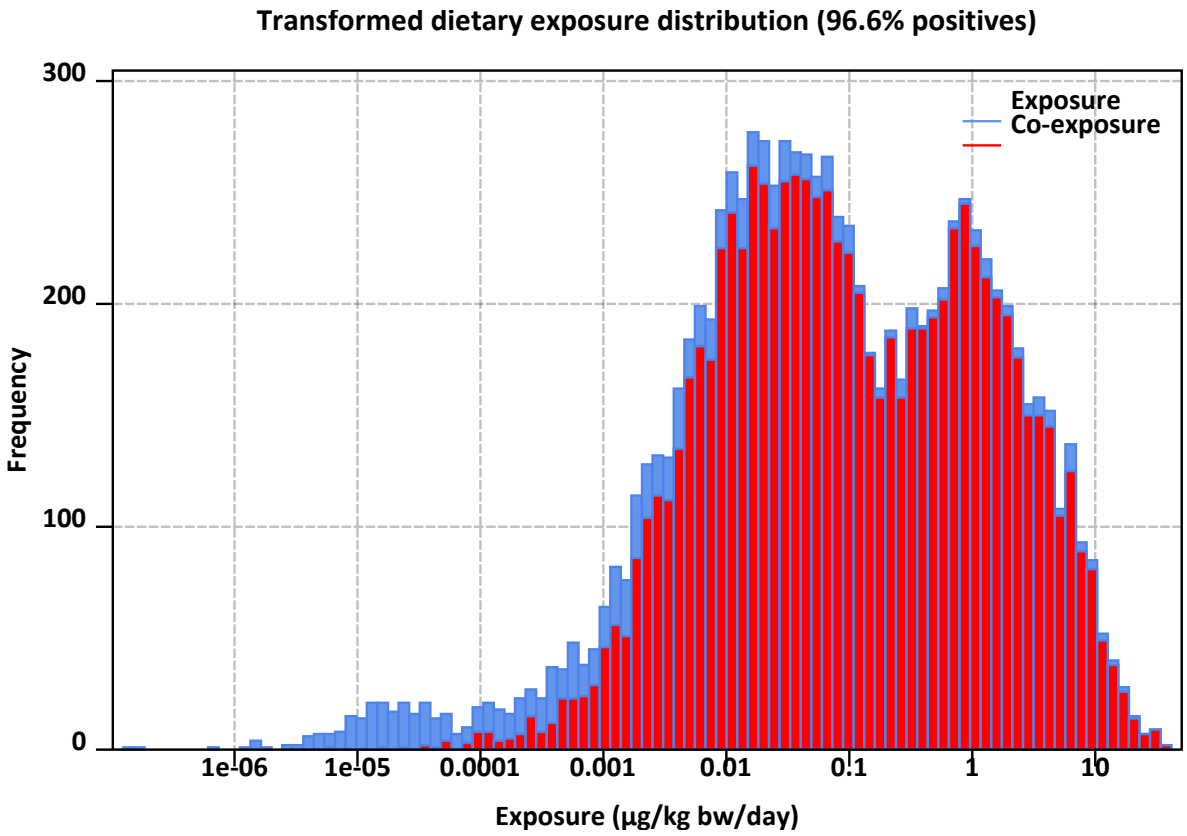



Figure 3.51: Example of co-exposure distribution (from >1 substance per individual-day, red) super-imposed on the total exposure distribution (blue).

### Sparse nonnegative matrix underapproximation

Starting point to identify major components of combinations of substances using exposure data was to use Non-negative Matrix Factorization (NMF). This algorithm was proposed by Lee and Seung (1999) and Saul and Lee (2002) and deals specifically with non-negative data that have excess zeros such as exposure data. Zetlaoui et al. (2011), introduced this method in food risk assessment to define diet clusters.

The NMF method was then implemented by Béchaux et al. (2013) in order to identify food consumption patterns and main components of combinations of pesticides to which the French population was exposed using *TDS* exposure to 26 priority pesticides.

At the start of the Euromix project ideas had evolved: to obtain less substances per component experiments were made using Sparse Nonnegative Matrix Factorization (SNMF) (Hoyer (2004)). This method was found not to give stable solutions. Better results were obtained with Sparse Nonnegative Matrix Underapproximation (SNMU) (Gillis and Plemmons (2013)). This model also fits better to the problem situation because also the residual matrix after extracting some components should be nonnegative. The SNMU method has been implemented in MCRA.

Indeed, NMF may be used to identify patterns or associations between substances in exposure data. NMF can be described as a method that finds a description of the data in a lower dimension. There are standard techniques available such as principal components analysis or factor analysis that do the same, but their lower rank representation is less suited because they contain negative values which makes interpretation hard and because of the modelling with a

Gaussian random vectors which do not correctly deal with the excess of 0 and non-negative data. The NMF solution approximates a non-negative input matrix (i.c. exposure data) by two constrained non-negative matrices in a lower dimension such that the product of the two is as close as possible to the original input matrix. In Figure 3.52, the exposure matrix $M$ with dimensions $m$ (number of substances) and $n$ (number of intake days or persons) is approximated by matrix $U$ and $V$ with dimensions $(m \times k)$ and $(k \times n)$ respectively, where $k$ represents the number of components. Matrix $U$ contains weights of the substances per component, matrix $V$ contains the coefficients of presence of components in exposure per intake day or person. $M$ is non-negative (zero or positive) and $U$ and $V$ are constraint to be non-negative. The minimization criterion is: $||M–UV||2$ such that $U \geq 0$ and $V \geq 0$.

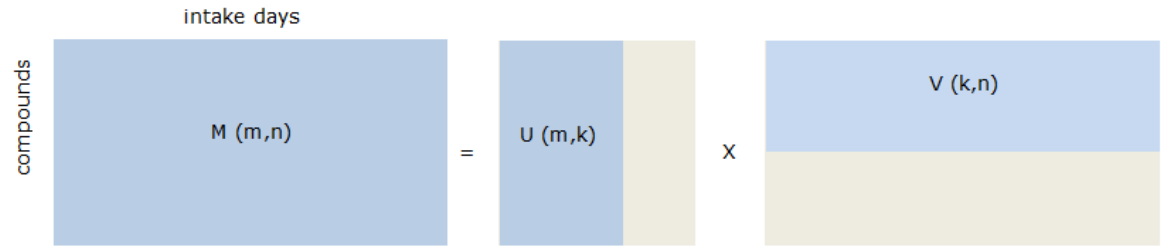



Figure 3.52: NMF approximation of exposure data

The solution found by NMF contains zeros, but components still contain many substances which complicates interpretability. Therefore, the Sparse Nonnegative Matrix Underapproximation (SNMU) (Gillis and Plemmons (2013)) which also provide sparse results was investigated. The SNMU has also some nice features well adapted to the objective of the Euromix project: the solution is independent of the initialization and the algorithm is recursive. Consequently, the SNMU method which is based on the same decomposition process as the NMF was the one implemented in MCRA.

SNMU is initialized using an optimal nonnegative rank-one approximation using the power method (https://en.wikipedia.org/wiki/Power_iteration). This initialization is based on a singular value decomposition and results in general in a unique solution that is sparse. The SNMU algorithm is called recursive because after identifying the first optimal rank-one underapproximation $u_1 v_1$, the next rank-one factor is recovered by subtracting $u_1 v_1$ from $M$ and applying the same factorization algorithm to the remainder $M - u_1 v_1$. The solution $u_1 v_1$ is called a rank-one underapproximation because an upper bound constraint is added to ensure that the remainder $M - u_1 v_1$ is non-negative. For Matlab code see: https://sites.google.com/site/nicolasgillis/code.

For each component, a percentage of explained variance is calculated. $M$ is the exposure matrix with $m$ rows (substances) and $n$ columns (individuals or individual days) $S_t$ is sum of squared elements of $M$:

$$S_t = ||M||^2 = \sum_{i,j}^{m,n} e_{i,j}^2$$

Apply SNMU on $M$, then for the first component:

- $u$ is $m \times 1$ vector, contains weights of the component.
- $v$ is $1 \times n$ vector, contains presence of component in exposure per individual.

Calculate residual matrix $R$:

$$R = M - uv$$

Calculate $S_r$, residual sum of squared elements of R:

$$S_r = ||R||^2 = \sum_{i,j}^{m,n} e_{i,j}^2$$

Percentage explained variance first component $(k = 1)$ is:

$$V_k = (1 - S_r)/S_t) \cdot 100$$

For the second component:

1. continue with residual matrix $R$ (replace $M$ by $R$),
2. estimate $u$ and $v$,
3. calculate new residual matrix $R$
4. calculate $S_r$, residual sum of squared elements of $R$

Percentage explained variance second component $(k = 2)$ is:

$$V_k = (1 - S_r)/S_t) \cdot 100 - \sum_{l=1}^{k-1} V_l$$

The last term is de percentage explained variance of the first component. Continue with the third component etc….

The given factorization by SNMU is not unique. A matrix $D$ and its inverse can be used to transform the two lower rank matrices $U$ and $V$ by, e.g.

$$M = UV = UDD^{-1}V$$

where matrix $D$ is non-negative and corresponds to a scaling of matrix $U$ and $V$ to matrix $\tilde{U} = UD$ and $\tilde{V} = D^{-1}V$.

In Figure 3.53, SNMU is applied on the exposure matrix. The SNMU solution after scaling results in a matrix that represents the mixture composition and a matrix representing the individual scores. The first matrix is interpreted as the set of contributions of the substances to a component., the second matrix, as the set of exposures of the individuals to the mixtures.

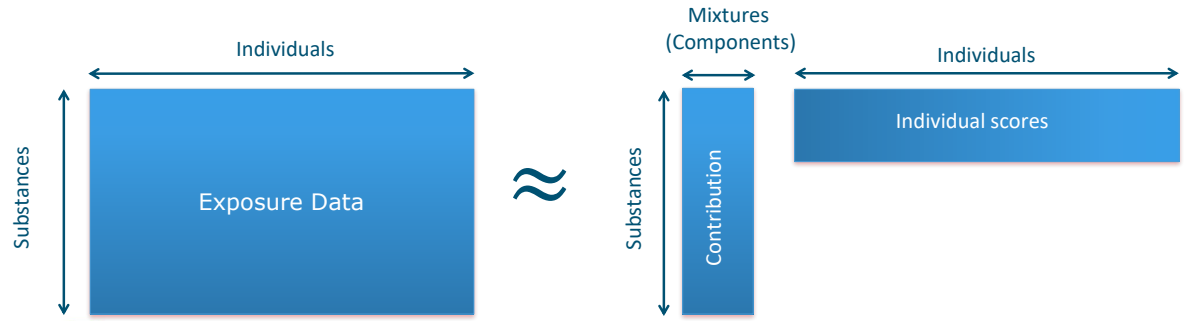



Figure 3.53: SNMU approximation of exposure data after scaling.

### Exposure matrix

Basically, exposure is calculated as consumption x concentration. By summing the exposures from the different foods for each substance per person day separately, the exposure matrix for component selection is estimated:

$$y_{ijc} = \frac{\sum_{k=1}^{p} x_{ijk} c_{ijkc}}{bw_i}$$

where $y_{ijc}$ is the exposure to substance $c$ by individual $i$ on day $j$ (in microgram substance per kg body weight), $x_{ijk}$ is the consumption by individual $i$ on day $j$ of food $k$ (in g), $c_{ijkc}$ is the concentration of substance $c$ in food $k$ eaten by individual $i$ on day $j$ (in mg/kg), and $bw_i$ is the body weight of individual $i$ (in kg). Finally, $p$ is the number of foods accounted for in the model. More precisely, for an *acute* or short term risk assessment, the exposure matrix summarises the $y_{ijc}$ with columns denoting the individual-days $(ij)$ and rows denoting the substances $(c)$. Each cell represents the sum of the exposures for a substance on that particular day. For a *chronic* or long term risk assessment, the exposure matrix is constructed as the sum of all exposures for a particular substance averaged over the total number of intake days of an individual (substances x persons). So each row represents a substance and a column an individual. Each cell represents the observed individual mean exposure for a substance for that individual. Note that in the exposure calculation, the concentration is the average of all residue values of a substance.

When *relative potency factors* (RPF) are available then exposures are multiplied by the RPF and thus exposures to the different substances are on the same and comparable scale (toxicological scale). In this case, the selection of the

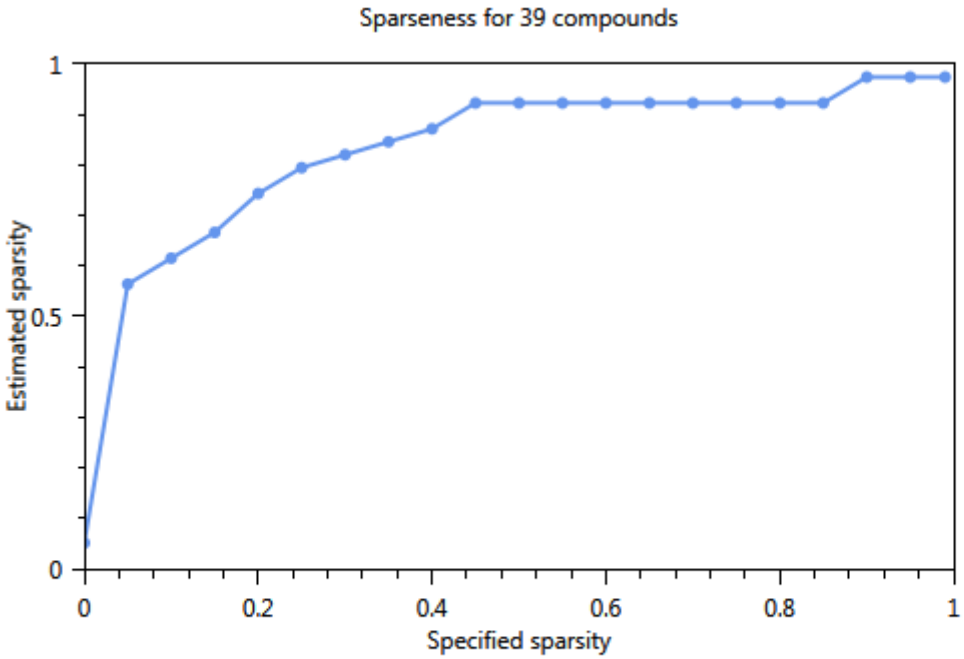
components is risk-based. In some cases, RPFs may not be available. In this case exposure to different substances, even in the same unit, may lead to very different effects. To give all substances an equal weight a priori and avoid scaling effects, a standardisation of the data can be applied as done in Béchaux et al. (2013). In this case, all substances are assigned equal mean and variance, and the selection of the components will work on patterns of correlation only. Then component selection is not risk-based anymore but, what could be called, co-exposure-based.

Finally, in the mixture selection module of MCRA, the SNMU expects RPF data for a risk-based selection. If not available, the user should provide alternative RPF data, e.g. values 1 for a purely exposure-based selection, or lower-tier estimates (e.g. a maximum value on RPF thought possible).

### Mechanisms to influence sparsity

Two mechanisms to *influence sparsity* are available. The SNMU algorithm incorporates a sparsity parameter and by increasing the value, the final components will be more sparse (sparsity close to 0: not sparse, many substances; sparsity close to 1: sparse, few substances). The other approach is by using a subset of the exposure matrix based on a cut-off value for the *MCR*. High ratios correspond to high co-exposure, so it is reasonable to focus on these (person) days and not include days where exposure is received from a single substance (ratio close to 1). To illustrate the combined use of MCR and the sparsity parameter, the French steatosis data (39 substances, 4079 persons) are used and person days with a ratio > 5 (see Figure 3.46) are selected yielding a subset of 139 records.

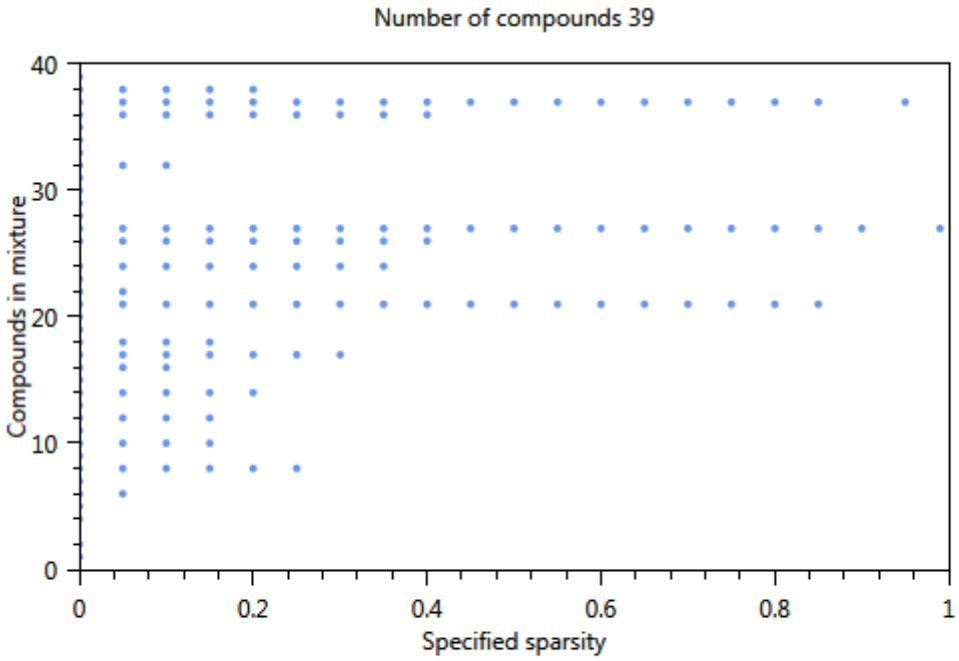
In Figure 3.54, the effect of using a cut-off level is immediately clear. The number of substances of the first component is 17 whereas in the unselected case (not shown) only 4 substances were found The three plots show the influence of increasing the sparsity parameter from 0 to 1 on the number of substances in the component. The first plot shows the estimated sparsity versus the specified sparsity. The second and third plot the the numer of substances in a component. For values close to 0, the component contains 17 substances. For values > 0.4 the number of substances in the component drops to 3 and for a sparsity close to 1, only one substance is found in a component.




### Substance contributions to components

The SNMU solution of matrix U can be displayed in a heatmap. The heatmap shows the relative contribution of each substance to a component.

In Figure 3.56 and Figure 3.57 the sparsity parameter is set to 0.1 (not sparse) and 0.8 (sparse), respectively. This



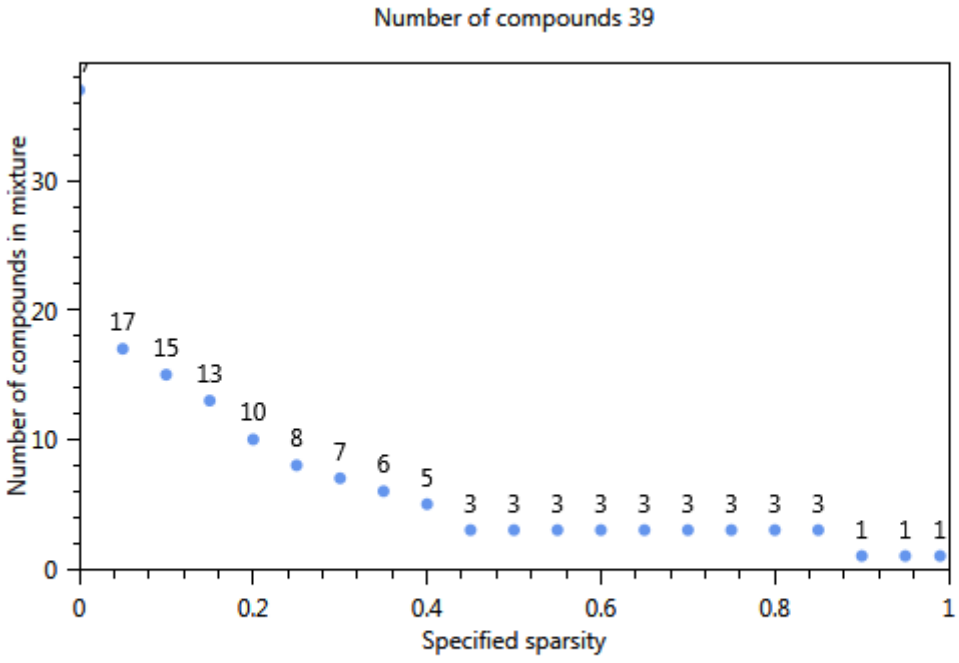




Figure 3.54: Influence of the specified sparsity parameter on the realized sparsity, n = 139.

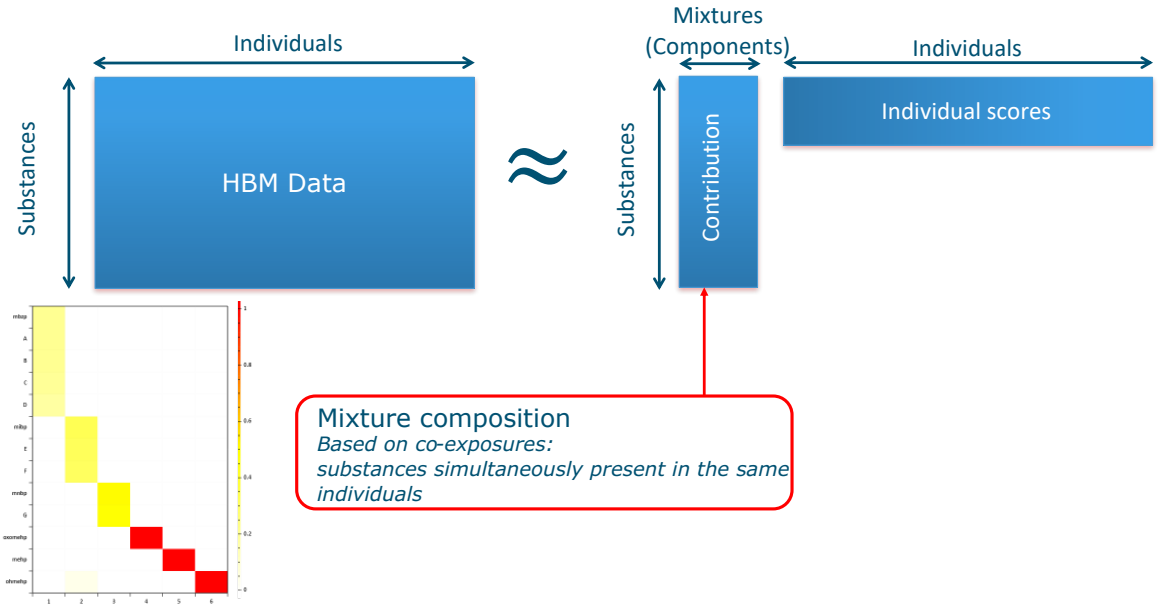



Figure 3.55: SNMU: matrix $U$, substance contributions to components.

leads to components containing different number of substances.

In Figure 3.58, the relative contributions of the substances to the first component are displayed in a piechart.

As mentioned before, one of the nice features of the SNMU algorithm is its recursive character which results in identical components. In Figure 3.59, the U matrix is visualized using three components. Compare this solution with Figure 3.57, the first three components are identical. Because of the ordering the plots look slightly different, but a closer inspection of the first 3 components of each solution shows that they are the same. In both figures, component 1 contains mbzp, A, B, C and D; component 2, mibp, E, F and ohmehp; and component 3 mnbp and G.

In paragraph *network analysis*, an alternative to the SNMU approach is proposed.

For selection of individual(day) exposures with a *maximum cumulative ratio* above a cutoff and/or above a cutoff percentage in the set of individual(day)s ranked on total exposure, see *'Cutoff MCR' and 'Cutoff percentage' settings*.

### Component exposures in population and subgroups

The SNMU solution of matrix V is used to group individuals with similar mixture exposure profiles. In Figure 3.60, the idea of clustering is shown.

Crépet et al. (2022) propose to identify components by coupling statistical criteria with the relevance of combined exposure profiles and component composition. First, the optimal choice for $k$, the number of components, is determined using a trade off between the decrease of the residual sum of squares and number of components. Then, hierarchical clustering was applied to the matrix of individual scores $V$ to group individual(day)s with similar exposure profiles to the $k$ components. This identification of components is repeated for different values of $k$ where inspection of components not relevant to characterize a cluster, or concerned with only a small part of the population leads to rejection of the mixture.

In MCRA, two clustering methods are availabe. The first, hierarchical clustering, is implemented as described in Crépet et al. (2022). Ward's clustering criterion is implemented using Euclidean distances (Ward.D2, Murtagh and Legendre (2014)) . Specification of the optimal number of clusters is not needed. Results of the clustering are displayed in a dendrogram, Figure 3.61. The second one, based on K-means, requires specification of the number of clusters. The results of the clustering are represented in a scatter plot using principal components and convex envelopes to identify the clusters, Figure 3.63.

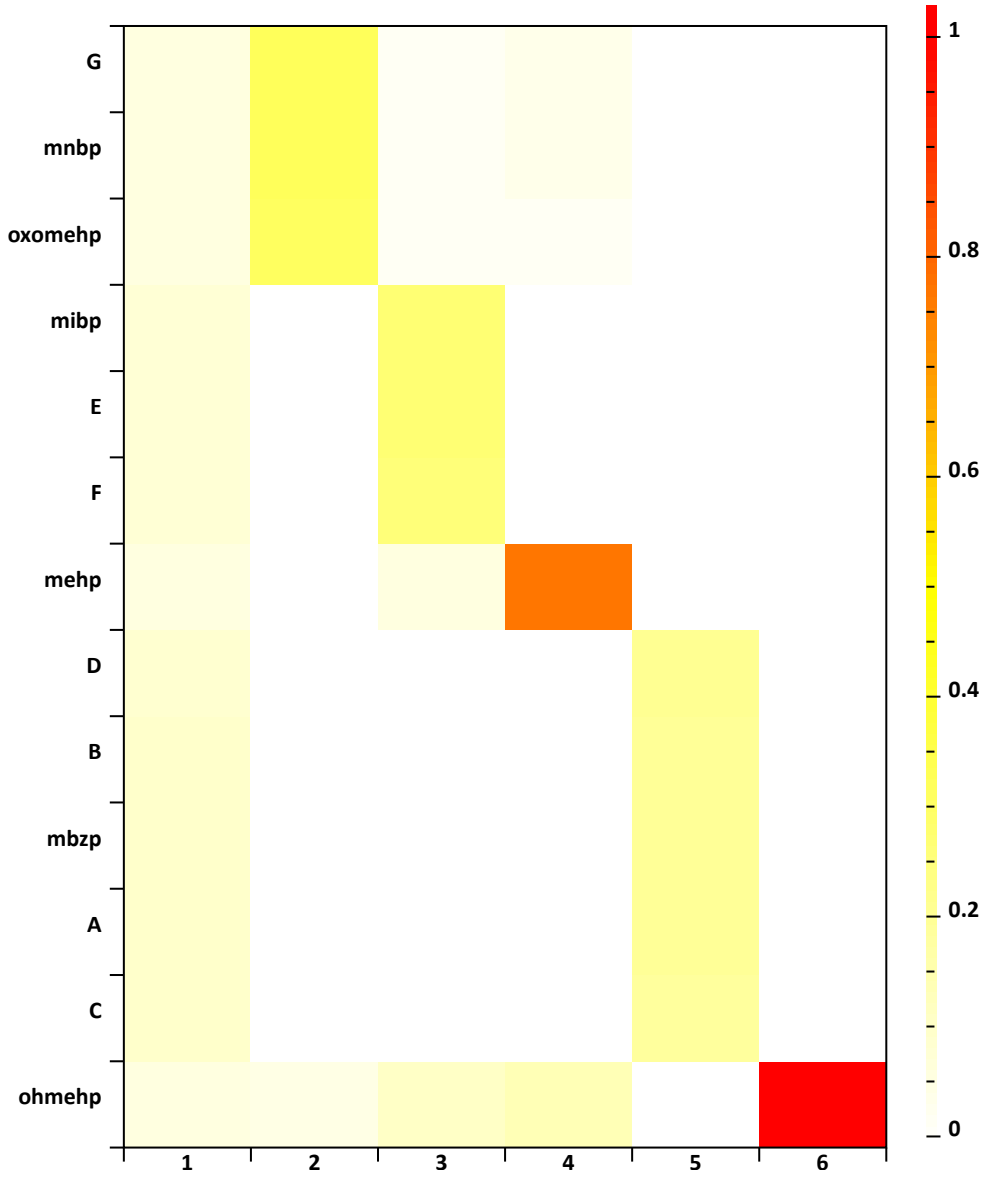



Figure 3.56: Co-exposure of substances. Heatmap for a solution with 6 components. The sparsity = 0.1. Each component, especially the first, contains many substances (see also Figure 3.57).

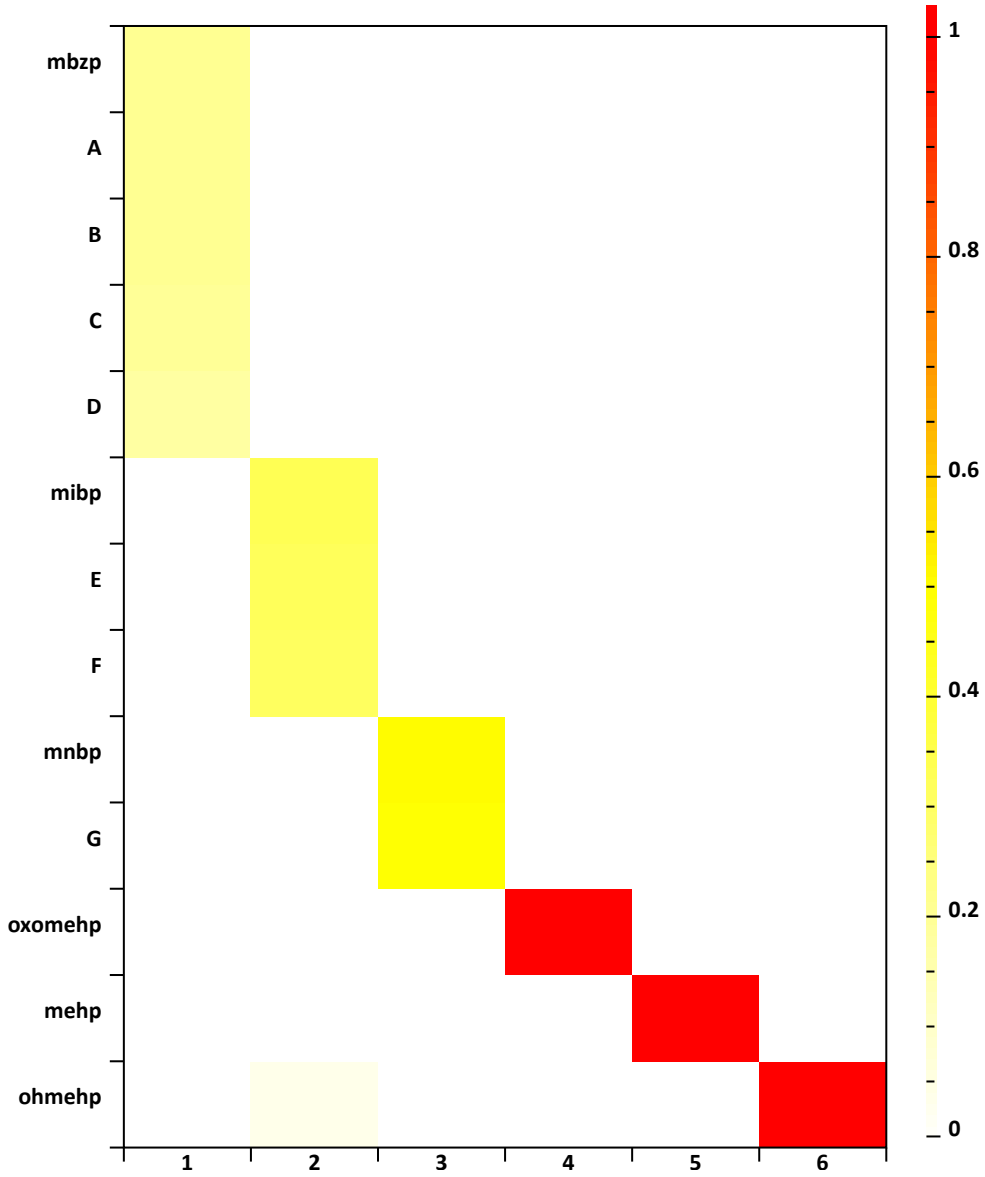



Figure 3.57: Co-exposure of substances. Heatmap for a solution with 6 components. The sparsity = 0.8. Components contain less substances compared to Figure 3.56.

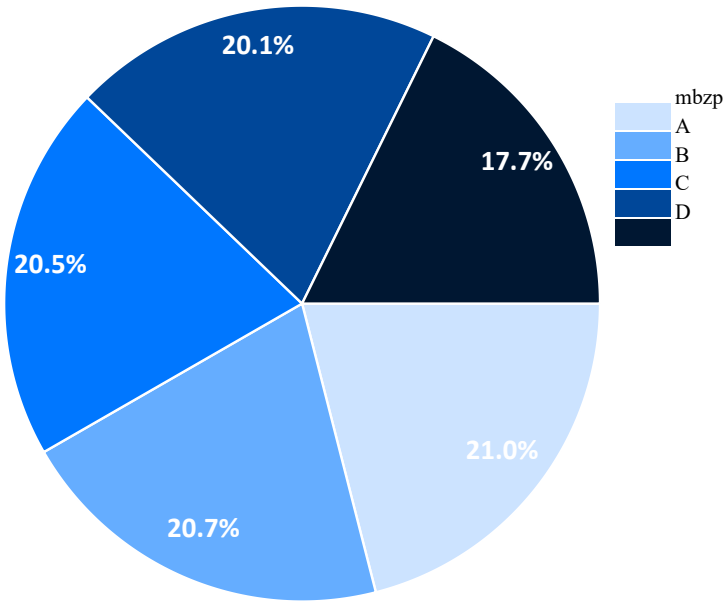



Figure 3.58: Relative contributions substances to component 1. The sparsity is set to 0.8 (sparse), estimated sparsity = 0.62.

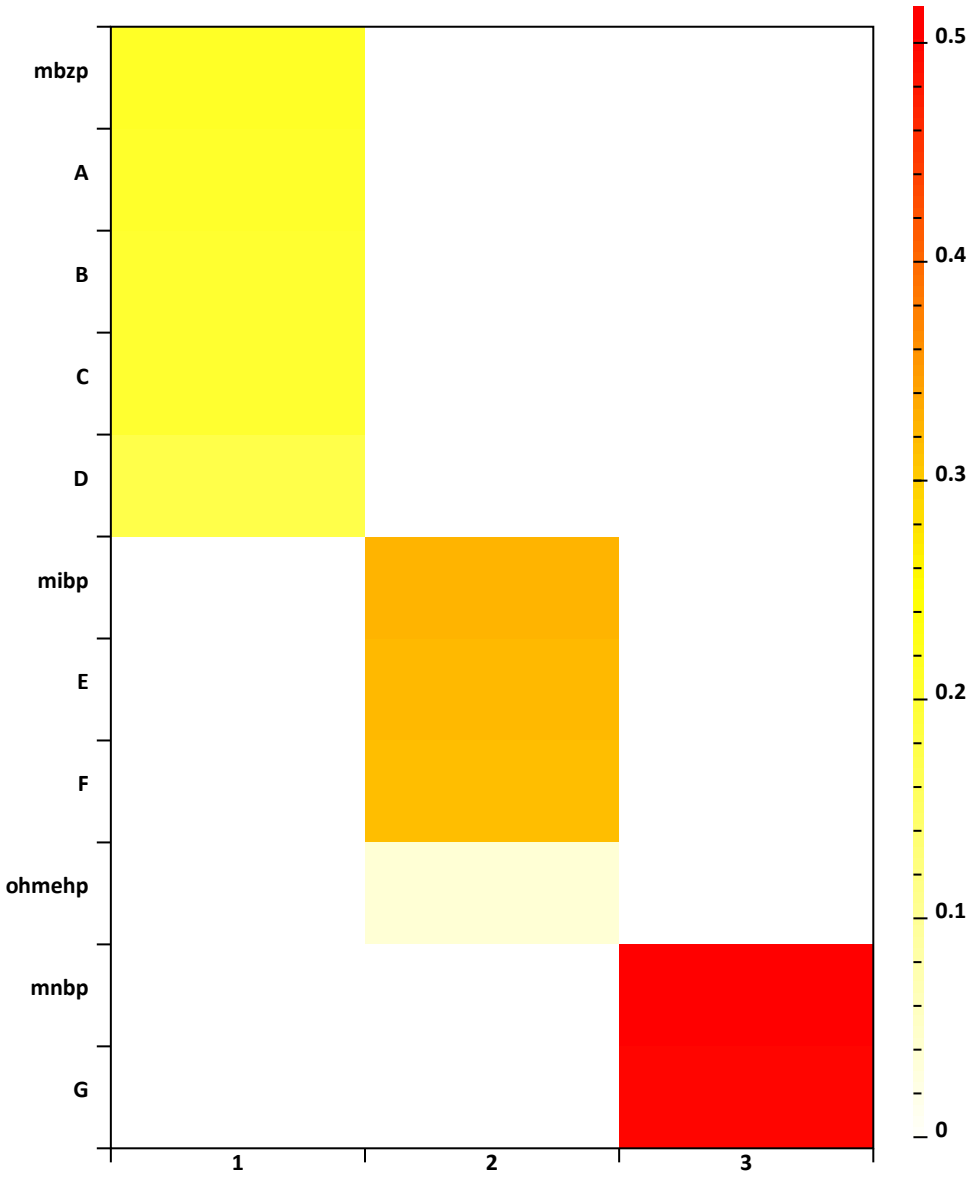



Figure 3.59: Heatmap for solution with 3 components. The first 3 components in Figure 3.59 and Figure 3.57 contain the same substances.

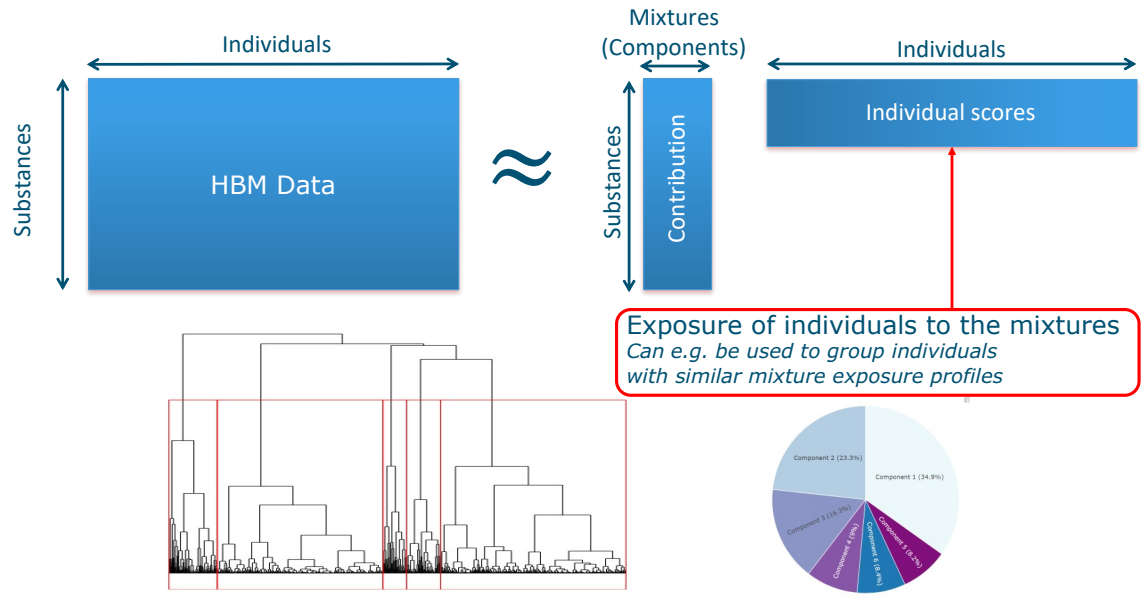



Figure 3.60: SNMU: matrix $V$, individual scores to components.

In Figure 3.62, the relative exposure to componaents in the total populations are shown. These plots are also available for the subgroups resulting from the clustering.

Advantages of K-means clustering is that it is simple and fast and large datasets can be handeled. Visualisation for large data sets is straightforward but for hierarchical clustering dendrograms maybe very dense. Disadvantage of K-means is that it requires the number of clusters set before. For large datasets, hierarchical clustering maybe slow, O(n^2), but for small datasets, the dendrogram helps in interpreting the results and in selecting the optimal number of clusters.

### Network analysis

As an alternative to *SNMU*, a network analysis is proposed. The outcome of a network analysis is graphically displayed by a network. This is a collection of nodes, that may have pairwise relationships. Each node represents a substance, and an edge represents pairwise dependence between substances (e.g. correlation or partial correlation). In MCRA, the network is estimated using a Gaussian graphical model (GLASSO) based on partial correlation and a sparseness penalty to control the number of nonzero edges (Friedman et al. (2008)). Parameters are automatically tuned. The communities are detected using a Walkman algorithm. In Figure 3.64, using HBM data, a network is displayed with 6 communities. The largest community contains 5 substances: mbzp, A, B, C and D. Compared to the results of the *SNMU mixture analysis*, the communities are almost identical to the components found in the SNMU approach.

The exposure data may be log transformed before the network analysis. Zeros are replaced by the logarithm of the minimum of the non-zero exposure values per substance multiplied by a factor 0.01.

### Exposure mixtures settings

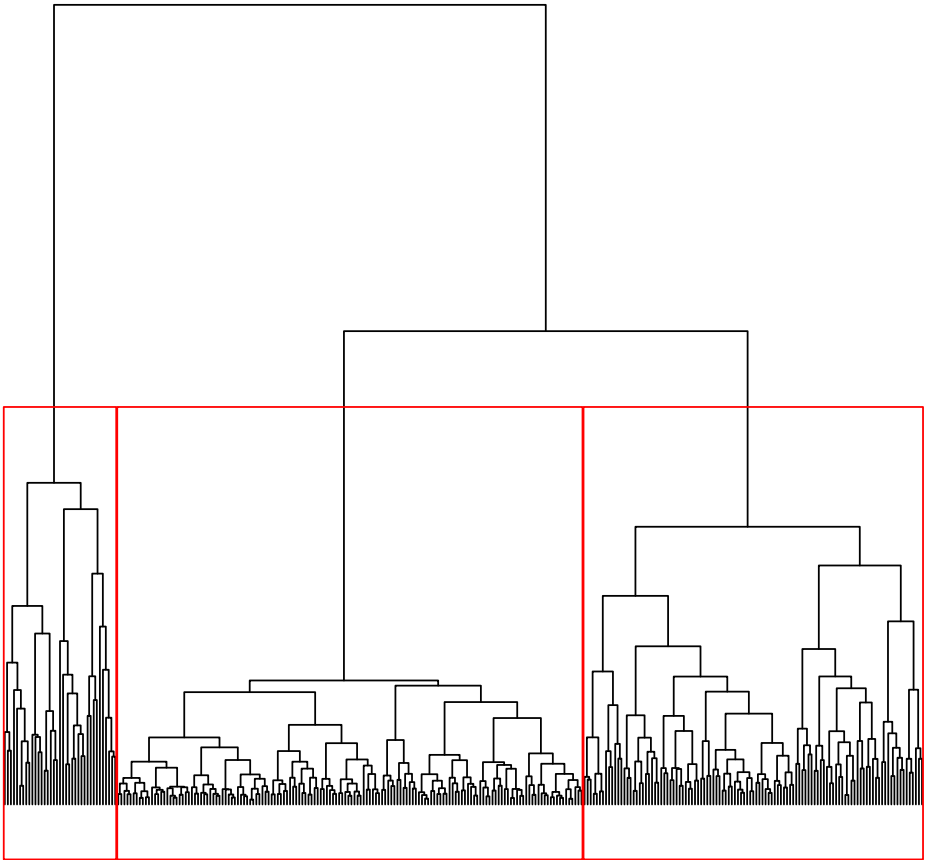


Figure 3.61: Hierarchical clustering of human monitoring data, 3 clusters, largest and smallest cluster contain 152 and 37 individuals, respectively

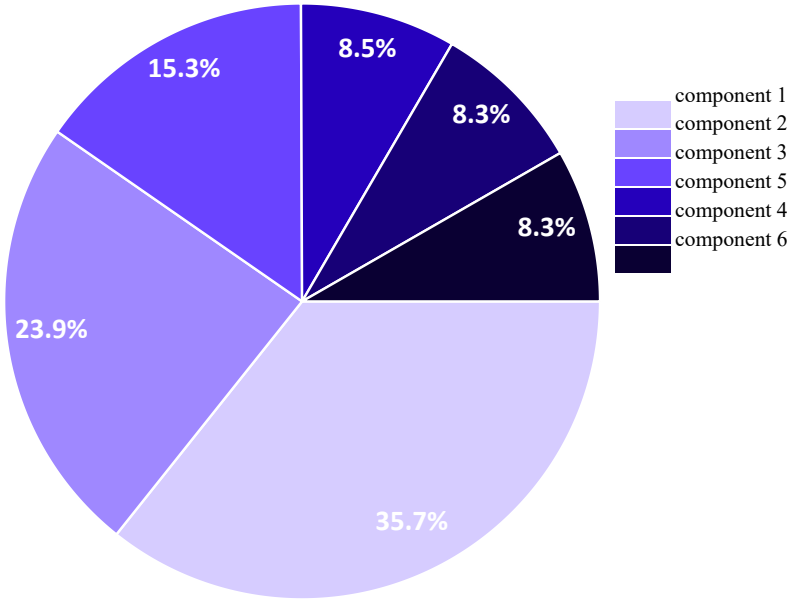



Figure 3.62: Relative exposure to components in the population

### Calculation settings

Table 3.282: Calculation settings for module Exposure mixtures.

| Name | Type | Description |
|---|---|---|
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Target level | *TargetLevelType* | Select whether the assessment is at the level of external dose, internal (target) concentration or internal (systemic) dose. For a aggregate assessment, combining dietary and nondietary exposures, the target level is always internal concentration or internal (systemic) dose. When only dietary exposures are available, the target level is optional and may be an external (administered) dose, an internal (tissue) concentration or an internal (absorbed) dose. |
| Exposure calculation method | *ExposureCalculationMethod* | Method for obtaining exposure estimates. These can be modelle exposures (e.g., external (dietary) exposures or internal exposur estimates obtained by aggregating dietary and non-dietary exposures) or exposure estimates derived from human (bio)monitoring data. |
| Report consumptions and exposures per individual instead of per kg body weight | Boolean | Specifies whether body weights should be ignored and consumptions and exposures should be expressed per individual Otherwise, the consumptions and exposures are per kg body weight. |
| Sampling method | AlphaNumeric | The sampling method that should be included in the action. |
| Substance weighting in mixtures | *ExposureApproachType* | Risk based: exposures in equivalents of the reference substance standardised: standardised exposures per substance have varian 1; or unweighted exposures: RPFs are equal to 1. |
| Number of components | Numeric | The number of components to select in SNMU. |
| Sparseness parameter | Numeric | Sparseness parameter. Value between 0 (not sparse, many substances) and 1 (sparse, few substances). |
| Iterations | Numeric | Maximum number of iterations, e.g. 1000. |
| Seed for pseudo-random number generator. | Numeric | Random seed for initialising matrix W and H. |

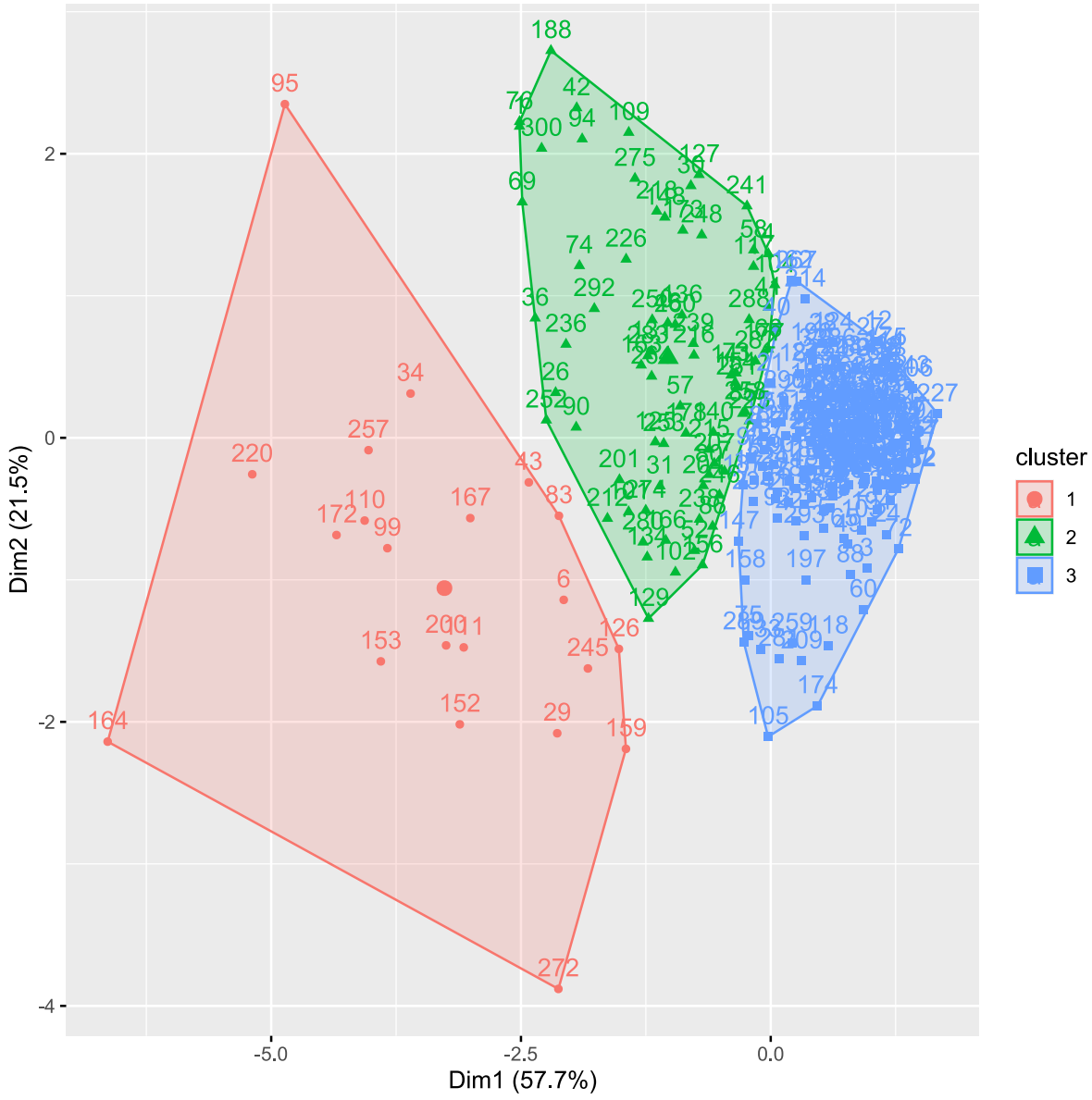



Figure 3.63: K-means clustering of human monitoring data, 3 clusters, largest and smallest cluster contain 204 and 21 individuals, respectively

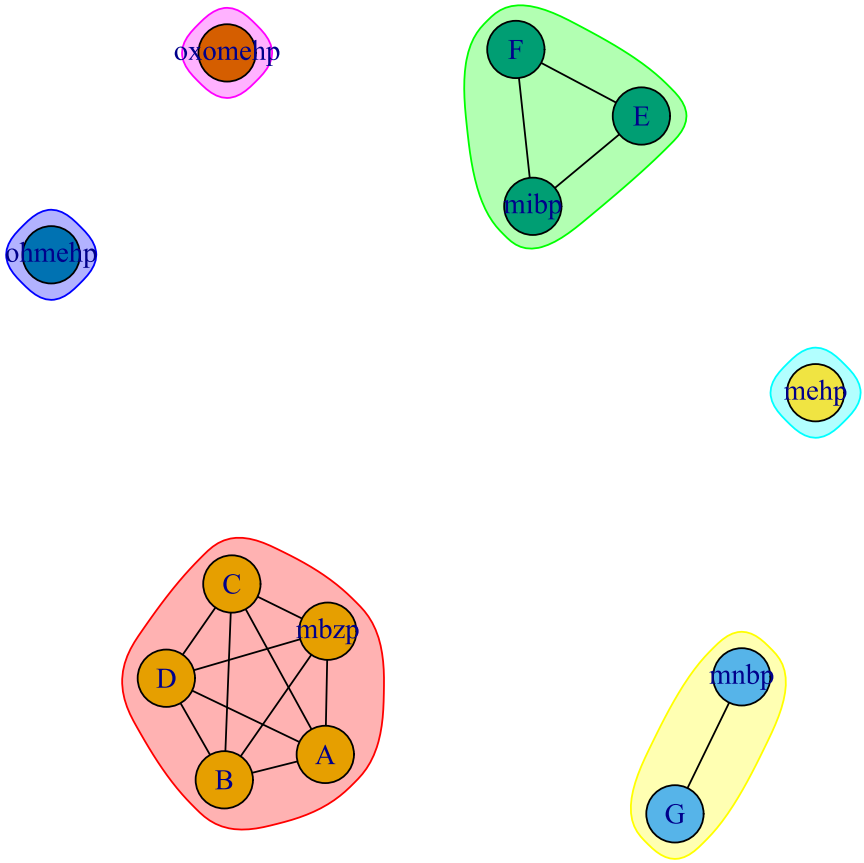



Figure 3.64: Network analysis.

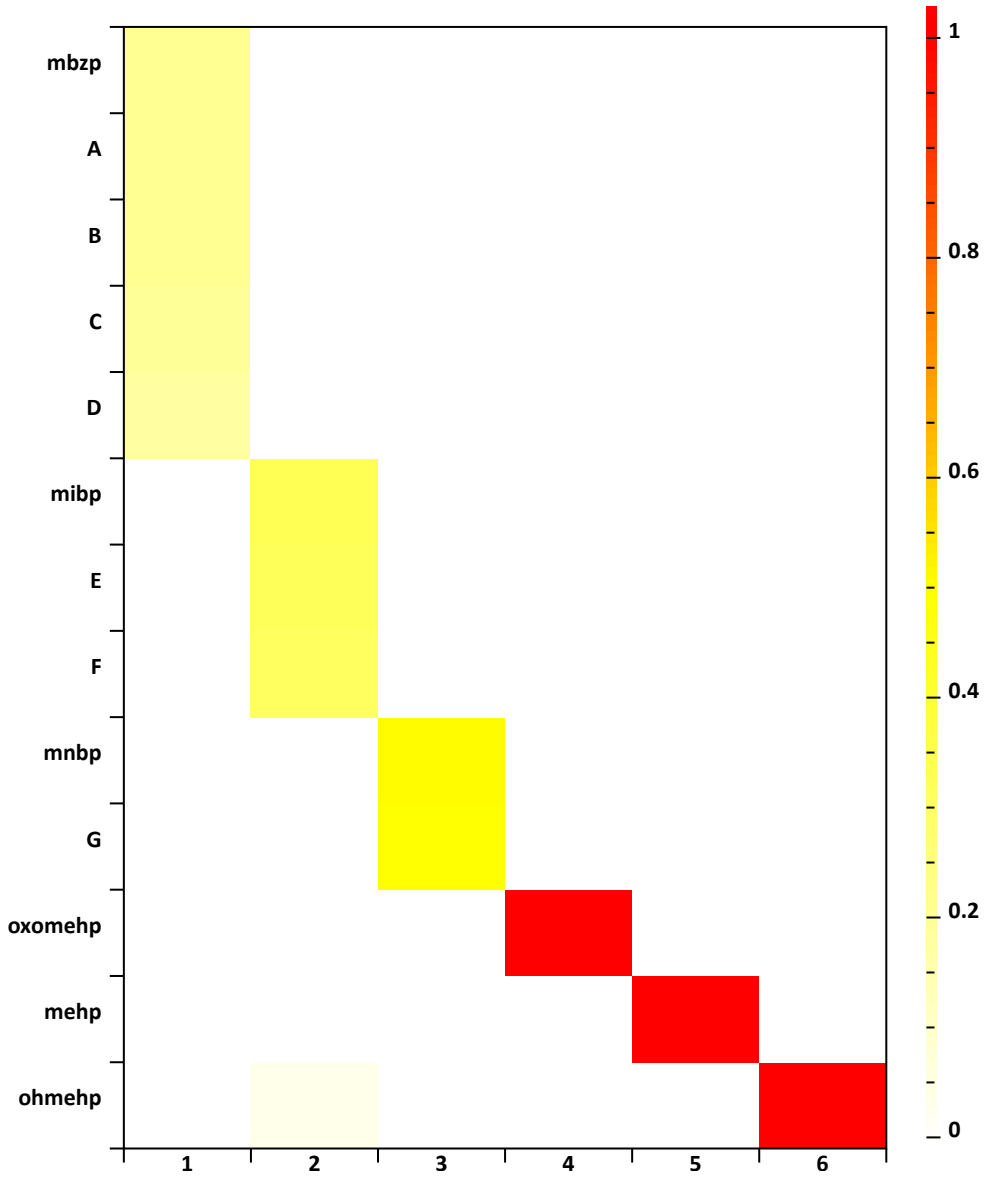



Figure 3.65: SNMU solution with 6 components. Sparsity = 0.8.

#### Calculation of exposure mixtures

Exposure mixtures or components can be computed from external dietary exposures, internal exposures (potentially combining dietary and non-dietary sources), or human biomonitoring concentrations. A multivariate decomposition method, sparse non-negative matrix underapproximation (SNMU), is applied to the exposure matrix—organized by substance and individual (chronic) or individual-day (acute) — to identify components containing the substances that contribute most to cumulative exposure. Prior to analysis, exposures per substance are preprocessed: they are either multiplied by relative potency factors (RPFs) for a risk-based analysis or standardized to unit variance for a correlation-based approach. An alternative to SNMU is network analysis, a method that identifies communities of substances based on their pairwise relationships.

- *Exposure mixtures calculation*

Inputs used: *Dietary exposures Internal exposures Relative potency factors HBM analysis*

Settings used

- *Calculation Settings*

### 3.4.15 Food conversions

Food conversions relate foods-as-eaten, as found in the consumption data, to modelled foods (foods-as-measured), which are the foods for which concentration data are available. A food-as-eaten can be linked to one, or multiple modelled foods using various conversion steps (e.g., using food recipes to translate a composite food into its ingredients). There are several types of conversion steps, and a conversion path may comprise multiple conversion steps between a food-as-eaten and a modelled food.

This module has as primary entities: *Foods Substances*

Output of this module is used by: *Consumptions by modelled food Dietary exposures*

#### Food conversions calculation

Food conversions are computed using a recursive search algorithm to link foods-as-eaten to modelled foods, possibly through intermediate conversion steps. For instance, if (unpeeled) apple and grapes are the modelled foods, the food-as-eaten apple pie contains peeled apple and raisins, peeled apple is linked to unpeeled apple, and raisins are dried grapes. Hence, for apple pie, there are two conversions, one to apple (with processing type 'peeled') and one to grapes (with processing type 'dried'), each with its own conversion path of intermediate conversion steps.

#### Substance independent conversion

The current implementation of the food conversion algorithm can be run substance independent. The *Find processing link (deprecated)* is skipped from the algorithm (default = false) and is only retained for backwards compatibility reasons only (see Advanced, set to true). Processed foods are easily recognized in the food translation step and retrieving the processing factor that belongs to a certain processing type is done outside the algorithm. In fact, finding processing types with corresponding processing factors is not a task of the conversion algorithm: conversion is about converting food codes to other food codes.

When the processing step is skipped, there is no need to run the conversion algorithm on a substance basis. The only information that is needed is whether a food code is a modelled food or not (i.c. is there a concentration available or not). This information can be computed beforehand: for each substance all modelled foods are collected and supplied to the conversion algorithm in a common dictionary containing all modelled food codes. As soon as a food code is found in the dictionary, the conversion ends and the next food code is converted.

For each food-as-eaten, the food conversion algorithm recursively builds up the conversion paths using the following procedure:

1. *Substance independent conversion:* the conversion algorithm is substance independent. Check whether the current food is a modelled food. If successful, the food has been found, and the current search stops.

2. Check whether the current food translates to one or more foods through composition or read-across. Identify any processing types of facets.

a. *Food recipe link:* try to find food translations for the current food (i.e., the ingredients of a composite food). This may result in one or more food codes for ingredients, and the iterative algorithm will proceed with each of the ingredient food codes in turn. Simultaneously check, whether the current food is a processed food or not. If so, determine the processing type or facets.

b. *TDS food sample composition link:* try to find the code in the *TDS food sample compositions* table (column idFood), a default translation proportion of 100% is assumed. The iterative algorithm will proceed with a TDS food (column idTDSFood) sample.

c. *Read-across link:* try to find a food extrapolation rule for the current food, a default translation proportion of 100% for 'idToFood' is assumed.

Note that in the *food recipe link* processed foods are recognized and that the translation proportion to correct for a weight reduction or increase is stored.

If successful, restart at the first step with each of the new codes of the ingredient foods, TDS foods or Read Across foods.

3. *Marketshares link:* try to find subtype codes, e.g. 'xxx$*' in the *Market shares* table. In general, marketshares should sum to 100%. Foods with marketshares not summing to 100% are ignored in the analysis unless the checkbox *Allow marketshares not summing to 100%* is checked. This step is optional, see advanced settings. If successful, restart at step 1 with each of the new codes of the subtype foods.

4. *Supertype link:* try to find supertypes, e.g. 'xxx$yyy' is converted to 'xxx'. This step is optional, see advanced settings if you want to use this. If successful, restart at step 1 with the new code of the supertype food.

5. *Default processing factor:* remove processing part (-xxx) of the code. If successful, restart at step 1 with the new code without processing part.

6. Check whether the food is a FoodEx 2 code. If so, strip all food facets of the code. The code that remains i.e the food base code of FoodEx 2 classification is returned and the algorithm restarts at step 1 with the base code (without facets).

### Substance dependent conversion

The original conversion algorithm contains two steps which are substance dependent. For each substance all food codes are supplied to the conversion algorithm and for each food code it is checked whether there is:

- a concentration,
- a processing type.

When a concentration is available for the food, this food is a modelled food (formerly known as food as measured). The food may be a food as eaten as such, like apple, or an ingredient of a food as eaten like tomato sauce on pizza which is converted to tomato. If concentrations are available, the food code is found and the conversion algorithm starts with converting the next food code. Otherwise, the conversion proceeds to the *processing link (deprecated)*. Here, basically, processed foods are converted to an unprocessed food and processing type with corresponding processing factor. This processing step may be substance specific and, occasionally, this results in different conversion paths for different substances. This is undesirable behaviour and normally not the case (dependent on the supplied data in the *Processing factors* table). However, on rare occasions this might happen.

*Find processing link (deprecated):* Check whether the current food can be considered to be a processed variant (e.g., cooked or peeled) of another food.

**Match processing factor:** try to find the code in the *Processing factors* table.

If successful, try to find the corresponding food translation proportion in the food recipes data to correct for a weight reduction or increase. Then, restart at the first step with the new code of the unprocessed food.

**Warning**: the *find processing link (deprecated)* step is not recommended and is currently maintained for backwards compatibility reasons only. Finding different conversions paths depending on the substance is undesirable behaviour.

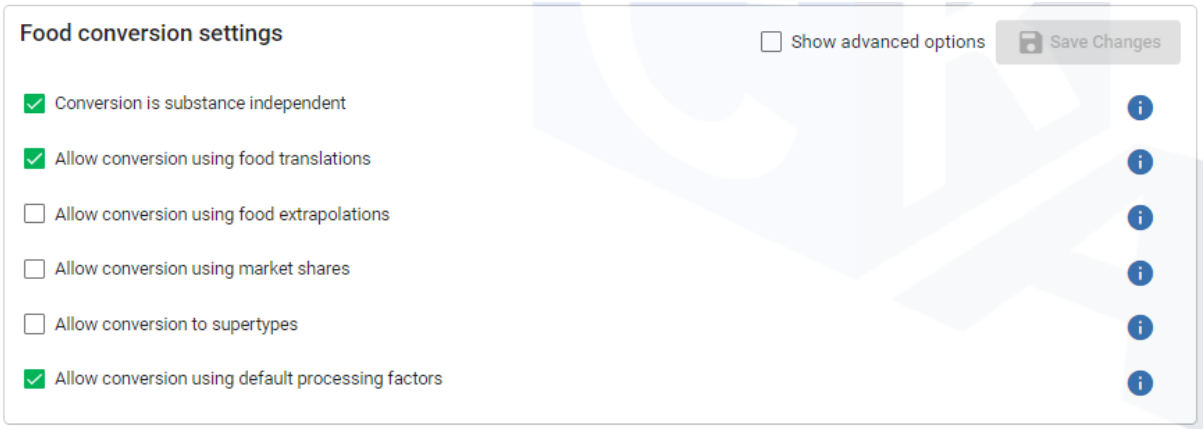



Figure 3.66: Default settings conversion.

### Food conversion settings

### Calculation settings

Table 3.283: Calculation settings for module Food conversions.

| Name | Type | Description |
|---|---|---|
| Selected tier | SettingsTemplateType | Specifies all module settings should be set according to a pre-defined tier or using custom settings. |
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Allow conversion using processing info | Boolean | Try to find the code in the processing table. When a match is found, then also a food translation record is searched for to also include information on weight reduction/increase (translation proportion). Warning: the processing step is deprecated and is currently only maintained for backwards compatibility reasons. |
| Allow conversion using food translations | Boolean | Try to find food translations for the current food (i.e. the ingredients of a composite food). This may result in one or mor food codes for ingredients, and the iterative algorithm will proceed with each of the ingredient food codes in turn. |
| Total diet study concentration data | Boolean | Specifies whether exposure is based on sampling data from tota diet studies. |
| Allow conversion using food extrapolations | Boolean | Try to find read across codes. If unchecked, read across table is ignored, default is 'Use read across info'. E.g. for pineapple no measurements are found but by specifying that pineapple is converted to FruitMix (with a default proportion of 100%), the TDS sample concentration value of FruitMix will be used for pineapple (as-eaten or as ingredient). |
| Allow conversion using market shares | Boolean | Try to find subtype codes, e.g. 'xxx$*' in the market shares tabl |
| Allow market shares not summing to 100% | Boolean | Specify whether to rescale market share percentages that do not sum to 100%. If checked, then foods with marketshares not summing to 100% are allowed. If not, then these foods are ignored in the analysis. |
| Allow conversion to supertypes | Boolean | Try to find supertypes, e.g. 'xxx$yyy' is converted to 'xxx'. If checked, allows for linkage of consumed foods coded at a lower hierarchical level to foods with measured concentrations at a higher hierarchical level e.g. consumed is Apple (code PF$App –> measured is Pome Fruit (code PF). Note: food codes are spl on '$'. Measurements of substances on food are available at a le detailed food coding level than consumption data. |
| Allow conversion using default processing | Boolean | Allow conversion from processed to unprocessed foods. Either matching to processing types specified as substrings separated using a '-' character or by matching FoodEx2 facet strings (separated by a '#' character) to processing types. |
| Substance independent conversion | Boolean | Conversion of foods is independent of the substance. |
| Derive modelled foods from concentration limits | Boolean | Derive modelled foods from concentration limits. |
| Include foods with only censored value measurements | Boolean | Specifies whether foods with only censored value measurements are part of the exposure assessment (default yes). |
| Include substances with only censored value measurements | Boolean | Specifies whether substances with only censored value measurements are part of the exposure assessment (default yes) |
| Include substances without measurements | Boolean | Specifies whether substances without any measurements should included. |

### Food conversions tiers

## Overview

Table 3.284: Tier overview for module Food conversions.

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFS 202 Chro Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| T ta di st co ce tr ti da | false | false | false | false | false | false | false | false | false | false |
| Ig no sa pl w | true | true | true | true | | | true | true | true | true |
| E cl in di vi u- al w le th N da | false | true | false | true | | | false | true | false | true |
| F te sa pl ex ce in th co ce tr ti li it | false | false | false | false | | false | false | false | false | false |
| U su st co ve si ru | true | true | true | true | | | true | true | true | true |
| S st co ve si m | UseMost-Toxic | UseMost-Toxic | DrawRandom | DrawRandom | | | UseMost-Toxic | UseMost-Toxic | DrawRandom | Draw dom |
| R | true | true | true | true | | | true | true | true | true |

### Retrospective dietary CRA (EC 2018) - Acute / Tier I

Table 3.285: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Consumptions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier I

Table 3.286: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Consumptions* |
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Consumptions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |

### Retrospective dietary CRA (EC 2018) - Acute / Tier II

Table 3.287: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Consumptions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier II

Table 3.288: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Consumptions* |
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Consumptions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |

### Retrospective dietary CRA (EFSA 2012) - Optimistic

Use the optimistic model settings according to the EFSA Guidance 2012. Concentration values are sampled using a sample-based empirical distribution. Available processing factors are applied. No unit variability model should be applied.

Table 3.289: Tier definition for Retrospective dietary CRA (EFSA 2012) - Optimistic.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | | |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2012) - Optimistic* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2012) - Optimistic* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EFSA 2012) - Optimistic* | *Processing factors* |

### Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic

Chronic probabilistic exposure assessment using the pessimistic model settings according to the EFSA Guidance 2012. Only processing factors > 1 are applied.

Table 3.290: Tier definition for Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | | |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Processing factors* |
| Ignore processing factors less than 1 | true | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Processing factors* |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier I

Table 3.291: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Consumptions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I

Table 3.292: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Consumptions* |
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Consumptions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier II

Table 3.293: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Consumptions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II

Table 3.294: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Consumptions* |
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Consumptions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |

### Prospective dietary CRA (EFSA 2023) - Acute / Tier II

Table 3.295: Tier definition for Prospective dietary CRA (EFSA 2023) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | | |
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Consumptions* |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |

### Prospective dietary CRA (EFSA 2023) - Chronic / Tier II

Table 3.296: Tier definition for Prospective dietary CRA (EFSA 2023) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | | |
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Consumptions* |
| N (number of days in survey) | 2 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Consumptions* |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |

### Prospective dietary CRA (EFSA 2024) - Acute / Tier II

Table 3.297: Tier definition for Prospective dietary CRA (EFSA 2024) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | | |
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Consumptions* |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |

### Prospective dietary CRA (EFSA 2024) - Chronic / Tier II

Table 3.298: Tier definition for Prospective dietary CRA (EFSA 2024) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | | |
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Consumptions* |
| N (number of days in survey) | 2 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Consumptions* |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |

### Calculation of food conversions

Food conversions are computed recursively, starting with a food-as-eaten and following a path to ingredients (food recipes), super/sup-type foods, etc. until either arriving at a modelled food (commonly the raw primary commodity) or concluding that the path does not lead to a modelled food.

- *Food conversions calculation*

Inputs used: *Consumptions Modelled foods Processing factors Food recipes Market shares Food extrapolations Total diet study sample compositions Active substances*

Settings used

- *Calculation Settings*

## 3.4.16 Exposure comparisons

Substances in the human body are absorbed, excreted without transformation, excreted after metabolization or stored in various tissues, bones or body fluids. The term biological matrix refers to all human specimens where concentrations of a chemical can be measured like bodily fluids, such as blood, urine, saliva, breast milk, sweat, and other specimens, such as faeces, hair, teeth, and nails. Exposure comparisons compares observed human monitoring data with predictions made for the same population of individuals from dietary survey data, concentration data and (optionally) non-dietary exposure data.

This module has as primary entities: *Populations Substances*

### Exposure comparisons calculation

In this module, concentration estimates from measurements in biological (human) matrices are compared with modelled or predicted concentrations obtained from *dietary* and/or *non-dietary* surveys via *exposure* assessments. This comparison provides insight into the coherence between modelled exposures and the measured reality. It is required that monitoring data and dietary/non-dietary exposure data are available for the same individual or individual-day. Figure 3.67 visualises summary statistics for the monitoring and modelled concentrations of the bisphenols BPA, BPS, and BPF.

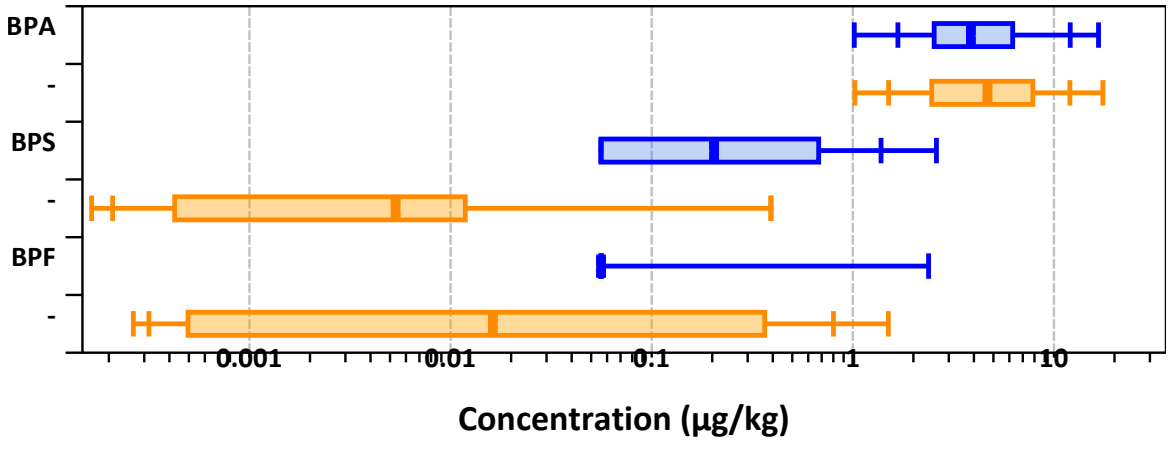



Figure 3.67: Boxplots for monitoring and modelled concentrations for bisphenols BPA, BPS and BPF. Lower whiskers indicate the p5 and p10 percentiles, upper whiskers the p90 and p95. The edges of the box indicate the p25 and p75 percentiles with the median in the centre of the box.

When both human monitoring data and exposure data are available for the same individuals within a population, a direct comparison can be made between the monitoring and modelled concentrations. Figure 3.68 shows an example of this.

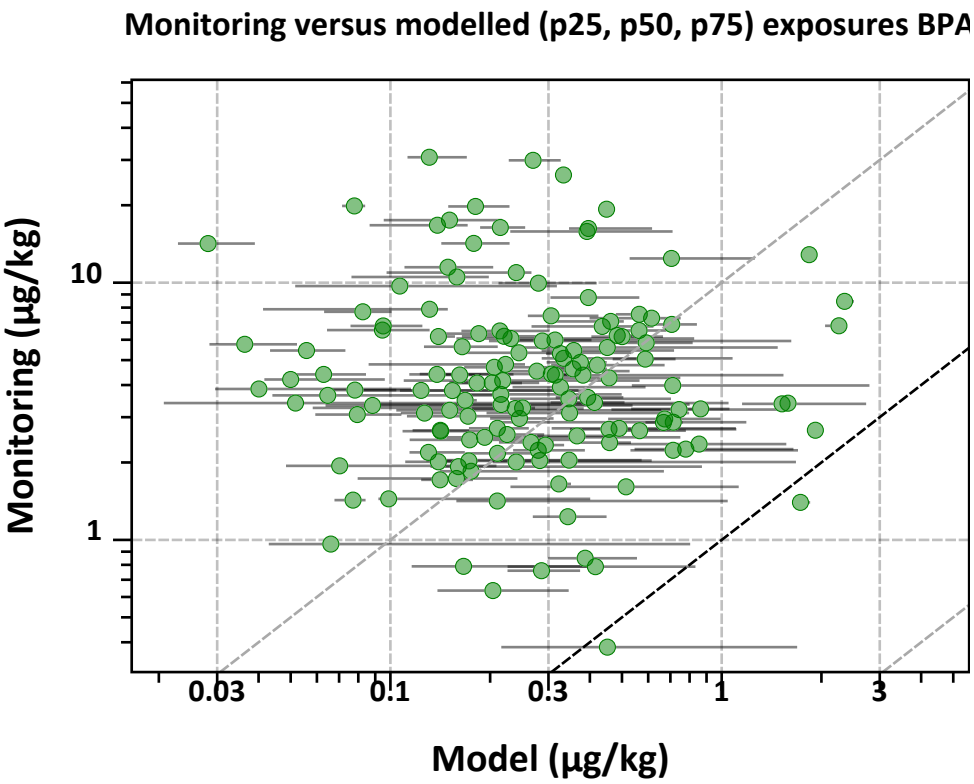



Figure 3.68: Monitoring versus modelled concentrations for bisphenol BPA

### Exposure comparisons settings

### Calculation settings

Table 3.299: Calculation settings for module Exposure comparisons.

| Name | Type | Description |
|---|---|---|
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Target level | *TargetLevelType* | Select whether the assessment is at the level of external dose, internal (target) concentration or internal (systemic) dose. For a aggregate assessment, combining dietary and nondietary exposures, the target level is always internal concentration or internal (systemic) dose. When only dietary exposures are available, the target level is optional and may be an external (administered) dose, an internal (tissue) concentration or an internal (absorbed) dose. |
| Correlate monitoring with modelled concentrations | Boolean | Correlate monitoring with modelled concentrations. This option prevents that monitoring and modelled individuals that are code unintentionally with identical id's or codes are correlated. |

### Output settings

Table 3.300: Output settings for module Exposure comparisons.

| Name | Type | Description |
|---|---|---|
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |
| Store simulated individual day exposures | Boolean | Store the simulated individual day exposures. If unchecked, no additional output will be generated. If checked, the output will contain an additional section with the simulated individual day exposures. |

### Calculation of exposure comparisons

Exposure comparisons calculations comprise two parts. The first part computes estimates of the human monitoring concentrations based on the biomonitoring data. The second part relates these human monitoring concentrations to modelled concentrations from exposure assessments.

- *Exposure comparisons calculation*

Inputs used: *HBM analysis Internal exposures*

Settings used

- *Calculation Settings*

## 3.4.17 Exposure biomarker conversions

Occasionally, the biomarker of interest (substance) is not measured. Exposure biomarker conversions specify how measured biomarkers are converted to the relevant biomarkers (substances). This type of conversion is within biological matrices.

This module has as primary entities: *Substances*

Output of this module is used by: *HBM analysis*

### Exposure biomarker conversions from data

In table *Exposure biomarker conversions*, conversion factors are specified to convert measured biomarkers to the biomarkers of interest. Conversion factors may be dependent on individual properties like age and gender. Specify in table *Exposure biomarker conversion subgroups* age and/or *gender* specific conversion factors.

For age, specify the lower bound of the age interval (in years) of the exposure biomarker conversion subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower age of the next subgroup.

Check option *Use exposure biomarker conversion factors subgroup* to use age and/or gender specific conversion factors in your assessment.

Column *VariabilityDistributionType* in table *Exposure biomarker conversions* is used to specify the variability distribution to sample from. When the column is left empty, the conversion factor itself is used. Currently, four distributions are available.

See also *uniform*, *lognormal*, *beta* and *inverse uniform* distribution.

### Exposure biomarker conversions data formats

Describes the exposure biomarker conversions (i.c. conversions within a biological matrix).

Download empty dataset template: Zipped CSV Excel

### Exposure biomarker conversions

Exposure biomarker conversions main table. Biomarker conversion is within a biological matrix.

Table 3.301: Table definition for Exposure biomarker conversions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExposure-Biomarker-Conversion | AlphaNumeric (50) | Id of the exposure biomarker conversion | idExposure-Biomarker-Conversion, idExposure-Biomarker-Factor, idEBCFactor | Yes |
| idSubstance-From | AlphaNumeric (50) | Identification code of substance of the 'from' substance. That is, the code of the (measured) substance for which concentrations need to be translated. | idSubstance-From, SubstanceId-From, SubstanceCode-From, SubstanceFrom | Yes |
| Biological matrix | *BiologicalMatrix* | The biological matrix (e.g., blood, urine) for which this conversion rule is defined. | Biological-Matrix, MatrixSource, SourceMatrix | Yes |
| Expression-TypeFrom | *ExpressionType* | The expression type (or adjustment method) of the 'from'-part. This field specifies how the dose unit (source) is expressed, e.g., for blood lipids for fat soluble biomarkers ('mg/g lipids') or the dilution level of the urine ('mg/g creatinine'). | ExpressionType-From, Adjustment-MethodFrom | No |
| UnitFrom | *DoseUnit* | The unit of the 'from'-part of the conversion rule. | UnitSource-From, SourceUnitFrom | Yes |
| idSubstanceTo | AlphaNumeric (50) | Identification code of substance of the 'to' substance. | idSubstanceTo, SubstanceIdTo, SubstanceCode-To, SubstanceTo | Yes |
| Expression-TypeTo | *ExpressionType* | TODO: to be removed. The expression type or adjustment method of 'to'-part of the conversion rule. This field specifies how the dose unit (target) is adjusted, e.g., for blood lipids for fat soluble biomarkers ('mg/g lipids') or the dilution level of the urine ('mg/g creatinine'). | ExpressionType-To, Adjustment-MethodTo | No |
| UnitTo | *DoseUnit* | TODO: to be removed. The unit of the 'to'-part of the conversion rule. | UnitSourceTo, SourceUnitTo | Yes |
| Conversion-Factor | Numeric | The conversion factor value. If the conversion is provided as a distribution, then this factor is the nominal value of the distribution. | Conversion-Factor, Factor | Yes |
| Variability-Distribution-Type | *Biomarker-Conversion-Distribution* | Distribution type (Uniform, LogNormal or Beta). If not specified, the conversion is assumed to be a constant factor. | Variability-Distribution-Type, Variability-Distribution, Distribution-Type, Distribution | No |
| Variability- | Numeric | The upper value of the | Variability- | No |

Accepted table names: ExposureBiomarkerConversions, ExposureBiomarkerConversion, BiomarkerConversions, BiomarkerConversion.

### Exposure biomarker conversion subgroups

Exposure biomarker conversion subgroups.

Table 3.302: Table definition for Exposure biomarker conversion subgroups.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExposureBiomarkerConversion | AlphaNumeric (50) | Id of the exposure biomarker conversion | idExposureBiomarkerConversion, idExposureBiomarkerFactor, idEBCFactor | Yes |
| ConversionFactor | Numeric | Conversion factor value | ConversionFactor, Factor | Yes |
| AgeLower | Numeric (50) | Specifies the lower bound of the age interval (in years) of the exposure biomarker conversion subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower age of the next subgroup. | AgeLower, LowerAge | No |
| Gender | *GenderType* | The gender of the exposure biomarker conversion subgroup. | Gender, Sex | No |
| VariabilityUpper | Numeric | The upper value of the distribution. If the distribution is uniform, then it is the upper bound of the uniform distribution. If the distribution is log-normal, then the upper value is assumed to correspond with the p95 percentile of the distribution. When a distribution is assumed, this value should be greater than the conversion factor. | VariabilityUpper, Upper | No |

Accepted table names: ExposureBiomarkerConversionSGs, BiomarkerConversionSGs, ExposureBiomarkerSGs, EBCFactorSubGroups.

#### Exposure biomarker conversions

#### Calculation settings

Table 3.303: Calculation settings for module Exposure biomarker conversions.

| Name | Type | Description |
|---|---|---|
| Use exposure biomarker conversion factors subgroup | Boolean | Exposure biomarker conversion factors are dependent on subgroups (e.g. based on age or gender, see dataformats ExposuerBiomarkerConversionsSgs). |

#### Exposure biomarker conversions as data

Exposure biomarkers conversions are provided as data in the form of a conversion factor for a substances (from) and substance (to).

- *Exposure biomarker conversions data formats*
- *Exposure biomarker conversions from data*

Settings used

- *Calculation Settings*

### 3.4.18 HBM analysis

Human biomonitoring concentrations are substance concentration estimates for a biological matrix (e.g., urine or blood) derived from data obtained from human monitoring studies.

This module has as primary entities: *Populations Substances*

Output of this module is used by: *Exposure mixtures Exposure comparisons Risks Environmental burden of disease*

#### HBM analysis calculation

Human monitoring analysis computes substance concentration estimates for a biological matrix (e.g., urine or blood) based on *human monitoring data*. These estimates are specified at the level of long term average concentrations for individuals in case of *chronic assessments*, or concentrations for individual-days in case of *acute assessments*. The concentrations are computed independently for each substance and biological matrix.

The main steps, and also performed in this order, for computing human monitoring concentration estimates are:

1. *Imputation of censored values*.
2. *Imputation of missing values*.
3. *Standardise blood for lipid content* (only available when data allows).
4. *Standardise/normalise urine for creatinine or specific gravity* (only available when data allows).
5. Filter for complete cases.
6. Combine urine from different sampling methods.
7. Apply *exposure biomarker conversion* of substance concentrations (within a biological matrix).
8. Apply *kinetic conversion* of substance concentrations from other biological matrices (only available when data allows).
9. Calculation of individual concentrations (*chronic*) or individual day concentrations (*acute*).

### Imputation of censored values

Similar to *concentrations measurements in food*, human monitoring measurements contain measurements below the limit of reporting and similar to *concentrations modelling in foods*, human monitoring analysis addresses these censored values and replaces them with imputed concentration values, see also *imputation methods*. Two approaches are available:

1. Impute using a *non-detects handling method*.
2. Impute using a draw from the left tail of the *censored lognormal distribution*. See also *concentration models* and *concentration model types*.

The available non-detects handling methods for deterministic imputation are:

- Replace censored values by zero.
- Replace censored values by a factor * *LOR*, the factor is set between zero and one.
- Replace non-detects by a factor * *LOD* and non-quantifications by *LOD* + factor * (*LOQ* - LOD), the factor is set between zero and one.
- Replace non-detects by zero and non-quantifications by factor * *LOQ*, the factor is set between zero and one.

For option 3, factor = 0, non-detects are replaced by zero, non-quantifications are replaced by *LOD*; for factor = 1, non-detects are replaced by *LOD*, non-quantifications are replaced by *LOQ*. See also PARC harmonised HBM data format: *Sample concentrations/measurements*.

Note, when LOD is not available then it is assumed to be 0. When LOQ is not available then it is assumed to be LOD (or zero if LOD is also not available).

For imputation based on the censored lognormal distribution, non-detect and non-quantification information is used. Non-detects are sampled from the entire left tail, e.g. the area below LOD. Non-quantifications are sampled from the intermediate segment, e.g. the area below LOQ and above LOD.

Note that for the option based on the censored lognormal distribution also a non-detects handling method has to be specified. Occasionally, fitting the censored lognormal model fails and the deterministic imputation method is used as fallback.

The *censored lognormal distribution*, with parameters $\mu$ and $\sigma$, is fitted using a likelihood function which is defined by contributions of the positive measurements (lognormal probability density function) and by contributions of the measurements below LOD and measeruments above LOD and below LOQ separately, e.g. the (cumulative) probabilities for LODs and LOQs.

In Figure 3.69, the *human monitoring concentration data* in urine are imputed with a factor * LOR and the summary statistics are visualized.

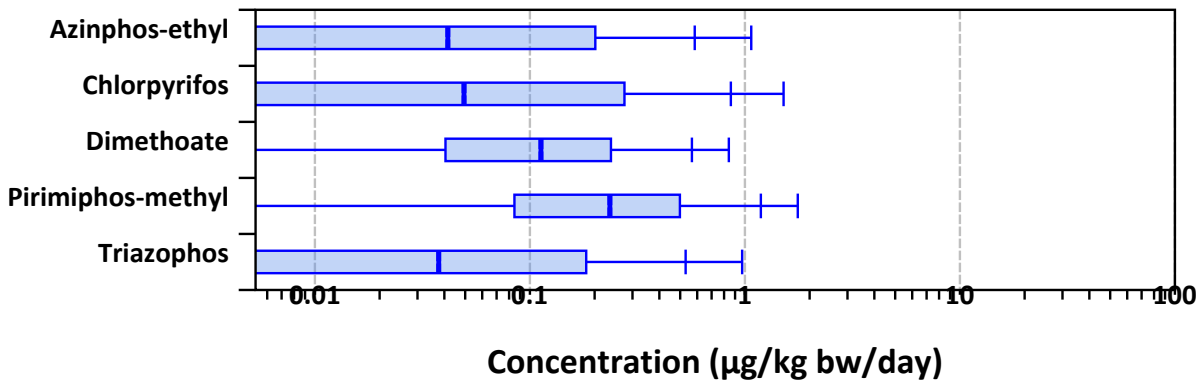



Figure 3.69: Boxplots for imputed concentration data for five pesticides. Lower whiskers indicate the p5 and p10 percentiles, upper whiskers the p90 and p95. The edges of the box indicate the p25 and p75 percentiles with the median in the centre of the box.

### Imputation of missing values

For missing concentration measurements, *three imputation methods* are available, see also *imputation methods*. The third opion ignores imputation and all missing values remain in the data set.

1. Replace missing values by zero. This is conditional on the specified minimum percentage of non-missing values.
2. For each substance and combination of biological matrix and sampling type, replace missing values by a random draw from the non-missing concentration values (samples). This is conditional on the specified minimum percentage of non-missing values.
3. Do not impute missing values.

Imputation of missing values by zeros or a random draw from the data is conditional on the specified percentage of non-missing values. When the percentage of non-missing values for a specific substance and combination of biological matrix and sampling type in the data is smaller than the specified percentage, imputation is ignored. This is to prevent that imputation takes place using a set of imputation values that is not representative or unrealistically small (e.g. one or a few values). Note that for the second imputation method, more refined methods could be used. E.g., when for a given day multiple samples are available and one is missing, then this sample might be neglected in the computation of an average exposure. Also, when samples have been taken at different time-slots, impute the missing records using samples from the same time-slot.

Note that imputation of missing values applies only to substances within the assessment scope, not to those used indirectly for standardisation and normalisation, such as creatinine, total cholesterol, and triglycerides.

### Standardise blood for lipid content

Lipid-soluble substances measured in blood data are typically standardised by total lipid content, see also *standardisation methods*. Three methods are in available, namely:

1. Standardisation based on *gravimatic analysis*.
2. Standardisation based on *enzymatic summation analysis*.
3. Standardisation based on Bernert et al. (2007), *total lipids (mg/dL) = 2.27 * total cholesterol + triglycerides + 62.3 mg/dL.*

The standardisation is only applied to lipid-soluble substances, see *Substances data formats*. After standardisation, the amount of substance is expressed per g lipid e.g. $\mu g/g$ `lipid`. Note that substance concentrations in blood samples with unmeasured lipid concentrations are set to missing after specifying option blood standardisation.

This option is only available to the user when the data contains substances that are soluble in lipid and when total lipid content (or cholesterol and triglycerides) is measured.

### Standardise/normalise urine for creatinine or specific gravity

Four methods are available for correcting spot urine measurements for creatinine of specific gravity, see also *standardisation methods*.

1. Normalisation based on *specific gravity*.
2. Standardisation based on *creatinine content*.
3. Normalisation based on *specific gravity derived from creatinine content, adults 18 - 68 years*.
4. Normalisation based on *specific gravity derived from nonlinear modelling of creatinine content, children 6 - 14 years*.
5. Normalisation based on *specific gravity derived from nonlinear modelling of creatinine content, age and gender dependent, children 6 - 14 years*.

Urine's specific gravity is determined by the concentration of excreted molecules in the urine. In adult humans, normal specific gravity values range from 1.010 to 1.030. The specific gravity normalisation used here (1) is equal to $(1.024 - 1)/(specific\,gravity - 1)$. The specific gravity value should be available in the HBM data, otherwise urine sample concentrations are set to missing.

After standardisation for creatinine content, the amount of substance is expressed per g creatinine e.g. $\mu g/g$ `creatinine`. Note that substance concentrations in urine samples where the creatinine content is not measured are set to missing values after specifying option urine standardisation.

Options 3 (Carrieri et al. (2000)) and 4 and 5 (Busgang et al. (2023)) are for specific subgroups in the population, e.g. adults (18 - 68 years) and children (6 - 14 years), respectively. For model 2 of Busgang et al. (2023), age and gender should be defined in the data, otherwise the sample concentration is set to missing.

The normalisation and standardisation methods are only available when the data contains creatinine or specific gravity values.

### Combine urine from different sampling methods

Different urine sampling methods (morning, spot, or 24-hour) are considered a single biological matrix for further analysis in MCRA. If the selected human biomonitoring data contains concentrations from different urine sampling methods, the concentration values are combined by taking the average of the concentration values from the various urine sampling methods.

### Filter for complete cases

After imputation of non-detects and missing values, standardisation and normalisation some individual day concentration records still contain missing values. The incomplete cases are removed from the dataset before the analysis continues.

Occasionally, removing all records with missing values results in empty datasets. Then a warning will be thrown 'All HBM individual day records were removed for having non-imputed missing substance concentrations'. To circumvent this warning, inspect your data and remove substances with too many missing values, lower the minimum percentage of non-missing values *(Impute from data)*, or *Impute with zero*.

Filtering for complete cases is always applied before conversion. In general, filtering has more impact when many substances are in scope, resulting in smaller subsets of complete cases. It is good practice to set the scope to the relevant substances. In the interface of the primary entity *substances*, select the relevant substances for the assessment.

### Apply exposure biomarker conversion of substance concentrations

Occasionally, the biomarkers of interest are not measured. *Exposure biomarker conversion* is used to convert measured biomarkers to the biomarker of interest and is applied within a *biological matrix*. Biomarker conversion is performed after imputation of censored and missing values and after normalisation/standardisation of urine/blood samples. For conversion factors that are dependent on age and/or *gender*, check option *Use exposure biomarker conversion factors subgroup* in the interface of the exposure biomarker conversion module.

### Apply kinetic conversion of substance concentrations from other biological matrices

Kinetic conversion of substances from other biological matrices is used when the number of substances in the matrix of interest is limited or for reverse dosimetry when exposures at external level are required. As an example of an internal-to-internal conversion, consider a scenario where five substances are measured in *urine (spot)* samples from individuals. Additionally, blood (serum) concentrations are analysed for the same individuals, resulting in another set of concentrations for, let's say, five different substances. The five substances measured in blood are then converted to urine matrix concentrations by checking the Apply kinetic conversions option. Then, the analysis continues with ten substances in urine (spot). Selecting specific substances for conversion is possible through multiplication factors defined in the *kinetic conversion factors data* of the Kinetic models module.

Enable the *Convert to single exposure surface (biological matrix or external route) matrices* option to compute exposures at a single target biological matrix or to compute exposures at the external level. Specify *the target level* (Internal or External) and *biological matrix* accordingly. *Kinetic conversion of substance concentrations* is performed after imputation of censored and missing values, and after normalisation/standardisation of urine/blood samples.

Note that kinetic conversion is applied only to substances that are not measured in the target matrix. For instance, kinetic conversion cannot be used for imputing missing values of substances that have one or more missing values.

For conversion factors that are dependent on age and/or *gender*, check option *Use kinetic conversion factors subgroup* in the interface of the kinetic models module.

### Calculation of acute human monitoring concentrations

For *acute* assessments, the monitoring concentrations are computed for each substance and biological matrix as average individual-day concentrations. The computation is done after imputation of censored and missing values, eventually followed by a conversion of biomarkers from other biological matrices. For a given substance and biological matrix, the acute individual-day concentration $c_{ij}$ for individual $i$ on day $j$ is:

$$c_{ij} = \frac{\sum_{k=1}^{n_{\texttt{samples}}} c_{ijk}}{n_{\texttt{samples}}}$$

where $n_{\texttt{samples}}$ is the number of samples available for individual $i$ on day $j$, and $c_{ijk}$ the concentration of the $k$-th sample of the individual day $j$.

After urine normalisation for specific gravity:

$$c'_{ij} = c_{ij} \cdot sg$$

where *sg* denotes the specific gravity correction factor for that individual day.

After standardisation for blood lipid content:

$$c'_{ij} = \frac{c_{ij}}{c_{ij}\,\texttt{lipid}}$$

where $c'_{ij}$ denotes the lipid concentration per $g$ `lipid`. The standardisation is only performed for lipid soluble substances. After standardisation the concentration of the substance is expressed as substance amount, with a user specified unit, per $g$ `lipid`.

The standardisation for creatinine is similar to the above equation replacing `lipid` by `creatinine`.

### Calculation of chronic human monitoring concentrations

For *chronic* assessments, the monitoring concentrations are computed as the average monitoring concentrations of multiple individual-days for each substance and biological matrix. The computation is done after imputation of censored and missing values, eventually followed by a conversion of biomarkers from other biological matrices. The chronic concentration $c_i$ for individual $i$ is computed as:

$$c_i = \frac{\sum_{j=1}^{n_{\texttt{days}}} c_{ij}}{n_{\texttt{days}}},$$

where $n_{\texttt{days}}$ is the number of days that individual $i$ was monitored (after removing missing individual days), and $c_{ij}$ denotes the average monitoring concentration of individual $i$ on day $j$.

Standardisation and normalisation of blood and urine samples, respectively, are similar to the expressions for the calculation of individual day concentrations (acute).

For co-exposure of substances, see *maximum cumulative ratio* (MCR) and the *exposure mixtures module*.

### Apply occupational exposure assessment

When human biomonitoring concentration data contain information about an individual's occupation (i.c., the occupational scenario), the human biomonitoring analysis is extended to assess how individuals are exposed across various scenarios. Specify in the PARC harmonized HBM data file in sheet 'SUBJECTUNIQUE', column 'idScenario' for each subject the requested information, see also *PARC HBM data format*. Note that 'idScenario' should exactly math the scenario codes used in the *occupational scenarios module*. The actual assessment is conducted after checking *occupational exposure assessment*. A menu unfolds and an additional 'pre-/post shift' and/or 'case-control analyis' is specified. The last option requires a selection of control scenario's (at least one).

In Figure 3.70, a chart of an artificial example of a case-control analysis is shown. In the corresponding table (not shown) all details are found.

A pre-post shift analysis is a standard method used in occupational health and human biomonitoring to measure a worker's exposure to chemical substances during a single work shift:

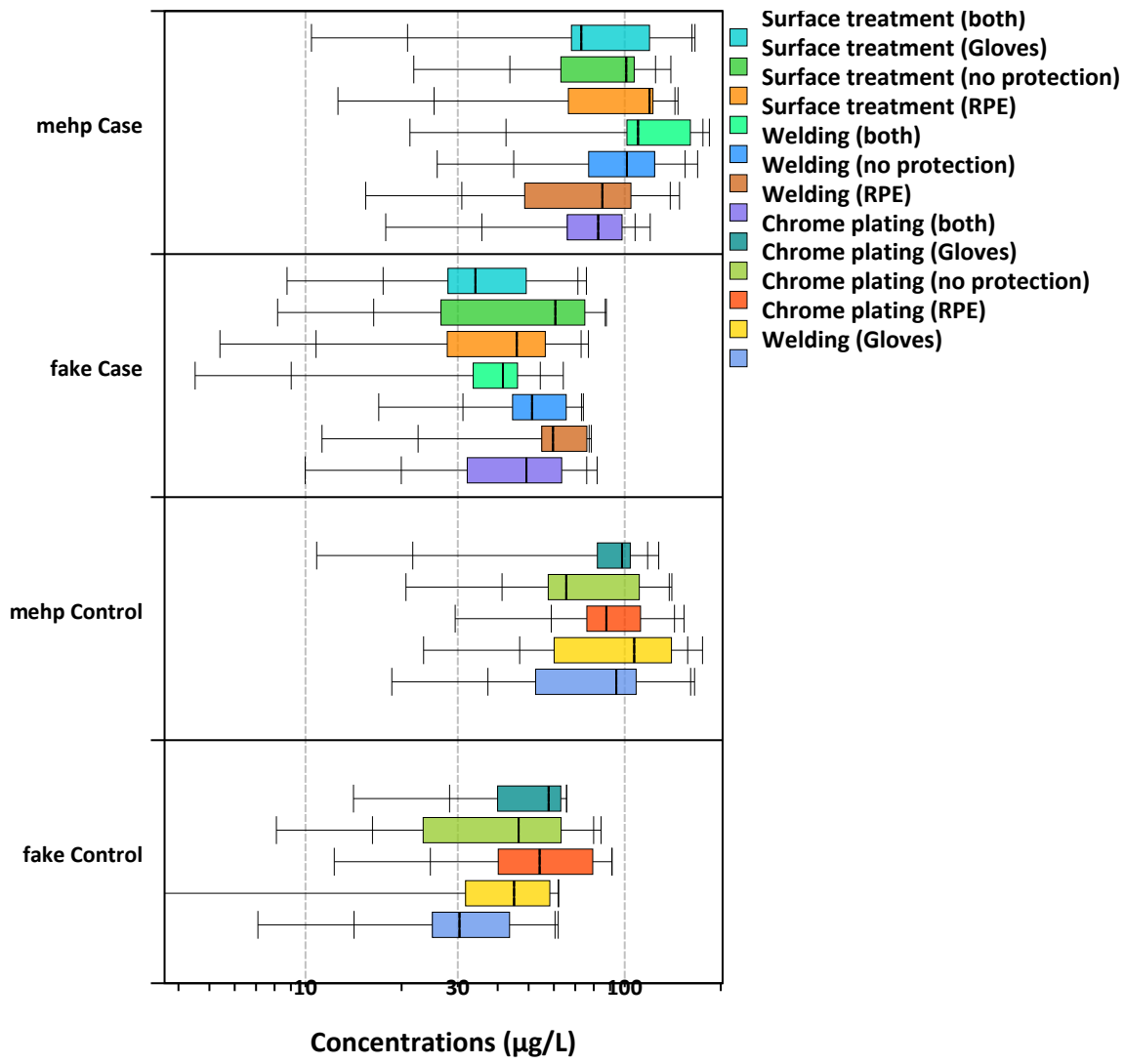



Figure 3.70: HBM exposure box plots for a case-control analysis, categorized by scenario. The lower whiskers indicate the 5th and 10th percentiles, while the upper whiskers indicate the 90th and 95th percentiles. The edges of the box indicate the 25th and 75th percentiles, with the median in the center of the box.

- Pre-shift: Collected before the worker starts their shift. This establishes the baseline level, showing what is already in their system from daily life or previous workdays.
- Post-shift: Collected immediately after the work shift ends. This captures the maximum concentration of the substance (or its metabolites) absorbed during that specific day.

Specify in the PARC harmonized HBM data file in sheet 'TIMEPOINT', column 'shift-type' for each time point the requested shift types *PreShift', 'PostShift'*, see also *perform pre-/post shift comparison*. Use the 'timepoint_description' column for an informative short message in the MCRA output.

### HBM analysis settings

### Calculation settings

Table 3.304: Calculation settings for module HBM analysis.

| Name | Type | Description |
|---|---|---|
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Compute cumulative exposures | Boolean | Specifies whether the assessment involves multiple substances a results should be cumulated over all substances. |
| Report consumptions and exposures per individual instead of per kg body weight | Boolean | Specifies whether body weights should be ignored and consumptions and exposures should be expressed per individual Otherwise, the consumptions and exposures are per kg body weight. |
| Sampling method | AlphaNumeric | The sampling method that should be included in the action. |
| Censored values handling method (also used as fallback for censored lognormal approach) | *NonDetectsHandlingMethod* | Method for dealing with censored value samples in human monitoring data. Note that this method is also used as a fallbac when fitting a censored lognormal model to the concentration d fails. |
| Fraction for censored value replacement | Numeric | Factor used for replacing the censored value. |
| Imputation method for non detect values | *NonDetectImputationMethod* | Imputation method for non detect values: replace nondetects based on by f*LOD/LOQ) or from left tail censored lognormal distribution. |
| Missing value imputation method | *MissingValueImputationMethod* | Imputation method for missing values: 1) By zero, 2) Impute from data, 3) No missing value imputation |
| Apply kinetic conversions | Boolean | Convert substance concentrations from other biological matrice using kinetic conversion models. The substances for conversion are designated within the kinetic models module. Substance conversion proves valuable when a biomarker was not directly measured for a matrix of interest. |
| Convert to single exposure surface (biological matrix or external route) | Boolean | Convert all substance concentrations from other biological matrices to the same target biological matrix. This conversion i applied when the number of substances measured on the target biological matrix is limited. Substances measured on other matrices can be converted using kinetic conversion models. |
| Target level | *TargetLevelType* | Select whether the assessment is at the level of external dose, internal (target) concentration or internal (systemic) dose. For a aggregate assessment, combining dietary and nondietary exposures, the target level is always internal concentration or internal (systemic) dose. When only dietary exposures are available, the target level is optional and may be an external (administered) dose, an internal (tissue) concentration or an internal (absorbed) dose. |

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Table 3.304 – continued from previous page

| Name | Type | Description |
|---|---|---|
| Exposure routes | ExposureRoutes | Exposure routes included in assessment. |
| Specify the minimum percentage of non-missing values (%) | Numeric | Specify the minimum percentage of non-missing values require for imputation. No imputation is done when the percentage of non-missing values in the data is smaller than the specified percentage. |
| Standardise blood concentrations for lipid-soluble substances | Boolean | Standardise blood concentrations for lipid-soluble substances: 1 Standardise by total lipid measured via gravimetric analysis, 2) Standardise by total lipid measured via enzymatic summation, 3 Standardise by derived total lipid content of Triglycerides/Cholesterol (Bernert et al. 2007). |
| Specify the standardisation method of blood concentrations for lipid-soluble substances | *StandardiseBloodMethod* | Specify the standardisation method of blood concentrations for lipid-soluble substances. |
| Subset selection: exclude substances from lipid standardisation | Boolean | Select this option to exclude one or more lipid-soluble substanc from standardisation. |
| Select substances to exclude from lipid standardisation | AlphaNumeric | The selected (lipid-soluble) substances will be excluded from li standardisation. |
| Normalise or standardise urine concentrations for specific gravity or creatinine | Boolean | Normalise or standardise urine concentrations for specific gravi or creatinine: 1) Normalise by specific gravity, 2) Standardise b creatinine concentration. |
| Specify the normalisation/standardisation method of urine concentrations for specific gravity or creatinine | *StandardiseUrineMethod* | Specify the normalisation/standardisation method of urine concentrations for specific gravity or creatinine. |
| Subset selection: exclude substances from urine normalisation/standardisation | Boolean | Select this option to exclude one or more substances from normalization for specific gravity or creatinine standardisation. |
| Select the substances to exclude from urine normalisation/standardisation | AlphaNumeric | The selected substances will be excluded from urine normalization/standardisation. |
| Substance weighting in mixtures | *ExposureApproachType* | Risk based: exposures in equivalents of the reference substance standardised: standardised exposures per substance have varian 1; or unweighted exposures: RPFs are equal to 1. |
| Perform MCR analysis | Boolean | Perform a Maximum Cumulative Ratio (MCR) analysis to determine co-exposure between substances. |
| Display ratio total exposure/ maximum (in MCR plot) | Numeric | For MCR plot: specify ratio total exposure/ maximum for individual(day) exposures . |
| Show tail percentiles (MCR plot) for: | Numeric | Give specific percentiles of exposure distribution (%), e.g. 97.5 99 (space separated). |
| Set minimum percentage contribution per substance to the tail exposure (MCR plot) | Numeric | Set minimum percentage contribution per substance to the tail exposure. |
| Cutoff MCR | Numeric | For selection of individual(day) exposures with maximum cumulative ratio (MCR = total exposure/maximum) above the cutoff. |
| Cutoff percentage in population ranked on total exposure | Numeric | For selection of individual(day) exposures above the cutoff percentage in the set of individual(day)s ranked on total exposu |

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Table 3.304 – continued from previous page

| Name | Type | Description |
|---|---|---|
| Apply exposure biomarker conversions | Boolean | Use this option to translate HBM concentrations derived from measured substances (biomarkers) to concentrations of other substances. This can be usefull when the measured substance is combination of multiple substances, e.g., to translate measured total arsenic (t-As) to toxicologically relevant arsenic (TRA). T option can also be used to translate between different expressio types (e.g., from measured urine concentration to urine concentrations standardized for specific gravity), but not for translation between different biological matrices. |
| Target biological matrix | *BiologicalMatrix* | The target biological matrix (internal compartment) for which exposures are computed. |
| Specific gravity conversion factor | Numeric | A specific gravity adjustment is applied by multiplying a creatinine adjusted concentration with a factor (default 1.48 for adults 18 - 68 year). |
| Kinetic conversion method | *KineticConversionMethodType* | Method for kinetic conversion. Use kinetic conversion factor models, PBK models, or a combination of both to convert substance concentrations from other biological matrices. |
| Exposure events and dose generation method | *ExposureEventsGeneration-Method* | Generates doses and events for PBK model |
| Number of simulated days | Numeric | The total duration (in days) of the PBK model simulations. |
| Number of initial days skipped | Numeric | The initial period (or burn-in period, specified in days) that nee to be skipped when calculating the steady-state or peak internal exposures from the simulated time series. |
| Use PBK model parameter variability | Boolean | When specified, use parameter variability. |
| Number of events per day for the DERMAL dose | Numeric | The daily dose is administered in equal portions (dose / number events) per event. |
| Number of events per day for the INHALATION dose | Numeric | The daily dose is administered in equal portions (dose / number events) per event. |
| Number of events per day for the ORAL dose | Numeric | The daily dose is administered in equal portions (dose / number events) per event. |
| Specify the hours (events). | Numeric | Specify the hours on which exposure events are simulated. Allowed numbers are 1, 2, 3, 4,…, 24 separated by spaces. |
| Specify event timings | Boolean | If checked, a specific sequence of hours on a day can be specifi on which exposure events are simulated. Otherwise the events a derived based on the number of exposure events per day. |
| PBK simulation method | *PbkSimulationMethod* | Specifies in which mode to run the PBK model |
| Lifetime start age in years | Numeric | The starting age (in years) for lifetime range simulation. |
| Lifetime end age in years | Numeric | The ending age (in years) for lifetime range simulation. |
| Lifetime window size in years | Numeric | The size of the time window (in years) for the lifetime window simulation. |
| Use bodyweight adjusted exposures | Boolean | Use bodyweight adjusted exposures in PBK model simulations. |
| Allow fallback to systemic dosing for missing exposure routes | Boolean | If the PBK model misses specific compartments for certain exposure routes, this setting allows the model to fallback to systemic dosing for those route. |
| PBK output resolution time unit | *PbkModelOutputResolution-TimeUnit* | Time unit in which the output resolution of PBK model simulations is specified. |
| PBK output resolution step size | Numeric | PBK model simulation output step size/length, specifying the evaluation resolution in terms of the step length (period) betwe two evaluations. For example, a step length of 12 with a resolut time unit of hours is interpreted as every 12 hours. |

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Table 3.304 – continued from previous page

| Name | Type | Description |
|---|---|---|
| Occupational exposure assessment | Boolean | Perform an occupational exposure assessment. If unchecked, no additional output will be generated. If checked, the output will contain an additional section with the occupational exposure assessment results. |
| Perform pre-/post shift comparison | Boolean | Perform a pre-/post shift comparison. If unchecked, no pre-/post shift comparison is performed. If checked, the output will contain an additional section with the pre-/post shift comparison results |
| Case control analysis | Boolean | Perform an occupational case control analysis. If unchecked, no additional output will be generated. If checked, the output will contain an additional section with the occupational case control results. |
| Case control selection | AlphaNumeric | Specify which scenarios to use for the controls (at least one scenario must be selected). |

### Output settings

Table 3.305: Output settings for module HBM analysis.

| Name | Type | Description |
|---|---|---|
| Exclude privacy sensitive data from outputs | Boolean | Use this setting to not report the parts of the results (i.e., figures, tables, or sections) that are marked as (potentially) privacy sensitive. |
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |
| Percentage for upper tail | Numeric | Gives detailed output for this upper percentage of the exposure distribution. |
| Stratify outputs | Boolean | This setting is used to get more details e.g. how exposures are distributed among males or females. |
| Stratification variable | *OutputStratificationVariable* | The variable used to categorise individuals into distinct subgroups for presentation of stratified outputs. |
| Age stratification boundaries | Numeric | Give specific age boundaries (years), e.g. 18 40 65 (space separated). |
| Store simulated individual day exposures | Boolean | Store the simulated individual day exposures. If unchecked, no additional output will be generated. If checked, the output will contain an additional section with the simulated individual day exposures. |

### Uncertainty settings

Table 3.306: Uncertainty settings for module HBM analysis.

| Name | Type | Description |
|---|---|---|
| Lower uncertainty limit (%) | Numeric | Percentage lower bound, e.g. 2.5%. |
| Upper uncertainty limit (%) | Numeric | Percentage upper bound, e.g. 97.5%. |
| Iterations uncertainty analysis | Numeric | Specifies the number of uncertainty cycles (default 100). |
| Monte Carlo iterations per uncertainty run | Numeric | Specifies the number of Monte Carlo iterations in each uncertainty cycle (default 10,000). |
| Resample HBM individuals | Boolean | HBM individual data are resampled from the original database using the bootstrap methodology (Efron 1979, Efron & Tibshirani 1993). |

### Calculation of hbm analysis

Human biomonitoring concentration estimates are computed from data collected in human monitoring studies. These concentration estimates are computed per substance for a selected (human) biological matrix. Modelling includes imputation of missing values and non-detects, as well as correction of concentrations for, e.g., specific gravity. Occasionally, the number of substances measured in the biological matrix of interest is limited or too low to perform a risk assessment or mixture analysis. In such cases, matrix conversion can be applied: substance concentrations measured in other biological matrices are translated to the matrix of interest using a kinetic conversion factor. Cumulative risks of multiple substances are calculated either by using RPFs weighted exposure or by using the sum of risk ratios method using hazard characterisations.

- *HBM analysis calculation*

Inputs used: *HBM concentrations Active substances Relative potency factors Kinetic conversion factors Exposure biomarker conversions PBK model parametrisations Occupational scenarios*

Settings used

- *Calculation Settings*

## 3.4.19 HBM concentrations

Human (bio)monitoring data quantify substance concentrations found in humans collected in human monitoring surveys.

This module has as primary entities: *Populations Substances*

Output of this module is used by: *HBM analysis*

### HBM concentrations from data

Human monitoring data characterise human exposure to substances, their metabolites in body fluids or tissues. In Figure 3.71, the positive (> zero) human monitoring concentrations for a number of pesticides in urine (morning) are visualised through summary statistics.

Find in Figure 3.72, boxplots for all human monitoring concentrations of 13 pesticides in urine (morning).

Note that all statistics are weighted using sampling weights.

### Selection on sampling method

The dropdown menu displays the available sampling methods as defined in the data source. Select one or more sampling methods here to include them in the action.

### Filter on repeated measurements

This option is only available when the survey contains two or more measurements or time points. It allows for the restriction of the action to one measurement to prevent the combination of unrelated samples. If there is only one measurement in the survey or if this option is not selected, all measurements are included in the action.

### Excluded substances from sampling method

Use this option to remove all samples of substances that are of no interest or have incomplete samples. This option can be combined with the "Use complete analysed samples" option. When "Use complete analysed samples" is selected, the resulting dataset might become very small due to some substances not being analysed. Excluding these non-analysed substances will result in a larger dataset.

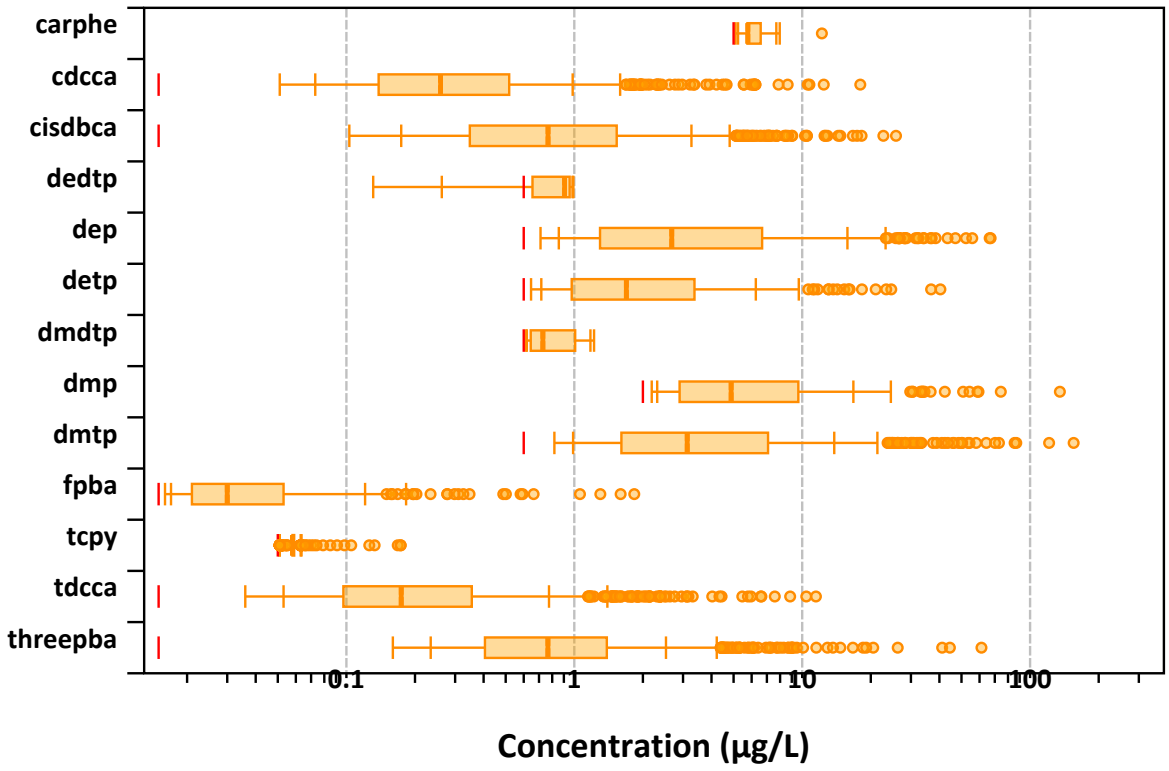


Figure 3.71: Boxplots for positive/quantified HBM substance concentration measurements of 13 pesticides. Lower whiskers indicate the p5 and p10 percentiles, upper whiskers the p90 and p95. The edges of the box indicate the p25 and p75 percentiles with the median in the centre of the box. LORs are displayed by a vertical red bar and outliers outside range (Q1 - 3 * IQR , Q3 + 3 * IQR).

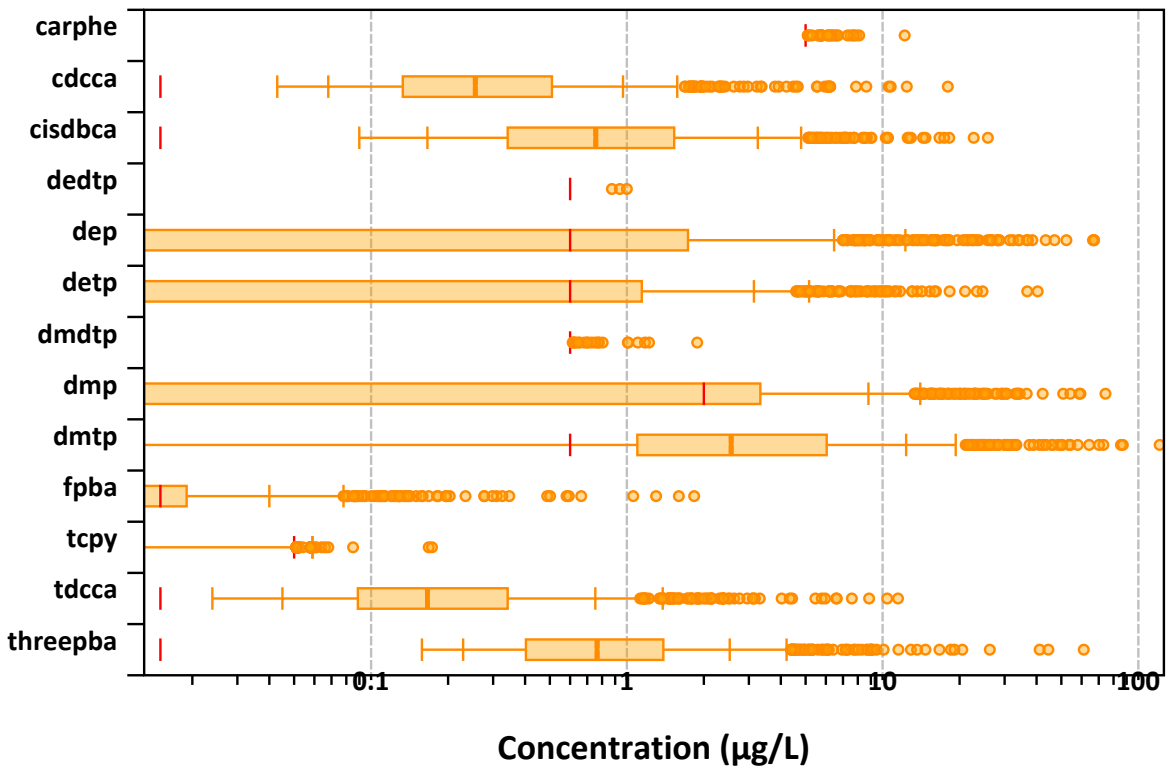


Figure 3.72: Boxplots for all of HBM substance concentration measurements of 13 pesticides. Lower whiskers indicate the p5 and p10 percentiles, upper whiskers the p90 and p95. The edges of the box indicate the p25 and p75 percentiles with the median in the centre of the box. LORs are displayed by a vertical red bar and outliers outside range (Q1 - 3 * IQR , Q3 + 3 * IQR).

### Use complete analysed samples

Select this option to remove samples from individuals for whom one or more of the selected substances have not been analysed.

### Use sampling weights

If checked, individual sampling weights are used. If unchecked, the individual sampling weights are not used in the calculations.

### HBM concentrations data formats

Human biomonitoring data are analytical measurements of chemical substances or markers of health effects in body fluids or tissues. This data can be used for assessing (combined) exposure to chemicals and the risks associated with this exposure. MCRA supports upload of this data in two formats: a relational table structure that matches the internal representation of MCRA and the PARC harmonized HBM data format.

### Relational human monitoring concentration data format

The relational human monitoring concentrations data format is the format that is used internally in MCRA. The data format consists of a number of tables for specification of the study, the individuals of the study (and their specific characteristics), and the human (bio)monitoring samples and sample analyses.

Download empty dataset template: Zipped CSV Excel

### Human biomonitoring surveys

Contains the definitions of the human (bio)monitoring surveys/studies.

Table 3.307: Table definition for Human biomonitoring surveys.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSurvey | AlphaNumeric (50) | Unique identification code of the survey. | idSurvey, idStudy | Yes |
| Name | AlphaNumeric (100) | Name of the study/survey. | Name | No |
| Description | AlphaNumeric (200) | Description of the study/survey. | Description | No |
| Location | AlphaNumeric (50) | The location or country where survey is held. It is recommended to use ISO Alpha-2 country codes. | Location, Country | No |
| BodyWeight-Unit | AlphaNumeric (50) | The unit of bodyweight of the individuals of the survey: kg (default) or g. | BodyWeight-Unit, UnitBody-Weight, WeightIn | No |
| AgeUnit | AlphaNumeric (50) | The unit of age, i.e., year or month. | UnitAge, agein, AgeUnit | No |
| StartDate | DateTime | The starting date of the survey. | StartDate | No |
| EndDate | DateTime | The end date of the survey. | EndDate | No |
| NumberOf-SurveyDays | Integer | The number of days each individual participated in the survey. | NumberOf-SurveyDays, NDaysInSurvey | Yes |
| idPopulation | AlphaNumeric (50) | Unique identification code of the population. | IdPopulation, PopulationId | No |
| Lipid-Concentration-Unit | *ConcentrationUnit* | The unit of the lipid concentration (defaults mg/dL). | Lipid-Concentration-Unit, LipidUnit | No |
| Triglyc-Concentration-Unit | *ConcentrationUnit* | The unit of the triglycerides concentration (defaults mg/dL). | Triglyc-Concentration-Unit, Triglycerides-Concentration-Unit, Triglycerides-Unit | No |
| Cholest-Concentration-Unit | *ConcentrationUnit* | The unit of the cholesterol concentration (defaults mg/dL). | Cholest-Concentration-Unit, Cholesterol-Concentration-Unit, CholesterolUnit | No |
| Creat-Concentration-Unit | *ConcentrationUnit* | The unit of the creatinine concentration (defaults mg/dL). | Creat-Concentration-Unit, Creatinine-Concentration-Unit, CreatinineUnit | No |

Accepted table names: HumanMonitoringSurveys, HumanMonitoringSurvey, HbmSurveys.

### Individuals

The individuals of a survey are recorded in the Individuals table. Add additional properties like Region, Breastfeeding to further describe an individual. In table IndividualProperties, each property in the Individuals table is described (recommended way). Note that only those properties that are available in the Individuals table are used in module Populations, table Populations or PopulationIndividualPropertyValues to subset the individuals. This is only relevant when the UseData option in the population module is used.

Table 3.308: Table definition for Individuals.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual | AlphaNumeric (50) | Unique identification code of the individual. | idIndividual, IndividualId, Individual, Id | Yes |
| idFoodSurvey | AlphaNumeric (50) | The identification code / short name of survey. | idSurvey, idFoodSurvey, Survey, FoodSurvey, SurveyId, FoodSurveyId, SurveyCode, idSet, SetCode, Code | Yes |
| BodyWeight | Numeric | The body weight of the individual. | BodyWeight, Weight | No |
| Sampling-Weight | Numeric | The sampling weight for an individual (default = 1). | SamplingWeight | No |
| NumberOf-SurveyDays | Integer | The number of days the individual participated in the survey. | NumberOf-SurveyDays, NumberOfDays-InSurvey, DaysInSurvey, NDaysInSurvey | No |
| Name | AlphaNumeric (100) | Name or label of the individual. | Name | No |
| Description | AlphaNumeric (200) | Additional description of the individual. | Description | No |
| Individual properties | | Other individual properties can be added like the fields Age, Gender, Region etc. These properties are automatically parsed as co-factors or co-variables. | | No |

Accepted table names: Individuals, SurveyIndividuals, ConsumptionSurveyIndividuals, FoodConsumptionSurveyIndividuals.

### Individual properties

This table is used to describe the properties used in the Populations or PopulationIndividualPropertyValues table characterising the population (table Populations) and/or the properties used in the Individuals table characterising an individual. Properties like Age, Gender, Region are describing an individual (PropertyLevel = Individual). Properties like Period (for populations) or Month (sampling date for an individual day) are describing an individual day (PropertyLevel = IndividualDay).

Table 3.309: Table definition for Individual properties.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual-Property | AlphaNumeric (50) | The code of the property. | idIndividual-Property, Individual-PropertyId, Individual-Property | Yes |
| Name | AlphaNumeric (100) | The name of the property. | Name | No |
| PropertyLevel | *PropertyLevelType* | The level of the property. This type follows a controlled terminology, with possible values: Individual or IndividualDay. | PropertyLevel, LevelProperty | No |
| Description | AlphaNumeric (200) | Description of the property. | Description | No |
| Type | *IndividualProperty-Type* | This field specifies the type of the values of this individual property. This type follows a controlled terminology, with possible values: Boolean, Categorical (default), Numeric, Nonnegative, Integer, NonnegativeInteger, Month, Datetime, Gender. | Type | No |

Accepted table names: IndividualProperties, IndividualProperty.

### Individual property values

Not recommended. This table describes individual property values. Property values are describing an individual for properties like e.g. Region, Breastfeeding. The recommended way is to add these columns as additional columns in the Individuals table. In table IndividualProperties, each property in the IndividualPropertyValues table is described.

Table 3.310: Table definition for Individual property values.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual | AlphaNumeric (50) | The identification number of the Individual. | Id | Yes |
| PropertyName | AlphaNumeric (50) | The name of the property. | Name | Yes |
| TextValue | AlphaNumeric (50) | The value of the property as text value. | | No |
| DoubleValue | Numeric | The value of the property as number. | | No |

Accepted table names: IndividualPropertyValues, IndividualPropertyValue.

### Analytical methods

The analytical methods used for analysing the samples are recorded in the analytical methods table. Each analytical method should have a unique identification code (idAnalyticalMethod). The description field may be used for a more detailed description of the analytical method. The records of this table should be linked to one or more analytical method substance properties table, which record the substances that are measured by this method (and their limits of reporting).

Table 3.311: Table definition for Analytical methods.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idAnalytical-Method | AlphaNumeric (50) | The code for the method of analysis. | idAnalytical-Method, Analytical-MethodId, Analytical-MethodName, Id | Yes |
| Name | AlphaNumeric (100) | Name of the analytical method. | Name | No |
| Description | AlphaNumeric (255) | Additional description of method of analysis. | Description | No |

Accepted table names: AnalyticalMethod, AnalyticalMethods.

### Analytical method properties for substances

This table describes the substances analysed by an analytical method. For each substance analysed by an analytical method a record should be included that describes the unit of measurement and the reporting limits (LOQ/LOD).

Table 3.312: Table definition for Analytical method properties for substances.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idAnalytical-Method | AlphaNumeric (50) | The code of method of analysis. | idAnalytical-Method, Analytical-MethodName, Analytical-MethodId | Yes |
| idSubstance | AlphaNumeric (50) | The substance code. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| LOD | Numeric | The limit of detection (LOD) is the lowest concentration of an substance in a sample that can be consistently detected. | LOD | No |
| LOQ | Numeric | The limit of quantification (LOQ) is the lowest concentration of a substance that can be quantified. The LOQ should be larger than the LOD. | LOQ, LOR | No |
| Concentration-Unit | *ConcentrationUnit* | The unit used for reporting the LOD, LOQ, and the substance concentrations. When not specified, then a default unit of mg/kg is assumed. | Concentration-Unit, Units, Unit | No |

Accepted table names: AnalyticalMethodSubstances, AnalyticalMethodSubstance, AnalyticalMethodCompounds, AnalyticalMethodCompound.

### Human biomonitoring samples

Describes the samples taken during the study. Each sample has a unique identifier/code.

Table 3.313: Table definition for Human biomonitoring samples.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSample | AlphaNumeric (50) | Unique identification code of the monitoring sample. | idSample, Sample | Yes |
| idIndividual | AlphaNumeric (50) | Unique identification code of the individual. | idIndividual, IndividualId, Individual, Id | Yes |
| DateSampling | DateTime | Date of sampling. | DateSampling, DateOf-Sampling, SamplingDate | No |
| DayOfSurvey | AlphaNumeric (50) | Identification code of the day of measurement. | Day, idDay, DayId, DayOfSurvey | Yes |
| TimeOf-Sampling | AlphaNumeric (50) | Identification code of the time of sampling. | TimeOf-Sampling, SamplingTime, TimeSampling | No |
| SampleType | AlphaNumeric (50) | Type of sample (e.g., pooled, 24h urine, spot urine, serum from blood, etc.). | SampleType, SamplingType | No |
| Compartment | AlphaNumeric (50) | If applicable, the measured compartment of the human body (e.g., blood, urine). When specified, the measurements are considered at the level of internal doses. | Compartment | No |
| ExposureRoute | *ExposureRoute* | If applicable, the measured exposure route, e.g., dermal (in case of skin wipes). When specified, the measurements are considered at the level of external doses. | ExposureRoute | No |
| SpecificGravity | Numeric | Specific gravity of the measured person for this particular sample. | SpecificGrafity, SpecificGravity | No |
| SpecificGravity-Correction-Factor | Numeric | Correction factor for the concentration to account for the specific gravity of the measured person for this particular sample. | SpecificGravity-Correction-Factor | No |
| Name | AlphaNumeric (100) | Name of the human monitoring sample. | Name | No |
| Description | AlphaNumeric (200) | Additional description of the human monitoring sample. | Description | No |
| LipidGrav | Numeric | Lipid content based on gravimatic analysis of the measured person for this particular sample. | LipidGrav, LipidGravimatic | No |
| LipidEnz | Numeric | Lipid content based on enzymatric summation of the measured person for this particular sample. | LipidEnz, LipidEnzymatic | No |
| Triglycerides | Numeric | Triglycerides total of the measured person for this particular sample. | Triglyc, Triglycerides | No |
| Cholesterol | Numeric | Cholesterol total of the measured person for this particular sample. | Cholest, Cholesterol | No |
| Creatinine | Numeric | Creatinine content of the measured person for this particular sample. | Creat, Creatinine | No |
| Osmotic- | Numeric | Osmotic concentration of the | Osm, Osmotic- | No |

Accepted table names: HumanMonitoringSamples, HumanMonitoringSample, HbmSamples.

### Human biomonitoring sample analyses

Contains the measurements of the samples of human biomonitoring studies.

Table 3.314: Table definition for Human biomonitoring sample analyses.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSample-Analysis | AlphaNumeric (50) | Unique identification code of the sample analysis. | idSample-Analysis, SampleAnalysis | Yes |
| idSample | AlphaNumeric (50) | Code of the measured monitoring sample. | idSample, Sample | Yes |
| idAnalytical-Method | AlphaNumeric (50) | The code of method of analysis. | idAnalytical-Method, Analytical-MethodName, Analytical-MethodId | Yes |
| AnalysisDate | DateTime | Date of analysis. | AnalysisDate, DateAnalysis | No |
| Substance concentration(s) | AlphaNumeric (100) | Substance concentrations can be uploaded via the sample concentrations table or via additional columns of the sample analyses table. For the latter, one or more columns with the measured concentrations of the substances in the unit as specified by the analytical method should be included in the data table. The column name(s) should match the substance codes of the substances measured by the analytical methods. Empty fields for substances that should have been measured by the analytical method are considered to be censored with measurement values below LOQ or LOD. | | No |
| Name | AlphaNumeric (100) | Name of the human monitoring sample analysis. | Name | No |
| Description | AlphaNumeric (200) | Additional description of the human monitoring sample analysis. | Description | No |

Accepted table names: HumanMonitoringSampleAnalyses, HumanMonitoringSampleAnalysis, HbmSampleAnalyses.

### Sample concentrations

The positive concentration values for substances from analysis in the unit specified in table human monitoring sample analyses. Censored values (i.e. results 'less than LOR') are not included, their existence can be inferred from the tables AnalysisSamples and AnalyticalMethodSubstances, and the LOR itself from the analytical method.

Table 3.315: Table definition for Sample concentrations.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idAnalysis-Sample | AlphaNumeric (50) | The identification number of the analysed sample. | idAnalysis-Sample, AnalysisSample-Id | Yes |
| idSubstance | AlphaNumeric (50) | The substance code. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Concentration | Numeric | The measured concentration. | Concentration | No |
| ResType | *ResType* | The type of residue. Should be VAL (= default), LOQ, LOD or MV. | ResType | No |

Accepted table names: HumanMonitoringSampleConcentrations, HumanMonitoringSampleConcentration, HumanMonitoringConcentrations, HbmSampleConcentrations.

### PARC HBM data format

The PARC HBM data format is the data format proposed in the EU Partnership for the Assessment of Risks from Chemicals (PARC) project. MCRA supports upload of files in this format, of which the data is mapped to the MCRA internal data format during the upload of the files.

### PARC harmonised HBM data format

> **Note**
>
> The PARC harmonised data format as well as the MCRA data format are under development and may be changed in the future.

In PARC, a harmonised data format for human biomonitoring data is being developed by VITO. Data harmonization improves the comparability of data from different HBM studies and interoperability for use with different analysis tools such as MCRA and the tool for the calculation of summary statistics of the HBM data, which can be made available via the IPCHEM portal and/or integrated into the European HBM dashboard. More information about this data format and instructions on preparing data files compliant with this format can be found at the PARC HBM data harmonization web page. This page also contains a tool for validating data files prepared in this format and an example data file that can be uploaded to and used in MCRA for testing.

Excel data files provided to MCRA in this format are mapped during the file upload process to the internal data structure/format of MCRA. For this, MCRA uses a custom mapping/conversion procedure. For a large part, this mapping is fairly straightforward. However, for some fields and entities explicit choices are made that users need to be aware of.

- **Survey/study**
  - Each data file corresponds to one HBM survey/study in MCRA.

- Survey *StartDate* refers to the first sampling date of all repeated samples.
- Survey *EndDate* refers to the last sampling date of all repeated samples.
- When all reported *country* values of the subjects are the same, then this is used as location of the survey/study.
- When a survey consists of two or more days, in case of repeated measurements or time points, the option to *Filter on repeated measurements* becomes available.

- **Subjects/individuals**
  - Each subject maps to MCRA individuals of the study/survey.
  - A selection of the subject/individual properties is mapped to the MCRA data format. Since MCRA does not support repeated properties, a choice has to be made when mapping individual properties that are repeated individual/subject properties in the harmonised HBM data format.
  - Repeated recordings for each subject's *weight* are averaged to one value: *BodyWeight* (missing values for *weight* are supported in MCRA).
    1) missing values for *BodyWeight* are replaced by the average of the population.
    2) if no *weight* values are available, a nominal bodyweight of 70kg is used instead.
  - Repeated recordings for each subject's *height* are averaged to one value: *Height*.
  - From the repeated recordings for *smoking* only the last recording is taken: *Smoking_status*.
- **Samples**
  - Each sample maps to an MCRA sample.
  - The *matrix* code is translated to a *biological matrix* and *sampling type*, e.g. *US* translates to *Urine* and *Spot*, *BP* to *Blood* and *Plasma*.
  - *id_timepoint* refers to the sampling time and is translated to *DayOfSurvey*.
- **Analytical methods**
  - MCRA analytical methods are derived/reconstructed from the concentration data sheets of the harmonised HBM data format based on the reported detection limits (LOQs/LODs) and substances and the matrix of the samples.
- **Sample concentrations/measurements**
  - Concentrations without value (blanks) are recorded as missing value (MV).
  - Concentrations recorded as -10 are recorded as missing value (MV).
  - When both LOD and LOQ are known, concentrations recorded as -1 are interpreted as a value below limit of detection (x < LOD).
  - When both LOD and LOQ are known, concentrations recorded as -2 are interpreted as a value below limit of quantification and above limit of detection (LOD <= x < LOQ).
  - When LOD is NaN and LOQ is known, concentrations recorded as -3 are interpreted as values below the limit of quantification (x < LOQ).
  - When LOD is known and LOQ is NaN, concentrations recorded as -1 are interpreted as values below the limit of detection (x < LOD).

### HBM concentrations settings

### Selection settings

Table 3.316: Selection settings for module HBM concentrations.

| Name | Type | Description |
|---|---|---|
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Sampling method | AlphaNumeric | The sampling method that should be included in the action. |
| Match HBM individuals selection to population definition options | *IndividualSubsetType* | Match HBM individuals selection to population definition. Use population definitions (default), ignore all population definitions use a selection of properties. |
| Select one or more individual(day) properties to filter the population | AlphaNumeric | Select one or more individual(day) properties to filter the individuals(days) in the population. |
| Use sampling weights | Boolean | If checked, individual sampling weights are used. If unchecked the individual sampling weights are not in the calculations. |
| Use complete analysed samples | Boolean | Select this option to remove samples from individuals for which one or more of the selected substances have not been analysed. |
| Exclude substances from sampling method | Boolean | Select this option to exclude one or more substances from the selected sampling methods. |
| Substances to exclude from a sampling method | HbmSamplingMethodSubstance | The data of the selected substances will be excluded from analy |
| Filter on repeated measurements | Boolean | Select this option to make a selection of the time points to be included in the action. By default, all time points are included. |
| Selected measurements | AlphaNumeric | The measurements that should be included in the action. |
| Define populations based on specified individual properties | Boolean | Define a population by selecting specific ranges/values of individual properties. E.g., the female population between ages and 45 is composed of the properties gender (female) and age (between 18 and 45). |
| Individual day subset | IndividualDaySubsetDefinition | Individual day subset definition. |
| Individuals subset definitions | IndividualsSubsetDefinition | Contains a list of subset definitions to filter the population's individuals based on an individual's properties, by property nam and a custom filter query, for example a value range or a list of keywords. |

### Output settings

Table 3.317: Output settings for module HBM concentrations.

| Name | Type | Description |
|---|---|---|
| Exclude privacy sensitive data from outputs | Boolean | Use this setting to not report the parts of the results (i.e., figure tables, or sections) that are marked as (potentially) privacy sensitive. |
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |

### Uncertainty settings

Table 3.318: Uncertainty settings for module HBM concentrations.

| Name | Type | Description |
|---|---|---|
| Resample HBM individuals | Boolean | HBM individual data are resampled from the original database using the bootstrap methodology (Efron 1979, Efron & Tibshir 1993). |

### HBM concentrations as data

Data are provided in the form of surveys consisting of individuals from which the human monitoring samples taken. Substance concentration measurements are linked to analyses performed on the human monitoring samples. The data should also include information about the analytical methods that were used.

- *HBM concentrations data formats*
- *HBM concentrations from data*

## 3.4.20 Non-dietary exposures

Non-dietary exposures are the amounts of substances to which individuals in a population are exposed to via any of three non-dietary routes: dermal, inhalation or oral. Non-dietary exposures are the input for the estimation of *aggregate (internal) exposure distributions* from both dietary and non-dietary routes of exposure. Depending on the period individuals are exposed, non-dietary exposures are short-term or acute exposure and are expressed per individual-day. When the exposure takes place over an unspecified longer time period, the exposure is long-term or chronic and is expressed as an average exposure per individual. Examples are presented as case studies in Kennedy et al. (Kennedy et al. (2012), Kennedy et al. (2015a), Kennedy et al. (2015b), Kennedy and Butler Ellis (2017)). The R-code to generate these examples is available for general use.

Datasets are typically generated by external programs, e.g. *BROWSE*, *BREAM* or *PACEM*. The BROWSE and BREAM2 models both simulate distributions of potential exposure of residents and bystanders to pesticides sprayed on crops. Probability distributions are included to quantify variations in input parameters representing conditions during a spray event. PACEM is a probabilistic exposure model for substances present in personal care products *PCPs* or house cleaning procucts *HCPs*. BROWSE was an EU FP7 project that, in addition to bystanders and residents from boom-sprayers, includes various arable and orchard scenarios. It includes dermal, oral and inhalation routes of exposure and generates exposure files in the correct format for MCRA non-dietary exposure calculations. The underlying simulation of dermal spray deposits on bystanders and residents was taken from BREAM, although BROWSE includes post-processing to model indirect exposures, multiple routes and long-term exposure, see Kennedy and Butler Ellis (2017). Volatilisation is also included through the PEARL-OPS model (van den Berg et al. (2016)) to account for inhalation of vapours. BREAM2 is an updated version of the original BREAM model (Kennedy et al. (2012)) and software is available online (http://www.ssau.co.uk/BREAM2-calculator). Results from BREAM had been used as part of EFSA guidance on bystander and resident exposure. BREAM2 was recently shown to produce more realistic exposure distributions, when compared to measured dermal exposure (Butler Ellis et al. (2018)). Currently, the BROWSE software is outdated and replaced by BREAM2.

This module has as primary entities: *Populations Substances*

Output of this module is used by: *Internal exposures*

### Non-dietary exposures from data

### Non-dietary exposures data formats

Non-dietary exposures may be specified for multiple routes of exposure (dermal, oral and inhalation), for multiple substances, and for multiple exposure sources. Also, they can be provided as single deterministic exposure levels or as probabilistic exposure estimates and it is possible, but not mandatory, to specify uncertainty. The non-dietary exposures may be short term (acute) or longer term averages (chronic), and the user must ensure to supply appropriate non-dietary data for the type of exposure assessment of interest. For chronic assessments this means the non-dietary exposure is averaged over an appropriate time interval.

Non-dietary exposures are defined by non-dietary surveys to which dietary exposures are linked. For these surveys, individual properties can be specified to define non-dietary exposures for particular sub-groups of the population (e.g., specific age groups, or a specific gender). For each non-dietary survey a percentage of the target population that is not exposed from this source can be specified by means of a percentage. Uncertainty about non-dietary exposures can be specified by specifying multiple records for each individual in an additional table.

The use of multiple surveys can be used when multiple sources are relevant. For example, when modelling individuals taking part in various activities involving pesticide use or incidental exposures as a resident. Each non-dietary source is characterised in a particular user-selected or user-supplied non-dietary survey. By default, exposures from separate non-dietary surveys (sources) are considered to be independent events, but as explained below correlations between substances and/or activity types per individual can be represented if generated prior to uploading to MCRA. When including multiple non-dietary surveys it is possible to supply some with uncertainty/variability and others without variability/uncertainty according to the requirements and data availability.

When the user supplies probabilistic non-dietary exposure estimates (i.e., there is a distribution for the non-dietary exposure rather than a single nominal value), then this information will be propagated as part of the *exposure assessment*. Distributions may be included to represent variability, uncertainty or both, and in these cases the aggregate exposure estimates are reported with variability and/or uncertainty as appropriate. Multiple (uncertain) values from the non-dietary exposure distribution may be supplied per individual and per substance.

Exposures within a non-dietary survey may be expressed as correlated or independent for the different substances. For example, if the exposures are a mixture of substances in a known ratio (e.g. from a specific tank mix of pesticides), or if exposure to one substance strongly implies that exposure to another is likely, these relationships may be included in the non-dietary data supplied by the user. Inference for the matched-case scenario with uncertainty analysis can use exposure sets. These are specific sets of exposures defined for each individual and in any uncertainty iteration an individual will receive exactly one of the exposure sets for that individual. Alternatively, independence may be represented by generating sets drawn from independent distributions when generating these tables.

Non-dietary exposure data is provided per non-dietary surveys. Each non-survey has some general information about the exposed population and the origin of the non-dietary exposure data. Also, a number of properties, such as specific age groups, can be specified for a survey. To each non-dietary survey, non-dietary exposures can be linked. These exposures may originate from dermal, oral and/or inhalatory exposure routes.

Download empty dataset template: Zipped CSV Excel

### Non-dietary surveys

This table provides detail about non-dietary surveys (source of non-dietary exposure): description, location, date and unit of exposure).

Table 3.319: Table definition for Non-dietary surveys.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idNonDietary-Survey | AlphaNumeric (50) | The survey identification number. | idSurvey, idNonDietary-Survey | Yes |
| Name | AlphaNumeric (100) | Name of the non-dietary survey. | Name | No |
| Description | AlphaNumeric (200) | Description of non-dietary survey. | Description | No |
| Location | AlphaNumeric (50) | The location of survey. | Location, Country | No |
| Date | DateTime | The date of survey. | Date | No |
| NonDietary-IntakeUnit | *ExternalExposure-Unit* | The unit of the non-dietary exposure. | Unit, ExposureUnit, NonDietary-IntakeUnit, NonDietary-ExposureUnit | Yes |
| Percentage-Zeros | Numeric | The proportion zeros, specified as a percentage (%). | PercentageZeros | No |
| idPopulation | AlphaNumeric (50) | Unique identification code of the population. | IdPopulation, PopulationId | No |

Accepted table names: NonDietarySurveys, NonDietarySurvey.

### Non-dietary survey properties

This table specifies demographic properties that apply to the individuals in the surveys. These properties could be used to link the individuals of a non-dietary survey with individuals from dietary surveys. That is, if demographic criteria are defined, only those individuals in the dietary survey that meet these criteria will be assigned non-dietary exposures. This table is not relevant when matching is switched on (i.e., when individuals are matched based on individual id).

Table 3.320: Table definition for Non-dietary survey properties.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| Individual-PropertyName | AlphaNumeric (50) | Name of demographic criteria for non-dietary exposures in a particular survey e.g. age, gender, height (must correspond to a column name in Individuals table). | Individual-PropertyName | Yes |
| idNonDietary-Survey | AlphaNumeric (50) | The code of survey (must correspond to values in id column of the non-dietary surveys table). | idNonDietary-Survey | Yes |
| Individual-PropertyText-Value | AlphaNumeric (50) | Text value of the property e.g. male or female, smoker or non-smoker. | Individual-PropertyText-Value | No |
| Individual-Property-DoubleValue-Min | Numeric | Inclusive lower bound value of the property. E.g., a value of “18” for an individual property name called Age would mean that only individuals aged 18 and above receive the non-dietary exposures. | Individual-PropertyDouble-ValueMin | No |
| Individual-Property-DoubleValue-Max | Numeric | Inclusive upper bound value of property e.g. a value of “65” for an IndividualPropertyName called Age would mean that only individuals aged 65 and below receive the non-dietary exposures. | Individual-PropertyDouble-ValueMax | No |

Accepted table names: NonDietarySurveyProperties, NonDietarySurveyProperty.

### Non-dietary exposures

This table defines nominal non-dietary exposure values (such as means) for individuals within the non-dietary surveys. It can also be used to specify non-dietary exposures for individuals within the food surveys. Each exposure comprises a non-dietary survey (source of exposure); a string identifying an individual, which may or may not correspond to the ID of an individual in a food survey; a substance; and dermal, oral and inhalation exposure values. Exposures are assumed to be external doses.

Table 3.321: Table definition for Non-dietary exposures.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual | AlphaNumeric (50) | Non-dietary individual identification number. This id may 1) match with the individual ids of the dietary survey (dietary exposures matched to food survey individuals), 2) not match with the individual ids of the dietary survey (unmatched individuals), or contain a default exposure (indicated by idIndividual = 'General') linking the dietary exposures to individuals based on the demographic criteria defined in the non-dietary survey properties table. | idIndividual | Yes |
| idNonDietary-Survey | AlphaNumeric (50) | The code of the survey (must correspond to values in id column of non-dietary surveys table). | idNonDietary-Survey | Yes |
| idSubstance | AlphaNumeric (50) | The substance code. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Dermal | Numeric | The dermal (non-dietary) exposure value. | Dermal | Yes |
| Oral | Numeric | The oral (non-dietary) exposure value. | Oral | Yes |
| Inhalation | Numeric | The inhalation (non-dietary) exposure value. | Inhalation | Yes |

Accepted table names: NonDietaryExposures, NonDietaryExposure.

### Non-dietary exposure uncertainty records

This table may be used to supply uncertainty sets of multiple (uncertain) non-dietary exposure values for individuals within the non-dietary surveys. Multiple non-dietary values are generated by probabilistic exposure calculations i.e. when there is a distribution for the non-dietary exposure rather than a single nominal value. If this table is supplied, aggregate exposure estimates will be reported with uncertainty using the uncertainty set approach. Each exposure set comprises a non-dietary survey (source of exposure); an individual ID; a substance; and dermal, oral and inhalation exposure values. In addition, the id column is used to define the uncertainty set. Summarizing, an uncertainty set is identified by column id and contains all exposure sets defined for each individual. In each uncertainty run (outer loop) an uncertainty set is sampled and in each iteration (inner loop) nondietary individuals are sampled from this set.

Table 3.322: Table definition for Non-dietary exposure uncertainty records.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idIndividual | AlphaNumeric (50) | Non-dietary individual identification number. The idIndividual value may correspond to an id in the Individuals table (dietary exposures matched to food survey individuals), may not correspond to an id in the Individuals table (unmatched individuals), or may contain a default exposure (indicated by idIndividual = 'General' - demographic criteria for the assignment of exposures are defined in the NonDietarySurveyProperties table). For matching to occur, the user will need to tick the option to 'match specific dietary survey individuals' in the user-interface. The software will then assign non-dietary exposures to the dietary individuals according to the values in this column. Any idIndividual values that do not correspond to individuals in the food survey will be ignored, unless a value 'General' is specified. Then the individual should meet the demographic criteria as defined in the NonDietarySurveyProperties table. If this box is left unticked, the non-dietary exposures will be randomly allocated to the dietary population provided they meet the demographic criteria. | idIndividual | Yes |
| idNonDietary-Survey | AlphaNumeric (50) | code of survey (must correspond to values in id column of NonDietarySurveys table) | idNonDietary-Survey | Yes |
| idCompound | AlphaNumeric (50) | Substance code (must correspond to values in id column of Substances table). | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| id | AlphaNumeric (50) | Uncertainty set identification number. | id | Yes |
| Dermal | Numeric | Dermal non-dietary exposure value. | Dermal | Yes |
| Oral | Numeric | Oral non-dietary exposure value. | Oral | Yes |
| Inhalation | Numeric | Inhalation (non-dietary) exposure value. | Inhalation | Yes |

Accepted table names: NonDietaryExposuresUncertain, NonDietaryExposureUncertain.

### Non-dietary exposures settings

### Calculation settings

Table 3.323: Calculation settings for module Non-dietary exposures.

| Name | Type | Description |
|---|---|---|
| NON-DIETARY: Population alignment method other non-dietary exposures | *PopulationAlignmentMethod* | Population aligment methods for nondietary exposure sources. |
| Match individuals of multiple non-dietary surveys | Boolean | If checked, then non-dietary exposures of individuals from different surveys with the same identifier (ID) are combined. |

### Uncertainty settings

Table 3.324: Uncertainty settings for module Non-dietary exposures.

| Name | Type | Description |
|---|---|---|
| Resample non-dietary exposures | Boolean | Specifies whether non-dietary exposures are resampled. Note th non-dietary uncertainty is only ignored when individual uncertainty is set to false (uncheck box: do NOT resample individuals). |

### Non-dietary exposures uncertainty

In an aggregate exposure assessment, dietary and nondietary data are combined into an aggregate exposure distribution. The nondietary data are supplied in table *Non-dietary exposures*. In an uncertainty analysis, MCRA provides two ways to assess the uncertainty:

1. the uncertainty set approach
2. the bootstrap algorithm.

When table *Non-dietary exposure uncertainty records* is not supplied, the nondietary data in table *Non-dietary exposures* is resampled and the bootstrapped sets are used in the uncertainty run. More precisely, in each outer loop of the 2D Monte Carlo, within each nondietary survey (multiple surveys may be supplied), the nondietary individuals are resampled. Each individual represents a nondietary exposure set containing dermal and/or oral and/or inhalation exposure values for multiple substances. Bootstrapping is the default behaviour when the *Non-dietary exposure uncertainty records* table is missing. When uncertainty distributions supplied in this table represent sampling uncertainty (individual exposure sets are repeatedly sampled using the same nondietary exposure generator without changing the input parameters), then bootstrapping the data performs equally well and is more efficient.

### Non-dietary exposures as data

Non-dietary exposures are collected in non-dietary surveys. Data may be specified on population level or individual level, and may or may not include variability and uncertainty.

- *Non-dietary exposures data formats*
- *Non-dietary exposures from data*

Inputs used: *Active substances*

Settings used

- *Calculation Settings*

See also *Combining exposure sources*.

### 3.4.21 Single value dietary exposures

Single value dietary exposures are based on the single value concentrations of substances, expressed per standard (kg) bodyweight and/or single value amounts of consumed modelled food. Depending on the exposure type, dietary exposures can be short-term/acute exposures.

This module has as primary entities: *Populations Foods Substances*

Output of this module is used by: *Single value risks*

#### Single value dietary exposures calculation

Either the short-(acute) or long-term (chronic) dietary exposure to a substances via food can be estimated as a single value calculated from single value inputs. This is often referred to as deterministic estimation. MCRA implements the IESTI, TMDI, IEDI and NEDI (Rees-Day) calculation methods that are also available in the EFSA PRIMo (Pesticide Residue Intake Model) tool revision 3 (EFSA (2018)).

The implementation in MCRA allows more choices than EFSA PRIMo by choosing other inputs or input combinations for the calculation formula. Moreover, the calculations can in all cases be adapted for processing factors or occurrence frequencies. For the chronic estimates, also the contributions per food or processed food are reported.

#### Acute single value dietary exposure assessment

The short term (acute) exposure assessment is usually the exposure related to a consumption of food over a single day. MCRA applies in principle the IESTI equations as shown in EFSA PRIMo revision 3 (EFSA (2018)), but the equations are extended with a factor $\mathtt{OF}$ to allow adaptation for an occurrence frequency lower than 1. So the inputs to the equations are not necessarily the same as used in PRIMo. For example, the large portion ($\mathtt{LP}$) and body weight ($\mathtt{BW}$) can be computed instead of just being standard values.

#### IESTI (International Estimated Short-Term Intake)

The IESTI (International Estimated Short-Term Intake) is calculated according to different equations depending on the unit weight of the raw agricultural commodity (RAC) and the unit weight of the edible portion (EP). The following cases are distinguished.

**Case 1**
: refers to commodities with unit weight of the raw agricultural commodity $\mathtt{U}_{\mathtt{RAC}} \leq 25$ g (e.g. walnuts, strawberries and peas. It is also used for meat, liver, kidney, edible offal, eggs and for post-harvest uses in cereal grains, oilseeds and pulses).

**Case 2a**
: for food product with a $\mathtt{U}_{\mathtt{RAC}} > 25$ g, where the meal portion is $> \mathtt{U}_{\mathtt{ep}}$ (unit weight edible portion).

**Case 2b**
: for food products with a $\mathtt{U}_{\mathtt{RAC}} > 25$ g, where the meal portion is $\leq \mathtt{U}_{\mathtt{ep}}$.

**Case 3**
: for food products that are usually bulked or blended before they are consumed (e.g. cereals, pulses, oilseeds and milk).

The calculations are as follows.

**Case 1**

$$\frac{\mathtt{LP} \cdot \mathtt{HR} \cdot \mathtt{PF} \cdot \mathtt{CF} \cdot \mathtt{OF}}{\mathtt{BW}}$$

**Case 2a**

$$\frac{\mathtt{U}_{\mathtt{ep}} \cdot \mathtt{HR} \cdot \mathtt{PF} \cdot \mathtt{CF} \cdot \mathtt{VF} \cdot \mathtt{OF} + \left(\mathtt{LP} - \mathtt{U}_{\mathtt{ep}}\right) \cdot \mathtt{HR} \cdot \mathtt{PF} \cdot \mathtt{CF} \cdot \mathtt{OF}}{\mathtt{BW}}$$

**Case 2b**

$$\frac{\mathrm{LP} \cdot \mathrm{HR} \cdot \mathrm{PF} \cdot \mathrm{CF} \cdot \mathrm{VF} \cdot \mathrm{OF}}{\mathrm{BW}}$$

**Case 3**

$$\frac{\mathrm{LP} \cdot \mathrm{STMR} \cdot \mathrm{PF} \cdot \mathrm{CF} \cdot \mathrm{OF}}{\mathrm{BW}}$$

**New Case 1 and 3:**

$$\frac{\mathrm{LP} \cdot \mathrm{MRL} \cdot \mathrm{PF} \cdot \mathrm{CF} \cdot \mathrm{OF}}{\mathrm{BW}}$$

**New Case 2a and 2b**

$$\frac{\mathrm{LP} \cdot \mathrm{MRL} \cdot \mathrm{PF} \cdot \mathrm{CF} \cdot \mathrm{VF} \cdot \mathrm{OF}}{\mathrm{BW}}$$

Parameters used in the equations

MRL: Maximum residue level for the RAC concerned (default in mg/kg);

STMR: Supervised Trials Median Residue for raw agricultural commodity (RAC) concerned (default in mg/kg);

CF: Conversion factor residue definition enforcement to residue definition risk assessment (calculated as the ratio of residues according to the residue definition for risk assessment divided by the residue concentration according to the residue definition for enforcement);

OF: Use Frequency of the raw agricultural commodity (RAC),

BW: body weight of the population related to the LP (default in kg);

LP: Large portion reported (in kg/day) (97.5th percentile of eaters (or alternative percentile, depending on the number of reported eating occasions);

HR: Highest residue according to residue definition for enforcement in composite sample (default in mg/kg);

$\mathrm{U_{ep}}$: Unit weight of edible portion (in kg), provided by the country from which the LP was reported (or mean unit weight calculated from all available unit weight data, if no unit weight is available from the country matching the highest LP;

PF: Processing factor or peeling factor (calculated as the ratio of residues in processed/peeled product, divided by residue concentration in unprocessed/unpeeled product);

VF: variability factor, depending on the unit weight of the whole product $(\mathrm{U_{RAC}})$, different default VF are used in the calculations.

$(\mathrm{U_{RAC}}) < 25$ g, the calculations are performed according to case 1 (VF = 1).

$(\mathrm{U_{RAC}})$ between 25 and 250 g: VF = 7.

$(\mathrm{U_{RAC}})$ greater than 250: VF = 5.

In $\mathrm{IESTI}_{new}$, a default VF of 3 is used.

In case the empirically derived variability factors are available, the default VF is to be replaced.

### Alternative IESTI-styled assessments

If consumption survey data for a specific population are available, the LP values in the IESTI equations may be replaced by statistics calculated from these data (at the consumed modelled food level).

If concentration monitoring data (retrospective) or concentration field trial data (prospective) are available, the MRL, HR, STMR values in the IESTI equations may be replaced by statistics calculated from these data (at the consumed modelled food level).

In the current use of IESTI, the occurrence frequency (use frequency) OF is assumed to be 1. In alternative assessments, a more realistic estimate may be used. Such an estimate could be derived for example as the highest occurrence frequency observed in a retrospective assessment for either the same substance or the same food.

### IESTI special cases

For some foods, chemicals are applied after harvest, i.c. post-harvest use. For those combinations of food and substance, Case 1 should be used in the calculation. However, commodities with post-harvest use like cereal grains, oilseeds and pulses are typically bulked or blended (Case 3). To overrule Case 3, specify in table *IESTI special cases* the food and substance combination with *PostHarvest* as application type. For those food and substance combinations with a unit weight of the raw agricultural commodity $\mathrm{U_{RAC}} \leq 25$ g, Case 1 is applied. When substances are applied before harvest, i.c. pre-harvest use, Case 1 should be overruled by Case 3. Specify in table *IESTI special cases* the food and substance combination with *PreHarvest* as application type.

### Chronic single value dietary exposure assessment

The long term (chronic) exposure assessment is usually the exposure related to a consumption over a longer period of time. MCRA applies in principle the TMDI, IEDI or NEDI (Rees-Day) equations as shown in EFSA PRIMo revision 3 (EFSA (2018)). However, the equations are extended with factors $PF_i$ and $OF_i$ to allow adaptation for processing factors and occurrence frequencies lower than 1. Also, the inputs to the equations are not necessarily the same as used in PRIMo. For example, the consumption statistics ($MC$, $p_{97.5}$) and body weight ($BW$) can be computed instead of just being standard values. Note that TMDI, IEDI and NEDI (Rees-Day) estimates are summations over foods (raw agricultural products). In addition to the summations, MCRA will also report the individual terms (single value dietary exposures per food).

### TMDI (Theoretical Maximum Dietary Intake)

$$\sum_{X=i}^{n} \frac{MRL_i \cdot CF_i \cdot PF_i \cdot OF_i \cdot MC_i}{BW}$$

$i, j, k, ...n$: individual raw agricultural products

### IEDI (International Estimated Dietary Intake)

$$\sum_{X=i}^{n} \frac{STMR_i \cdot CF_i \cdot PF_i \cdot OF_i \cdot MC_i}{BW}$$

$i, j, k, ...n$: individual raw agricultural products

### NEDI (National Estimated Dietary Intake): Rees-Day model (I)

$$\sum_{X=i}^{j} \frac{MRL_i \cdot CF_i \cdot PF_i \cdot OF_i \cdot p_{97.5} consumption_i}{BW} + \sum_{X=k}^{n} \frac{MRL_k \cdot CF_k \cdot PF_i \cdot OF_i \cdot MC_k}{BW}$$

$i, j$: two raw agricultural products leading to the highest intake;

$k, l, m, ...n$: remaining raw agricultural commodities consumed

### NEDI (National Estimated Dietary Intake): Rees-Day model (II)

$$\sum_{X=i}^{j} \frac{STMR_i \cdot CF_i \cdot PF_i \cdot OF_i \cdot p_{97.5}consumption_i}{BW} + \sum_{X=k}^{n} \frac{STMR_k \cdot CF_i \cdot PF_i \cdot OF_i \cdot MC_k}{BW}$$

$i, j$: two raw agricultural products leading to the highest intake;

$k, l, m, ...n$: remaining raw agricultural commodities consumed

Parameters used in the equations

$MRL_i$: Maximum residue level for the RAC concerned (default in mg/kg);

$STMR_i$: Supervised Trials Median Residue for raw agricultural commodity (RAC) concerned (default in mg/kg);

$CF_i$: Conversion factor residue definition enforcement to residue definition risk assessment (calculated as the ratio of residues according to the residue definition for risk assessment divided by the residue concentration according to the residue definition for enforcement);

$MC_i$: mean consumption for a given raw agricultural product (RAC) calculated for the whole survey/subgroup of the survey, including processed products (recalculated to the unprocessed RAC) (default in kg/day);

$p_{97.5}$ $consumption_i$ for a given raw agricultural product (RAC), calculated from the individual consumption reported by the participants of the whole survey/subgroup of the survey, including processed products (recalculated to the unprocessed RAC) (default in kg/day);

$BW$: mean body weight of the population related to the $LP$ or mean consumption (default in kg).

$OF_i$: Occurrence Frequency of the substance on the food (typically, a raw agricultural commodity, RAC),

$PF_i$: Processing factor or peeling factor (calculated as the ratio of residues in processed/peeled product, divided by residue concentration in unprocessed/unpeeled product);

### Alternative TMDI-, IEDI- or NEDI-styled assessments

If consumption survey data for a specific population are available, the $MC, p_{97.5}consumption$ values in the IESTI equations may be replaced by statistics calculated from these data (at the consumed modelled food level).

If concentration monitoring data (retrospective) or concentration field trial data (prospective) are available, the $MRL, STMR$ values in the IESTI equations may be replaced by statistics calculated from these data (at the consumed modelled food level).

In the current use of IESTI, the occurrence frequency (use frequency) $OF$ is assumed to be 1. In alternative assessments, a more realistic estimate may be used. Such an estimate could be derived for example as the highest occurrence frequency observed in a retrospective assessment for either the same substance or the same food.

### Single value dietary exposures data formats

Single value dietary exposures are IESTI etc.

Dietary exposure data is specified through dietary exposure models. To each dietary exposure model, exposure distributions are linked.

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### Dietary exposure models

High level description of the dietary exposure models, specifying the id, name, description and the (reference) substance and exposure unit used for reporting the exposures. To this models, exposure percentiles and bootstrap values of the percentile may be linked.

Table 3.325: Table definition for Dietary exposure models.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idDietary-ExposureModel | AlphaNumeric (50) | Identifier of the dietary exposure model. | id, idDietary-Exposure, idExposure-Model | Yes |
| Name | AlphaNumeric (100) | The name of the dietary exposure model. | Name | No |
| Description | AlphaNumeric (200) | Description of dietary exposure model. | Description | No |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| ExposureUnit | AlphaNumeric (50) | The intake/exposure unit of the dietary exposures reported by this model. If not specified, then a default exposure unit of mg/kg BW/day is assumed. | Unit, ExposureUnit, IntakeUnit | Yes |

Accepted table names: DietaryExposureModels, DietaryExposures.

### Dietary exposure percentiles

Exposure percentiles linked to a dietary exposure model. The percentiles are reported in the unit specified by the exposure model to which they belong.

Table 3.326: Table definition for Dietary exposure percentiles.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idDietary-ExposureModel | AlphaNumeric (50) | The code of the dietary exposure model to which this record belongs. | idDietary-ExposureModel | Yes |
| Percentage | Numeric | The percentage to which the percentile value belongs. | Individual-PropertyDouble-ValueMin | Yes |
| Exposure | Numeric | The percentile value. I.e., the exposure value belonging to the specified percentage. | Exposure | Yes |

Accepted table names: DietaryExposurePercentiles.

### Dietary exposure percentile bootstrap values

Uncertainty values, obtained from bootstrap runs, of the dietary exposure percentiles.

Table 3.327: Table definition for Dietary exposure percentile bootstrap values.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idDietary-ExposureModel | AlphaNumeric (50) | The code of the dietary exposure model to which this record belongs. | idDietary-ExposureModel | Yes |
| idUncertainty-Set | AlphaNumeric (50) | The uncertainty set identifier. | idUncertainty-Set, UncertaintyId | Yes |
| Percentage | Numeric | The percentage to which the percentile value belongs. | Individual-PropertyDouble-ValueMin | Yes |
| Exposure | Numeric | The percentile value. I.e., the exposure value belonging to the specified percentage. | Exposure | Yes |

Accepted table names: DietaryExposurePercentilesUncertain, DietaryExposurePercentileUncertains.

### Single value dietary exposures settings

### Selection settings

Table 3.328: Selection settings for module Single value dietary exposures.

| Name | Type | Description |
|---|---|---|
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Selected tier | SettingsTemplateType | Specifies all module settings should be set according to a pre-defined tier or using custom settings. |

### Calculation settings

Table 3.329: Calculation settings for module Single value dietary exposures.

| Name | Type | Description |
|---|---|---|
| Single value dietary exposure calculation method | *SingleValueDietaryExposuresCalculationMethod* | Method for computing single value dietary exposures. |
| Apply processing factors | Boolean | Specified in table ProcessingFactor. If checked, processing fact are applied. Concentrations in the consumed food may be different from concentrations in the modelled food in monitorin programs (typically raw food) due to processing, such as peelin washing, cooking etc. If unchecked, no processing information used. This is in most (though not all) cases a worst-case assumption |
| Report consumptions and exposures per individual instead of per kg body weight | Boolean | Specifies whether body weights should be ignored and consumptions and exposures should be expressed per individual Otherwise, the consumptions and exposures are per kg body weight. |
| Use occurrence frequencies | Boolean | Account for occurrence frequencies for combinations of food a substance in the exposure calculations. |
| Use unit variability | Boolean | Controls whether to use unit variability. |
| Derived modelled foods for concentration source | *ModelledFoodsCalculationSource* | The derived modelled foods for the specified concentration sou that is used in the conversion algorithm to determine for which modelled food concentrations are available. This source is 1) a single value concentrations data source or 2) a sampled concentrations data source. |

### Output settings

Table 3.330: Output settings for module Single value dietary exposures.

| Name | Type | Description |
|---|---|---|
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |

### Uncertainty settings

Table 3.331: Uncertainty settings for module Single value dietary exposures.

| Name | Type | Description |
|---|---|---|
| Lower uncertainty limit (%) | Numeric | Percentage lower bound, e.g. 2.5%. |
| Upper uncertainty limit (%) | Numeric | Percentage upper bound, e.g. 97.5%. |

### Calculation of single value dietary exposures

Single value dietary exposures are calculated from single value consumptions per modelled food and single value concentrations. Optionally, also processing factors, unit variability models and use frequencies are applied.

- *Single value dietary exposures calculation*

Inputs used: *Single value consumptions Single value concentrations Processing factors Unit variability factors Occurrence frequencies*

Settings used

- *Calculation Settings*

### 3.4.22 Single value non-dietary exposures

Single value non-dietary exposures are based on the single value concentrations or amounts of substances, as opposed to the distribution-based exposures of individuals in the non-dietary exposure module. Exposures are via any of the non-dietary routes: dermal, inhalation, or oral. Depending on the exposure type, single value non-dietary exposures can be short-term/acute or long term/chronic exposures. The exposures can be modelled as external exposures or internal exposures.

This module has as primary entities: *Populations Substances*

#### Single value non-dietary exposures from data

#### Single value non-dietary exposures calculation

Either the short-(acute) or long-term (chronic) non-dietary exposures to substances via inhalation, dermal or oral routes can be estimated.

#### Acute single value non-dietary exposure assessment

The short term (acute) exposure assessment is usually the exposure related to inhalation, dermal or oral contact of substances over a single day.

#### Chronic single value non-dietary exposure assessment

The long term (chronic) exposure assessment is the exposure related to dermal, oral or inhalation route(s) over a longer period of time (months or years).

#### Single value non-dietary exposures data formats

Single value non-dietary exposure estimates are supported from external exposures or internal exposures.

Single value non-dietary exposure data is provided per exposure scenario.

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#### Exposure scenarios

This table provides details about exposure scenarios.

Table 3.332: Table definition for Exposure scenarios.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExposure-Scenario | AlphaNumeric (50) | The identifier of the exposure scenario. | idExposure-Scenario, Exposure-ScenarioId | Yes |
| Name | AlphaNumeric (100) | Name of the exposure scenario. | Name | No |
| Description | AlphaNumeric (200) | Description of exposure scenario. | Description | No |
| idPopulation | AlphaNumeric (50) | Unique identification code of the population. | IdPopulation, PopulationId | No |
| ExposureType | *ExposureType* | The exposure type associated with the exposure scenario (i.e., chronic or acute). | ExposureType | Yes |
| ExposureLevel | *TargetLevelType* | The target level. I.e., internal or external. If omitted, external is assumed. | ExposureLevel, LevelExposure | No |
| ExposureRoutes | AlphaNumeric (100) | The exposure route(s) (only applicable if exposure level is external) for which exosure estimates are collected. | ExposureRoutes, Routes | No |
| ExposureUnit | *ExternalExposure-Unit* | The unit of the non-dietary exposure. | Unit, NonDietary-IntakeUnit, NonDietary-ExposureUnit | Yes |

Accepted table names: ExposureScenarios, ExposureScenarios.

### Exposure determinants

This table is used to describe the custom properties used in the exposure estimates table.

Table 3.333: Table definition for Exposure determinants.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExposure-Determinant | AlphaNumeric (50) | The code of the exposure determinant. | IdExposure-Determinant, Exposure-DeterminantId | Yes |
| Name | AlphaNumeric (100) | The name of the exposure determinant. | Name | No |
| Description | AlphaNumeric (200) | Description of the exposure determinant. | Description | No |
| Type | *IndividualProperty-Type* | This field specifies the type of the values of this exposure determinant. This type follows a controlled terminology, with possible values: Boolean, Categorical (default), Numeric, Nonnegative, Integer, NonnegativeInteger, Month, Datetime, Gender. If not specified, categorical is assumed. | Type | No |

Accepted table names: ExposureDeterminants.

### Exposure determinant combinations

This table is used to fill in the values of the exposure determinants.

Table 3.334: Table definition for Exposure determinant combinations.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExposure-Determinant-Combination | AlphaNumeric (50) | The code of the exposure determinant combination. | IdExposure-Determinant-Combination, Exposure-Determinant-CombinationId, Exposure-Determinant-Combination | Yes |
| Name | AlphaNumeric (100) | The name of the exposure determinant combination. | Name | No |
| Description | AlphaNumeric (200) | Description of the exposure determinant combination. | Description | No |

Accepted table names: ExposureDeterminantCombinations.

### Exposure determinant values

This table describes exposure determinant values, for example determinants like face shields or application techniques like vehicle-mounted application of pesticides.

Table 3.335: Table definition for Exposure determinant values.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExposure-Determinant-Combination | AlphaNumeric (50) | The code of the exposure determinant combination to which the determinant value is attached. The provided exposure estimate code should match with a code of the exposure estimate table. | idExposure-Determinant-Combination, Exposure-Determinant-CombinationId, Exposure-Determinant-Combination, Exposure-Determinant-Combination-Code | Yes |
| PropertyName | AlphaNumeric (50) | The identifier of the exposure determinant. | IdExposure-Determinant, idExposure-Determinant | Yes |
| TextValue | AlphaNumeric (100) | The value of the determinant as text value. | | No |
| DoubleValue | Numeric | The value of the determinant as number. | | No |

Accepted table names: ExposureDeterminantValues, ExposureDeterminantVal.

### Exposure estimates

This table defines non-dietary exposure values (such as means) for exposure scenarios. Exposures can be internal and external. Exposures are assumed to be external doses.

Table 3.336: Table definition for Exposure estimates.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExposure-Scenario | AlphaNumeric (50) | The identifier of an exposure scenario. | idExposure-Scenario, Exposure-ScenarioId | Yes |
| idExposure-Determinant-Combination | AlphaNumeric (50) | The identifier of an exposure determinant combination. | idExposure-Determinant-Combination, Exposure-Determinant-CombinationId, Exposure-Determinant-Combination | No |
| ExposureSource | AlphaNumeric (100) | The origin of substance or a mixture for the purposes of an exposure assessment, in immediate contact with outer surfaces of exposure, to which individuals in the target population may be exposed. Examples are food, drinking water, consumer products, indoor air, outdoor air, dust and soil. | Source | No |
| idSubstance | AlphaNumeric (50) | The substance code. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| ExposureRoute | *ExposureRoute* | The exposure route (only applicable if exposure level is external). If not specified and external level, then Dietary is assumed. | ExposureRoute | No |
| Value | Numeric | The exposure value. | Value, ExposureValue | Yes |
| EstimateType | AlphaNumeric (100) | An indication of the measure by which the exposure value has been obtained, e.g. a 95th percentile (P95) or as a mean (Mean). | Source | No |

Accepted table names: ExposureEstimates, ExposureEstimate.

### Single value non-dietary exposures settings

### Selection settings

Table 3.337: Selection settings for module Single value non-dietary exposures.

| Name | Type | Description |
|---|---|---|
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |

### Calculation settings

Table 3.338: Calculation settings for module Single value non-dietary exposures.

| Name | Type | Description |
|---|---|---|
| Configuration | AlphaNumeric | Select the configuration for computing the non-dietary exposure |

### Single value non-dietary exposures as data

Single-value non-dietary exposures estimates are collected in exposure scenarios.

- *Single value non-dietary exposures data formats*
- *Single value non-dietary exposures from data*

Settings used

- *Calculation Settings*

### Calculation of single value non-dietary exposures

Single value non-dietary exposures are calculated from single value exposure values.

- *Single value non-dietary exposures calculation*

Settings used

- *Calculation Settings*

## 3.4.23 HBM single value exposures

Human (bio)monitoring (HBM) population exposure estimates specified as (single value) percentile points of the exposure distribution.

This module has as primary entities: *Populations Substances*

Output of this module is used by: *Environmental burden of disease*

### HBM single value exposures from data

Human monitoring data characterise human exposure to substances, their metabolites in body fluids or tissues. Human monitoring data privacy requires organizations to balance their legitimate interests with individuals' fundamental right to privacy by adhering to data protection laws like the *GDPR*, which mandates lawful bases for processing, transparent practices, minimizing data collection, and performing Data Protection Impact Assessments, *DPIA*, for high-risk monitoring activities. For summary statistics like percentiles, regulations are less strict and these data can be used instead. Probability distributions are fitted to discrete data allowing estimation of the parameters for that distribution.

For more info: what is GDPR, the EU's new data protection law?.

### HBM single value exposures data formats

HBM single value exposures data are exposure data from HBM surveys/studies, specified with percentile points of the exposure distributions for different combinations of matrix and substance.

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### HBM single value exposure surveys

Contains the definitions of the human (bio)monitoring surveys/studies.

Table 3.339: Table definition for HBM single value exposure surveys.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| id | AlphaNumeric (50) | Unique identification code of the survey. | idSurvey, id | Yes |
| Name | AlphaNumeric (100) | Name of the study/survey. | Name | No |
| Description | AlphaNumeric (200) | Description of the study/survey. | Description | No |
| Country | AlphaNumeric (50) | Unique identification code of the country. | Country | No |

Accepted table names: HbmSingleValueExposureSurveys, HbmSVExposureSurveys, HbmPointEstimateSurveys.

### HBM single value exposure sets

High level description of the HBM single value exposure sets, specifying the id, name, description and the (reference) substance and exposure unit used for reporting the exposures.

Table 3.340: Table definition for HBM single value exposure sets.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| id | AlphaNumeric (50) | Identifier of the HBM single exposure set. | id, idExposureSet | Yes |
| idSurvey | AlphaNumeric (50) | Unique identification code of the survey. | idSurvey, Survey | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Biological matrix | *BiologicalMatrix* | The biological matrix (e.g., blood, urine) for which this exposure response function is defined. | Biological-Matrix, MatrixSource, SourceMatrix | No |
| DoseUnit | *DoseUnit* | The unit of the result of the exposure response function. | DoseUnit, Unit | No |
| ExpressionType | *ExpressionType* | The expression type or adjustment method of the unit. This field specifies how the unit (target) is adjusted, e.g. for blood lipids for fat soluble biomarkers ('mg/g lipids') or the dilution level of the urine ('mg/g creatinine'). | ExpressionType, Adjustment-Method | No |

Accepted table names: HbmSingleValueExposureSets, HbmSVExposureSets, HbmPointEstimateExposureSets.

### HBM single value exposures

HBM single value exposure linked to a HBM single value exposure sets. The percentiles are reported in the unit specified by the HBM single value exposure sets to which they belong.

Table 3.341: Table definition for HBM single value exposures.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExposureSet | AlphaNumeric (50) | The code of the HBM exposure set to which this record belongs. | idExposureSet, idHbmSV-ExposureSet | Yes |
| Percentage | Numeric | The percentage to which the percentile value belongs. | Percentage | Yes |
| Value | Numeric | The percentile value. I.e., the concentration value belonging to the specified percentage. | Value, Concentration | Yes |

Accepted table names: HbmSingleValueExposures, HbmSVExposures, HbmPointEstimates.

### HBM single value exposures settings

### Selection settings

Table 3.342: Selection settings for module HBM single value exposures.

| Name | Type | Description |
|---|---|---|
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |

### Output settings

Table 3.343: Output settings for module HBM single value exposures.

| Name | Type | Description |
|---|---|---|
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |

### Uncertainty settings

Table 3.344: Uncertainty settings for module HBM single value exposures.

| Name | Type | Description |
|---|---|---|
| Lower uncertainty limit (%) | Numeric | Percentage lower bound, e.g. 2.5%. |
| Upper uncertainty limit (%) | Numeric | Percentage upper bound, e.g. 97.5%. |

### HBM single value exposures as data

Human (bio)monitoring (HBM) population exposure estimates specified as (single value) percentile points of the exposure distribution. For each HBM survey/study, exposure estimates for different biological matries (e.g. blood, urine) and substance can be reported via exposure sets.

- *HBM single value exposures data formats*

- *HBM single value exposures from data*

## 3.5 Hazard modules

Hazard data exist at two levels: at a lower level *dose response data* give *responses* measured in *test systems* from doses of *active substances*. Such data can be modelled with *dose response models*.

At a higher level *responses* can be linked to *effects*, optionally via *AOP networks*, using *effect representations*. If benchmark responses (BMRs) have been specified, *dose response models* can calculate Benchmark Doses (BMDs), which are the preferred Points of departure in hazard assessments. In addition, or alternatively, external *points of departure* can be specified for *active substances* and *effects*.

BMDs from *dose response models* and/or other *points of departure* can be converted to *hazard characterisations* at the intended level (external or internal dose, without or with safety factors), using *kinetic models*, *inter-species conversions* and/or *intra-species factors*. Finally, *hazard characterisations* can be translated to *relative potency factors*.

### 3.5.1 Active substances

Active substances are the substances that may lead with non-zero probability (P (AG)>0) to a specific *health effect* (adverse outcome). In the simplest case, all substances in the scope of the action will form one assessment group (AG) of active substances. In more advanced cases, the list of active substances is derived from possibly multiple assessment group memberships, which are scores for substances that determine whether a substance is included (score > 0) or excluded (score = 0) in the set of active substances. Substances with membership 0 are excluded from the list of active substances. Memberships scores between 0 and 1 are treated as probabilities of being in the set of active substances. Assessment group memberships can be either specified directly as data or derived from *QSAR membership models*, *molecular docking models*, or from availability of *points of departure*.

This module has as primary entities: *Effects Substances*

Output of this module is used by: *Food concentrations Single value concentrations Occurrence patterns Occurrence frequencies Substance conversions Non-dietary exposures Dust exposures Soil exposures Air exposures Consumer product exposures Occupational exposures Absorption factors PBK model parametrisations Kinetic conversion factors Relative potency factors Hazard characterisations Inter-species conversions Intra species factors Food concentration models Food conversions High exposure food-substance combinations Dietary exposures Internal exposures HBM analysis*

#### Active substances from data

#### Active substances calculation

Depending on the *model settings*, the set of active substances for a specified effect is computed in several ways:

1. From the list of substances with available *points of departure (POD) data* for the specified effect. If there is a POD, then the substance is considered an active substance with membership 1. If not, the membership is 0, and the substance is excluded from the list of active substances.
2. From one or more in-silico (QSAR and/or molecular docking) models. The results of the in-silico models should be provided as *QSAR membership models data* and/or *molecular docking models data*. Binding energies from molecular docking models are first translated to crisp memberships using a threshold value. The results from multiple in-silico models can be combined in any of four membership calculation methods:
    1. (crisp, any) the substance is considered an active substance if any in-silico model indicates activity;
    2. (crisp, majority) the substance is considered an active substance if the majority of in-silico models indicates activity;
    3. (probabilistic, ratio) the membership probability is the fraction of in-silico models that indicate activity;
    4. (probabilistic, Bayesian) the membership probability is calculated using a Bayesian model according to Kennedy et al. (2020) and a specified prior probability (which is by default 0.5).

    For substances within the scope of the assessment but without in-silico data, the default is to omit them from the assessment group. Set option *Include substances without membership information* to include them in the assessment group.

3. From a combination of 1 and 2, using either the union (OR) method or the intersection (AND method) of results.

### Active substances data formats

Active substances as data have to be specified via assessment group (AG) memberships in an AG membership model. For each effect one or more AG membership models can be available, one of which should be chosen in assessments. The AG memberships can be crisp, i.e. a positive list of active substances (with default memberships 1, although it is also allowed to include the negative memberships with membership 0 explicitly) or probabilistic ( $0 \leq P \leq 1$ ).

Assessment group membership models contain substance membership definitions for a given (health) effect. This data is described using two tables: the assessment group membership models table and the assessment group memberships table. The groups for a specified health effect are defined in the assessment group membership models table. The assessment group memberships table describes the substance memberships (or membership probabilities) in each group.

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### Assessment group membership models

This table contains the definitions of the assessment group membership models. Each model contains a id, name, an optional description, and refers to its related health effect.

Table 3.345: Table definition for Assessment group membership models.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| id | AlphaNumeric (50) | The unique identification code of the assessment group membership model. | id, idModel, Model, idAssessment-GroupModel, Assessment-GroupModel, idGroup-Membership-Model, Group-Membership-Model | Yes |
| Name | AlphaNumeric (100) | The name of the assessment group membership model. | Name | No |
| Description | AlphaNumeric (200) | Description of the assessment group membership model. | Description | No |
| idEffect | AlphaNumeric (50) | The effect code. | idEffect, EffectId, Effect | Yes |
| idIndex-Substance | AlphaNumeric (50) | The id/code of the index substance. | idIndex-Substance, idReference-Substance, IndexSubstance-Id, Reference-SubstanceId | No |
| Accuracy | Numeric | If applicable, the accuracy of the assessment group membership model memberships. | Accuracy | No |
| Sensitivity | Numeric | If applicable, the sensitivity of the assessment group membership model. | Sensitivity | No |
| Specificity | Numeric | If applicable, the specificity of the assessment group membership model. | Specificity | No |
| Reference | AlphaNumeric (200) | External reference(s) to sources containing more information about the assessment group model. | References | No |

Accepted table names: AssessmentGroupMembershipModels, AssessmentGroupMembershipModel.

### Assessment group memberships

Substances belong to an assessment group with certainty (probability 1), or the membership are uncertain. This table allows to specify membership probabilities for assessment group membership models. The probability should be a value between zero and one. For example, set to 1 or 0, or prior probabilities, or probabilities or 0/1 values estimated from QSAR, from Molecular Docking or from expert elicitation. The table can contain prior or posterior memberships. Default membership are specified with an empty idSubstance field.

Table 3.346: Table definition for Assessment group memberships.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idGroup-Membership-Model | AlphaNumeric (50) | The id of the assessment group memberships model or source. | Model, idModel, idAssessment-Group-Membership-Model, Assessment-Group-Membership-Model, idGroup-Membership-Model, Group-Membership-Model, idGroup | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Group-Membership | Numeric | Probability of the substance for belonging to the assessment group for the effect. If omitted, the default is 1, i.e. certain membership. | Group-Membership, Membership, Membership-Probability, Probability, Assessment-Group-Membership | Yes |

Accepted table names: AssessmentGroupMemberships, AssessmentGroupMembership.

### Active substances settings

### Selection settings

Table 3.347: Selection settings for module Active substances.

| Name | Type | Description |
|---|---|---|
| Multiple effects analysis | Boolean | Specifies whether the analysis should consider multiple effects. Otherwise, a single focal effect should be selected. |
| Include related effects of AOP network | Boolean | Include all related key events of the AOP network. |

### Calculation settings

Table 3.348: Calculation settings for module Active substances.

| Name | Type | Description |
|---|---|---|
| Filter by certain assessment group membership | Boolean | Filter substances by certain assessment group membership. |
| Restrict active substances to substances with available PODs | Boolean | Restrict assessment group membership based on presence/abser of points of departure. |
| Restrict active substances to substances with available hazard characterisations | Boolean | Restrict assessment group membership based on presence/abser of hazard characterisations. |
| Exclude the selected substances | AlphaNumeric | Exclude the selected substances using the substance code. |
| Derive memberships from QSAR membership data | Boolean | Specifies whether QSAR membership data is used for computi the assessment group memberships. |
| Derive memberships from molecular docking data | Boolean | Specifies whether molecular docking data is used for computing the assessment group memberhips. |
| Include substances without membership information | Boolean | For non-probabilistic methods: specifies whether substances for which no membership information is available in the specified inputs should be included in the assessment group. |
| Combination method memberships from available PODs and in-silico data | *CombinationMethodMembershipInfoAndPodPresence* | Specifies whether to take the intersection or the union of the set substances with available PoDs and the set of substances with positive/probable (in-silico) membership score. |
| Membership calculation method | *AssessmentGroupMembershipCalculationMethod* | Calculation method for computing assessment group memberships: majority/any (crisp methods), ratio/Bayesian (probabilistic methods) |
| Default/prior membership probability | Numeric | Default substance membership probability for which no membership information is available in the specified inputs. Pri probability for Bayesian method. |
| Use probabilistic assessment group memberships | Boolean | Specifies whether substance memberships should be expressed terms of probabilities (probabilistic). Otherwise, substance memberships are expressed as in or out (crisp). |

### Uncertainty settings

Table 3.349: Uncertainty settings for module Active substances.

| Name | Type | Description |
|---|---|---|
| Resample assessment group memberships | Boolean | Specifies whether assessment group memberships of substances should be resampled using the assessment group membership probabilities. |

### Active substances as data

When provided as data, in the form of assessment group memberships, the active substances are derived from the specified memberships.

- *Active substances data formats*
- *Active substances from data*

Inputs used: *AOP networks Points of departure Hazard characterisations*

Settings used

- *Calculation Settings*

#### Calculation of active substances

Active substances and assessment group memberships may be computed from PoD presence of in-silico data.

- *Active substances calculation*

Inputs used: *Molecular docking models QSAR membership models*

Settings used

- *Calculation Settings*

### 3.5.2 AOP networks

Effects are related to each other using the toxicological concept of adverse outcome pathways (AOPs) and adverse outcome pathway networks (see https://aopwiki.org). Adverse Outcome Pathway (AOP) Networks specify how biological events (effects) can lead to an adverse outcome (AO) in a qualitative way through relations of upstream and downstream key events (KEs), starting from molecular initiating events (MIEs). Using AOPs, the adverse outcome (AO), e.g., liver steatosis, is linked to key events (KEs), e.g., triglyceride accumulation in the liver, and to molecular initiating events (MIEs), e.g., PPAR-alpha receptor antagonism. In general, multiple AOPs may lead to the same AO, and therefore AOP networks can be identified.

This module has as primary entities: *Effects*

Output of this module is used by: *QSAR membership models Molecular docking models Active substances Relative potency factors Hazard characterisations Points of departure Effect representations*

#### AOP networks from data

#### AOP Networks calculation

Find below a simplified AOP network based on a MCRA analysis for focal effect Steatosis-liver and related effects Fatty liver cells (tissue level), Cytoplasm displacement liver, Endoplasmatic reticulum stress liver, Mitochondrial disruption liver, Nucleus distortion liver and Triglyceride accumulation liver (cellular level).

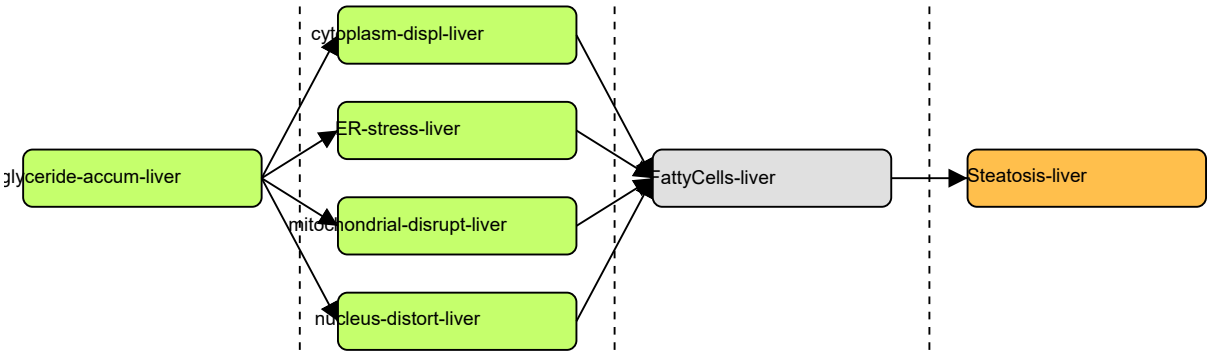


Figure 3.73: AOP network liver steatosis

#### AOP networks data formats

AOP networks are described using two tables: the AOP networks table, and the effect relations table. The AOP networks table records the ids, names, descriptions, and other metadata of the AOP networks. The effect relations table describes the effects and effect relations (i.e., upstream and downstream key event relations) that are part of the AOP network.

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### AOP networks

Data format for specification of adverse outcome pathway (AOP) networks.

Table 3.350: Table definition for AOP networks.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idAdverse-Outcome-Pathway-Network | AlphaNumeric (50) | Unique identification code of the AOP network. | idAOPN, idAOPNetwork, AOPN, AOPNetwork, Id | Yes |
| Name | AlphaNumeric (100) | Name of the AOP network. | Name | No |
| Description | AlphaNumeric (200) | Additional description or label of the AOP network. | Description | No |
| Reference | AlphaNumeric (200) | External reference(s) to sources containing more information about the AOP network. E.g., the AOP wiki, and the associated AOP wiki Ids. | Reference, References | No |
| idAdverse-Outcome | AlphaNumeric (50) | The identification code of the effect representing the adverse outcome of this AOP network. | idAdverse-Outcome, idAO, idEffect, Adverse-Outcome | Yes |
| RiskType | *ExposureType* | The exposure type of the adverse outcome. Acute or chronic. | RiskType | No |

Accepted table names: AOPNetworks, AOPNetwork.

### Effect relations

Dataformat for specification of the effect (key event) relationships of adverse outcome pathway (AOP) networks.

Table 3.351: Table definition for Effect relations.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idAdverse-Outcome-Pathway-Network | AlphaNumeric (50) | Identification code of the AOP network for which this link is defined. | idAdverse-Outcome-Pathway-Network, idAOPN, idAOPNetwork, AOPN, AOPNetwork | Yes |
| idDownstream-KeyEvent | AlphaNumeric (50) | Identification code of the (triggered) effect of this relationship. | idDownstream-KeyEvent, idEffect, idKeyEvent, Effect, KeyEvent | Yes |
| idUpstream-KeyEvent | AlphaNumeric (50) | Identification code of the triggering effect of this relationship. | idTrigger, idUpstreamKey-Event, Trigger | Yes |
| Reference | AlphaNumeric (200) | External reference(s) to sources containing more information about the effect (key event) relationships. | Reference, References | No |

Accepted table names: EffectRelations, EffectRelation, EffectRelationships, EffectRelationship, KeyEventRelationships, KeyEventRelationship.

### AOP networks settings

### Selection settings

Table 3.352: Selection settings for module AOP networks.

| Name | Type | Description |
|---|---|---|
| AOP Network | AlphaNumeric | The AOP networks of interest. |
| Restrict AOP network by focal upstream event | Boolean | Restrict the AOP network to a specific sub-network, containing only the AOPs that include both the focal key event (KE) defined here (which must be upstream of the AO) and the focal effect (adverse outcome, AO). |
| Focal upstream event | AlphaNumeric | The focal key event used for restricting the AOP network to a specific sub-network of interest. |

### AOP networks as data

AOP networks can only be provided as data in the form of network definitions containing effect relations (key-event relationships) collections.

- *AOP networks data formats*
- *AOP networks from data*
- *AOP networks calculation*

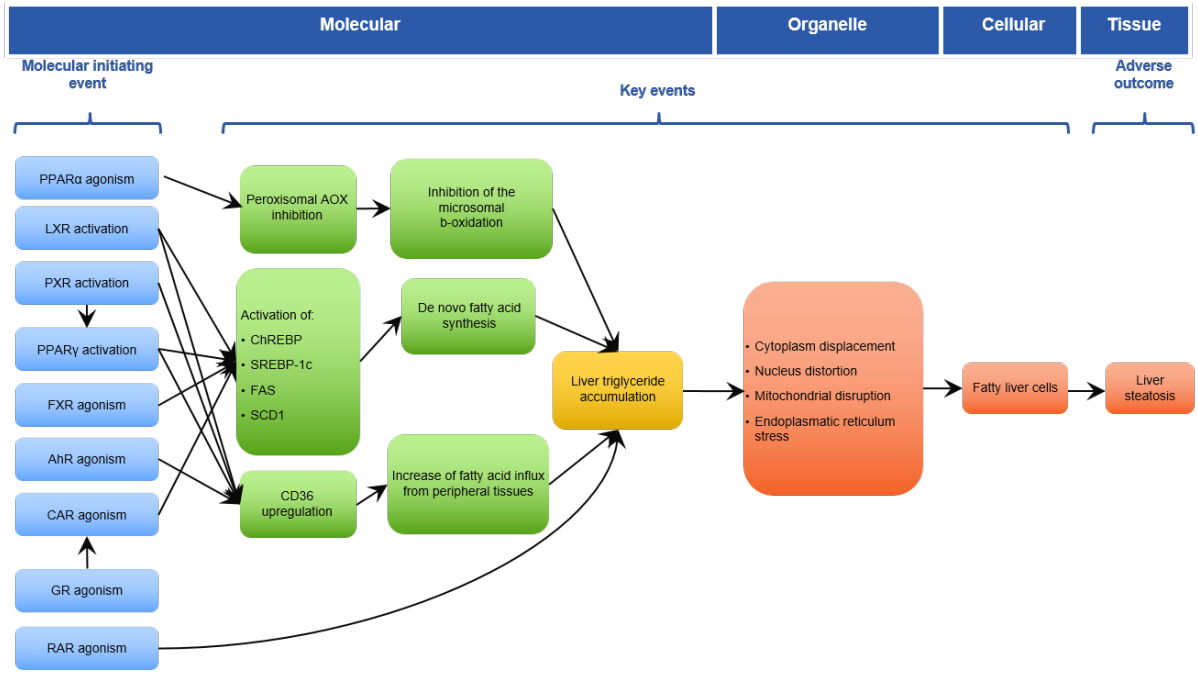


Figure 3.74: AOP network

### 3.5.3 Burden of disease

Burden of disease data specify the burden of disease information related to specific effects and burden of disease indicators in specific populations.

This module has as primary entities: *Populations Effects*

Output of this module is used by: *Environmental burden of disease*

#### Burden of disease from data

#### Burden of disease data formats

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### Burden of disease

Table 3.353: Table definition for Burden of disease.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| Population | AlphaNumeric (50) | The population linked to this burden of disease. | Population | Yes |
| idEffect | AlphaNumeric (50) | Code of the effect linked to this burden of disease. | idEffect, EffectId, Effect, EffectCode | Yes |
| BodIndicator | *BodIndicator* | The burden of disease indicator linked to this burden of disease. | BodIndicator, Indicator, BurdenOf-DiseaseIndicator | Yes |
| Value | Numeric | The value of the burden of disease indicator. | Value | Yes |
| BodIndicator-Uncertainty-Distribution | *BodIndicator-DistributionType* | Distribution type (Uniform, Triangular or LogNormal). If not specified, the burden of disease indicator is assumed to be a constant factor. | BodUncertainty-Distribution, BodDistribution | No |
| BodIndicator-Lower | Numeric | Burden of disease indicator lower uncertainty bound. | BodIndicator-Lower, BodLower | No |
| BodIndicator-Upper | Numeric | Burden of disease indicator upper uncertainty bound. | BodIndicator-Upper, BodUpper | No |

Accepted table names: BurdenOfDisease, BurdensOfDisease.

### Burden of disease indicator conversions

Table 3.354: Table definition for Burden of disease indicator conversions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| FromIndicator | *BodIndicator* | The source burden of disease indicator (from). | FromIndicator, FromBod, From | Yes |
| FromUnit | AlphaNumeric (50) | The unit of the burden of disease indicator (from). | FromUnit, UnitFrom | No |
| ToIndicator | *BodIndicator* | The target burden of disease indicator (to). | ToIndicator, ToBod, To | Yes |
| ToUnit | AlphaNumeric (50) | The unit of the burden of disease indicator (to). | ToUnit, UnitTo | No |
| Value | Numeric | The value/conversion factor for converting from source to target. | Value | Yes |

Accepted table names: BodIndicatorConversions, BodIndicatorConversion.

### Burden of disease settings

### Calculation settings

Table 3.355: Calculation settings for module Burden of disease.

| Name | Type | Description |
|---|---|---|
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |

### Uncertainty settings

Table 3.356: Uncertainty settings for module Burden of disease.

| Name | Type | Description |
|---|---|---|
| Resample burden of disease values | Boolean | Specifies whether the burden of disease values are resampled from a parametric uncertainty distribution. |

### Burden of disease as data

Burden of disease definitions are provided as lists/catalogues of burden of disease information.

- *Burden of disease data formats*
- *Burden of disease from data*

Settings used

- *Calculation Settings*

## 3.5.4 Dose response data

Dose response data are data on response values of test systems at specified doses of substances (or mixtures of substances) from dose response experiments.

This module has as primary entities: *Substances Test systems Responses*

Output of this module is used by: *Dose response models*

### Dose response data from data

### Dose response data data formats

The meta-data of dose response experiments (such as name, description, etc.) are specified in the DoseResponseExperiments table.

For presenting the data of these experiments to the system, there are two formats: a single table format, see table *Dose response data* and a relational data format (three tables: *Dose response experiment doses*, *Experimental unit properties* and *Dose response experiment measurements*). Usually, the single table format will be the easier one. For internal use in MCRA, this single table data is converted to the relational data format.

Dose response data are used to extract assessment group membership or hazard doses . The meta-data of dose response experiments (such as name, description, etc.) are specified in the DoseResponseExperiments table. For presenting the data of these experiments to the system, there are two formats: a tabular format and a relational data format (three tables). Usually, the single table format will be the easier one. For internal use in MCRA, this single table data is converted to the relational data format.

### Tabular dose response data format

In the tabular dose response data format, the substance doses and response measurements are provided in the same data table as columns and automatically parsed based on the specification of the substances and responses of the experiments in the dose response experiments table.

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### Dose response experiments

General information about the dose response experiments, such as the (unique) identifier, name, description, the used test-system, and the dose unit is stored in the table DoseResponseExperiments. If the data of an experiment is provided in a single table format, then the fields Time, Covariates, Substances, and Responses are used to map the column header names of the columns of the single data table to these their respective types.

Table 3.357: Table definition for Dose response experiments.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExperiment | AlphaNumeric (50) | Unique identification code of the dose effect experiment. | idExperiment, Id, Code | Yes |
| Name | AlphaNumeric (100) | Name of the dose effect experiment. | Name | No |
| Description | AlphaNumeric (200) | Description of the dose effect experiment. | Description | No |
| Date | DateTime | The starting date of the experiment. | Date | No |
| Reference | AlphaNumeric (200) | External reference, for instance, to the experiment protocol and/or supporting material. | Reference | No |
| Experimental-Unit | AlphaNumeric (100) | The name of the experimental unit of the experiment, e.g., rat, cage, litter, vial, cup, petridish. | Experimental-Unit | No |
| DoseRoute | AlphaNumeric (50) | For in-vivo test systems, the route in which the dose was administered | DoseRoute | No |
| Substances | AlphaNumeric | Code or comma separated list of the codes of the substances measured in the experiment. E.g., 'Cyproconazole, Thiram'. Required when presenting the dose-response data in a single table. Make sure that in table DoseResponseData the column headers exactly match these names. | idSubstance, SubstanceId, SubstanceCode, Substance, idSubstances, SubstanceIds, SubstanceCodes, Substances | Yes |
| DoseUnit | *DoseUnit* | Unit of the doses administered in this experiment. | DoseUnit | Yes |
| Responses | AlphaNumeric | Code or comma separated list of codes of the responses measured in the experiment. E.g., 'AngleM_PQ, Mortality'. Required when presenting the dose-response data in a single table. Make sure that in table DoseResponseData the column headers exactly match these names. | Responses, Response, idResponses, idResponse | Yes |
| Time | AlphaNumeric (100) | Identifier of the time field of the experiment. Required when presenting the dose-response data in a single table and responses are measured at multiple times. Make sure that in the table DoseResponseData the column header of the time-column exactly matches this name. | Time, Times | No |
| TimeUnit | *TimeUnit* | Unit of the time scale used in the experiments. | TimeUnit | No |
| Covariates | AlphaNumeric (200) | Comma separated list of the names/codes of the covariates of the experiment. E.g. 'Gender, Inhibitor | Covariates, Covariate | No |

Accepted table names: DoseResponseExperiments, DoseResponseExperiment.

### Dose response data

Single (two-way) table data format for specifying data of dose response experiments (as alternative for the relational format). The column headers are dynamic and should be defined in the table DoseResponseExperiments through fields Substances and Responses (and, optionally, Covariates and Time). For responses given as aggregated statistics, also SD, CV, N and Uncertainty are specified as [Datatype:Response]. E.g., 'SD:Y', 'CV:Y', 'N:Y'. Uncertainty upper 95%limits are specified as 'UncertaintyUpper:Y'. For each quantal response an additional column 'N:[responsename]'is required with binomial totals (e.g. Mortality = 3, N:Mortality = 10).

Table 3.358: Table definition for Dose response data.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExperiment | AlphaNumeric (50) | Unique identification code of the dose effect experiment. | idExperiment, Experiment, Code | No |
| Experimental unit | AlphaNumeric (50) | Experimental unit numbers or identifiers. The column name of the experimental unit should be as specified in the dose response experiment record. | Experimental-Unit, Experimental-Units, Experimental unit | No |
| Substance(s) | AlphaNumeric (100) | One or more columns with doses for each substance, in the unit as specified in the dose response experiment table. The column name(s) should match the substance codes listed in the comma-separated list of the substances field of the dose response experiment record. | | Yes |
| Response(s) | AlphaNumeric (100) | One or more columns with results for each response, in the unit(s) as specified in the dose response experiment table. The column name(s) should match the response codes listed in the comma-separated list of the responses field of the dose response experiment record. | | Yes |
| Time | Numeric | The column containing the observed response times. The column name (header) should match that of the Time column in the dose response experiment record. | | No |
| Covariate(s) | AlphaNumeric (100) | The column(s) containing additional properties of the experimental unit. The column name (header) should match the codes of the comma-separated covariates list in the dose response experiment record. | | No |

Accepted table names: TwoWayDoseResponseData, DoseResponseDataTwoWay, DoseResponseData.

### Relational dose response data format

The relational dose response data format is the internal format of MCRA. In this format, the dose response experiments, doses, responses, and experimental units are provided in separate data tables.

Download empty dataset template: Zipped CSV Excel

### Dose response experiments

General information about the dose response experiments, such as the (unique) identifier, name, description, the used test-system, and the dose unit is stored in the table DoseResponseExperiments. If the data of an experiment is provided in a single table format, then the fields Time, Covariates, Substances, and Responses are used to map the column header names of the columns of the single data table to these their respective types.

Table 3.359: Table definition for Dose response experiments.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExperiment | AlphaNumeric (50) | Unique identification code of the dose effect experiment. | idExperiment, Id, Code | Yes |
| Name | AlphaNumeric (100) | Name of the dose effect experiment. | Name | No |
| Description | AlphaNumeric (200) | Description of the dose effect experiment. | Description | No |
| Date | DateTime | The starting date of the experiment. | Date | No |
| Reference | AlphaNumeric (200) | External reference, for instance, to the experiment protocol and/or supporting material. | Reference | No |
| Experimental-Unit | AlphaNumeric (100) | The name of the experimental unit of the experiment, e.g., rat, cage, litter, vial, cup, petridish. | Experimental-Unit | No |
| DoseRoute | AlphaNumeric (50) | For in-vivo test systems, the route in which the dose was administered | DoseRoute | No |
| Substances | AlphaNumeric | Code or comma separated list of the codes of the substances measured in the experiment. E.g., 'Cyproconazole, Thiram'. Required when presenting the dose-response data in a single table. Make sure that in table DoseResponseData the column headers exactly match these names. | idSubstance, SubstanceId, SubstanceCode, Substance, idSubstances, SubstanceIds, SubstanceCodes, Substances | Yes |
| DoseUnit | *DoseUnit* | Unit of the doses administered in this experiment. | DoseUnit | Yes |
| Responses | AlphaNumeric | Code or comma separated list of codes of the responses measured in the experiment. E.g., 'AngleM_PQ, Mortality'. Required when presenting the dose-response data in a single table. Make sure that in table DoseResponseData the column headers exactly match these names. | Responses, Response, idResponses, idResponse | Yes |
| Time | AlphaNumeric (100) | Identifier of the time field of the experiment. Required when presenting the dose-response data in a single table and responses are measured at multiple times. Make sure that in the table DoseResponseData the column header of the time-column exactly matches this name. | Time, Times | No |
| TimeUnit | *TimeUnit* | Unit of the time scale used in the experiments. | TimeUnit | No |
| Covariates | AlphaNumeric (200) | Comma separated list of the names/codes of the covariates of the experiment. E.g. 'Gender, Inhibitor | Covariates, Covariate | No |

Accepted table names: DoseResponseExperiments, DoseResponseExperiment.

### Dose response experiment doses

The table DoseResponseExperimentDoses describes the experiment design, being a complete specification of which doses of which substances were applied to which experimental unit and if relevant at what time.

Table 3.360: Table definition for Dose response experiment doses.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExperiment | AlphaNumeric (50) | Identification code of the experiment to which this design record belongs. | idExperiment, Experiment | Yes |
| idExperimental-Unit | AlphaNumeric (50) | Identification code of the experimental unit to which the dose is applied. | idExperimental-Unit, Experimental-Unit | Yes |
| Time | Numeric | The time of administration of the dose. | Time | No |
| idSubstance | AlphaNumeric (50) | Code of the substance that was administered. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Dose | Numeric | The dose that was administered. | Dose | Yes |

Accepted table names: DoseResponseExperimentDoses, DoseResponseExperimentDose.

### Experimental unit properties

The table ExperimentalUnitProperties are used to specify additional properties of the experimental units of the experiment. For instance, the gender of the rat, in case rats are the experimental units.

Table 3.361: Table definition for Experimental unit properties.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExperiment | AlphaNumeric (50) | Identification code of the experiment. | idExperiment, Experiment | Yes |
| idExperimental-Unit | AlphaNumeric (50) | Identification code of the experimental unit. | idExperimental-Unit, Experimental-Unit | Yes |
| PropertyName | AlphaNumeric (50) | Name of the experimental unit property. | Property, Name | Yes |
| Value | AlphaNumeric (100) | Value of the experimental unit property. | PropertyValue | No |
| OtherProperty | | Other properties of experimental units are automatically parsed, using the column name (header) as property name. | | No |

Accepted table names: ExperimentalUnitProperties, ExperimentalUnitProperty.

### Dose response experiment measurements

The table DoseResponseMeasurements describes the measurements that were done in the experiments. That is, for each response and experimental unit, at each observation time, one measurement should be recorded. If the response is an aggregated statistic, then this record may also include a standard deviation and number of units over which was aggregated.

Table 3.362: Table definition for Dose response experiment measurements.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idExperiment | AlphaNumeric (50) | Identification code of the experiment to which this measurement belongs. | idExperiment, Experiment | Yes |
| idExperimental-Unit | AlphaNumeric (50) | Identification code of the experimental unit from which the measurement is taken. | idExperimental-Unit, Experimental-Unit | Yes |
| idResponse | AlphaNumeric (50) | Identifier of the response that is measured. | idResponse, Response | Yes |
| Time | Numeric | Time of observation. | Time | No |
| ResponseValue | Numeric | The measured response. | ResponseValue, Value | Yes |
| SD:Response | Numeric | For aggregated responses, the standard deviation of the measurement. | SD:Response, ResponseSD | No |
| CV:Response | Numeric | For aggregated responses, the coefficient of variation (cv) of the measurement. | CV:Response, ResponseCV | No |
| N:Response | Numeric | For aggregated responses, the number of units over which was aggregated. | N:Response, ResponseN | No |
| Uncertainty-Upper:Response | Numeric | Optionally, measurement uncertainty quantification in terms of the upper value (i.e., an estimate of 95th percentile). | Uncertainty-Upper:Response, Response-Uncertainty-Upper, Uncertainty-Upper, Upper | No |

Accepted table names: DoseResponseExperimentMeasurements, DoseResponseExperimentMeasurement, DoseResponseMeasurements, DoseResponseMeasurement.

### Dose response data settings

### Selection settings

Table 3.363: Selection settings for module Dose response data.

| Name | Type | Description |
|---|---|---|
| Merge dose response data of multiple experiments | Boolean | Specifies whether the dose response data of multiple experimen should be merged into one large dose response data set. |

#### Dose response data as data

Dose response data are provided per experiment or study in which several responses (on in-vitro or in-vivo test systems) are measured from several administered substance doses.

- *Dose response data data formats*
- *Dose response data from data*

### 3.5.5 Dose response models

Dose response models are models fitted to dose response data and can be provided as data or calculated using a local or remote version of PROAST. The main results for hazard and risk assessment are benchmark doses (BMDs), related to a specified substance, response, optionally covariate value, and the benchmark response (BMR). Dose response models can be uploaded as data, retrieved from PROASTweb through *linked remote repositories*, or *calculated using an internal version of PROAST*.

This module has as primary entities: *Test systems Responses Substances*

Output of this module is used by: *Hazard characterisations*

#### Dose response models from data

#### Dose response models calculation

Dose response models are uploaded as data or retrieved from the PROASTweb through *linked remote repositories*. A second possibility is to compute dose response models using an integrated version of PROAST: for each response in a dose response experiment a dose response model is fitted. Depending on the type of data (e.g., response type, covariates y/n, single or multiple substances) a PROAST run is configured and executed. If *effect representations* are provided, then benchmark responses specified by the effect representations data are used, otherwise only the model fits will be computed without benchmark doses.

PROAST (copyright RIVM National Institute for Public Health and the Environment) is a software package for the statistical analysis of dose-response data. Its main purpose is dose-response modelling of toxicological data, and the derivation of a Benchmark dose (*BMD* or *BMDL*) in human risk assessment (or an ECx in ecotoxicological risk assessment). More generally, it can be used for (nonlinear) regression (with covariates) (see Slob (2002), Slob and Setzer (2013))

When PROAST is run without uncertainty, the *BMD* is estimated and the *BMDL* and *BMDU* are based on the profile likelihood method where the Fisher information matrix indicates the estimate's precision. When uncertainty is specified,the setting *Calculate a parametric benchmark dose confidence interval* becomes relevant.

1. checked: a benchmark dose interval (90% confidence) based on the profile likelihood method is estimated,
2. unchecked: the BMDL (p5) and BMDU (p95) are based on the 90% confidence interval of the bootstrapped BMD values.

In module *hazard characterisations* specify with setting *Use lower limit of BMD* whether a BMD or BMDL is used in the risk assessment.

#### Proast models

In Proast, a family of (nested) dose-response models are available that can be used for describing the change in any continuous endpoint as a function of dose. The likelihood ratio test is used to select one of the available models (model selection to prevent overparameterization).

- Model 1: $y = a$ with $a > 0$
- Model 2: $y = a \cdot exp(x/b)$ with $a > 0$
- Model 3: $y = a \cdot exp(\pm(x/b)^d)$ with $a > 0, b > 0, d \geq 1$
- Model 4: $y = a[c - (c-1)exp(-x/b)]$ with $a > 0, b > 0, c > 0$
- Model 5: $y - (c-1)exp(-(x/b)^d)]$ with $a > 0, b > 0, c > 0, d \geq 1$

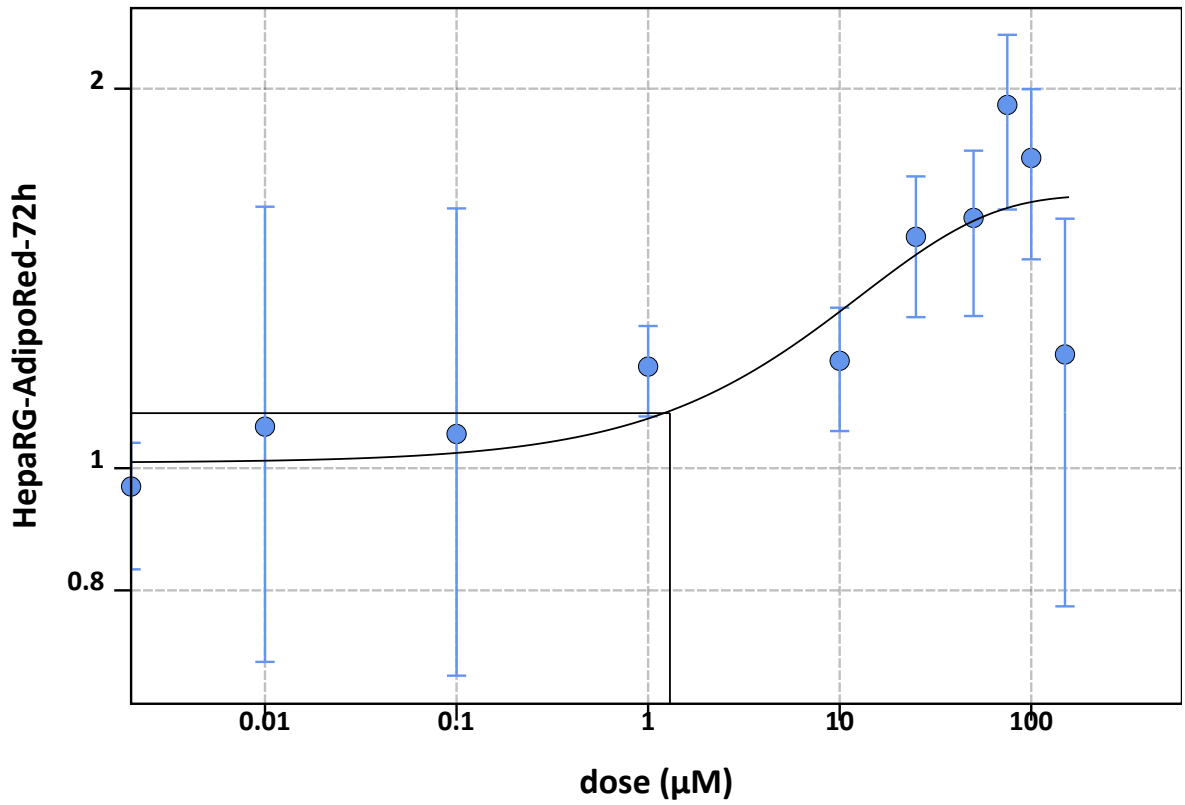


Figure 3.75: Dose response model: HepaRG Adipo72 72h.

where $y$ is any continuous endpoint and $x$ denotes the dose. In all models parameter $a$ represents the level of the endpoint at dose 0, and $b$ is considered as the parameter reflecting the efficacy of the substance or the sensitivity of the subject. At high doses model 4 and 5 level of to the value $a \cdot c$, so the parameter $c$ can be interpreted as the maximum relative change. Model 3 and 5 have the flexibility to mimic threshold-like responses. All these model are nested to each other, except models 3 and 4, which both have three parameters.

In all models the parameter $a$ is constrained to being positive for obvious reasons (it denotes the value of the endpoint at dose 0). The parameter $d$ is constrained to values larger than (or equal to) 1, to prevent the slope of the function at dose 0 being infinite, which seems biologically implausible. The parameter $b$ is constrained to be positive in all models. Parameter $c$ in models 4 and 5 determines whether the function increases or decreases, by being larger or smaller than unity, respectively. To make model 3 a decreasing function a minus sign has to be inserted in the exponent (Slob (2002), Slob and Setzer (2013)).

### Dose response models data formats

Dose response models are specified using three tables: the dose response models table holds the dose response model definitions (id, name, description) and other information about the dose response models. The dose response model benchmark doses table records the benchmark doses and (optionally) the model parameters for specific substances and covariates. The dose response model benchmark doses uncertainty table records results from bootstrap runs for the benchmark doses per substance/covariate combination.

Download empty dataset template: Zipped CSV Excel

### Dose response models

Each dose response model has a unique id, a name (optional), and description (optional). Also, each dose response model is associated with a specific dose response experiment (idExperiment) from which the data used to create the model is obtained, a response (idResponse), one or more substances, and, optionally, specific covariates considered by the dose response model. The combination of the benchmark response type and the associated value define the benchmark response of the model. The dose unit specifies the unit used for the doses, and if applicable, the model equation can be specified.

Table 3.364: Table definition for Dose response models.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idDose-ResponseModel | AlphaNumeric (50) | The unique identification code of the fitted dose response model. | idDose-ResponseModel, idModel | Yes |
| idExperiment | AlphaNumeric (50) | The identification code of the experiment from the dose response model. | experiment-Code, experimentId | Yes |
| Name | AlphaNumeric (100) | The name of the dose response model. | Name | No |
| Description | AlphaNumeric (200) | Description of the dose response model. | Description | No |
| Substances | AlphaNumeric | Code or comma separated list of the codes of the substances in the Dose Response Model. E.g., 'Cyproconazole, Thiram'. | Substances | Yes |
| idResponse | AlphaNumeric (50) | The response of the dose response model. | idResponse, Response | Yes |
| Covariates | AlphaNumeric | The covariates considered by the dose response model. | Covariates, Covariate | No |
| Benchmark-Response | Numeric | The value of the benchmark response or critical effect size. | Benchmark-Response, CriticalEffect-Size, CES | Yes |
| Benchmark-ResponseType | *Benchmark-ResponseType* | Specifies how the benchmark response is expressed. E.g., using a percent change in mean response or, for quantal response types, in terms of extra risk, additional risk, or ED50. | Benchmark-ResponseType, HazardEffect-SizeType, CriticalEffect-SizeType | No |
| LogLikelihood | Numeric | Loglikelihood of the model fit. | LogLikelihood | No |
| DoseUnit | AlphaNumeric (50) | The dose unit (if not specified, then mg/kg is assumed). | DoseUnit, UnitDose | No |
| ModelEquation | AlphaNumeric (500) | If available, the model equation of the dose response model (R model equation) or the identifier of the dose response model type. | ModelEquation, DoseResponse-ModelEquation, Equation | No |

Accepted table names: DoseResponseModels, DoseResponseModel.

### Dose response model benchmark doses

The benchmark responses and benchmark doses belonging to the dose response models are recorded per substance/covariate in the dose response model benchmark doses table. Optionally, if the model equation of the dose response model has been specified in the dose response models table, the model parameter values for this specific substance/covariate can be specified here.

Table 3.365: Table definition for Dose response model benchmark doses.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idDose-ResponseModel | AlphaNumeric (50) | The identification code of the dose response model to which this record belongs. | idDose-ResponseModel | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Covariates | AlphaNumeric (500) | Comma separated list of the covariate values for which this benchmark dose applies. | Covariates, Covariate | No |
| Benchmark-Dose | Numeric | The (nominal) benchmark dose (BMD). | Benchmark-Dose, BMD, CED | Yes |
| Benchmark-DoseLower | Numeric | Benchmark dose lower uncertainty bound (BMDL). | Benchmark-DoseLower, BMDL, CEDL | No |
| Benchmark-DoseUpper | Numeric | Benchmark dose upper uncertainty bound (BMDU). | Benchmark-DoseUpper, BMDU, CEDU | No |
| Model-Parameter-Values | AlphaNumeric (500) | Parameter values for dose response models. | ParameterValues | No |

Accepted table names: DoseResponseModelBenchmarkDoses.

### Dose response model benchmark dose bootstraps

Empirical uncertainty values of the benchmark benchmark doses of dose response models can be recorded in the dose response model benchmark doses bootstraps table. The uncertainty set identifier (idUncertaintySet) can be specified to retain correlations between uncertainty records that originate from the same bootstrap run.

Table 3.366: Table definition for Dose response model benchmark dose bootstraps.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idDose-ResponseModel | AlphaNumeric (50) | The identification code of the dose response model to which this record belongs. | idDose-ResponseModel | Yes |
| idUncertainty-Set | AlphaNumeric (50) | The uncertainty set identifier. | idUncertainty-Set, UncertaintyId | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Covariates | AlphaNumeric (500) | Comma separated list of the covariate values for which this benchmark dose applies. | Covariates | No |
| Benchmark-Dose | Numeric | Benchmark dose (BMD). | Benchmark-Dose, BMD, CED | Yes |

Accepted table names: DoseResponseModelBenchmarkDosesBootstraps, DoseResponseModelBenchmarkDosesUncertain, DoseResponseModelBmdsUncertain.

### Dose response models settings

### Calculation settings

Table 3.367: Calculation settings for module Dose response models.

| Name | Type | Description |
|---|---|---|
| Index substance | AlphaNumeric | The substance of interest or index substance. |
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Calculate a parametric benchmark dose confidence interval | Boolean | A parametric benchmark dose confidence interval (90%) is calculated by the profile likelihood method. If unchecked, the confidence interval is based on a bootstrap sample with uncertainty bounds p5 and p95. |

### Uncertainty settings

Table 3.368: Uncertainty settings for module Dose response models.

| Name | Type | Description |
|---|---|---|
| Perform uncertainty analysis | Boolean | In probabilistic risk assessment of dietary exposure, distributio describe the variability in consumption within a given populatio of individuals and the variability of the occurrence and level of substances in the consumed foods. However, these calculations not consider the amount of uncertainty that is due to the limite size of the underlying datasets. |
| Resample hazard characterisations or RPFs | Boolean | Specifies whether to resample the hazard characterisations or relative potency factors. Requires hazard characterisation or RP uncertainty to be quantified in DoseResponseModelsUncertain RelativePotencyFactorsUncertain tables. |
| Iterations uncertainty analysis | Numeric | Specifies the number of uncertainty cycles (default 100). |

#### Dose response models as data

Dose response models as data contain the details of fitted dose response models. The main elements for hazard and risk assessment are the benchmark doses (BMDs, BMDLs) related to specified substances, responses, and optionally covariate values for specified benchmark responses (BMR). These specifications can be provided in data files or can be retrieved/imported from PROAST output files on the PROAST website https://proastweb.rivm.nl/user/login using a PROASTweb user account and an application access key.

- *Dose response models data formats*
- *Dose response models from data*

Inputs used: *Dose response data*

Settings used

- *Calculation Settings*

#### Calculation of dose response models

Used as a calculator, dose response models are fitted to dose response data using an MCRA-internal version of PROAST. Currently, all available models appropriate for the response type will be fitted, and for the Hill and Exponential model families, the best fitting model based on maximum likelihood will be selected. The set of results for the calculation will include BMD(L)s etc. for all fitted models.

- *Dose response models calculation*

Inputs used: *Effect representations*

Settings used

- *Calculation Settings*

### 3.5.6 Effect representations

Effect representations specify the responses that can be used to measure specified effects and which response levels, the benchmark response (BMR), define the hazard limits for the effects.

This module has as primary entities: *Effects Responses*

Output of this module is used by: *Hazard characterisations Dose response models*

#### Effect representations from data

#### Effect representations data formats

Effect representations specify responses that may represent the effect.

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#### Effect representations

One response can be set as the canonical response (golden standard). For a quantitative or stochastically qualitative canonical response a benchmark response should be defined.

Table 3.369: Table definition for Effect representations.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idEffect | AlphaNumeric (50) | Identifier of the effect | idEffect | Yes |
| idResponse | AlphaNumeric (50) | Identifier of the response | idResponse | Yes |
| Benchmark-Response | Numeric | The threshold response value that defines a hazard. For numeric responses (Continuous, Quantal, Count) the value that defines a hazard. For Binary responses 1 defines a hazard by default, unless redefined here. | BenchMark-Response, HazardEffect-Size, BMR, CriticalEffect-Size, CES | No |
| Benchmark-ResponseType | *Benchmark-ResponseType* | Specifies how the BenchMarkResponse is expressed, relative to the response at zero dose, or absolute. Required for numeric response types (Continuous, Quantal, Count). For qualitative responses (Ordinal, Categorical) Absolute is used. | Benchmark-ResponseType, HazardEffect-SizeType, CriticalEffect-SizeType | No |

Accepted table names: EffectRepresentations, EffectRepresentation.

#### Effect representations settings

#### Calculation settings

Table 3.370: Calculation settings for module Effect representations.

| Name | Type | Description |
|---|---|---|
| Multiple effects analysis | Boolean | Specifies whether the analysis should consider multiple effects. Otherwise, a single focal effect should be selected. |
| Include related effects of AOP network | Boolean | Include all related key events of the AOP network. |

#### Effect representations as data

Effect representations are provided as data in the form of specified combinations of effect and response, optionally with a benchmark response that defines a hazard limit for the effect.

- *Effect representations data formats*
- *Effect representations from data*

Inputs used: *AOP networks*

Settings used

- *Calculation Settings*

### 3.5.7 Exposure response functions

Exposure response functions define the relation between percentiles and percentile specific ratios for exposure effect related to environmental burden of disease.

This module has as primary entities: *Substances Effects*

Output of this module is used by: *Environmental burden of disease*

### Exposure response functions from data

### Exposure response functions data formats

Download empty dataset template: Zipped CSV Excel

### Exposure response functions

Table 3.371: Table definition for Exposure response functions.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idModel | AlphaNumeric (50) | The unique identifier of the exposure response model. | idModel, Model, ModelId | Yes |
| Name | AlphaNumeric (100) | Name of the exposure response model. | Name | No |
| Description | AlphaNumeric (200) | Additional description or label of the exposure response model. | Description | No |
| idSubstance | AlphaNumeric (50) | The substance code. | idSubstance, Substance, SubstanceId | Yes |
| idEffect | AlphaNumeric (50) | Code of the effect linked to this exposure response function. | idEffect, EffectId, Effect, EffectCode | Yes |
| TargetLevel | *TargetLevelType* | The target level. I.e., internal or external. If omitted, external is assumed. | TargetLevel, LevelTarget | No |
| ExposureRoute | *ExposureRoute* | The exposure route(s) (only applicable if exposure level is external) for which this exposure response function is defined. | ExposureRoute, Route | No |
| Biological matrix | *BiologicalMatrix* | The biological matrix (e.g., blood, urine) for which this exposure response function is defined. | Biological-Matrix, MatrixSource, SourceMatrix | No |
| DoseUnit | *DoseUnit* | The unit of the result of the exposure response function. | DoseUnit, Unit | Yes |
| ExpressionType | *ExpressionType* | The expression type or adjustment method of the unit. This field specifies how the unit (target) is adjusted, e.g. for blood lipids for fat soluble biomarkers ('mg/g lipids') or the dilution level of the urine ('mg/g creatinine'). | ExpressionType, Adjustment-Method | No |
| Population-Characteristic | *Population-CharacteristicType* | Population characteristic type. | Characteristic, idCharacteristic, Population-Characteristic, IdPopulation-Characteristic | No |
| Effect-ThresholdLower | Numeric (50) | Lower threshold for the effect for the specified population characteristic. | EffectThreshold-Lower | No |
| Effect-ThresholdUpper | Numeric (50) | Upper threshold for the effect for the specified population characteristic. | EffectThreshold-Upper | No |
| Effect metric | *EffectMetric* | The type of risk for which this exposure response function is defined. | EffectMetric, ResponseMetric, Metric | Yes |
| Exposure-ResponseType | *ExposureResponse-Type* | The type of specification used to define the relation between the exposure and the exposure response. | Exposure-ResponseType, ErType, ErfType | Yes |
| Exposure-Response-Specification | AlphaNumeric (200) | The specification for the exposure response. Either a mathematical expression when the exposure response type is function, or a single | Exposure-Response-Specification, ErfSpecification, ErSpecification | Yes |

Accepted table names: ExposureResponseFunctions, ResponseFunctions, ExposureEffectFunctions.

### Exposure response function subgroups

Exposure response functions defined per exposure category.

Table 3.372: Table definition for Exposure response function subgroups.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idModel | AlphaNumeric (50) | The unique identifier of the exposure response model. | idModel | Yes |
| idSubgroup | AlphaNumeric (50) | The unique identifier of the subgroup. | idSubgroup | Yes |
| ExposureUpper | Numeric (50) | Specifies the upper bound of the exposure percentile of the exposure response function subgroup. Exposure belong to a subgroup when the exposure is equal or lower than the specified upper bound and larger than the specified upper bound of the previous subgroup. | ExposureUpper, UpperExposure | No |
| Exposure-Response-Specification | AlphaNumeric (200) | The specification for the exposure response. Either a mathematical expression when the exposure response type is function, or a single value if the exposure response type is constant, perDoubling, or perUnit. | ErfSpecification, Exposure-Response-Specification, Exposure-Response-Function-Specification | Yes |
| Exposure-Response-Specification-Lower | AlphaNumeric (200) | Exposure response lower uncertainty bound. Either a mathematical expression when the exposure response type is function, or a single value if the exposure response type is constant, perDoubling, or perUnit. | Exposure-Response-Specification-Lower, ErfLower | No |
| Exposure-Response-Specification-Upper | AlphaNumeric (200) | Exposure response upper uncertainty bound. Either a mathematical expression when the exposure response type is function, or a single value if the exposure response type is constant, perDoubling, or perUnit. | Exposure-Response-Specification-Upper, ErfUpper | No |

Accepted table names: ErfSubgroups, ErfSubgroup.

### Exposure response functions settings

### Calculation settings

Table 3.373: Calculation settings for module Exposure response functions.

| Name | Type | Description |
|---|---|---|
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |
| Exposure grouping method | *ExposureGroupingMethod* | Specify the method by which the exposures are grouped in bins For 'Custom bins', the specified bins are used for all exposure response functions. For 'ERF-defined bins', the bins defined for subgroups are used and for exposure response functions withou subgroups, the specified custom bins are used. |

### Uncertainty settings

Table 3.374: Uncertainty settings for module Exposure response functions.

| Name | Type | Description |
|---|---|---|
| Resample exposure response function values | Boolean | Specifies whether exposure response function values are resampled. |
| Resample counter factual values | Boolean | Specifies whether the counter factual values are resampled from parametric uncertainty distribution. |

### Exposure response functions as data

Exposure response function definitions are provided as lists/catalogues of exposure response function definitions.

- *Exposure response functions data formats*
- *Exposure response functions from data*

Settings used

- *Calculation Settings*

## 3.5.8 Hazard characterisations

Hazard characterisations are reference exposure values for active substances at the chosen biological target level (external or internal). Hazard characterisations may be specified for specific effects or for the critical effect as defined in hazard characterisation. Hazard characterisations are specified as external values (e.g. human based guidance values, such as ADI or ARfD) or are based on points of departure, such as BMD(L)s from dose-response models or externally specified points of departure (NOAEL, LOAEL, MDS). The computation may involve assessment factors, e.g. for inter-species conversion, intra-species variation or additional sources of uncertainty. The calculation may also use kinetic conversion factors, PBK models or absorption factors to convert external doses to internal concentration/doses or vice versa.

This module has as primary entities: *Substances Effects Populations*

Output of this module is used by: *Active substances Relative potency factors Risks Single value risks*

### Hazard characterisations from data

In table *Hazard characterisations subgroups*, hazard characterisations are specified that are dependent on individual properties like age and/or *gender*.

For age, specify the lower bound of the age interval (in years) of the hazard characterisation subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower age of the next subgroup.

Check option *Use hazard characterisations subgroup* (default) to use age and/or gender specific hazard characterisations (only visible when the datasource contains age/gender specific hazard characterisations information).

### Hazard characterisations calculation

Hazard characterisations are defined as deterministic threshold values, e.g., *ADI*, *ARfD*, or as distributions (using probabilistic models). They are linked to an effect of interest or alternatively are defined for the critical effect. Hazard characterisations depend on the *exposure type* (acute or chronic) and the *target level* of the human body (external via some route of exposure or internal for a specific defined organ or biological matrix). Hazard characterisations are derived from *points of departure* provided as data and/or from *dose-response models*. The procedure for computing hazard characterisations has two main phases: 1) collection of all available hazard characterisation candidates and alignment with the target system, and 2) aggregation over multiple available hazard characterisations and imputation of missing hazard characterisations.

Collection of available hazard characterisation candidates involves collecting the appropriate points of departure data and/or dose-response models that are used for deriving the hazard characterisations. In MCRA, a distinction is made between three *methods for computing hazard characterisations*:

1. Calculation of hazard characterisations from *in-vivo* points of departure (*PoD*, e.g. *BMD*, *BMDL*, *NOAEL*, *LOAEL*).
2. Calculation of hazard characterisations from PoDs (in this case BMD) calculated from dose response data.
3. Calculation of hazard characterisations based on an *in-vivo PoD for the index substance and in-vitro RPFs from dose-response models for the other substances (IVIVE model)* (cumulative assessments only) .

For all three methods, the collected points of departure and benchmark doses should be aligned with the target system. This alignment may involve various conversion steps for each point of departure and specific substance, and can be formally specified as:

$$HC = f_{\texttt{expression-type}} \cdot f_{\texttt{kinetic}} \cdot \frac{1}{f_{\texttt{inter-species}}} \cdot \frac{1}{f_{\texttt{intra-species}}} \cdot \frac{1}{f_{\texttt{additional}}} \cdot PoD$$

where:

- *HC* denotes the hazard characterisation.
- $f_{\texttt{expression-type}}$ denotes the *expression type correction factor*, e.g., for extrapolation from LOAEL or NOAEL, or from NOAEL to BMD.
- $f_{\texttt{kinetic}}$ denotes the kinetic conversion factor for *conversion from internal to external or external to internal hazard characterisations*.
- $f_{\texttt{inter-species}}$ denotes the inter-species factor for *extrapolation from animal to human (inter-species)*.
- $f_{\texttt{intra-species}}$ denotes the intra-species factor for *extrapolation from the average to the sensitive human or probabilistic calculation of the distribution of human individuals (intra-species)*.
- $f_{\texttt{additional}}$ denotes the additional assessment factor for *extrapolation from the POD to the hazard characterisation in humans for sources where appropriate data or information is scarce or missing (additional)*.
- *PoD* denotes the point of departure.

Note that inter- and intra-species extrapolation and the use of an *additional assessment factor* are optional. However, expression type correction and the kinetic conversion are always applied (when relevant) whatever option is chosen.

Occasionally, for some substances multiple hazard characterisations are available (e.g., obtained from multiple experiments) and for others substance hazard characterisations are still missing. Hence, two final steps remain to come to the final set of hazard characterisation:

- *Aggregation over multiple available hazard characterisations*. Set the *selection method in case of multiple candidate hazard characterisations* from *MostToxic* to *Aggregate*.
- *Imputation of missing hazard characterisations*. Check the option *Imput missing hazard characterisations*, to select the Imputation method.

Specify with setting *Use lower limit of BMD* whether a BMD or BMDL is used in the risk assessment. The BMDL is a parametric estimate based on the profile likelihood method or is the p5 estimate of the bootstrapped BMD values in an uncertainty run. See module *dose response models* for more information on the estimation of the BMDL.

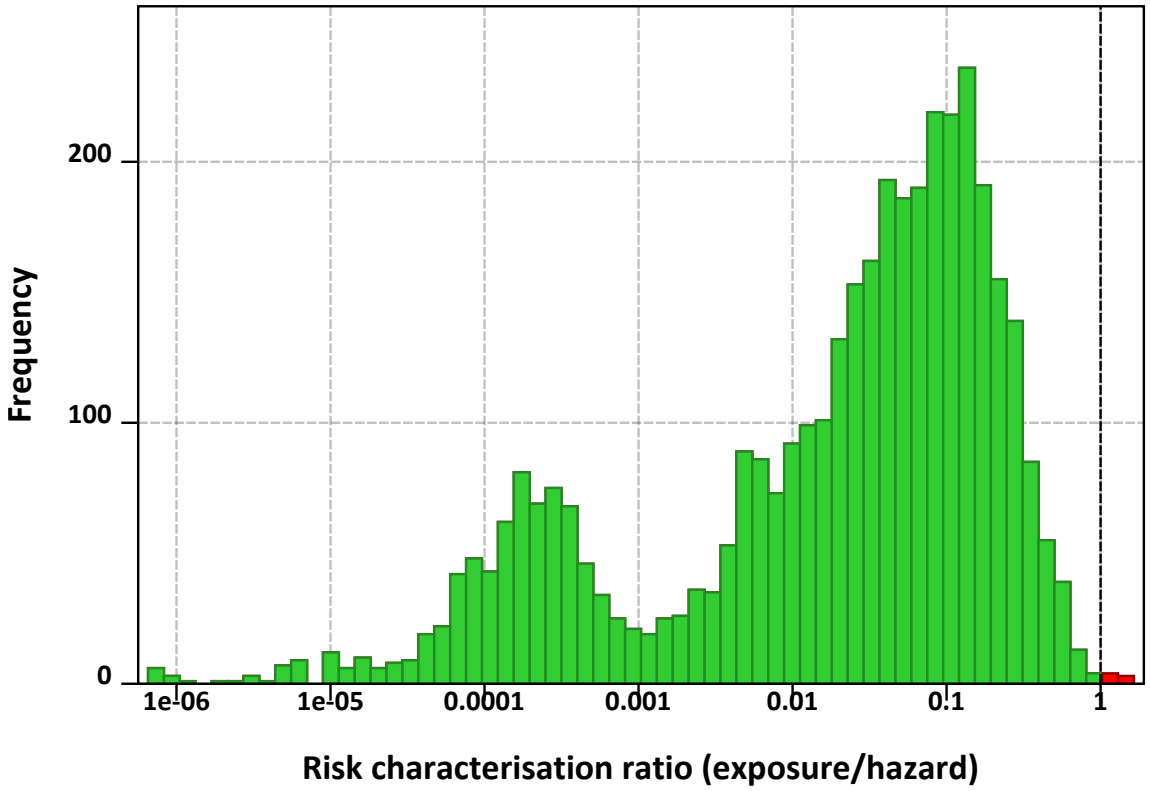


Figure 3.76: Risk characterisation ratio (exposure/hazard) based on BMD, *POCE* = 0.18%.

In above figures the risk characterisation ratio (exposure/hazard) based on a BMDL is conservative compared to the ratio based on the BMD.

### Hazard characterisation type extrapolation

Hazard doses, or points of departure can be of *various types*. E.g., *BMD* s, *NOAEL* s, or *LOAEL* s. When computing hazard characterisations, the type in which the hazard characterisations are expressed (i.e., the *hazard characterisation expression type*) should be specified explicitly. When points of departure from types different from the expression type are provided, these should be translated to the specified expression level. In the current implementation, the simple conversion factors shown in Table 3.375 are used, roughly based on the WHO guidance document on evaluating and expressing uncertainty in hazard characterisation, see WHO (2018).

Table 3.375: Conversion factors for hazard characterisation types.

| From | To | Conversion factor |
|---|---|---|
| BMD | NOAEL | 1/3 |
| BMD | LOAEL | 1 |
| NOAEL | BMD | 3 |
| NOAEL | LOAEL | 1/3 |
| LOAEL | BMD | 1 |
| LOAEL | NOAEL | 1/3 |

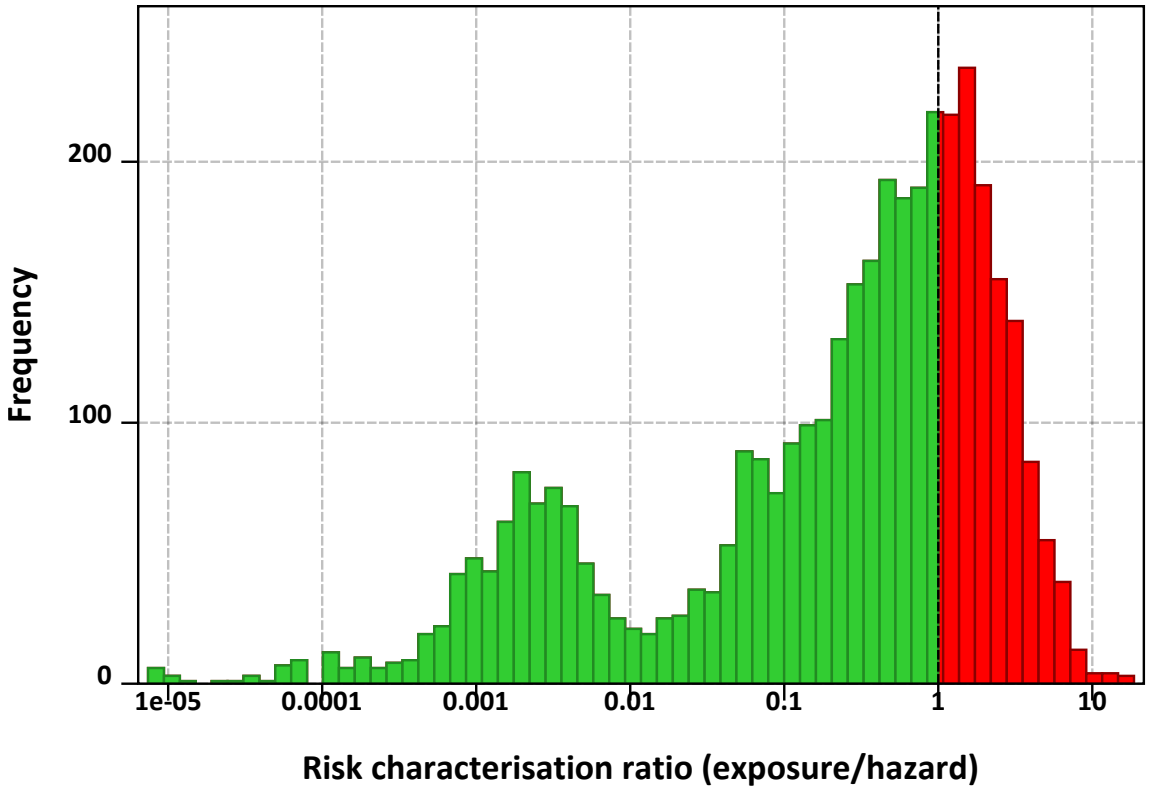


Figure 3.77: Risk characterisation ratio (exposure/hazard) based on BMDL, *POCE* = 32%.

### Inter-species extrapolation

Hazard doses, or points of departure, are commonly only determined for animals, not for humans. In order to derive hazard characterisations for humans, the animal hazard doses need to be converted to toxicologically equivalent doses for humans. This extrapolation is usually expressed as a multiplication factor, and traditionally a factor of 10 is used (which is roughly obtained from the product of a factor of 3.2 for toxicokinetic variability and a factor 3.2 for toxicodynamic variability).

The following methods are available within MCRA:

1. **No inter-species extrapolation:** Assume that for all available points of departure, the animal hazard dose is equal to the human hazard dose. Effectively, this is equivalent to using a conversion factor of 1.
2. **Default distribution:** Use a conversion factor drawn from a default, substance and species independent log-normal uncertainty distribution specified (as *model settings*) by a geometric mean (GM) and geometric standard deviation (GSD). In the *nominal run*, the nominal value of this distribution (i.e., the geometric mean) is used as a conversion factor. In the *uncertainty analysis loop*, provided that inter-species extrapolation uncertainty is *included in the uncertainty analysis*, a single factor is drawn from the lognormal distribution.
3. **Substance/species specific distributions:** Use conversion factors drawn from substance/species specific log-normal uncertainty distributions specified (as *data*) by a geometric mean (GM) and geometric standard deviation (GSD). In the *nominal run*, a factor equal to the geometric mean is used for all combinations of substance and species. In the *uncertainty analysis loop*, provided that inter-species extrapolation uncertainty is *included in the uncertainty analysis*, a uncertainty factor is drawn from the lognormal distribution with $\mu = 0$ and $\sigma^2 = 1$, which is used to obtain correlated draws for all available inter-species conversion factor distributions. If the distribution parameters are missing for a specific substance/species, then the default distribution is used as a fallback.

### Intra-species extrapolation of hazard characterisations

There is variation between individuals concerning their individual sensitivities to experience health effects. In some scenarios the aim is to perform assessments for the sensitive individuals instead of the average individuals for which the points of departure are derived. If this is the case, then extrapolation is required to translate hazard characterisations derived for the average individual to hazard characterisations for a sensitive individual. In traditional exposure assessments, a safety of 100 is commonly used as a margin of safety, that is assumed to be composed of a interspecies extrapolation factor (factor 10), and inter-individual extrapolation factor (factor 10). I.e., the hazard characterisation defined for the sensitive individual is defined as

$$HC_{\mathtt{sens}} = \frac{1}{f_{\mathtt{intra-species}}} \cdot HC_{\mathtt{avg}}$$

Here $f_{\mathtt{inter-species}}$ denotes the intra-species factor. An alternative to using a fixed safety factor, is to define intra-species variability explicitly using *a lognormal distribution*, characterised by a geometric mean (GM) equal to 1 and a geometric standard deviation (GSD). For *risks calculations*, this distribution could be used to sample individual hazard characterisations. This effectively converts the description of hazard characterisations to include variability, with an unbiased central value.

### Additional assessment factors

In cases where where appropriate data or information is scarce or missing, an additional assessment factor (*AF*) is used for extrapolation from the *POD* to the hazard characterisation in humans. This factor can be used as a worst case value (preferably AF = 100) for inter- and intra-species extrapolation, but it may equally well serve as an additional extrapolation factor next to inter- and/or intra-species extrapolation. In the latter case the factor merely serves to account for differences in for example route to route, metabolic rates in interspecies, completeness and consistency of available data, reliability of alternative data (e.g. read-across) or quality of data in general.

### In-vitro in-vivo extrapolation (IVIVE)

The in-vitro in-vivo extrapolation method implemented in MCRA is based on the following prerequisites:

1. For one substance, the index substance, a reliable point of departure is available for the adverse outcome of interest obtained from an *in-vivo* assay (i.e., external dose).
2. There are other substances for which there is a dose-response model available from an *in-vitro* assay on a response representing an early key event of the adverse outcome for these substances and the index substance.

In *IVIVE*, these RPFs, in combination with the known hazard characterisation of the index substance, can be used to derive hazard characterisations for the other substances as well. Figure 3.78 shows the conceptual model that forms the basis of the IVIVE methodology of MCRA.

### IVIVE for calculating internal hazard characterisations

1. Translate the (external) PoD of the index substance substance to an internal hazard characterisation for the human target system/*biological matrix*.
2. If the RPFs are obtained are obtained using mol-based specification of the doses, then convert the mol-based RPFs to mass-based RPFs. I.e.,

$$RPF_{\mathtt{mass-based},i} = RPF_{\mathtt{mol-based},i} \cdot \frac{MW_{\mathtt{ref}}}{MW_i}$$

3. Derive internal hazard characterisations for the human target system for the other substances by multiplying the RPF obtained from dose-response modelling with the hazard characterisation of the index substance. I.e.,

$$HC_i = HC_{\mathtt{ref}} \cdot RPF_{\mathtt{mass-based},i}$$

### IVIVE for calculating external hazard characterisations

1. Translate the PoD of the index substance to an external human hazard characterisation (dietary/oral exposure route).

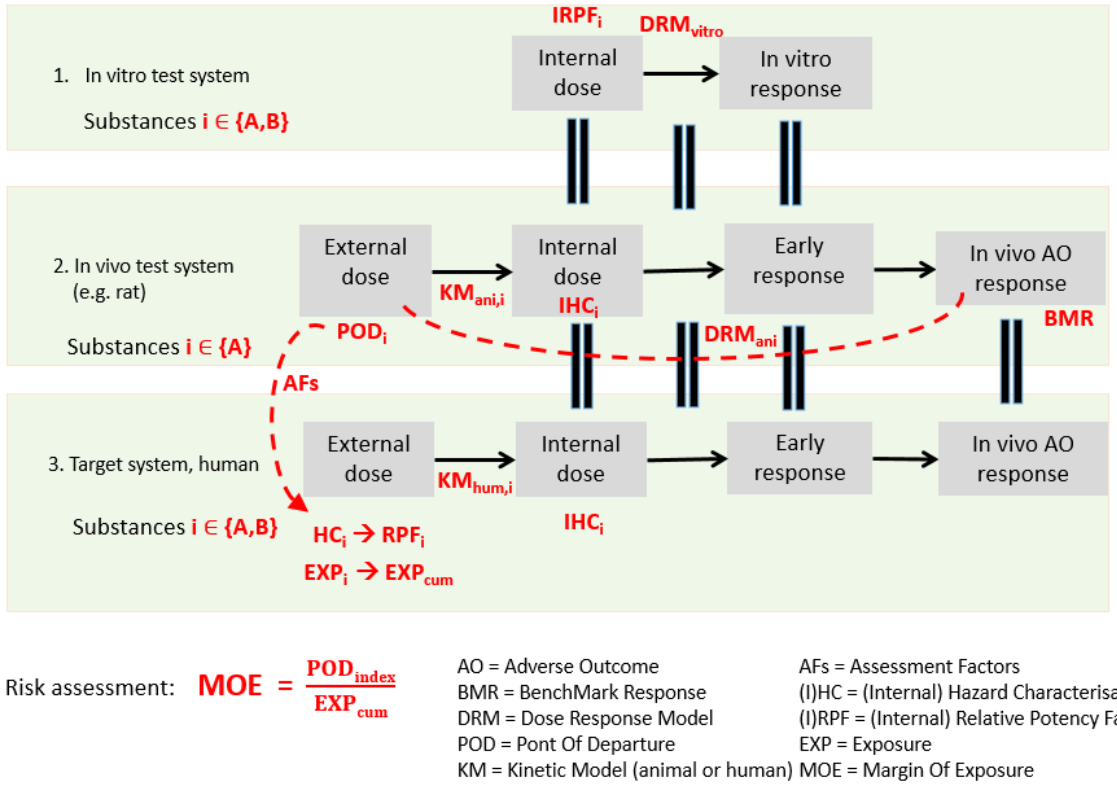


Figure 3.78: Conceptual model IVIVE.

2. Derive an internal hazard characterisation for the index substance, with a target biological matrix representative for the response of the dose-response model.
3. If the RPFs are obtained are obtained using mol-based specification of the doses, then convert the mol-based RPFs to mass-based RPFs.
4. Derive internal hazard characterisations for the human target system for the other substances by multiplying the RPF obtained from dose-response modelling with the hazard characterisation of the index substance.
5. Convert the internal hazard characterisations of the other substance to external hazard characterisations for the dietary/oral exposure route using.

### Absorption or kinetic conversion of hazard characterisations

When the *hazard characterisation level* is internal and points of departure are available for external exposures (e.g., NOAELs from in-vivo animal studies) or when the hazard characterisation level is external and benchmark doses are available at the internal level, then *kinetic conversion factors* or *PBK models* are needed to translate the external doses to *equivalent internal doses at the target* or *biological matrix* of interest or *vice-versa*.

In MCRA, this alignment from internal to external or from external to internal is generally termed *conversion*, associated with a *kinetic conversion factor* or *PBK model*. The kinetic conversion factor is a multiplication factor needed to obtain a hazard characterisation on the target level from a hazard characterisation of the point of departure or benchmark dose. Depending on the chosen kinetic modelling tier, this kinetic conversion factor may be 1) assumed to be one, or derived from 2) absorption factors, 3) kinetic conversion factors or 4) using *PBK* models.

An important detail in the use of kinetic conversion factors for computing hazard characterisations is the order between kinetic conversion and inter-species extrapolation. Notice that when points of departure are determined for animals, a choice should be made regarding the order of inter-species extrapolation and kinetic modelling. That is, one may first choose to convert animal external point of departure to an internal hazard characterisation for that animal, using the available animal kinetic model. Alternatively, one may first extrapolate the animal external point

of departure to a human external hazard characterisation, and thereafter apply the human kinetic model to obtain internal hazard characterisations. Currently, in MCRA only the latter approach is implemented.

### Extrapolation from external to internal hazard characterisations

The calculation of internal hazard characterisations based on external hazard characterisations is similar to the procedure for *computing internal exposures*. In the simplest tier, equivalence can be assumed between internal and external hazard characterisations, and in higher tiers absorption factors, respectively PBK models can be used.

### Calculation of internal doses using absorption factors

In the simplest form, internal doses are obtained from external exposure concentrations using absorption factors that are specified per combination of substance and route. That is, for a given substance, the internal hazard characterisation $HC_{\mathtt{int,dose}}$ can be derived from an external hazard characterisation $HC_{\mathtt{ext}}$ as

$$HC_{\mathtt{int,dose}} = f_{\mathtt{abs},r} \cdot HC_{\mathtt{ext},r}$$

Here, $r$ denotes the route of the external exposure $HC_{\mathtt{ext}}$, and $f_{\mathtt{abs},r}$ denotes the absorption factor of route $r$. Note that this model assumes that the external hazard characterisations are specified as concentrations (i.e., substance amount divided by the body weight).

### Calculation of internal concentration using human PBK models

A more detailed alternative to absorption factors is to use kinetic conversion factors or one of the *advanced PBK models* available in MCRA. In the last approach, for each substance independently, an external exposure equivalent to the dose of the external hazard characterisation is presented to a representative simulated individual for a number of simulated days to the PBK model of the individual. This representative individual should represent the "average" individual of the population, with nominal physiological properties (e.g., an average bodyweight of 70kg). This yields a time course of the internal substance amount at the specified target or biological matrix from which a long term average substance amount (chronic) or peak substance amount (acute) can be obtained. By dividing this substance amount by the weight of the biological matrix, an internal concentration is obtained, which then represents the internal hazard characterisation.

More details on computing internal concentrations from external doses can be found in the description of the calculation of internal concentrations from external exposures in section *kinetic conversion factors* or *PBK models*. For both tasks, the procedure for computing internal exposures/doses is exactly and the same *kinetic model settings*, such as *dosing patterns* and *non-stationary period* period apply for calculation of internal hazard characterisations as well.

### Calculation of internal doses using animal PBK models

In the above methods, the assumption is that the external points of departure (often obtained from experiments on animals) are first converted to external hazard characterisations for humans, and a human kinetic model is used for obtaining the internal hazard characterisations. As mentioned, an alternative approach is to use first the animal PBK models to derive an internal hazard characterisation specific for the tested animal species and thereafter extrapolate to humans. When there are more precise kinetic models available for the animal used in the experiments for obtaining the point of departure, this could be a preferred path.

> **Note**
>
> Notice that this procedure is not yet implemented.

### Extrapolation from internal to external hazard characterisations

In some cases, hazard characterisations are available at the internal level whereas the specified *hazard characerisation level* is external. This situation may occur, for instance, in *in-vitro in-vivo extrapolation (IVIVE)*. Then, conversion is needed from the internal level to the external level, where the external level is implicitly defined as coming from the dietary/oral route of exposure.

For absorption factors, the external (dietary) hazard characterisation of a substance is simply computed by dividing the internal hazard characterisation by the dietary absorption factor, i.e.,

$$HC_{\text{ext,diet}} = \frac{HC_{\text{int,dose}}}{f_{\text{abs,diet}}}$$

For PBK models, reverse dosimetry is needed to find the corresponding external (dietary) dose that yields the internal concentration specified by the internal hazard characterisation. In MCRA, this is done using a bisection algorithm: external doses are systematically fed into the PBK model and convergence is reached when the resulting dose is within a specified precision of the value derived from the hazard characterisation.

### Hazard characterisation imputation

Occasionally, for some substances causing the effect of interest, no data are available to determine the hazard characterisations, HCs, (e.g. no points of departure or dose response models). Instead of excluding these substances in quantitative analyses, missing HCs are imputed based on known HCs of similar substances. The imputed HCs are used for calculating relative potency factors or used in a risk assessment.

### Munro P5 (TTC approach)

The Threshold of Toxicological Concern (TTC) is an example of a tier for extrapolation of hazard characterisations from other substances that is already in common use (see Munro et al. (1996)). The *Munro collection of NOELs/LOAELs* is a collection of *NOEL* s/*LOAEL* s for chemicals for the critical (i.e., first occurring) effect. In the TTC approach, the toxicity of an unknown substance is, depending on its Cramer class (see Cramer et al. (1976)), imputed by the 5th percentile NOAEL of the sub-collection of the corresponding Cramer class.

Two variations of this approach are to use the empirical NOAEL distribution itself (just sample from the NOAEL data), or to fit a distribution (e.g. lognormal) to the empirical data and sample from the parametric distribution. MCRA provides an implementation of the TTC approach that uses the empirical distribution. In the nominal run, this implementation imputes the hazard characterisations with a value equivalent to the TTC. In the uncertainty runs, NOAELs are sampled from the empirical distribution.

The TTC is a conservative estimate of the NOAEL for at least two reasons:

1. TTCs are calculated from a collection of NOELs for the critical (i.e., first occurring) effect within each study and often the effect of interest will not be the critical effect, and therefore higher NOAELs are expected.
2. The TTC is a low percentile and therefore a conservative estimate for a random class member with unknown NOAEL.

### Munro central value

To avoid the conservatism of taking the 5th percentile in the Munro P5 approach, alternatively, a nominal (or central) value could be taken from the Munro collection for each Cramer class. For a nominal run without uncertainty, the expected contribution of a substance with missing hazard characterisation to the risk as quantified in the hazard index is obtained from

$$HI = SF \cdot \sum_{i}^{n} \frac{\exp_i}{HC_i}$$

Here SF are all combined safety factors. It follows from this equation that an unbiased estimate for the contribution from a substance with missing hazard characterisations is obtained by taking the harmonic mean from the available NOAELs:

$$NOAEL = \left( \sum_{i=1}^{n} \frac{1}{NOAEL_i} \right)^{-1}$$

This is the value to use in a nominal run without uncertainty for the Munro central value approach. For the uncertainty runs, this approach also uses random sampling from the empirical distribution of the corresponding Cramer class.

### Available hazard characterisations distribution P5

Another conservative aspect of the TTC approach is that the Munro set lists NOELs/LOAELs for critical effects, not for the specific effect under study. Therefore an alternative is to use the effect-specific hazard characterisations of the substances for which these are available. This collection will have on average higher NOAELs than those of the Munro NOEL collection, because for many substances, the effect of interest will not be the critical effect.

### Available hazard characterisations distribution central value

Similar to the Munro central value approach, a central value could also be obtained from the set of effect-specific hazard characterisations distribution for imputation of hazard characterisations. This approach may yield the most realistic, or unbiased imputation value for missing hazard characterisations.

### Aggregation over multiple available hazard characterisations

In some scenarios, for a given substance and effect, multiple hazard characterisations are available e.g. different studies yield different *NOAEL* s. In such cases, a single hazard characterisation should be derived from the available candidates.

In a conservative approach, choose the lowest hazard characterisation (HC) of the available hazard characterisations. I.e.,

$$\mathrm{HC} = \min_{i=1,\ldots,n} \mathrm{HC}_i$$

Alternatively, the candidates are aggregated into a new "average" hazard characterisation. For this, the harmonic mean, also used for obtaining central value estimates in the *imputation of missing hazard characterisations*, is a suitable approach.

$$\mathrm{HC} = \left( \sum_{i}^{n} \frac{1}{\mathrm{HC}_i} \right)^{-1}$$

### Hazard characterisations data formats

Hazard characterisations provide reference threshold values associated with the hazard of interest. Examples are health-based guidance values such as ADI or ARfD, and points of departure such as BMD or NOAEL. Hazard characterisations may be dependent on e.g. age (or gender not implemented yet)

Download empty dataset template: Zipped CSV Excel

### Hazard characterisations

Hazard characterisations are specified for combinations of hazard characterisation type, effect, substance, population type, target level, and exposure route (for external) or target organ (for internal). Effects can be specific, but can also be labelled as being the critical effect and used as such if this has been specified in the hazard characterisation settings.

Table 3.376: Table definition for Hazard characterisations.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idHazard-Characterisation | AlphaNumeric (50) | Id of the hazard characterisation. | id, idHazard-Characterisation | Yes |
| idEffect | AlphaNumeric (50) | Code of the (critical) effect linked to this hazard characterisation. | idEffect, EffectId, Effect, EffectCode | No |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceCode, SubstanceId, Substance | Yes |
| idPopulation-Type | AlphaNumeric (50) | The code of the population type for which this reference value is defined. If not specified, PS06A, Consumers is assumed. | idPopulation-Type, PopulationType, Population-Group, Population-Subgroup | No |
| TargetLevel | *TargetLevelType* | The target level. I.e., internal or external. If omitted, external is assumed | TargetLevel | No |
| ExposureRoute | *ExposureRoute* | The exposure route (only applicable if target level is external). If not specified, Dietary is assumed. | ExposureRoute | No |
| Matrix | *BiologicalMatrix* | The biological matrix or organ (should be specified when target level is internal). | Matrix, BiologicalMatrix | No |
| Expression type | *ExpressionType* | The expression type for (internal) hazard characterisations of which the concentrations are not directly specified at the level of the biological matrix. For instance, urinary expressions expressed in terms of the amount excreted per gram of creatinine or blood concentration expressed per gram of lipids. | ExpressionType | No |
| IsCriticalEffect | Boolean | Specifies whether this value is the value associated with the critical effect. If omitted, No is assumed | IsCriticalEffect | No |
| ExposureType | *ExposureType* | The exposure type associated with the hazard characterisation (i.e., chronic or acute). | ExposureType | Yes |
| Hazard-Characterisation-Type | *Hazard-Characterisation-Type* | The type of the hazard characterisation (e.g., ARfD, ADI, NOAEL, BMD). | Hazard-Characterisation-Type | Yes |
| Qualifier | *ValueQualifier* | Qualifier of the hazard characterisation value, e.g. equal-to (=) or smaller-than (<). If omitted, = is assumed. | QualifierType | No |
| Value | Numeric | Reference value that characterises the hazard. | Value, Hazard-Characterisation-Value | Yes |
| DoseUnit | *DoseUnit* | Unit of the hazard characterisation value. | DoseUnit, Unit | Yes |
| idPointOf-Departure | AlphaNumeric (50) | The code of the point of departure from which this hazard characterisation was | idHazardDose, idPod | No |

Accepted table names: HazardCharacterisations.

### Hazard characterisations uncertainty

Often, the hazard characterisations found for a substance are uncertain. This table facilitates in specifying the hazard characterisation uncertainty in the form of a set of uncertainty values that may additionally be specified for a hazard characterisation model - substance combination.

Table 3.377: Table definition for Hazard characterisations uncertainty.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idHazard-Characterisation | AlphaNumeric (50) | The hazard characterisation model code (must correspond to values in id column of Hazard characterisations table). | idHazard-Characterisation | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Hazard-Characterisation-Value | Numeric | Reference value that characterises the hazard. | Hazard-Characterisation, Hazard-Characterisation-Value | Yes |

Accepted table names: HazardCharacterisationsUncertain, HazardCharacterisationsUncertai, HazardDoseUncertain, HCUncertain.

### Hazard characterisations subgroups

Hazard characterisations are dependent on e.g. age.

Table 3.378: Table definition for Hazard characterisations subgroups.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubgroup | AlphaNumeric (50) | The id of the subgroup. | idSubgroup | Yes |
| idHazard-Characterisation | AlphaNumeric (50) | Id of the hazard characterisation. | idHazard-Characterisation | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| AgeLower | Numeric (50) | Specifies the lower bound of the age interval (in years) of the hazard characterisation subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower age of the next subgroup. | AgeLower, LowerAge | No |
| Gender | *GenderType* | The gender of the subgroup. | Gender | No |
| Value | AlphaNumeric (50) | The hazard characterisation of the subgroup. | Value | Yes |

Accepted table names: HCSubgroups, HCSubgroup.

### Hazard characterisations subgroups uncertainty sets

Hazard characterisations are dependent on e.g. age and may be uncertain.

Table 3.379: Table definition for Hazard characterisations subgroups uncertainty sets.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idSubgroup | AlphaNumeric (50) | The id of the subgroup. | idSubgroup | Yes |
| idHazard-Characterisation | AlphaNumeric (50) | Id of the hazard characterisation. | idHazard-Characterisation | Yes |
| idUncertainty-Set | AlphaNumeric (50) | The id of the ucertainty set. | idUncertainty-Set, idUncertainty-Set, idUncertainty | Yes |
| Value | AlphaNumeric (50) | The uncertain hazard characterisation of the subgroup. | Value | Yes |

Accepted table names: HCSubgroupsUncertain, HCSubgroupUncertain.

### Hazard characterisations settings

### Selection settings

Table 3.380: Selection settings for module Hazard characterisations.

| Name | Type | Description |
|---|---|---|
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Multiple effects analysis | Boolean | Specifies whether the analysis should consider multiple effects. Otherwise, a single focal effect should be selected. |
| Target level | *TargetLevelType* | Select whether the assessment is at the level of external dose, internal (target) concentration or internal (systemic) dose. For a aggregate assessment, combining dietary and nondietary exposures, the target level is always internal concentration or internal (systemic) dose. When only dietary exposures are available, the target level is optional and may be an external (administered) dose, an internal (tissue) concentration or an internal (absorbed) dose. |
| Consider critical effect | Boolean | Specifies whether the analysis should look at critical effects such as specified in the Hazard characterisation data source. |
| Restrict active substances to substances with available hazard characterisations | Boolean | Restrict assessment group membership based on presence/absence of hazard characterisations. |
| Include related effects of AOP network | Boolean | Include all related key events of the AOP network. |

### Calculation settings

Table 3.381: Calculation settings for module Hazard characterisations.

| Name | Type | Description |
|---|---|---|
| Selected tier | SettingsTemplateType | Specifies all module settings should be set according to a pre-defined tier or using custom settings. |
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a value 0 will provide the same results in a repeated run. |
| Index substance | AlphaNumeric | The substance of interest or index substance. |
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Point of departure source | *TargetDosesCalculationMethod* | Point of departure source for computing the hazard characterisations: from points of departure (data), dose respons models or both. |
| Exposure routes | ExposureRoutes | Exposure routes included in assessment. |
| Apply kinetic conversions | Boolean | Convert substance concentrations from other biological matrice using kinetic conversion models. The substances for conversion are designated within the kinetic models module. Substance conversion proves valuable when a biomarker was not directly measured for a matrix of interest. |
| Restrict to single target | Boolean | Restrict to one biological matrix when computing substance hazard characterisations at the internal level. |
| Target biological matrix | *BiologicalMatrix* | The target biological matrix (internal compartment) for which exposures are computed. |
| Specify the type of kinetic model | *InternalModelType* | Specify the type of model to convert external exposure to the internal level. |
| Expression type | *PointOfDeparture* | Specifies how hazard characterisations are expressed: as BMD, NOAEL, or the expression type is ignored. |

continues on next pa

Table 3.381 – continued from previous page

| Name | Type | Description |
|---|---|---|
| Selection method in case of multiple candidate hazard characterisations | *TargetDoseSelectionMethod* | Choose either the most toxic (default) or an aggregated hazard characterisation when in nominal runs there are multiple availal candidates. In uncertainty runs, multiple candidates are resampled. |
| Impute missing hazard characterisations | Boolean | If checked, missing hazard characterisations are imputed based Munro NOELs or on other available points of departure. |
| Imputation method | *HazardDoseImputationMethod-Type* | Imputation of Hazard characterisations: use low percentile (P5) unbiased central estimate from either the Munro set or the available POD collection. |
| Use lower limit of BMD | Boolean | Use the lower uncertainty limit of the benchmark dose. For an uncertainty run, the lower limit is the p5 of the bootstrap sampl otherwise it is a parametric estimate based on the parameters o the dose response curve. |
| Use inter-species conversions | Boolean | Use inter-species conversion factors (default value, e.g. 10, or data). |
| Use intra-species factors | Boolean | Use intra-species conversion factors (default value, e.g. 10, or data). |
| Additional assessment factor | Numeric | Additional assessment factor for extrapolation of PODs to (human) hazard characterisations. |
| Use additional assessment factor | Boolean | Use additional assessment factor for extrapolation of PODs to (human) hazard characterisations. |
| Use hazard characterisations subgroup | Boolean | Hazard characterisations are dependent on subgroups (e.g. base on age or gender, see dataformats HCSubgroups). |
| Exposure events and dose generation method | *ExposureEventsGeneration-Method* | Generates doses and events for PBK model |
| Number of simulated days | Numeric | The total duration (in days) of the PBK model simulations. |
| Number of initial days skipped | Numeric | The initial period (or burn-in period, specified in days) that nee to be skipped when calculating the steady-state or peak internal exposures from the simulated time series. |
| Use PBK model parameter variability | Boolean | When specified, use parameter variability. |
| Number of events per day for the DERMAL dose | Numeric | The daily dose is administered in equal portions (dose / number events) per event. |
| Number of events per day for the INHALATION dose | Numeric | The daily dose is administered in equal portions (dose / number events) per event. |
| Number of events per day for the ORAL dose | Numeric | The daily dose is administered in equal portions (dose / number events) per event. |
| Specify the hours (events). | Numeric | Specify the hours on which exposure events are simulated. Allowed numbers are 1, 2, 3, 4,…, 24 separated by spaces. |
| Specify event timings | Boolean | If checked, a specific sequence of hours on a day can be specifi on which exposure events are simulated. Otherwise the events a derived based on the number of exposure events per day. |
| Allow fallback to systemic dosing for missing exposure routes | Boolean | If the PBK model misses specific compartments for certain exposure routes, this setting allows the model to fallback to systemic dosing for those route. |
| PBK output resolution time unit | *PbkModelOutputResolution-TimeUnit* | Time unit in which the output resolution of PBK model simulations is specified. |
| PBK output resolution step size | Numeric | PBK model simulation output step size/length, specifying the evaluation resolution in terms of the step length (period) betwe two evaluations. For example, a step length of 12 with a resolut time unit of hours is interpreted as every 12 hours. |

### Uncertainty settings

Table 3.382: Uncertainty settings for module Hazard characterisations.

| Name | Type | Description |
|---|---|---|
| Resample intra-species factor | Boolean | Specifies whether intra-species factors are resampled from a parametric uncertainty distribution. |
| Resample hazard characterisations or RPFs | Boolean | Specifies whether to resample the hazard characterisations or relative potency factors. Requires hazard characterisation or RF uncertainty to be quantified in DoseResponseModelsUncertain RelativePotencyFactorsUncertain tables. |
| Lower uncertainty limit (%) | Numeric | Percentage lower bound, e.g. 2.5%. |
| Upper uncertainty limit (%) | Numeric | Percentage upper bound, e.g. 97.5%. |

### Hazard characterisations tiers

### Overview

Table 3.383: Tier overview for module Hazard characterisations.

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| T ge le | External | External | External | External | External | External | External | External | External | Exte |

### Retrospective dietary CRA (EC 2018) - Acute / Tier I

Table 3.384: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier I.

| Name | Setting |
|---|---|
| Target level | External |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier I

Table 3.385: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier I.

| Name | Setting |
|---|---|
| Target level | External |

### Retrospective dietary CRA (EC 2018) - Acute / Tier II

Table 3.386: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier II.

| Name | Setting |
|---|---|
| Target level | External |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier II

Table 3.387: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Target level | External |

### Retrospective dietary CRA (EFSA 2012) - Optimistic

Use the optimistic model settings according to the EFSA Guidance 2012. Concentration values are sampled using a sample-based empirical distribution. Available processing factors are applied. No unit variability model should be applied.

Table 3.388: Tier definition for Retrospective dietary CRA (EFSA 2012) - Optimistic.

| Name | Setting |
|---|---|
| Target level | External |

### Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic

Acute probabilistic exposure assessment using the pessimistic model settings according to the EFSA Guidance 2012. Only processing factors > 1 are applied. For unit variability, the Beta distribution is applied.

Table 3.389: Tier definition for Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic.

| Name | Setting |
|---|---|
| Target level | External |

### Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic

Chronic probabilistic exposure assessment using the pessimistic model settings according to the EFSA Guidance 2012. Only processing factors > 1 are applied.

Table 3.390: Tier definition for Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic.

| Name | Setting |
|---|---|
| Target level | External |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier I

Table 3.391: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier I.

| Name | Setting |
|---|---|
| Target level | External |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I

Table 3.392: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I.

| Name | Setting |
|---|---|
| Target level | External |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier II

Table 3.393: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier II.

| Name | Setting |
|---|---|
| Target level | External |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II

Table 3.394: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Target level | External |

### Prospective dietary CRA (EFSA 2023) - Acute / Tier II

Table 3.395: Tier definition for Prospective dietary CRA (EFSA 2023) - Acute / Tier II.

| Name | Setting |
|---|---|
| Target level | External |

### Prospective dietary CRA (EFSA 2023) - Chronic / Tier II

Table 3.396: Tier definition for Prospective dietary CRA (EFSA 2023) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Target level | External |

### Prospective dietary CRA (EFSA 2024) - Acute / Tier II

Table 3.397: Tier definition for Prospective dietary CRA (EFSA 2024) - Acute / Tier II.

| Name | Setting |
|---|---|
| Target level | External |

#### Prospective dietary CRA (EFSA 2024) - Chronic / Tier II

Table 3.398: Tier definition for Prospective dietary CRA (EFSA 2024) - Chronic / Tier II.

| Name | Setting |
|---|---|
| Target level | External |

#### Hazard characterisations as data

Hazard characterisations (HCs) can be provided as data e.g., in the form of ADI or ARfD. For age dependent hazard characterisations, specify the HCs in table HCSubgroups and HCSubgroupsUncertain. Currently, only age dependent HCs are implemented.

- *Hazard characterisations data formats*
- *Hazard characterisations from data*

Inputs used: *AOP networks Active substances Points of departure*

Settings used

- *Calculation Settings*

#### Calculation of hazard characterisations

Hazard characterisations can be computed from points of departure. The computation may involve assessment factors, e.g. for inter-species conversion, intra-species variation or additional sources of uncertainty. The additional assessment factor can be used to bypass inter- and intra species conversion, or as an additional assessment factor to account for extrapolation for sources where appropriate data or information is scarce or missing (e.g. to implement a mixture assessment factor). The hazard characterisation calculation may also use kinetic conversion factors, PBK models or absorption factors to convert external doses to internal doses/concentrations or vice versa.

- *Hazard characterisations calculation*

Inputs used: *Dose response models Effect representations Inter-species conversions Intra species factors Absorption factors Kinetic conversion factors PBK model parametrisations*

Settings used

- *Calculation Settings*

### 3.5.9 Inter-species conversions

Inter-species conversions specify how to convert a hazard characterisation for a given species to a hazard characterisation for humans. In the simplest approach, this specifies a fixed inter-species factor. In a higher tier, this specifies a geometric mean (GM) and geometric standard deviation (GSD) for a lognormal uncertainty distribution of the interspecies factor. Inter-species conversion are specified per effect and can be general or substance-specific.

This module has as primary entities: *Substances Effects*

Output of this module is used by: *Hazard characterisations*

#### Inter-species conversions from data

#### Inter-species conversions data formats

Inter-species conversion models specify how to convert a hazard dose for a given species to a hazard dose for humans.

Download empty dataset template: Zipped CSV Excel

### Inter-species model parameters

Inter-species extrapolation factors are described using a lognormal distribution specified by a geometric mean (GM) and geometric standard deviation (GSD). Inter-species factors are defined for an effect and a species and may optionally be specified specifically for a substance.

Table 3.399: Table definition for Inter-species model parameters.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idEffect | AlphaNumeric (50) | The code of the effect for which this inter-species model is defined. | idEffect, EffectId, Effect | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance for which this inter-species model is defined. | idSubstance, SubstanceId, SubstanceCode, Substance | No |
| Species | AlphaNumeric (50) | Species | Species | Yes |
| InterSpecies-GeometricMean | Numeric | Interspecies geometric mean. | InterSpecies-GeometricMean, InterSpeciesGM | Yes |
| InterSpecies-Geometric-Standard-Deviation | Numeric | Interspecies geometric standard deviation. | InterSpecies-Geometric-Standard-Deviation, InterSpeciesGS-D | Yes |
| Standard-HumanBody-Weight | Numeric | The standard human body weight. | Standard-HumanBody-Weight | Yes |
| HumanBody-WeightUnit | *BodyWeightUnit* | The unit of the human body weight specification (kg is assumed if not defined). | HumanBody-WeightUnit | No |
| Standard-AnimalBody-Weight | Numeric | The standard animal body weight. | Standard-AnimalBody-Weight | Yes |
| AnimalBody-WeightUnit | *BodyWeightUnit* | The unit of the animal body weight specification (kg is assumed if not defined). | AnimalBody-WeightUnit | No |

Accepted table names: InterSpeciesModelParameters, InterSpeciesModelParameter, InterSpeciesFactors, InterSpeciesFactor.

### Inter-species conversions settings

### Selection settings

Table 3.400: Selection settings for module Inter-species conversions.

| Name | Type | Description |
|---|---|---|
| Interspecies factor geometric mean | Numeric | Interspecies factor geometric mean. |
| Interspecies factor geometric standard deviation | Numeric | Interspecies factor geometric standard deviation. |
| Restrict active substances to substances with available hazard characterisations | Boolean | Restrict assessment group membership based on presence/abse of hazard characterisations. |

### Calculation settings

Table 3.401: Calculation settings for module Inter-species conversions.

| Name | Type | Description |
|---|---|---|
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Use inter-species conversions | Boolean | Use inter-species conversion factors (default value, e.g. 10, or data). |

### Uncertainty settings

Table 3.402: Uncertainty settings for module Inter-species conversions.

| Name | Type | Description |
|---|---|---|
| Resample inter-species factor | Boolean | Specifies whether inter-species factors are resampled from a parametric uncertainty distribution. |

### Inter-species conversions as data

Data are provided in the form of a geometric mean (GM) and geometric standard deviation (GSD)

- *Inter-species conversions data formats*
- *Inter-species conversions from data*

Inputs used: *Active substances*

Settings used

- *Calculation Settings*

## 3.5.10 Intra species factors

Intra-species factors describe variation between individuals concerning their individual sensitivities to experience well-defined health effects. Traditionally the intraspecies factor is a fixed value, but the true distribution might be (very) uncertain. There is some support for assuming a lognormal distribution to describe the variability between individuals. In MCRA, intraspecies factors are sampled from a lognormal distribution, characterised by a geometric mean (GM) equal to 1 and a geometric standard deviation (GSD) thats needs to be given a value representing the intraspecies variability. GM is 1 by definition (50% of the population is assumed to be less sensitive than the average, 50% is mor sensitive) and has no uncertainty. On the other hand, there is uncertainty about the GSD. In MCRA it is assumed that this uncertainty is described by a Chi-square distribution with df degrees of freedom. By specifying a lower and upper bound for the p95 sensitive individual e.g. a lower value 2 and upper value 10 (meaning, the p95 individuals are between 2 and 10 times more sensible than the average human), a Chi-square distribution can be estimated where 1) the GSD specifies the variability and 2) the degrees of freedom specifies the uncertainty around the GSD.

This module has as primary entities: *Substances Effects*

Output of this module is used by: *Hazard characterisations*

### Intra species factors from data

### Intra species factors calculation

There is variation between individuals concerning their individual sensitivities to experience health effects. In some scenarios the aim is to perform assessments for the sensitive individuals instead of the average individuals for which the points of departure are derived. If this is the case, then extrapolation is required to translate hazard characterisations derived for the average individual to hazard characterisations for a sensitive individual.

Traditionally a fixed safety factor describes the variation between individuals. Little information is available about the true distribution of human sensitivities, so there is also a large uncertainty. In MCRA, the intra-species variability is modelled explicitly using *a lognormal distribution*, characterised by a geometric mean (GM) equal to 1 and a geometric standard deviation (GSD). This distribution is used to sample individual hazard characterisations. This effectively converts the description of hazard characterisations to include variability, with an unbiased central value. GM is 1 by definition (50% of the population is assumed to be less sensitive and 50% more sensitive than the average individual) and has no uncertainty. On the other hand, there is uncertainty about the GSD or *SD* = log(GSD). This uncertainty is described by a chi-square distribution with *df* degrees of freedom:

$$\frac{df \cdot SD^2}{\sigma^2} \sim \chi^2_{df}$$

where $\sigma$ is the true standard deviation and $\chi^2_{df}$ denotes a chi-square distribution with $df$ degrees of freedom. Thus $df$ characterises the amount of uncertainty regarding the intra species variation quantified by (G)SD.

It is difficult to specify values for GSD and $df$. A practical way to do this is, define a p95-sensitive individual having an intra-species factor corresponding to the p95 percentile of the distribution describing the variability.

Assume that the p95-sensitive individuals are between e.g. 2 and 10 times more sensitive than the average human. The values 2 and 10 are to be interpreted as uncertainty bounds, the 2.5th and 97.5th percentiles of the uncertainty distribution for the $F_{intra,\,p95}$.

Then, p95-sensitive individuals are between $F_{intra,\,p95\,p2.5}$ and $F_{intra,\,p95\,p97.5}$ more sensitive than the average human, where the first index indicate the variability distribution and the second the uncertainty distribution.

For the lognormal distribution we have:

$$ln(F_{intra,\,p95}) = ln(GM) + 1.645 \cdot \sigma = 1.645 \cdot \sigma$$

And thus $\sigma = \frac{ln(F_{intra,\,p95})}{1.645}$. The uncertainty statement can be re-expressed as a 95% confidence interval for $\sigma$:

$$\frac{ln(F_{intra,\,p95\,p2.5})}{1.645} \leq \sigma \leq \frac{ln(F_{intra,\,p95\,p97.5})}{1.645}$$

A standard two-sided 95% confidence interval for $\sigma$ derived from the $\chi^2$ distribution is:

$$SD \cdot \sqrt{\frac{df}{\chi^2_{df,0.975}}} \leq \sigma \leq SD \cdot \sqrt{\frac{df}{\chi^2_{df,0.025}}}$$

Equating the two lower bounds as well as the two upper bounds we obtain two equations with two unknowns. Substituting for SD and rearranging we find that $df$ can be found from:

$$\frac{\chi^2_{df,0.975}}{\chi^2_{df,0.025}} = \left(\frac{ln(F_{intra,\,p95\,p97.5})}{ln(F_{intra,\,p95\,p2.5})}\right)^2$$

And then GSD can be calculated as:

$$GSD = exp(SD) = (F_{intra,\,p95\,p97.5})^{\sqrt{\frac{\chi^2_{df,0.025}}{df}}/1.645}$$

A bisection algorithm can be used to find the value for $df$ for which the chi-square ratio in the example is

$$\frac{\chi^2_{df,0.975}}{\chi^2_{df,0.025}} = \left(\frac{ln(10)}{ln(2)}\right)^2 = 11.035$$

This value is attained for $df$ = 6.25. See also van der Voet et al. (2009)

### Intra-species factors data formats

Intra-species factors.

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### Intra-species model parameters

Intra species factors.

Table 3.403: Table definition for Intra-species model parameters.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idEffect | AlphaNumeric (50) | The effect code. | idEffect, EffectId, Effect | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | No |
| IntraSpecies-Lower-VariationFactor | Numeric | The lower uncertainty bound. The p95-sensitive-individual is 'lower bound' times more sensitive than the average individual.The lower and upper bounds are used to derive a geometric standard deviation (gsd) and degrees of freedom (df). | IntraSpecies-LowerVariation-Factor | No |
| IntraSpecies-UpperVariation-Factor | Numeric | The upper uncertainty bound. The p95-sensitive-individual is 'upper bound' times more sensitive than the average individual. The lower and upper bounds are used to derive a geometric standard deviation (gsd) and degrees of freedom (df). | IntraSpecies-UpperVariation-Factor | Yes |
| idPopulation | AlphaNumeric (50) | Unique identification code of the population. | IdPopulation, PopulationId | No |

Accepted table names: IntraSpeciesModelParameters, IntraSpeciesModelParameter, IntraSpeciesFactors, IntraSpeciesFactor.

### Intra species factors settings

### Selection settings

Table 3.404: Selection settings for module Intra species factors.

| Name | Type | Description |
|---|---|---|
| Intra-species factor | Numeric | Intra-species factor. |
| Restrict active substances to substances with available hazard characterisations | Boolean | Restrict assessment group membership based on presence/absen of hazard characterisations. |

### Calculation settings

Table 3.405: Calculation settings for module Intra species factors.

| Name | Type | Description |
|---|---|---|
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |

#### Uncertainty settings

Table 3.406: Uncertainty settings for module Intra species factors.

| Name | Type | Description |
|---|---|---|
| Resample intra-species factor | Boolean | Specifies whether intra-species factors are resampled from a parametric uncertainty distribution. |

#### Intra species factors as data

In the simplest approach, intra-species factors are fixed factors. In a higher tier, lower and upper values for the intra-species factor are used to derive a variability distribution (log-normal around 1) and an uncertainty distribution for the geometric standard deviation related to human variability in sensitivity.

- *Intra species factors data formats*
- *Intra species factors from data*
- *Intra species factors calculation*

Inputs used: *Active substances*

Settings used

- *Calculation Settings*

### 3.5.11 Points of departure

Externally specified points of departure can be used as an alternative to calculated BMDs from dose response models. Points of departure can be of various types, such as NOAEL, LOAEL or BMD. They can be used to construct the list of active substances, to derive relative potency factors, and to perform health impact assessments.

This module has as primary entities: *Substances Effects*

Output of this module is used by: *Active substances Hazard characterisations*

#### Points of departure from data

#### Points of departure data formats

Points of departure, such as NOAELS and BMDs, describe the critical/reference levels of substance dose in relation to the presence or absence of an effect. If available, the uncertainty of externally specified points of departure can be specified with uncertainty sets (empirical distributions representing possible values) in the points of departure uncertainty table.

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#### Points of departure

Nominal points of departure should be presented in this table. Each point of departure should be linked to an effect using the effect code (idEffect) and to substances using the substance code (idSubstance).

Table 3.407: Table definition for Points of departure.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idModel | AlphaNumeric (50) | The dose response model code. | idDose-ResponseModel, idModel, idPod, idPointOf-Departure | No |
| idEffect | AlphaNumeric (50) | The effect code. | idEffect, EffectId, Effect | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Species | AlphaNumeric (50) | The species used to obtain this point of departure. | Species, System | No |
| Value | Numeric | Point of departure, can be of various types, e.g. NOAEL, LOAEL, BMD, CED | PointOf-Departure, LimitDose, HazardDose, Value, CED | Yes |
| Type | *PointOfDeparture-Type* | The type of the point of departure, e.g. NOAEL, LOAEL, BMD. | Type, PODType, HazardDose-Type, LimitDoseType | No |
| DoseUnit | *DoseUnit* | The dose unit (if not specified, then mg/kg is assumed). | DoseUnit, Unit, UnitDose | No |
| Benchmark-Response | AlphaNumeric (100) | The benchmark response or effect size. | Benchmark-Response, CriticalEffect-Size, HazardEffect-Size | No |
| ExposureRoute | *ExposureRoute* | The route of dose administration used in the study to obtain this point of departure. If not specified exposure route = Dietary is assumed. | ExposureRoute, RouteExposure | No |
| IsCriticalEffect | Boolean | Specifies whether this value is the value associated with the critical effect. If omitted, No is assumed. | IsCriticalEffect | No |
| TargetLevel | *TargetLevelType* | The target level, i.e., internal or external. If omitted, external is assumed. | TargetLevel | No |
| Matrix | *BiologicalMatrix* | The biological matrix or organ (should be specified when target level is internal). | Matrix, BiologicalMatrix | No |
| Expression type | *ExpressionType* | The expression type for (internal) hazard characterisations of which the concentrations are not directly specified at the level of the biological matrix. For instance, urinary expressions expressed in terms of the amount excreted per gram of creatinine or blood concentration expressed per gram of lipids. | ExpressionType | No |
| PublicationTitle | AlphaNumeric (250) | Title of the publication of the study in which this hazard | PublicationTitle, Title | No |

Accepted table names: PointsOfDeparture, PointOfDeparture, HazardDoses, HazardDose.

### Points of departure uncertainty

Often, the PODs found for a substance/effect combination are uncertain. This table facilitates in specifying the POD uncertainty in the form of a set of uncertainty values that may additionally be specified for a substance/effect combination.

Table 3.408: Table definition for Points of departure uncertainty.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idDose-ResponseModel | AlphaNumeric (50) | The dose response model code (must correspond to values in id column of DoseResponseModels table). | idDose-ResponseModel | Yes |
| idUncertainty-Set | AlphaNumeric (50) | The identification code of the uncertainty set. During an uncertainty iteration one set will be picked to be the POD value. | idUncertainty-Set, UncertaintyId | Yes |
| idEffect | AlphaNumeric (50) | The effect code. | idEffect, EffectId, Effect | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Point of departure | Numeric | Point of departure, can be of various types, e.g. NOAEL, LOAEL, BMD, CED | PointOf-Departure, HazardDose, LimitDose, CED | Yes |
| DoseResponse-Model-Parameter-Values | AlphaNumeric (200) | A comma separated list of the values of the parameters of the model, format: a=1.2,b=3.4,c=5.6 | DoseResponse-Model-Parameter-Values, ParameterValues | No |

Accepted table names: PointsOfDepartureUncertain, PointOfDepartureUncertain, HazardDosesUncertain, HazardDoseUncertain.

### Points of departure settings

### Selection settings

Table 3.409: Selection settings for module Points of departure.

| Name | Type | Description |
|---|---|---|
| Multiple effects analysis | Boolean | Specifies whether the analysis should consider multiple effects. Otherwise, a single focal effect should be selected. |
| Include related effects of AOP network | Boolean | Include all related key events of the AOP network. |

### Uncertainty settings

Table 3.410: Uncertainty settings for module Points of departure.

| Name | Type | Description |
|---|---|---|
| Perform uncertainty analysis | Boolean | In probabilistic risk assessment of dietary exposure, distributio describe the variability in consumption within a given populatio of individuals and the variability of the occurrence and level of substances in the consumed foods. However, these calculations not consider the amount of uncertainty that is due to the limite size of the underlying datasets. |
| Resample hazard characterisations or RPFs | Boolean | Specifies whether to resample the hazard characterisations or relative potency factors. Requires hazard characterisation or RF uncertainty to be quantified in DoseResponseModelsUncertain RelativePotencyFactorsUncertain tables. |

### Points of departure as data

Points of departure are provided as data for combinations of substance and effect and each is minimally described by a reference value and a type (e.g., NOAEL or LOAEL). In addition, the exposure route, specifies, and references may be specified.

- *Points of departure data formats*
- *Points of departure from data*

Inputs used: *AOP networks*

## 3.5.12 Relative potency factors

Relative potency factors (RPFs) quantify potencies of substances with respect to a defined effect, relative to the potency of a chosen index substance. RPFs can be used to express combined exposures of multiple substances in terms of a the exposure value of the chosen index substance (i.e., in index substance equivalents). In MCRA, hazard characterisations, and therefore also RPFs are based on mass units (e.g., µg), and not on mol units. RPFs can be different for different levels of the human organism (external, internal, specific compartment). RPFs can be given as data or computed from hazard characterisations. RPFs can be specified with uncertainty. Computation from uncertain hazard characterisations allows to include correlations between uncertain RPFs which originate from using the same index substance.

This module has as primary entities: *Substances Effects*

Output of this module is used by: *Food concentrations Food concentration models High exposure food-substance combinations Dietary exposures Internal exposures Exposure mixtures HBM analysis Risks Environmental burden of disease*

### Relative potency factors from data

### Relative potency factors calculation

Relative potency factors (*RPF* s) describe the potency of substances with respect to a defined effect, relative to the potency of a chosen index or reference substance. RPFs are provided as data or computed from *hazard characterisations*. The RPF for substance $i$ is defined by the ratio of hazard characterisation value (*POD*) for the index substance ($\texttt{ref}$) and the hazard characterisation value for substance $i$. That is,

$$\texttt{RPF}_i = \texttt{POD}_{\texttt{ref}} / \texttt{POD}_i.$$

When hazard characterisations are resampled in the uncertainty runs, RPFs are recomputed based on the bootstrapped hazard characterisations. In this way, RPF uncertainty is included in the uncertainty analysis.

### Relative potency factors data formats

Relative potency factors quantify relative potencies of substances with respect to an effect and can be used to express combined exposures of multiple substances in terms of the exposure value of the chosen index substance (i.e., as index substance equivalents). Relative potency factors can be provided in case hazard characterisations are missing. If available, the uncertainty of externally specified RPFs can be specified with uncertainty sets (empirical distributions representing possible values) in an additional table.

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### Relative potency factors

Relative potency factors are linked to an effect using the effect code (idEffect) and to substances using the substance code (idSubstance).

Table 3.411: Table definition for Relative potency factors.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idCompound | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| idEffect | AlphaNumeric (50) | The effect code. | idEffect, EffectId, Effect | Yes |
| RPF | Numeric | The relative potency factor. | RPF, Relative-PotencyFactor, Value | Yes |
| PublicationTitle | AlphaNumeric (250) | Title of the publication of the study in which this relative potency factor was established. | PublicationTitle, Title | No |
| Publication-Authors | AlphaNumeric | Author(s) of the publication of the study in which this relative potency factor was established. | Publication-Authors, Publication-Author, Author, Authors | No |
| PublicationYear | Integer | Year of the publication of the study in which this relative potency factor was established. | PublicationYear, Year | No |
| PublicationUri | AlphaNumeric | Uniform resource identifier of the reference publication. | URI, URL, PublicationURI, PublicationURL | No |
| Description | AlphaNumeric (200) | Additional description of the relative potency factor. | Description, Remark | No |

Accepted table names: RelativePotencyFactors, RelativePotencyFactor.

### Relative potency factor uncertainty

This table contains sets of values representing the uncertainty for relative potency factors.

Table 3.412: Table definition for Relative potency factor uncertainty.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idUncertainty-Set | AlphaNumeric (50) | The uncertainty set identification number. During each uncertainty iteration one set is used. | idUncertainty-Set, UncertaintyId | Yes |
| idEffect | AlphaNumeric (50) | The effect code (must correspond to values in id column of Effects table). | idEffect, EffectId, Effect | Yes |
| idSubstance | AlphaNumeric (50) | The substance code (must correspond to values in id column of Substances table). | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| RPF | Numeric | The relative potency factor. | RPF, Relative-PotencyFactor, Value | Yes |

Accepted table names: RelativePotencyFactorsUncertain, RelativePotencyFactorUncertain.

### Relative potency factors settings

### Calculation settings

Table 3.413: Calculation settings for module Relative potency factors.

| Name | Type | Description |
|---|---|---|
| Multiple effects analysis | Boolean | Specifies whether the analysis should consider multiple effects. Otherwise, a single focal effect should be selected. |
| Include related effects of AOP network | Boolean | Include all related key events of the AOP network. |
| Index substance | AlphaNumeric | The substance of interest or index substance. |

### Uncertainty settings

Table 3.414: Uncertainty settings for module Relative potency factors.

| Name | Type | Description |
|---|---|---|
| Resample hazard characterisations or RPFs | Boolean | Specifies whether to resample the hazard characterisations or relative potency factors. Requires hazard characterisation or RF uncertainty to be quantified in DoseResponseModelsUncertain RelativePotencyFactorsUncertain tables. |
| Lower uncertainty limit (%) | Numeric | Percentage lower bound, e.g. 2.5%. |
| Upper uncertainty limit (%) | Numeric | Percentage upper bound, e.g. 97.5%. |

### Relative potency factors as data

Data are provided in the form of a RPF for a specific substance and effect.

- *Relative potency factors data formats*
- *Relative potency factors from data*

Inputs used: *Active substances AOP networks*

Settings used

- *Calculation Settings*

#### Calculation of relative potency factors

RPFs are computed from hazard characterisations.

- *Relative potency factors calculation*

Inputs used: *Hazard characterisations*

Settings used

- *Calculation Settings*

## 3.6 In-silico modules

Two types of *in-silico* models are available: QSAR models specify assessment group memberships for active substances, as numbers in the interval [0,1]. This allows both crisp (0 or 1) and probabilistic memberships. Molecular docking models specify binding energies and thresholds which can be used to convert binding energies to assessment group memberships for active substances.

### 3.6.1 Molecular docking models

Molecular docking models specify binding energies for substances in specific molecular docking models related to a specific health effect (adverse outcome).

This module has as primary entities: *Substances Effects*

Output of this module is used by: *Active substances*

#### Molecular docking models from data

'In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when a ligand and a target are bound to each other to form a stable complex.[1] Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using, for example, scoring functions….'

See In Wikipedia.

#### Molecular docking models data formats

**Required data tables:**

- Molecular docking models, to identify models for a specified effect (receptor)
- Molecular docking binding energies, to specify the binding energies per substance for the receptor

Contains definitions of molecular docking models for a given effect (molecular initiating event), for example parameters needed in the conversion of binding energies to group memberships or to relative potency factors. Substance specific binding energies are specified in the binding energies table.

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#### Molecular docking models

Each docking model has a unique identifier, and optionally a name and a description. Each model is linked to an effect using the idEffect field and optionally a binding threshold and the number of receptors can be added. A reference to the source of the data can be stored in the reference field.

Table 3.415: Table definition for Molecular docking models.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| id | AlphaNumeric (50) | The unique identification code of the molecular docking model. | idMolecular-DockingModel, idBinding-EnergyModel | Yes |
| Name | AlphaNumeric (100) | The name of the molecular docking model. | Name | No |
| Description | AlphaNumeric (200) | Description of the molecular docking model. | Description | No |
| idEffect | AlphaNumeric (50) | The effect code, typically for the Molecular Initiating Event that is modelled | idEffect, EffectId, Effect | Yes |
| Threshold | Numeric | Threshold Molecular Docking binding energy (group membership = 1 when higher). | | Yes |
| NumberOf-Receptors | Integer | Example parameter needed for translating Molecular Docking binding energies to RPFs. | | No |
| Reference | AlphaNumeric (200) | External reference(s) to sources containing more information about the molecular docking model. | References | No |

Accepted table names: MolecularDockingModels, MolecularDockingModel, BindingEnergyModels, BindingEnergyModel.

### Molecular docking binding energies

Molecular docking model binding energies per substance

Table 3.416: Table definition for Molecular docking binding energies.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idMolecular-DockingModel | AlphaNumeric (50) | The id of the molecular docking model or source. | idMolecular-Docking, Molecular-DockingModel | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| BindingEnergy | Numeric | Molecular Docking binding energy. | Molecular-Docking-BindingEnergy | Yes |

Accepted table names: MolecularBindingEnergies, MolecularBindingEnergy, BindingEnergies, BindingEnergy, MolecularDockingBindingEnergies, MolecularDockingBindingEnergy.

#### Molecular docking models

#### Calculation settings

Table 3.417: Calculation settings for module Molecular docking models.

| Name | Type | Description |
|---|---|---|
| Multiple effects analysis | Boolean | Specifies whether the analysis should consider multiple effects. Otherwise, a single focal effect should be selected. |
| Include related effects of AOP network | Boolean | Include all related key events of the AOP network. |

#### Molecular docking models as data

Binding energies for substances in specific molecular docking models related to a specific health effect (adverse outcome) are provided as data.

- *Molecular docking models data formats*
- *Molecular docking models from data*

Inputs used: *AOP networks*

Settings used

- *Calculation Settings*

### 3.6.2 QSAR membership models

QSAR membership models specify assessment group memberships for active substances related to a specific health effect (adverse outcome). Memberships should be derived externally from Quantitative Structure-Activity Relationship (QSAR) models.

This module has as primary entities: *Substances Effects*

Output of this module is used by: *Active substances*

#### QSAR membership models from data

'Quantitative structure-activity relationship models (QSAR models) are regression or classification models used in the chemical and biological sciences and engineering. Like other regression models, QSAR regression models relate a set of "predictor" variables (X) to the potency of the response variable (Y), while classification QSAR models relate the predictor variables to a categorical value of the response variable….'

See In Wikipedia.

#### QSAR membership models data formats

Required data tables:

- QSAR membership models, to identify QSAR models for a specified health effect
- QSAR membership scores, to specify the memberships per substance per QSAR model

Note that only memberships 1 (include) and 0 (exclude) are allowed.

Substance membership models obtained from QSAR for a given (health) effect. The models are defined in the membership models table, and substance specific memberships are specified in the QSAR memberships table.

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### QSAR membership models

This table contains the definitions of the QSAR membership models. Each model contains a id, name, an optional description, and refers to its related health effect.

Table 3.418: Table definition for QSAR membership models.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| id | AlphaNumeric (50) | The unique identification code of the QSAR membership model. | id, Model, ModelCode, idModel, QSARModel, idQSARModel, QSAR-Membership-Model, idQSAR-Membership-Model, Membership-Model, idMembership-Model | Yes |
| Name | AlphaNumeric (100) | The name of the QSAR membership model. | Name | No |
| Description | AlphaNumeric (200) | Description of the QSAR membership model. | Description | No |
| idEffect | AlphaNumeric (50) | The effect code. | idEffect, EffectId, Effect | Yes |
| Accuracy | Numeric | Accuracy of the QSAR membership model. | Accuracy | No |
| Sensitivity | Numeric | Sensitivity of the QSAR membership model. | Sensitivity | No |
| Specificity | Numeric | Specificity of the QSAR membership model. | Specificity | No |
| Reference | AlphaNumeric (200) | External reference(s) to sources containing more information about the QSAR model. | References | No |

Accepted table names: QSAR, QSARMembershipModels, QSARMembershipModel, QSARModels, QSARModel.

### QSAR membership scores

Substance membership score according to the QSAR model.

Table 3.419: Table definition for QSAR membership scores.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idQSAR-Membership-Model | AlphaNumeric (50) | The id of the QSAR model. | Model, ModelCode, idModel, QSARModel, idQSARModel, QSAR-Membership-Model, idQSAR-Membership-Model, Membership-Model, idMembership-Model | Yes |
| idSubstance | AlphaNumeric (50) | The code of the substance. | idSubstance, SubstanceId, SubstanceCode, Substance | Yes |
| Membership-Score | Numeric | QSAR membership score. Value should be 1 for positive membership, or 0 for negative membership. | Membership-Score, Membership, QSARScore, Score | Yes |

Accepted table names: QSARMembershipScores, QSARMembershipScore, QSARMemberships, QSARMembership.

### QSAR membership models

### Calculation settings

Table 3.420: Calculation settings for module QSAR membership models.

| Name | Type | Description |
|---|---|---|
| Multiple effects analysis | Boolean | Specifies whether the analysis should consider multiple effects. Otherwise, a single focal effect should be selected. |
| Include related effects of AOP network | Boolean | Include all related key events of the AOP network. |

### QSAR membership models as data

QSAR memberships models are provided as data, per QSAR model assessment group memberships for active substances related to a specific health effect are specified.

- *QSAR membership models data formats*
- *QSAR membership models from data*

Inputs used: *AOP networks*

Settings used

- *Calculation Settings*

## 3.7 Kinetic modules

Kinetic models convert exposures or hazard characterisations from one or more external routes or compartments to an internal compartment or biological matrix. Internal exposure can be systemic or related to a specific biological matrix in a kinetic model (target). The reverse conversion from internal to external is called reverse dosimetry.

In a simple tier, kinetic models are specified as absorption factors (systemic). In a higher tier, physiologically based (toxico)kinetic (PBK) models of a specified type (currently available is the EuroMix generic PBK model) are linked to MCRA. Kinetic model instances for specific substances and test systems (e.g. cypermethrin in the rat) are specified with parameter sets for the chosen kinetic model.

There are 3 tiers for relating external to internal exposures (doses):

1. Assume conservative absorption factors as suggested by *EFSA* (EFSA (2014), EFSA (2017a)): oral and inhalation 100%, dermal 50%. The internal exposure is systemic (*absorption factors data tables*).
2. Use externally provided kinetic conversion factors, converting the exposure to an internal target (biological matrix) or organ (*kinetic conversion factors data tables*).
3. Use *PBK models*, with instances for specific substances defined in data table *kinetic model instances* and model parameters specified in data table *kinetic model instance parameters*.

Given a chosen tier, the calculation will fall back to the next lower tier in case of missing data.

### 3.7.1 Absorption factors

Absorption factors are simple kinetic conversion factors used to convert external exposure from one or more routes to an internal dose (systemic).

This module has as primary entities: *Substances*

Output of this module is used by: *Internal exposures Hazard characterisations*

#### Absorption factors from data

#### Absorption factors data formats

**Data tables:**

- Absorption factors

Absorption factors are chemical- and route-specific values representing the fraction of external exposures passing the absorption barrier.

#### Kinetic absorption data format

Absorption factor data format.

Download empty dataset template: Zipped CSV Excel

#### Absorption factors

Absorption factors translating external (daily) exposures for specific routes to the resulting internal (systemic, daily) intakes.

Table 3.421: Table definition for Absorption factors.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idCompound | AlphaNumeric (50) | code of substance (must correspond to values in id column of Substances table) | idSubstance, SubstanceId, SubstanceCode, Substance | No |
| Route | *ExposurePathType* | Non-dietary route or pathway, use 'Oral', 'Dermal', or 'Inhalation' to specify the route. | Route, Pathway | Yes |
| Absorption-Factor | Numeric | absorption factor value | Absorption-Factor, Factor | Yes |

Accepted table names: KineticAbsorptionFactors, KineticAbsorptionFactor, AbsorptionFactors, AbsorptionFactor.

### Absorption factors settings

### Calculation settings

Table 3.422: Calculation settings for module Absorption factors.

| Name | Type | Description |
|---|---|---|
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Exposure routes | ExposureRoutes | Exposure routes included in assessment. |
| Restrict active substances to substances with available hazard characterisations | Boolean | Restrict assessment group membership based on presence/absen of hazard characterisations. |
| Default oral absorption factor | Numeric | When there is no kinetic model and absorption factors are not specified in file, oral exposures (external doses) are multiplied b this factor to determine the absorbed (internal) dose. |
| Default dermal absorption factor for non-dietary exposure | Numeric | When there is no kinetic model and absorption factors are not specified in file, dermal exposures (external doses) are multiplie by this factor to determine the absorbed (internal) dose. |
| Default inhalation absorption factor for non-dietary exposure | Numeric | When there is no kinetic model and absorption factors are not specified in file, inhalation exposures (external doses) are multiplied by this factor to determine the absorbed (internal) do |

### Absorption factors as data

Absorption factors are chemical- and route-specific values representing the fraction of external exposures passing the absorption barrier. The corresponding exposure is referred to as internal dose.

- *Absorption factors data formats*
- *Absorption factors from data*

Inputs used: *Active substances*

Settings used

- *Calculation Settings*

## 3.7.2 Kinetic conversion factors

External exposure can be from one or more exposure routes: oral (dietary or non-dietary), dermal or inhalation and is converted to an internal concentration by a kinetic conversion factor. The internal concentration is related to a specific compartment *(biological matrix)* in a kinetic model.

This module has as primary entities: *Substances*

Output of this module is used by: *Internal exposures HBM analysis Hazard characterisations*

### Kinetic conversion factors from data

In table *Kinetic conversion factors*, conversion factors are specified to convert biomarkers from one *biological matrix* to another biological matrix. This specification may include *expression type* and/or *exposure route*.

Kinetic conversion factors may be dependent on individual properties like age and *gender*. Specify in table *Kinetic conversion factor subgroups* (kinetic conversion factor subgroups) age and/or gender specific kinetic conversion factors.

For age, specify the lower bound of the age interval (in years) of the kinetic conversion factor subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower age of the next subgroup.

Check option *Use kinetic conversion factors subgroup* (default) to use age and/or gender specific kinetic conversion factors in your assessment (only visible when the datasource contains age/gender specific subgroup information).

For more information, see *internal concentrations using kinetic conversion factors* in module Internal exposures for conversion to blood standardised concentrations by lipids and/or urine standardised or normalised concentrations by repectively creatinine or specific gravity.

For kinetic conversion factor uncertainty distributions see *uniform*, *lognormal*, *beta* and *inverse uniform* distribution.

### Kinetic conversion factors calculation

Specify the compartments and routes, and estimate kinetic conversion factors using PBK models to compute internal concentrations from external exposures.

### Kinetic conversion factors data formats

**Data tables:**

- Kinetic conversion factors

Kinetic conversion factors convert external exposures from one or more external routes (dietary, non-dietary oral, dermal, inhalation) to an internal (target) compartment.

### Kinetic conversion data format

The kinetic conversion factor data format.

Download empty dataset template: Zipped CSV Excel

### Kinetic conversion factors

Kinetic conversion factors translating external (daily) exposures for specific routes to the resulting internal target intakes.

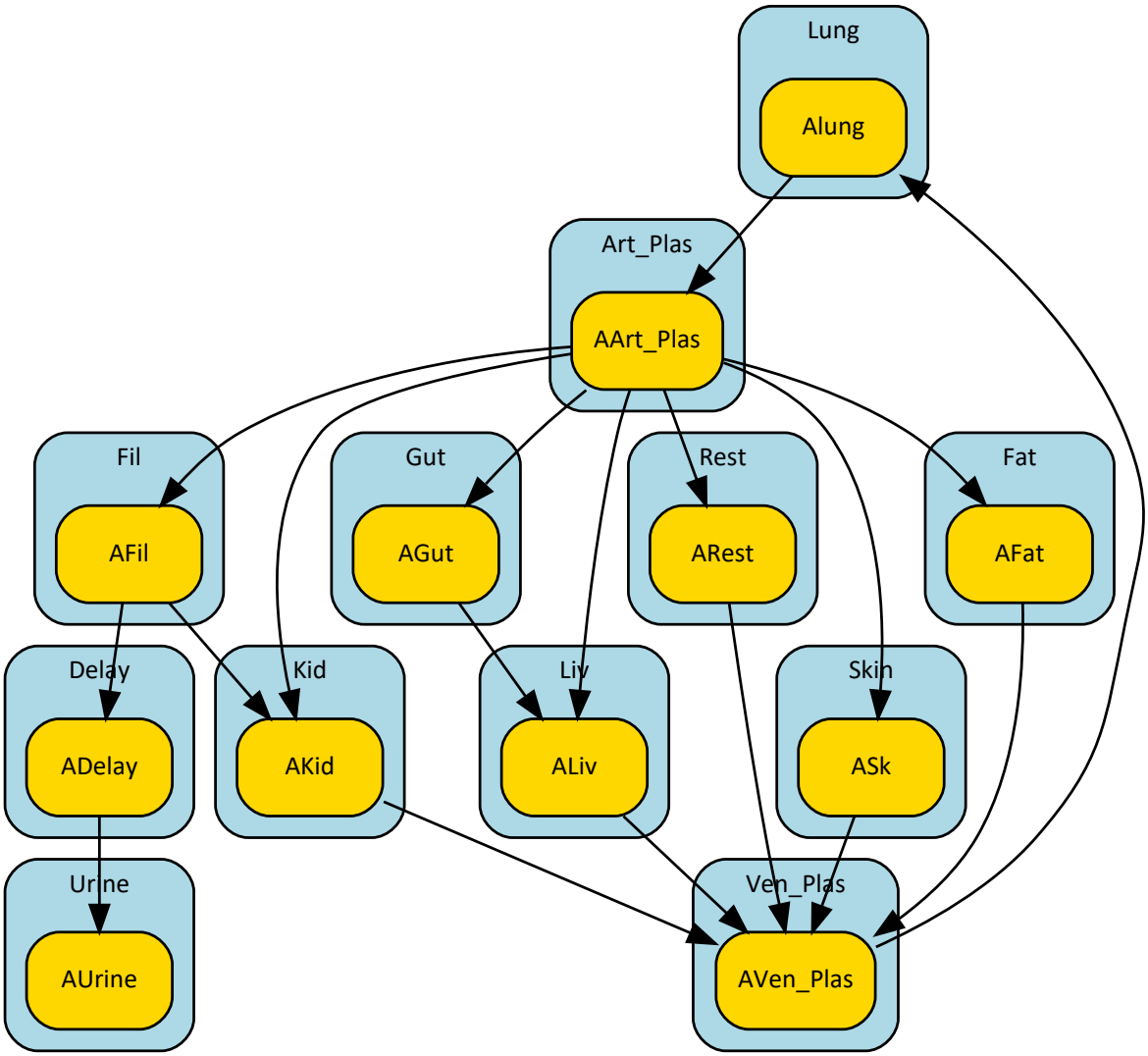


Figure 3.79: Kinetic compartments

Table 3.423: Table definition for Kinetic conversion factors.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idKinetic-Conversion-Factor | AlphaNumeric (50) | Id of the kinetic conversion factor | idKinetic-Conversion-Factor, idConversion-Factor, idKCFactor | Yes |
| idSubstance-From | AlphaNumeric (50) | Code of substance (must correspond to values in id column of Substances table) | idSubstance-From, SubstanceId-From, SubstanceCode-From, SubstanceFrom | Yes |
| ExposureRoute-From | *ExposureRoute* | The exposure route (only applicable if target level is external). If not specified, Dietary is assumed. | ExposureRoute | No |
| Biological matrix from | *BiologicalMatrix* | If applicable, the source matrix of the human body (e.g., blood, urine) to convert from. When specified, the measurements are considered at the level of internal doses. | MatrixSource, SourceMatrix | No |
| DoseUnitFrom | *DoseUnit* | The unit of the substance dose to convert from. | UnitSource, SourceUnit | Yes |
| Expression-TypeFrom | *ExpressionType* | The expression type or adjustment method of the dose unit (from). This field specifies how the dose unit (source) is adjusted, e.g. for blood lipids for fat soluble biomarkers ('mg/g lipids') or the dilution level of the urine ('mg/g creatinine'). | ExpressionType-From, Adjustment-MethodFrom | No |
| idSubstanceTo | AlphaNumeric (50) | Code of substance (must correspond to values in id column of Substances table) | idSubstanceTo, SubstanceIdTo, SubstanceCode-To, SubstanceTo | Yes |
| ExposureRoute-To | *ExposureRoute* | The exposure route (only applicable if target level is external) to convert to. If not specified, Dietary is assumed. | ExposureRoute | No |
| Biological matrix to | *BiologicalMatrix* | If applicable, the matrix of the human body (e.g., blood, urine) to convert to. When specified, the measurements are considered at the level of internal doses. | MatrixTarget, TargetMatrix | No |
| DoseUnitTo | *DoseUnit* | The unit of the substance dose to convert to. | UnitTarget, TargetUnit | Yes |
| Expression-TypeTo | *ExpressionType* | The expression type or adjustment method of the dose unit (to). This field specifies how the dose unit (target) is adjusted, e.g. for blood lipids for fat soluble biomarkers ('mg/g lipids') or the dilution level of the urine ('mg/g creatinine'). | ExpressionType-To, Adjustment-MethodTo | No |
| Conversion-Factor | Numeric | Conversion factor value | Conversion-Factor, Factor | Yes |

Accepted table names: KineticConversionFactors, KineticConversionFactor.

### Kinetic conversion factor subgroups

Kinetic conversion factor subgroups.

Table 3.424: Table definition for Kinetic conversion factor subgroups.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idKinetic-Conversion-Factor | AlphaNumeric (50) | Id of the kinetic conversion factor | idKinetic-Conversion-Factor, idConversion-Factor, idKCFactor | Yes |
| Conversion-Factor | Numeric | Conversion factor value | Conversion-Factor, Factor | Yes |
| AgeLower | Numeric (50) | Specifies the lower bound of the age interval (in years) of the kinetic conversion factor subgroup. Individuals belong to a subgroup when the age of the individual is equal or greater than the specified lower bound and smaller than the specified lower age of the next subgroup. | AgeLower, LowerAge | No |
| Gender | *GenderType* | The gender of the kinetic conversion factor subgroup. | Gender, Sex | No |
| Uncertainty-Upper | Numeric | The upper value of the distribution. If the distribution is uniform, then it is the upper bound of the uniform distribution. If the distribution is log-normal, then the upper value is assumed to correspond with the p95 percentile of the distribution. When a distribution is assumed, this value should be greater than the conversion factor. | Uncertainty-Upper, Upper | No |

Accepted table names: KineticConversionFactorSGs, KCFactorSubGroups.

### Kinetic conversion factors settings

### Calculation settings

Table 3.425: Calculation settings for module Kinetic conversion factors.

| Name | Type | Description |
|---|---|---|
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Exposure routes | ExposureRoutes | Exposure routes included in assessment. |
| Restrict active substances to substances with available hazard characterisations | Boolean | Restrict assessment group membership based on presence/abser of hazard characterisations. |
| Use kinetic conversion factors subgroup | Boolean | Kinetic conversion factors are dependent on subgroups (e.g. bas on age or gender, see dataformats KineticConversionfactorsSGs |
| Target biological matrix | *BiologicalMatrix* | The internal target/matrices for which kinetic conversion factor are to be computed. |
| PBK model simulations | Numeric | Number of PBK model simulations used to derive kinetic conversion factors from PBK model simulations. |
| Exposure range minimum | Numeric | Minimum of the external exposure range for PBK model simulations used to derive kinetic conversion factors from PBK model simulations. |
| Exposure range maximum | Numeric | Maximum of the external exposure range for PBK model simulations used to derive kinetic conversion factors from PBK model simulations. |
| Compute between internal target conversion factors | Boolean | Compute kinetic conversion factors to extrapolate exposures/concentrations between internal targets/matrices. |
| Number of simulated days | Numeric | The total duration (in days) of the PBK model simulations. |
| Exposure events and dose generation method | *ExposureEventsGeneration-Method* | Generates doses and events for PBK model |
| Number of initial days skipped | Numeric | The initial period (or burn-in period, specified in days) that nee to be skipped when calculating the steady-state or peak internal exposures from the simulated time series. |
| Use PBK model parameter variability | Boolean | When specified, use parameter variability. |
| PBK simulation method | *PbkSimulationMethod* | Specifies in which mode to run the PBK model |
| Lifetime start age in years | Numeric | The starting age (in years) for lifetime range simulation. |
| Lifetime end age in years | Numeric | The ending age (in years) for lifetime range simulation. |
| Lifetime window size in years | Numeric | The size of the time window (in years) for the lifetime window simulation. |
| Use bodyweight adjusted exposures | Boolean | Use bodyweight adjusted exposures in PBK model simulations. |
| Allow fallback to systemic dosing for missing exposure routes | Boolean | If the PBK model misses specific compartments for certain exposure routes, this setting allows the model to fallback to systemic dosing for those route. |
| PBK output resolution time unit | *PbkModelOutputResolution-TimeUnit* | Time unit in which the output resolution of PBK model simulations is specified. |
| PBK output resolution step size | Numeric | PBK model simulation output step size/length, specifying the evaluation resolution in terms of the step length (period) betwe two evaluations. For example, a step length of 12 with a resolut time unit of hours is interpreted as every 12 hours. |
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |

#### Uncertainty settings

Table 3.426: Uncertainty settings for module Kinetic conversion factors.

| Name | Type | Description |
|---|---|---|
| Resample kinetic conversion factors | Boolean | Specifies whether kinetic conversion factors are resampled. |

#### Kinetic conversion factors as data

Specify kinetic conversion factors as data.

- *Kinetic conversion factors data formats*
- *Kinetic conversion factors from data*

Inputs used: *Active substances*

Settings used

- *Calculation Settings*

#### Calculation of kinetic conversion factors

By specifying compartments and routes, PBK models can be used to estimate kinetic conversion factors and compute internal concentrations based on external exposures

- *Kinetic conversion factors calculation*

Inputs used: *PBK model parametrisations*

Settings used

- *Calculation Settings*

### 3.7.3 PBK model definitions

Output of this module is used by: *PBK model parametrisations*

#### PBK model definitions from data

PBK models can either be uploaded as data (in the SBML format) or can be selected from the collection of embedded models

#### PBK model definitions data formats

PBK models can also be uploaded to the data repository in the Systems Biology Markup Language (SBML) file format (with extension *.sbml*). Currently only level 3 version 2 is supported.

SBML has three main purposes:

- enable the use of multiple software tools without having to rewrite models to conform to every tool's idiosyncratic file format;
- enable models to be shared and published in a form that other researchers can use even when working with different software environments;
- ensure the survival of models beyond the lifetime of the software used to create them.

### PBK model definitions as data

PBK models can either be uploaded as data (in the SBML format) or can be selected from the collection of embedded models

- *PBK model definitions data formats*
- *PBK model definitions from data*

Physiologically based kinetic (PBK) models are mathematical representations of the animal or human body aimed at describing and predicting the time course distribution of chemicals in tissues and organs. Those internal dose metrics can usefully replace external exposure dose in the derivation of the quantitative dose-response relationships and following risk assessments. PBK models can simulate both internal doses from exposure scenarios (forward dosimetry) and external dose from biomonitoring data (reverse dosimetry).

This module provides two ways for including PBK models: 1) use uploaded PBK models implemented in SBML as data, or 2) use one of the available PBK models embedded in MCRA.

### Embedded PBK models

The following generic PBK models are currently implemented in MCRA:

- *EuroMix generic PBK model* of Tebby et al. (2020).
- *Bisphenol PBK model ETHZ* of Karrer et al. (2019).

The MCRA interface allows to run PBK models for any number of days and supplies an option to skip an initial number of days (build-up phase PBK model) in the calculation of the internal exposure.

In the original bisphenol PBK model of Karrer et al. (2019), doses were applied on fixed time points and only for the first four days. For oral exposure, three dosings per day with t = 0, 6 and 12 h, for dermal exposure to PCPs and TP, two dosings per day with t = 0 and 12 h. The steady state was reached after dosing on four consecutive days. Therefore, the bisphenol PBK model described in *Karrer et al.* should be run for four days to reached steady state and the number of initial days to be skipped should be set to 0. Note, no dosing is applied from day 5th onwards.

These restrictions were relaxed in a new implementation of the bisphenol PBK model (General Model BPA Re-implementation). In this new version the number of days is unlimited. Dosings are specified through the user interface including the definition on the non-stationary period, see *settings PBK models*.

### EuroMix generic PBK model

Reference: Tebby et al. (2020)

In MCRA updated versions (version 4b, 6) of the PBK model developed at INERIS in the framework of the COSMOS project is used. The model describes the distribution of chemicals in venous blood, arterial blood, adipose tissues, poorly perfused tissues (muscles), gut lumen, liver, richly perfused tissues (other viscera), and skin. Each of those is described as a compartment (homogeneous virtual volume) in which distribution is instantaneous and limited only by the incoming blood flow or rate of entry in the compartment. Exposure can occur through the dermal route, ingestion or inhalation. The absorbed molecules can be excreted to urine, exhaled through the lung, or metabolized in liver.

The EuroMix generic PBK model is coded as a set of ordinary differential equations. There is one such equation per time-dependent chemical quantity of the model (so-called state variables). There are 13 state variables in the model: the quantity of chemical in venous blood ($Q_{ven}$), in arterial blood ($Q_{art}$), in adipose tissues ($Q_{fat}$), in poorly perfused tissues ($Q_p$), in well perfused tissues ($Q_r$), in liver ($Q_{liv}$), in unexposed skin ($Q_{s,u}$), in exposed skin ($Q_{s,e}$), in the stratum corneum of unexposed skin ($Q_{sc,u}$), in exposed stratum corneum ($Q_{sc,e}$), in gut lumen ($Q_{gut}$), the quantity excreted to urine ($Q_{ex}$), and the quantity metabolized ($Q_{met}$). The model can predict, as a function of time, for given oral, dermal and/or inhalation exposures, all the above quantities and the corresponding concentrations as a function of time. Concentrations are obtained by dividing quantities by compartment volumes Tebby et al. (2020).

In Figure 3.81 a time course of the internal substance amount ($\mu g$) for Clothianidin in the liver is shown. For 50 consecutive days a bolus per day is submitted. The red line shows the substance amount varying over time. The green line displays the average of the peaks representing acute exposure, the blue line displays the steady state representing chronic exposure, all after skipping a nonstationary period of 10 days (the vertical black line).

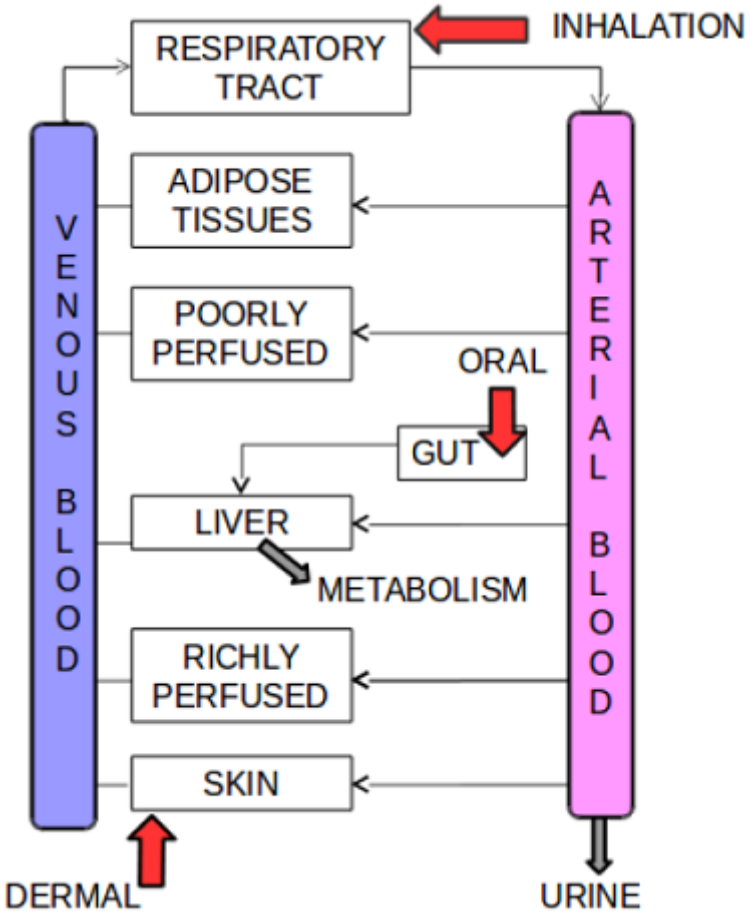


Figure 3.80: Schematic representation of the EuroMix Generic PBK model.

From the substance amount, a concentration is computed by dividing it by the total compartment weight (i.e., the mass/volume of the compartment/organ).

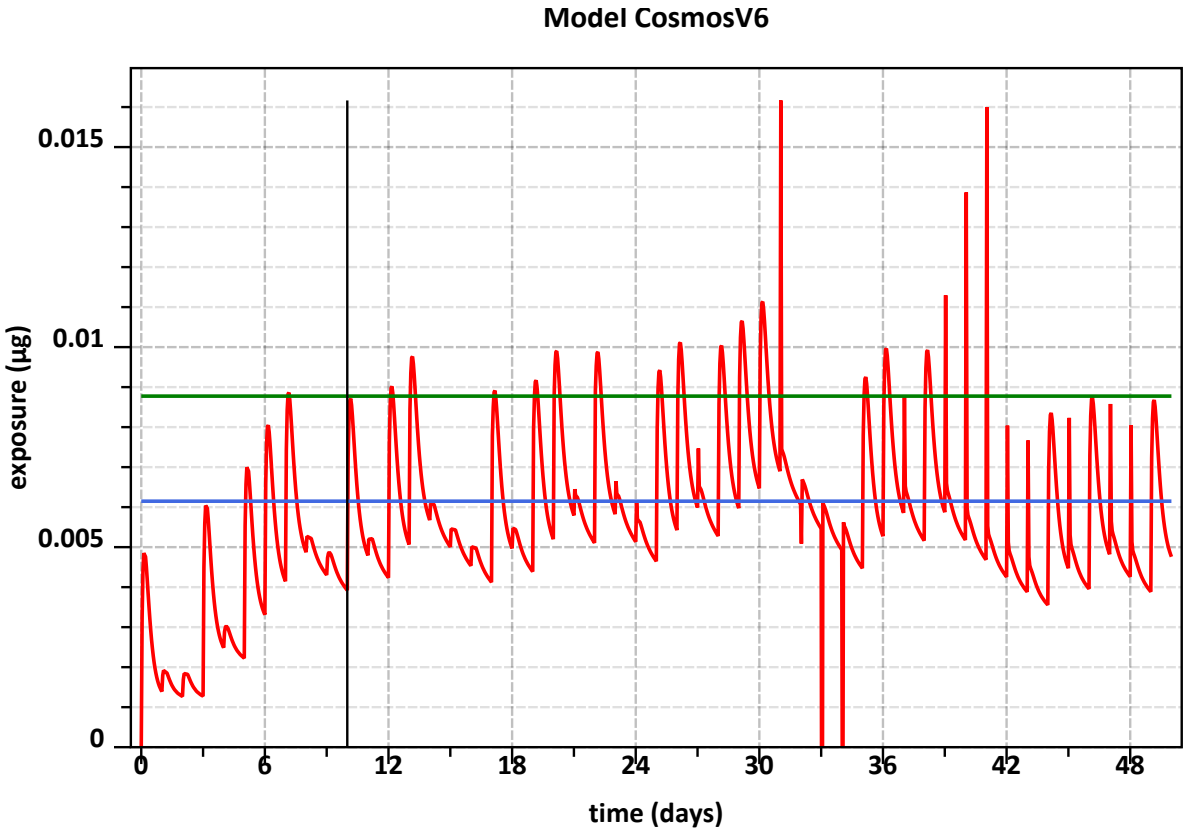


Figure 3.81: Time course of exposure ($\mu g$) for Clothianidin in the liver (EuroMix generic PBK model version 6).

In Figure 3.82, for a large number of individuals the internal exposure (acute, green dots) in the liver is plotted versus the external exposure ($\mu g/kgbw$). The diagonal represents the 1:1 ratio of internal vs external exposure.

### Bisphenol model

Reference: Karrer et al. 2019: Karrer et al. (2019)

'Structural analogs such as the bisphenols S, F, and AF (BPS, BPF, BPAF) are used to replace the endocrine disrupting chemical bisphenol A (BPA), but they exert estrogenic effects in the same order of magnitude. In order to investigate the consequences of BPA restrictions, we assessed the cumulative risk from BPA, BPS, BPF, and BPAF in Europe before and after the first BPA restrictions in 2011. We modelled external exposures from food, personal care products (PCPs), thermal paper, and dust, using the models MCRA and PACEM for food and PCPs, respectively. We calculated internal concentrations of unconjugated BPs with substance-specific PBK models and cumulated concentrations by taking into account relative estrogenic potencies. Average cumulative exposure to unconjugated BPs was 3.8 and 2.1 ng/kg bw/day before and after restrictions, respectively. The decline was mostly caused by the replacement of BPA with BPS in thermal paper. Therefore, the margins of exposure (MOEs) for estrogenic effects were mostly higher after the restrictions. However, in high uncertainty percentiles the MOEs were partly lower than before (e.g. the MOEs for the uncertainty P97.5 of the variability P99 were 2.6 and 1.9 before and after restrictions, respectively), which shows the higher uncertainty around exposures for substitutes compared to BPA.'

Abstract: Linking probabilistic exposure and pharmacokinetic modelling to assess the cumulative risk from the bisphenols BPA, BPS, BPF, and BPAF for Europeans. Authors: Cecile Karrer, Waldo de Boer, Christiaan Delmaar, Yaping Cai, Amélie Crépet, Konrad Hungerbühler, Natalie von Goetz

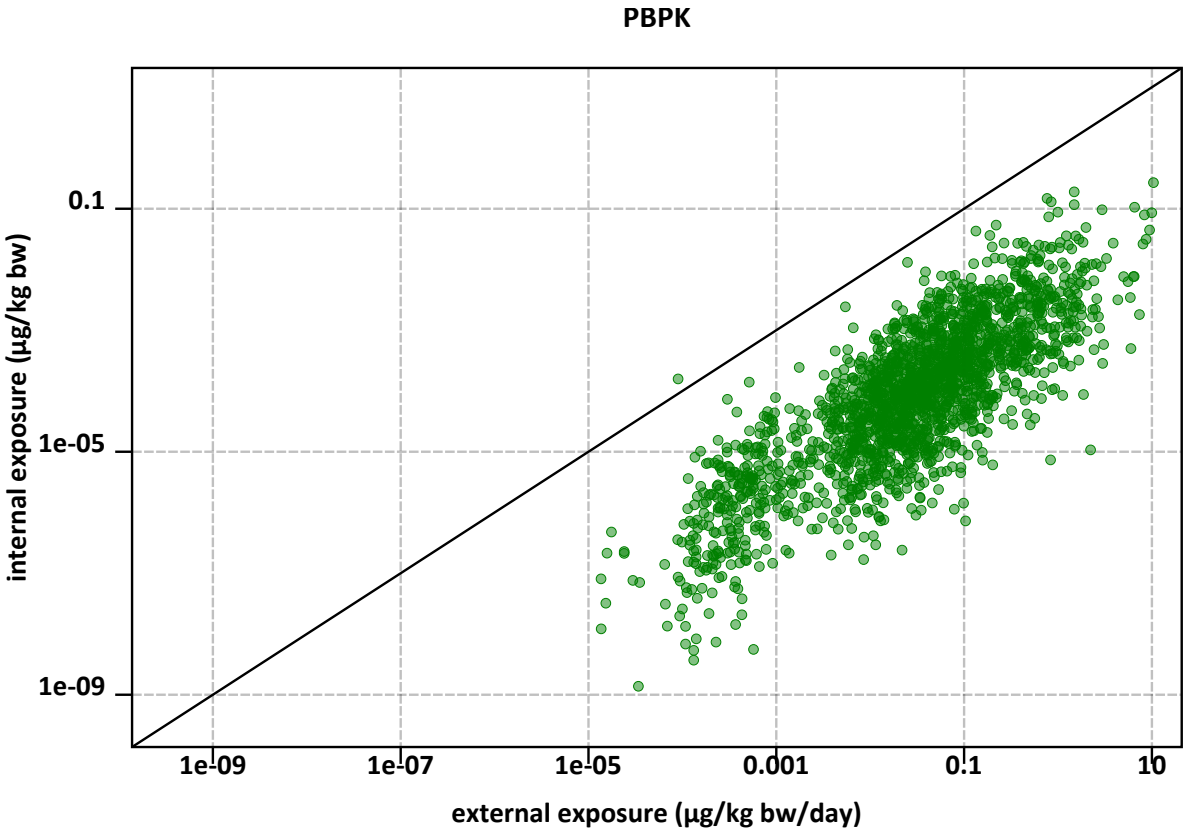


Figure 3.82: Internal versus external exposure for Clothianidin in the liver (EuroMix Generic PBK model version 6).

### Embedded model specifications

This section serves as a reference, providing the technical specifications for using/linking the PBK models embedded in MCRA.

### EuroMix Bisphenols PBPK model (v1)

EuroMix Bisphenols PBPK model by Karrer et al. (23 July 2018).

Table 3.427: Exposure routes (forcings)

| Id | Description | Unit |
|---|---|---|
| Oral | Oral exposure | nmoles |
| Dermal | Dermal exposure | nmoles |
| Inhalation | Inhalation exposure | nmoles |

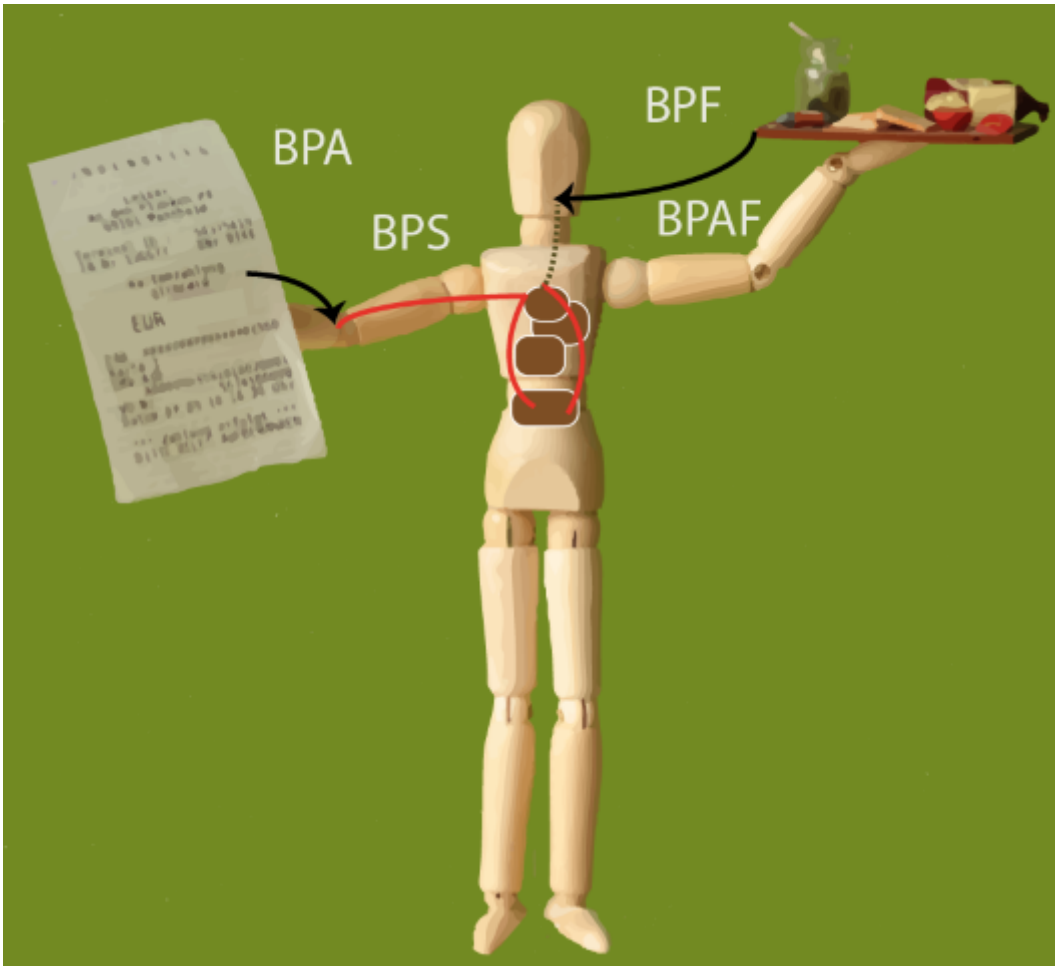


Figure 3.83: Graphical abstract 'Linking probabilistic exposure and pharmacokinetic modelling to assess the cumulative risk from the bisphenols BPA, BPS, BPF, and BPAF for Europeans.'

Table 3.428: Model outputs

| Id | Description | ScalingFactor | Multiplication-Factor | Unit |
|---|---|---|---|---|
| CPlasmaOut | Concentration in plasma | | | nmol/L |
| CGonadOut | Concentration in gonads | | | nmol/L |
| AurinebpaOut | Cumulative excretion of BPA in urine | | | nmoles |
| AurinegOut | Cumulative excretion of BPA-g in urine | | | nmoles |
| AurineTotalOut | Cumulative excretion of BPA and metabolites in urine | | | nmoles |

Table 3.429: Model parameters

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| BW | Bodyweight | | kg | BodyWeight |
| QCC | Cardiac output | | L/min | Physiological |
| QgonadC | Fractional blood flow to gonads | | | Physiological |
| QliverC | Fractional blood flow to liver | | | Physiological |
| QfatC | Fractional blood flow to fat tissue | | | Physiological |
| QbrainC | Fractional blood flow to brain | | | Physiological |
| QskinC | Fractional blood flow to skin | | | Physiological |
| QmuscleC | Fractional blood flow to gonads | | | Physiological |
| VplasmaC | Fractional volume of plasma | | | Physiological |
| VfatC | Fractional volume of fat tissue | | | Physiological |
| VliverC | Fractional volume of liver tissue | | | Physiological |
| VbrainC | Fractional volume of brain tissue | | | Physiological |
| VskinC | Fractional volume of skin tissue | | | Physiological |
| VgonadC | Fractional volume of gonads | | | Physiological |
| VmuscleC | Fractional volume of muscle tissue | | | Physiological |
| VrichC | Fractional volume of richly perfused tissue | | | Physiological |
| VbodygC | Distribution volume of BPA-g | | | Physiological |

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Table 3.429 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| VbodysC | Distribution volume of BPA-s | | | Other |
| MW | Molecular weight | | g/mol | MolecularWeight |
| pliver | Partition coefficient liver to blood | | | PartitionCoefficient |
| pfat | Partition coefficient fat to blood | | | PartitionCoefficient |
| pslow | Partition coefficient slowly perfused tissue to blood | | | PartitionCoefficient |
| prich | Partition coefficient richly perfused tissue to blood | | | PartitionCoefficient |
| pgonad | Partition coefficient gonads to blood | | | PartitionCoefficient |
| pbrain | Partition coefficient brain to blood | | | PartitionCoefficient |
| pskin | Partition coefficient skin to blood | | | PartitionCoefficient |
| geC | Gastric emptying | | 1/h/kg bw^-0.25 | Physicochemical |
| k0C | Oral uptake from the stomach into the liver | | 1/h/kg bw^-0.25 | Physicochemical |
| k1C | Oral uptake from the small intestine into the liver | | 1/h/kg bw^-0.25 | Physicochemical |
| k4C | Fecal elimination from small intestine after oral administration | | 1/h/kg bw^-0.25 | Physicochemical |
| kGIingC | Transport of glucuronide from enterocytes into serum | | 1/h/kg bw^-0.25 | Physicochemical |
| kGIinsC | Transport of sulfate from enterocytes into serum | | 1/h/kg bw^-0.25 | Physicochemical |
| kmgutg | Km of Glucuronidation in the gut | | nM | Physicochemical |
| vmaxgutgC | Vmax of Glucuronidation in the gut | | nmol/h/kg bw | Physicochemical |
| fgutg | Correction factor of glucuronidation in the gut | | | Physicochemical |
| kmguts | Km of Sulfation in the gut | | nM | Physicochemical |
| vmaxgutsC | Vmax of Sulfation in the gut | | nmol/h/kg bw | Physicochemical |
| fguts | Correction factor of sulfation in the gut | | | Physicochemical |

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Table 3.429 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| met1g | Fraction of glucuronide in the liver taken up directly into serum (the rest undergoes EHR) | | | Physicochemical |
| met1s | Fraction of sulfate in the liver taken up directly into serum | | | Physicochemical |
| enterocytes | Sum of enterocytes weights in duodenum, jejunum and ileum | | L | Physicochemical |
| kmliver | Km of Glucuronidation in the liver | | nM | Physicochemical |
| vmaxliverC | Vmax of Glucuronidation in the liver | | nmol/h/g liver | Physicochemical |
| fliverg | Correction factor of glucuronidation in the liver | | | Physicochemical |
| kmlivers | Km of Sulfation in the liver | | nM | Physicochemical |
| vmaxliversC | Vmax of Sulfation in the liver | | nmol/h/g liver | Physicochemical |
| flivers | Correction factor of sulfation in the liver | | | Physicochemical |
| EHRtime | Time until EHR occurs | | h | Physicochemical |
| EHRrateC | EHR of glucuronide | | 1/h/kg bw^-0.25 | Physicochemical |
| k4C_IV | Fecal elimination of glucuronide from the EHR compartment | | 1/h/kg bw^-0.25 | Physicochemical |
| kurinebpaC | Clearance, urine excretion of parent compound | | L/h/kg bw^0.75 | Physicochemical |
| kurinebpagC | Clearance, urine excretion of glucuronide | | L/h/kg bw^0.75 | Physicochemical |
| kurinebpasC | Clearance, urine excretion of sulfate | | L/h/kg bw^0.75 | Physicochemical |
| vreabsorptiong-C | Vmax for renal reabsorption of glucuronide | | nmol/h/kg bw^0.75 | Physicochemical |
| vreabsorptionsC | Vmax for renal reabsorption of sulfate | | nmol/h/kg bw^0.75 | Physicochemical |
| kreabsorptiong | Km for renal reabsorption of glucuronide | | nM | Physicochemical |
| kreabsorptions | Km for renal reabsorption of sulfate | | nM | Physicochemical |

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Table 3.429 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| kenterobpagC | EHR of parent compound due to biliary excretion of glucuronide | | 1/h/kg bw^-0.25 | Physicochemical |
| kenterobpasC | EHR of parent compound due to biliary excretion of sulfate | | 1/h/kg bw^-0.25 | Physicochemical |
| D_o | oral dose | | ng/kg bw/dosing | Other |
| dose_O | oral dose | | nmol/kg bw/dosing | Other |
| EoA_O | Extent of oral absorption | | | Physiological |
| uptake_O | amount of oral uptake | | nmol/dosing | Other |
| period_O | uptake period | | h | Other |
| koa | uptake rate | | nmol/h | Other |
| t0_O | time point at which dosing starts | | h | Other |
| t1_O | time point at which dosing ends | | h | Other |
| D_d | dermal dose from thermal paper (TP) | | ng/kg bw/dosing | Other |
| EoA_D | Extent of dermal absorption from TP | | | Physiological |
| dose_D | dermal dose from TP | | nmol/kg bw/dosing | Other |
| aHL_D | Half-life for dermal penetration | | h | Other |
| uptake_D | amount of dermal uptake from TP | | nmol/dosing | Other |
| period_D | Uptake period dermal exposure from TP | | h | Other |
| kda | Uptake rate of dermal exposure from TP | | nmol/h | Other |
| t0_D | Time points at which dermal dosing from TP starts | | h | Other |
| t1_D | Time points at which dermal dosing from TP ends | | h | Other |
| D_d2 | Dermal dose from PCPs | | ng/kg bw/dosing | Other |
| EoA_D2 | Extent of dermal absorption from PCPs | | | Physiological |
| dose_D2 | Dermal dose from PCPs | | nmol/kg bw/dosing | Other |
| aHL_D2 | Half-life for dermal penetration from PCPs | | h | Other |

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Table 3.429 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| uptake_D2 | amount of dermal uptake from PCPs | | nmol/dosing | Other |
| period_D2 | Uptake period dermal exposure from PCPs | | h | Other |
| kda2 | uptake rate of dermal exposure from PCPs | | nmol/h | Other |
| t0_D2 | Time points at which dermal dosing from PCPs starts | | h | Other |
| t1_D2 | time points at which dermal dosing from TP ends | | h | Other |
| QC | Cardiac output | | L/h | Other |
| Qfat | Blood flow to the fat tissue | | L/h | Other |
| Qliver | Blood flow to the liver tissue | | L/h | Other |
| Qgonad | Blood flow to the gonads | | L/h | Other |
| Qbrain | Blood flow to the brain | | L/h | Other |
| Qskin | Blood flow to the skin tissue | | L/h | Other |
| Qslow | Blood flow to the slowly perfused tissue | | L/h | Other |
| Qrich | Blood flow to the richly perfused tissue | | L/h | Other |
| Vliver | Volume of the liver | | L | Other |
| Vfat | Volume of the fat tissue | | L | Other |
| Vgonad | Volume of the gonads | | L | Other |
| Vplasma | Volume of the plasma | | L | Other |
| Vbrain | Volume of the brain | | L | Other |
| Vskin | Volume of the skin | | L | Other |
| Vslow | Volume of the slowly perfused tissue | | L | Other |
| Vrich | richly perfused tissue | | L | Other |
| Vbodyg | Volume of the distribution for BPAG | | L | Other |
| Vbodys | Volume of the distribution for BPAS | | L | Other |
| BW075 | BW^0.75 | | kg^0.75 | Other |
| BW025 | BW^0.25 | | kg^0.25 | Other |
| vmaxlivers-Cnew | scaled Vmax of Sulfation of BPA in the liver | | nmol/h/kg bw^0.75 | Other |

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Table 3.429 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| vmaxliverCnew | scaled Vmax of Glucuronidation of BPA in the liver | | nmol/h/kg bw^0.75 | Other |
| vmaxgutgCnew | scaled Vmax of Glucuronidation of BPA in the gut | | nmol/h/kg bw^0.75 | Other |
| vreabsorptiong | scaled vmax of renal resorption of BPAG | | nmol/h | Other |
| vreabsorptions | scaled vmax of renal resorption of BPAS | | nmol/h | Other |
| EHRrate | scaled EHR of BPAG | | 1/h | Other |
| k0 | scaled Uptake of BPA from the stomach into the liver | | 1/h | Other |
| ge | scaled Gastric emptying of BPA | | 1/h | Other |
| k1 | scaled Uptake of BPA from small intestine into the liver | | 1/h | Other |
| k4 | scaled Fecal excretion of BPA after oral administration from small intestine | | 1/h | Other |
| k4_IV | scaled Fecal excretion of BPAG from the EHR compartment | | 1/h | Other |
| vmaxliver | rescaled and corrected vmax of BPA glucuronidation in the liver | | nmol/h | Other |
| kGIing | scaled Uptake of BPAG from small intestine into serum | | 1/h | Other |
| met2g | Fraction of BPAG formed subject to EHR | | | Other |
| met2s | Fraction of BPAS formed subject to EHR | | | Other |
| kurinebpa | scaled Clearance of BPA via urine | | L/h | Other |
| kurinebpag | scaled Clearance of BPAg via urine | | L/h | Other |
| kurinebpas | scaled Clearance of BPAs via urine | | L/h | Other |
| vmaxlivers | rescaled and corrected vmax of BPA sulfation in the liver | | nmol/h | Other |

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Table 3.429 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| kGIins | scaled Uptake of BPAS from small intestine into serum | | 1/h | Other |
| vmaxgutg | rescaled and corrected vmax of BPA glucuronidation in the gut | | nmol/h | Other |
| vmaxguts | rescaled and corrected vmax of BPA sulfation in the gut | | nmol/h | Other |
| kenterobpag | scaled EHR of BPA due to biliary excretion of BPAG | | 1/h | Other |
| kenterobpas | scaled EHR of BPA due to biliary excretion of BPAS | | 1/h | Other |
| t0_D1_day1 | time points at which dermal dosing from Thermal paper starts | | h | Other |
| t0_D2_day1 | time points at which dermal dosing from Thermal paper starts | | h | Other |
| t0_D1_day2 | time points at which dermal dosing from Thermal paper starts | | h | Other |
| t0_D2_day2 | time points at which dermal dosing from Thermal paper starts | | h | Other |
| t0_D1_day3 | time points at which dermal dosing from Thermal paper starts | | h | Other |
| t0_D2_day3 | time points at which dermal dosing from Thermal paper starts | | h | Other |
| t0_D1_day4 | time points at which dermal dosing from Thermal paper starts | | h | Other |
| t0_D2_day4 | time points at which dermal dosing from Thermal paper starts | | h | Other |
| t0_D21_day1 | time points at which dermal dosing from PCPs starts | | h | Other |
| t0_D22_day1 | time points at which dermal dosing from PCPs starts | | h | Other |
| t0_D21_day2 | time points at which dermal dosing from PCPs starts | | h | Other |
| t0_D22_day2 | time points at which dermal dosing from PCPs starts | | h | Other |

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Table 3.429 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| t0_D21_day3 | time points at which dermal dosing from PCPs starts | | h | Other |
| t0_D22_day3 | time points at which dermal dosing from PCPs starts | | h | Other |
| t0_D21_day4 | time points at which dermal dosing from PCPs starts | | h | Other |
| t0_D22_day4 | time points at which dermal dosing from PCPs starts | | h | Other |
| t0_O1_day1 | time points at which oral dosing starts | | h | Other |
| t0_O2_day1 | time points at which oral dosing starts | | h | Other |
| t0_O3_day1 | time points at which oral dosing starts | | h | Other |
| t0_O1_day2 | time points at which oral dosing starts | | h | Other |
| t0_O2_day2 | time points at which oral dosing starts | | h | Other |
| t0_O3_day2 | time points at which oral dosing starts | | h | Other |
| t0_O1_day3 | time points at which oral dosing starts | | h | Other |
| t0_O2_day3 | time points at which oral dosing starts | | h | Other |
| t0_O3_day3 | time points at which oral dosing starts | | h | Other |
| t0_O1_day4 | time points at which oral dosing starts | | h | Other |
| t0_O2_day4 | time points at which oral dosing starts | | h | Other |
| t0_O3_day4 | time points at which oral dosing starts | | h | Other |
| ksiLiver | Ksi of glucuronidation in liver | | nM | Other |
| ksiGut | Ksi of glucuronidation in gut | | nM | Other |
| age | age | 30 | | Age |
| gender | gender | 0 | | Sex |
| QCC_adult_f | QCC_adult_f | | | Other |
| Qgonad-C_adult_f | QgonadC_adult_f | | | Other |
| QliverC_adult_f | QliverC_adult_f | | | Other |
| QfatC_adult_f | QfatC_adult_f | | | Other |
| Qbrain-C_adult_f | QbrainC_adult_f | | | Other |
| QskinC_adult_f | QskinC_adult_f | | | Other |
| Qmuscle-C_adult_f | QmuscleC_adult_f | | | Other |

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Table 3.429 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| Vplasma-C_adult_f | VplasmaC_adult_f | | | Other |
| VfatC_adult_f | VfatC_adult_f | | | Other |
| VliverC_adult_f | VliverC_adult_f | | | Other |
| Vbrain-C_adult_f | VbrainC_adult_f | | | Other |
| VskinC_adult_f | VskinC_adult_f | | | Other |
| Vgonad-C_adult_f | VgonadC_adult_f | | | Other |
| Vmuscle-C_adult_f | VmuscleC_adult_f | | | Other |
| VrichC_adult_f | VrichC_adult_f | | | Other |
| Vbodyg-C_adult_f | VbodygC_adult_f | | | Other |
| Vbodys-C_adult_f | VbodysC_adult_f | | | Other |
| QCC_adult_m | QCC_adult_m | | | Other |
| Qgonad-C_adult_m | QgonadC_adult_m | | | Other |
| Qliver-C_adult_m | QliverC_adult_m | | | Other |
| QfatC_adult_m | QfatC_adult_m | | | Other |
| Qbrain-C_adult_m | QbrainC_adult_m | | | Other |
| Qskin-C_adult_m | QskinC_adult_m | | | Other |
| Qmuscle-C_adult_m | QmuscleC_adult_m | | | Other |
| Vplasma-C_adult_m | VplasmaC_adult_m | | | Other |
| VfatC_adult_m | VfatC_adult_m | | | Other |
| Vliver-C_adult_m | VliverC_adult_m | | | Other |
| Vbrain-C_adult_m | VbrainC_adult_m | | | Other |
| Vskin-C_adult_m | VskinC_adult_m | | | Other |
| Vgonad-C_adult_m | VgonadC_adult_m | | | Other |
| Vmuscle-C_adult_m | VmuscleC_adult_m | | | Other |
| Vrich-C_adult_m | VrichC_adult_m | | | Other |
| Vbodyg-C_adult_m | VbodygC_adult_m | | | Other |
| Vbodys-C_adult_m | VbodysC_adult_m | | | Other |
| QC-C_adolescent_f | QCC_adolescent_f | | | Other |
| Qgonad-C_adolescent_f | Qgonad-C_adolescent_f | | | Other |
| Qliver-C_adolescent_f | Qliver-C_adolescent_f | | | Other |
| Qfat-C_adolescent_f | QfatC_adolescent_f | | | Other |

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Table 3.429 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| Qbrain-C_adolescent_f | Qbrain-C_adolescent_f | | | Other |
| Qskin-C_adolescent_f | Qskin-C_adolescent_f | | | Other |
| Qmuscle-C_adolescent_f | Qmuscle-C_adolescent_f | | | Other |
| Vplasma-C_adolescent_f | Vplasma-C_adolescent_f | | | Other |
| Vfat-C_adolescent_f | VfatC_adolescent_f | | | Other |
| Vliver-C_adolescent_f | Vliver-C_adolescent_f | | | Other |
| Vbrain-C_adolescent_f | Vbrain-C_adolescent_f | | | Other |
| Vskin-C_adolescent_f | Vskin-C_adolescent_f | | | Other |
| Vgonad-C_adolescent_f | Vgonad-C_adolescent_f | | | Other |
| Vmuscle-C_adolescent_f | Vmuscle-C_adolescent_f | | | Other |
| Vrich-C_adolescent_f | Vrich-C_adolescent_f | | | Other |
| Vbodyg-C_adolescent_f | Vbodyg-C_adolescent_f | | | Other |
| Vbodys-C_adolescent_f | Vbodys-C_adolescent_f | | | Other |
| QC-C_adolescent_m | QCC_adolescent_m | | | Other |
| Qgonad-C_adolescent_m | Qgonad-C_adolescent_m | | | Other |
| Qliver-C_adolescent_m | Qliver-C_adolescent_m | | | Other |
| Qfat-C_adolescent_m | Qfat-C_adolescent_m | | | Other |
| Qbrain-C_adolescent_m | Qbrain-C_adolescent_m | | | Other |
| Qskin-C_adolescent_m | Qskin-C_adolescent_m | | | Other |
| Qmuscle-C_adolescent_m | Qmuscle-C_adolescent_m | | | Other |
| Vplasma-C_adolescent_m | Vplasma-C_adolescent_m | | | Other |
| Vfat-C_adolescent_m | VfatC_adolescent_m | | | Other |
| Vliver-C_adolescent_m | Vliver-C_adolescent_m | | | Other |
| Vbrain-C_adolescent_m | Vbrain-C_adolescent_m | | | Other |
| Vskin-C_adolescent_m | Vskin-C_adolescent_m | | | Other |
| Vgonad-C_adolescent_m | Vgonad-C_adolescent_m | | | Other |
| Vmuscle-C_adolescent_m | Vmuscle-C_adolescent_m | | | Other |

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Table 3.429 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| Vrich-C_adolescent_m | Vrich-C_adolescent_m | | | Other |
| Vbodyg-C_adolescent_m | Vbodyg-C_adolescent_m | | | Other |
| Vbodys-C_adolescent_m | Vbodys-C_adolescent_m | | | Other |
| QCC_child_f | QCC_child_f | | | Other |
| Qgonad-C_child_f | QgonadC_child_f | | | Other |
| QliverC_child_f | QliverC_child_f | | | Other |
| QfatC_child_f | QfatC_child_f | | | Other |
| Qbrain-C_child_f | QbrainC_child_f | | | Other |
| QskinC_child_f | QskinC_child_f | | | Other |
| Qmuscle-C_child_f | QmuscleC_child_f | | | Other |
| Vplasma-C_child_f | VplasmaC_child_f | | | Other |
| VfatC_child_f | VfatC_child_f | | | Other |
| VliverC_child_f | VliverC_child_f | | | Other |
| Vbrain-C_child_f | VbrainC_child_f | | | Other |
| VskinC_child_f | VskinC_child_f | | | Other |
| Vgonad-C_child_f | VgonadC_child_f | | | Other |
| Vmuscle-C_child_f | VmuscleC_child_f | | | Other |
| VrichC_child_f | VrichC_child_f | | | Other |
| Vbodyg-C_child_f | VbodygC_child_f | | | Other |
| Vbodys-C_child_f | VbodysC_child_f | | | Other |
| QCC_child_m | QCC_child_m | | | Other |
| Qgonad-C_child_m | QgonadC_child_m | | | Other |
| Qliver-C_child_m | QliverC_child_m | | | Other |
| QfatC_child_m | QfatC_child_m | | | Other |
| Qbrain-C_child_m | QbrainC_child_m | | | Other |
| Qskin-C_child_m | QskinC_child_m | | | Other |
| Qmuscle-C_child_m | QmuscleC_child_m | | | Other |
| Vplasma-C_child_m | VplasmaC_child_m | | | Other |
| VfatC_child_m | VfatC_child_m | | | Other |
| Vliver-C_child_m | VliverC_child_m | | | Other |
| Vbrain-C_child_m | VbrainC_child_m | | | Other |
| Vskin-C_child_m | VskinC_child_m | | | Other |
| Vgonad-C_child_m | VgonadC_child_m | | | Other |

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Table 3.429 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| Vmuscle-C_child_m | VmuscleC_child_m | | | Other |
| Vrich-C_child_m | VrichC_child_m | | | Other |
| Vbodyg-C_child_m | VbodygC_child_m | | | Other |
| Vbodys-C_child_m | VbodysC_child_m | | | Other |

Model aliases: EuroMix_Bisphenols_PBPK_model_V1, PBPKModel_BPA.

### EuroMix Bisphenols PBPK model (v2)

EuroMix Bisphenols PBPK model by Karrer et al. (2019).

Table 3.430: Exposure routes (forcings)

| Id | Description | Unit |
|---|---|---|
| Oral | Oral exposure | nmoles |
| Dermal | Dermal exposure | nmoles |
| Inhalation | Inhalation exposure | nmoles |

Table 3.431: Model outputs

| Id | Description | ScalingFactor | Multiplication-Factor | Unit |
|---|---|---|---|---|
| CPlasmaOut | Concentration in plasma | | | nmol/L |
| CGonadOut | Concentration in gonads | | | nmol/L |
| AurinebpaOut | Cumulative excretion of BPA in urine | | | nmoles |
| AurinegOut | Cumulative excretion of BPA-g in urine | | | nmoles |
| AurineTotalOut | Cumulative excretion of BPA and metabolites in urine | | | nmoles |

Table 3.432: Model parameters

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| BW | Bodyweight | | kg | BodyWeight |
| QCC | Cardiac output | | L/min | Physiological |
| QgonadC | Fractional blood flow to gonads | | | Physiological |
| QliverC | Fractional blood flow to liver | | | Physiological |
| QfatC | Fractional blood flow to fat tissue | | | Physiological |

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Table 3.432 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| QbrainC | Fractional blood flow to brain | | | Physiological |
| QskinC | Fractional blood flow to skin | | | Physiological |
| QmuscleC | Fractional blood flow to gonads | | | Physiological |
| VplasmaC | Fractional volume of plasma | | | Physiological |
| VfatC | Fractional volume of fat tissue | | | Physiological |
| VliverC | Fractional volume of liver tissue | | | Physiological |
| VbrainC | Fractional volume of brain tissue | | | Physiological |
| VskinC | Fractional volume of skin tissue | | | Physiological |
| VgonadC | Fractional volume of gonads | | | Physiological |
| VmuscleC | Fractional volume of muscle tissue | | | Physiological |
| VrichC | Fractional volume of richly perfused tissue | | | Physiological |
| VbodygC | Distribution volume of BPA-g | | | Physiological |
| VbodysC | Distribution volume of BPA-s | | | Other |
| pliver | Partition coefficient liver to blood | | | PartitionCoefficient |
| pfat | Partition coefficient fat to blood | | | PartitionCoefficient |
| pslow | Partition coefficient slowly perfused tissue to blood | | | PartitionCoefficient |
| prich | Partition coefficient richly perfused tissue to blood | | | PartitionCoefficient |
| pgonad | Partition coefficient gonads to blood | | | PartitionCoefficient |
| pbrain | Partition coefficient brain to blood | | | PartitionCoefficient |
| pskin | Partition coefficient skin to blood | | | PartitionCoefficient |
| geC | Gastric emptying | | 1/h/kg bw^-0.25 | Physicochemical |
| k0C | Oral uptake from the stomach into the liver | | 1/h/kg bw^-0.25 | Physicochemical |
| k1C | Oral uptake from the small intestine into the liver | | 1/h/kg bw^-0.25 | Physicochemical |
| k4C | Fecal elimination from small intestine after oral administration | | 1/h/kg bw^-0.25 | Physicochemical |

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Table 3.432 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| kGIingC | Transport of glucuronide from enterocytes into serum | | 1/h/kg bw^-0.25 | Physicochemical |
| kGIinsC | Transport of sulfate from enterocytes into serum | | 1/h/kg bw^-0.25 | Physicochemical |
| kmgutg | Km of Glucuronidation in the gut | | nM | Physicochemical |
| vmaxgutgC | Vmax of Glucuronidation in the gut | | nmol/h/kg bw | Physicochemical |
| fgutg | Correction factor of glucuronidation in the gut | | | Physicochemical |
| kmguts | Km of Sulfation in the gut | | nM | Physicochemical |
| vmaxgutsC | Vmax of Sulfation in the gut | | nmol/h/kg bw | Physicochemical |
| fguts | Correction factor of sulfation in the gut | | | Physicochemical |
| met1g | Fraction of glucuronide in the liver taken up directly into serum (the rest undergoes EHR) | | | Physicochemical |
| met1s | Fraction of sulfate in the liver taken up directly into serum | | | Physicochemical |
| enterocytes | Sum of enterocytes weights in duodenum, jejunum and ileum | | L | Physicochemical |
| kmliver | Km of Glucuronidation in the liver | | nM | Physicochemical |
| vmaxliverC | Vmax of Glucuronidation in the liver | | nmol/h/g liver | Physicochemical |
| fliverg | Correction factor of glucuronidation in the liver | | | Physicochemical |
| kmlivers | Km of Sulfation in the liver | | nM | Physicochemical |
| vmaxliversC | Vmax of Sulfation in the liver | | nmol/h/g liver | Physicochemical |
| flivers | Correction factor of sulfation in the liver | | | Physicochemical |
| EHRtime | Time until EHR occurs | | h | Physicochemical |
| EHRrateC | EHR of glucuronide | | 1/h/kg bw^-0.25 | Physicochemical |

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Table 3.432 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| k4C_IV | Fecal elimination of glucuronide from the EHR compartment | | 1/h/kg bw^-0.25 | Physicochemical |
| kurinebpaC | Clearance, urine excretion of parent compound | | L/h/kg bw^0.75 | Physicochemical |
| kurinebpagC | Clearance, urine excretion of glucuronide | | L/h/kg bw^0.75 | Physicochemical |
| kurinebpasC | Clearance, urine excretion of sulfate | | L/h/kg bw^0.75 | Physicochemical |
| vreabsorptiong-C | Vmax for renal reabsorption of glucuronide | | nmol/h/kg bw^0.75 | Physicochemical |
| vreabsorptionsC | Vmax for renal reabsorption of sulfate | | nmol/h/kg bw^0.75 | Physicochemical |
| kreabsorptiong | Km for renal reabsorption of glucuronide | | nM | Physicochemical |
| kreabsorptions | Km for renal reabsorption of sulfate | | nM | Physicochemical |
| kenterobpagC | EHR of parent compound due to biliary excretion of glucuronide | | 1/h/kg bw^-0.25 | Physicochemical |
| kenterobpasC | EHR of parent compound due to biliary excretion of sulfate | | 1/h/kg bw^-0.25 | Physicochemical |
| koa | uptake rate | | nmol/h | Other |
| EoA_D | Extent of dermal absorption from TP | | | Physiological |
| aHL_D | Half-life for dermal penetration | | h | Other |
| kda | Uptake rate of dermal exposure from TP | | nmol/h | Other |
| EoA_D2 | Extent of dermal absorption from PCPs | | | Physiological |
| aHL_D2 | Half-life for dermal penetration from PCPs | | h | Other |
| kda2 | Uptake rate of dermal exposure from PCPs | | nmol/h | Other |
| QC | Cardiac output | | L/h | Other |
| Qfat | Blood flow to the fat tissue | | L/h | Other |
| Qliver | Blood flow to the liver tissue | | L/h | Other |
| Qgonad | Blood flow to the gonads | | L/h | Other |

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Table 3.432 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| Qbrain | Blood flow to the brain | | L/h | Other |
| Qskin | Blood flow to the skin tissue | | L/h | Other |
| Qslow | Blood flow to the slowly perfused tissue | | L/h | Other |
| Qrich | Blood flow to the richly perfused tissue | | L/h | Other |
| Vliver | Volume of the liver | | L | Other |
| Vfat | Volume of the fat tissue | | L | Other |
| Vgonad | Volume of the gonads | | L | Other |
| Vplasma | Volume of the plasma | | L | Other |
| Vbrain | Volume of the brain | | L | Other |
| Vskin | Volume of the skin | | L | Other |
| Vslow | Volume of the slowly perfused tissue | | L | Other |
| Vrich | richly perfused tissue | | L | Other |
| Vbodyg | Volume of the distribution for BPAG | | L | Other |
| Vbodys | Volume of the distribution for BPAS | | L | Other |
| vreabsorptiong | scaled vmax of renal resorption of BPAG | | nmol/h | Other |
| vreabsorptions | scaled vmax of renal resorption of BPAS | | nmol/h | Other |
| EHRrate | scaled EHR of BPAG | | 1/h | Other |
| k0 | scaled Uptake of BPA from the stomach into the liver | | 1/h | Other |
| ge | scaled Gastric emptying of BPA | | 1/h | Other |
| k1 | scaled Uptake of BPA from small intestine into the liver | | 1/h | Other |
| k4 | scaled Fecal excretion of BPA after oral administration from small intestine | | 1/h | Other |
| k4_IV | scaled Fecal excretion of BPAG from the EHR compartment | | 1/h | Other |

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Table 3.432 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| vmaxliver | rescaled and corrected vmax of BPA glucuronidation in the liver | | nmol/h | Other |
| kGIing | scaled Uptake of BPAG from small intestine into serum | | 1/h | Other |
| met2g | Fraction of BPAG formed subject to EHR | | | Other |
| met2s | Fraction of BPAS formed subject to EHR | | | Other |
| kurinebpa | scaled Clearance of BPA via urine | | L/h | Other |
| kurinebpag | scaled Clearance of BPAg via urine | | L/h | Other |
| kurinebpas | scaled Clearance of BPAs via urine | | L/h | Other |
| vmaxlivers | rescaled and corrected vmax of BPA sulfation in the liver | | nmol/h | Other |
| kGIins | scaled Uptake of BPAS from small intestine into serum | | 1/h | Other |
| vmaxgutg | rescaled and corrected vmax of BPA glucuronidation in the gut | | nmol/h | Other |
| vmaxguts | rescaled and corrected vmax of BPA sulfation in the gut | | nmol/h | Other |
| kenterobpag | scaled EHR of BPA due to biliary excretion of BPAG | | 1/h | Other |
| kenterobpas | scaled EHR of BPA due to biliary excretion of BPAS | | 1/h | Other |
| ksiLiver | Ksi of glucuronidation in liver | | nM | Other |
| ksiGut | Ksi of glucuronidation in gut | | nM | Other |
| age | age | 30 | | Age |
| gender | gender | 0 | | Sex |
| QCC_adult_f | QCC_adult_f | | | Other |
| Qgonad-C_adult_f | QgonadC_adult_f | | | Other |
| QliverC_adult_f | QliverC_adult_f | | | Other |
| QfatC_adult_f | QfatC_adult_f | | | Other |
| Qbrain-C_adult_f | QbrainC_adult_f | | | Other |

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Table 3.432 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| QskinC_adult_f | QskinC_adult_f | | | Other |
| QmuscleC_adult_f | QmuscleC_adult_f | | | Other |
| VplasmaC_adult_f | VplasmaC_adult_f | | | Other |
| VfatC_adult_f | VfatC_adult_f | | | Other |
| VliverC_adult_f | VliverC_adult_f | | | Other |
| VbrainC_adult_f | VbrainC_adult_f | | | Other |
| VskinC_adult_f | VskinC_adult_f | | | Other |
| VgonadC_adult_f | VgonadC_adult_f | | | Other |
| VmuscleC_adult_f | VmuscleC_adult_f | | | Other |
| VrichC_adult_f | VrichC_adult_f | | | Other |
| VbodygC_adult_f | VbodygC_adult_f | | | Other |
| VbodysC_adult_f | VbodysC_adult_f | | | Other |
| QCC_adult_m | QCC_adult_m | | | Other |
| QgonadC_adult_m | QgonadC_adult_m | | | Other |
| QliverC_adult_m | QliverC_adult_m | | | Other |
| QfatC_adult_m | QfatC_adult_m | | | Other |
| QbrainC_adult_m | QbrainC_adult_m | | | Other |
| QskinC_adult_m | QskinC_adult_m | | | Other |
| QmuscleC_adult_m | QmuscleC_adult_m | | | Other |
| VplasmaC_adult_m | VplasmaC_adult_m | | | Other |
| VfatC_adult_m | VfatC_adult_m | | | Other |
| VliverC_adult_m | VliverC_adult_m | | | Other |
| VbrainC_adult_m | VbrainC_adult_m | | | Other |
| VskinC_adult_m | VskinC_adult_m | | | Other |
| VgonadC_adult_m | VgonadC_adult_m | | | Other |
| VmuscleC_adult_m | VmuscleC_adult_m | | | Other |
| VrichC_adult_m | VrichC_adult_m | | | Other |
| VbodygC_adult_m | VbodygC_adult_m | | | Other |
| VbodysC_adult_m | VbodysC_adult_m | | | Other |
| QCC_adolescent_f | QCC_adolescent_f | | | Other |
| Qgonad-C_adolescent_f | Qgonad-C_adolescent_f | | | Other |

continues on next page

Table 3.432 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| Qliver-C_adolescent_f | Qliver-C_adolescent_f | | | Other |
| Qfat-C_adolescent_f | QfatC_adolescent_f | | | Other |
| Qbrain-C_adolescent_f | Qbrain-C_adolescent_f | | | Other |
| Qskin-C_adolescent_f | Qskin-C_adolescent_f | | | Other |
| Qmuscle-C_adolescent_f | Qmuscle-C_adolescent_f | | | Other |
| Vplasma-C_adolescent_f | Vplasma-C_adolescent_f | | | Other |
| Vfat-C_adolescent_f | VfatC_adolescent_f | | | Other |
| Vliver-C_adolescent_f | Vliver-C_adolescent_f | | | Other |
| Vbrain-C_adolescent_f | Vbrain-C_adolescent_f | | | Other |
| Vskin-C_adolescent_f | Vskin-C_adolescent_f | | | Other |
| Vgonad-C_adolescent_f | Vgonad-C_adolescent_f | | | Other |
| Vmuscle-C_adolescent_f | Vmuscle-C_adolescent_f | | | Other |
| Vrich-C_adolescent_f | Vrich-C_adolescent_f | | | Other |
| Vbodyg-C_adolescent_f | Vbodyg-C_adolescent_f | | | Other |
| Vbodys-C_adolescent_f | Vbodys-C_adolescent_f | | | Other |
| QC-C_adolescent_m | QCC_adolescent_m | | | Other |
| Qgonad-C_adolescent_m | Qgonad-C_adolescent_m | | | Other |
| Qliver-C_adolescent_m | Qliver-C_adolescent_m | | | Other |
| Qfat-C_adolescent_m | Qfat-C_adolescent_m | | | Other |
| Qbrain-C_adolescent_m | Qbrain-C_adolescent_m | | | Other |
| Qskin-C_adolescent_m | Qskin-C_adolescent_m | | | Other |
| Qmuscle-C_adolescent_m | Qmuscle-C_adolescent_m | | | Other |
| Vplasma-C_adolescent_m | Vplasma-C_adolescent_m | | | Other |
| Vfat-C_adolescent_m | VfatC_adolescent_m | | | Other |
| Vliver-C_adolescent_m | Vliver-C_adolescent_m | | | Other |
| Vbrain-C_adolescent_m | Vbrain-C_adolescent_m | | | Other |
| Vskin-C_adolescent_m | Vskin-C_adolescent_m | | | Other |

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Table 3.432 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| Vgonad-C_adolescent_m | Vgonad-C_adolescent_m | | | Other |
| Vmuscle-C_adolescent_m | Vmuscle-C_adolescent_m | | | Other |
| Vrich-C_adolescent_m | Vrich-C_adolescent_m | | | Other |
| Vbodyg-C_adolescent_m | Vbodyg-C_adolescent_m | | | Other |
| Vbodys-C_adolescent_m | Vbodys-C_adolescent_m | | | Other |
| QCC_child_f | QCC_child_f | | | Other |
| Qgonad-C_child_f | QgonadC_child_f | | | Other |
| QliverC_child_f | QliverC_child_f | | | Other |
| QfatC_child_f | QfatC_child_f | | | Other |
| Qbrain-C_child_f | QbrainC_child_f | | | Other |
| QskinC_child_f | QskinC_child_f | | | Other |
| Qmuscle-C_child_f | QmuscleC_child_f | | | Other |
| Vplasma-C_child_f | VplasmaC_child_f | | | Other |
| VfatC_child_f | VfatC_child_f | | | Other |
| VliverC_child_f | VliverC_child_f | | | Other |
| Vbrain-C_child_f | VbrainC_child_f | | | Other |
| VskinC_child_f | VskinC_child_f | | | Other |
| Vgonad-C_child_f | VgonadC_child_f | | | Other |
| Vmuscle-C_child_f | VmuscleC_child_f | | | Other |
| VrichC_child_f | VrichC_child_f | | | Other |
| Vbodyg-C_child_f | VbodygC_child_f | | | Other |
| Vbodys-C_child_f | VbodysC_child_f | | | Other |
| QCC_child_m | QCC_child_m | | | Other |
| Qgonad-C_child_m | QgonadC_child_m | | | Other |
| Qliver-C_child_m | QliverC_child_m | | | Other |
| QfatC_child_m | QfatC_child_m | | | Other |
| Qbrain-C_child_m | QbrainC_child_m | | | Other |
| Qskin-C_child_m | QskinC_child_m | | | Other |
| Qmuscle-C_child_m | QmuscleC_child_m | | | Other |
| Vplasma-C_child_m | VplasmaC_child_m | | | Other |
| VfatC_child_m | VfatC_child_m | | | Other |
| Vliver-C_child_m | VliverC_child_m | | | Other |
| Vbrain-C_child_m | VbrainC_child_m | | | Other |

continues on next page

Table 3.432 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| Vskin-C_child_m | VskinC_child_m | | | Other |
| Vgonad-C_child_m | VgonadC_child_m | | | Other |
| Vmuscle-C_child_m | VmuscleC_child_m | | | Other |
| Vrich-C_child_m | VrichC_child_m | | | Other |
| Vbodyg-C_child_m | VbodygC_child_m | | | Other |
| Vbodys-C_child_m | VbodysC_child_m | | | Other |

Model aliases: EuroMix_Bisphenols_PBPK_model_V2, PBPKModel_BPA_Reimplementation.

### EuroMix Generic PBTK model (v5)

Cosmos version 5 (adapted 9/11/2018)

Table 3.433: Exposure routes (forcings)

| Id | Description | Unit |
|---|---|---|
| Oral | Oral exposure | mmoles |
| Dermal | Dermal exposure | mmoles |
| Inhalation | Inhalatory exposure | mmoles |

Table 3.434: Model outputs

| Id | Description | ScalingFactor | Multiplication-Factor | Unit |
|---|---|---|---|---|
| CVen | Venous blood | scVBlood | 0.66667 | mM |
| CArt | Arterial blood | scVBlood | 0.33333 | mM |
| CFat | Fat tissues | scVFat | | mM |
| CPoor | Muscle tissues | | | mM |
| CRich | Viscera | scVRich | | mM |
| CLiver | Liver | scVLiver | | mM |
| CSkin_u | Viable skin, unexposed | | | mM |
| CSkin_e | Viable skin, exposed | BSA, Height_vs, fsA_exposed | | mM |
| CSkin_sc_u | Skin stratum corneum, unexposed | | | mM |
| CSkin_sc_e | Skin stratum corneum, exposed | BSA, Height_vs, fsA_exposed | | mM |

Table 3.435: Model parameters

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| BM | Body mass | | kg | BodyWeight |
| BSA | Body skin surface area | | dm2 | BodySurfaceArea |

continues on next page

Table 3.435 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| scVFat | Fat as fraction of total body volume | | | Physiological |
| scVRich | Richly perfused tissues (viscera) as fraction of total body volume | | | Physiological |
| scVLiver | Liver as fraction of total body volume | | | Physiological |
| scVBlood | Blood as fraction of total body volume | | | Physiological |
| Height_sc | Skin thickness | | decimeter | Physiological |
| Height_vs | Viable skin | | | Physiological |
| scFBlood | Total blood flow per unit mass | | L/h/kg | Physiological |
| scFFat | Fat fraction of total blood flow going to compartments | | | Physiological |
| scFPoor | Poorly perfused tissues (muscles) fraction of total blood flow going to compartments | | | Physiological |
| scFLiver | Liver fraction of total blood flow going to compartments | | | Physiological |
| scFSkin | Skin fraction of total blood flow going to compartments | | | Physiological |
| Falv | Alveolar ventilation rate | | L/h | Physiological |
| mic | Microsomal proteins content | | mg/gr liver | Physiological |
| PCAir | Partition coefficient: blood over air | | | PartitionCoefficient |
| log_PCFat | Scaled parameter, partition coefficient: fat over blood | | | PartitionCoefficient |
| log_aPoor | Scaled parameter, partition coefficient: muscle over blood (poorly perfused tissue) | | | PartitionCoefficient |
| log_aRich | Scaled parameter, partition coefficient: viscera over blood (richly perfused tissue) | | | PartitionCoefficient |
| log_aLiver | Scaled parameter, partition coefficient: liver over blood | | | PartitionCoefficient |
| log_aSkin | Scaled parameter, partition coefficient: viable skin / blood | | | PartitionCoefficient |

continues on next page

Table 3.435 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| log_aSkin_sc | Scaled parameter, partition coefficient: viable skin / stratum corneum | | | PartitionCoefficient |
| Kp_sc_vs | Diffusion rate from stratum corneum to viable skin | | decimeter/h | Physicochemical |
| Ke | Renal excretion rate | | L/h | Physicochemical |
| Michaelis | Flag for Michaelis-Menten vs linear metabolism (0 = linear) | | | Physicochemical |
| Vmax | Maximum rate of metabolism | | mmoles/h/L liver | Physicochemical |
| Km | Michaelis-Menten constant | | mM | Physicochemical |
| CLH | Hepatic clearance | | | Physicochemical |
| fup | Unbound fraction in blood | | | Physicochemical |
| Frac | Fraction absorbed by the gut | | | Physicochemical |
| kGut | Oral 1st order absorption rate constant | | 1/h | Physicochemical |
| Cinh | Inhalation | | | Other |
| Tinh | Inhalation duration | | | Other |
| OralDose | | | mmol | Other |
| DermalDose | | | mmol | Other |
| fSA_exposed | Fraction of skin surface area actually exposed | | | Physicochemical |
| FBlood | Blood flow | | | Other |
| FFat | Scaled parameters | | | Other |
| FPoor | Scaled parameters | | | Other |
| FRich | Scaled parameters | | | Other |
| FLiver | Scaled parameters | | | Other |
| FSkin | Scaled parameters | | | Other |
| VFat | Scaled parameters | | | Other |
| VRich | Scaled parameters | | | Other |
| VLiver | Scaled parameters | | | Other |
| VSkin_e | Scaled parameters | | | Other |
| VSkin_u | Scaled parameters | | | Other |
| VSkin_sc_e | Scaled parameters | | | Other |
| VSkin_sc_u | Scaled parameters | | | Other |
| VBlood | Scaled parameters | | | Other |
| VPoor | Scaled parameters | | | Other |
| VArt | Scaled parameters | | | Other |
| VVen | Scaled parameters | | | Other |
| FSkin_e | Scaled parameters | | | Other |
| FSkin_u | Scaled parameters | | | Other |
| PCFat | Partition coefficient: fat over blood | | | PartitionCoefficient |

continues on next page

Table 3.435 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| PCPoor | Partition coefficient: muscle over blood (poorly perfused tissue) | | | PartitionCoefficient |
| PCRich | Partition coefficient: viscera over blood (richly perfused tissue) | | | PartitionCoefficient |
| PCLiver | Partition coefficient: liver over blood | | | PartitionCoefficient |
| PCSkin | Partition coefficient: viable skin / blood | | | PartitionCoefficient |
| PCSkin_sc | Partition coefficient: viable skin / stratum corneum | | | PartitionCoefficient |
| ResampledPC-Fat | Resampled value PCFat | | | PartitionCoefficient |

Model aliases: EuroMix_Generic_PBTK_model_V5, CosmosV4, CosmosV5.

### EuroMix Generic PBTK model (v6)

Cosmos version 6 (received 3/27/2019)

Table 3.436: Exposure routes (forcings)

| Id | Description | Unit |
|---|---|---|
| Oral | Oral exposure | mmoles |
| Dermal | Dermal exposure | mmoles |
| Inhalation | Inhalatory exposure | mmoles |

Table 3.437: Model outputs

| Id | Description | ScalingFactor | Multiplication-Factor | Unit |
|---|---|---|---|---|
| CTotal | Total concentration | | | mM |
| CVen | Venous blood concentration | scVBlood | 0.66667 | mM |
| CArt | Arterial blood concentration | scVBlood | 0.33333 | mM |
| CFat | Fat (adipose) tissue concentration | scVFat | | mM |
| CPoor | Poorly perfused tissue (muscle) concentration | | | mM |
| CRich | Richly perfused tissue (viscera) concentration | scVRich | | mM |
| CLiver | Liver concentration | scVLiver | | mM |
| CSkin_u | Viable unexposed skin concentration | | | mM |
| CSkin_e | Viable exposed skin concentration | BSA, Height_vs, fsA_exposed | | mM |
| CSkin_sc_u | Skin unexposed stratum corneum concentration | | | mM |
| CSkin_sc_e | Skin exposed stratum corneum concentration | BSA, Height_vs, fsA_exposed | | mM |

Table 3.438: Model parameters

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| BM | Body mass | | kg | BodyWeight |
| BSA | Body surface area (internally scaled by an allometric scaling factor s = 70/BM^0.3) | | dm2 | BodySurfaceArea |
| scVFat | Fat as fraction of total body volume | | | Physiological |
| scVRich | Richly perfused tissues (viscera) as fraction of total body volume | | | Physiological |
| scVLiver | Liver as fraction of total body volume | | | Physiological |
| scVBlood | Blood as fraction of total body volume | | | Physiological |
| Height_sc | Skin thickness | | decimeter | Physiological |
| Height_vs | Viable skin | | | Physiological |
| scFBlood | Total blood flow per unit mass | | L/h/kg | Physiological |
| scFFat | Fat fraction of total blood flow going to compartments | | | Physiological |

continues on next page

Table 3.438 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| scFPoor | Poorly perfused tissues (muscles) fraction of total blood flow going to compartments | | | Physiological |
| scFLiver | Liver fraction of total blood flow going to compartments | | | Physiological |
| scFSkin | Skin fraction of total blood flow going to compartments | | | Physiological |
| Falv | Alveolar ventilation rate | | L/h | Physiological |
| mic | Microsomal proteins content | | mg/gr liver | Physiological |
| PCAir | Partition coefficient: blood over air | | | PartitionCoefficient |
| log_PCFat | Scaled parameter, partition coefficient: fat over blood | | | PartitionCoefficient |
| log_aPoor | Scaled parameter, partition coefficient: muscle over blood (poorly perfused tissue) | | | PartitionCoefficient |
| log_aRich | Scaled parameter, partition coefficient: viscera over blood (richly perfused tissue) | | | PartitionCoefficient |
| log_aLiver | Scaled parameter, partition coefficient: liver over blood | | | PartitionCoefficient |
| log_aSkin | Scaled parameter, partition coefficient: viable skin over blood | | | PartitionCoefficient |
| log_aSkin_sc | Scaled parameter, partition coefficient: viable skin stratum corneum over blood | | | PartitionCoefficient |
| Kp_sc_vs | Diffusion rate from stratum corneum to viable skin | | decimeter/h | Physicochemical |
| Ke | Renal excretion rate | | L/h | Physicochemical |
| Michaelis | Flag for Michaelis-Menten vs linear metabolism (0 = linear) | | | Physicochemical |
| Vmax | Maximum rate of metabolism | | mmoles/h/L liver | Physicochemical |
| Km | Michaelis-Menten constant for metabolism | | mM | Physicochemical |

continues on next page

Table 3.438 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| CLH | Hepatic Physicochemical clearance | | | Physicochemical |
| fub | Unbound fraction in blood | | | Physicochemical |
| Frac | Fraction absorbed by the gut | | | Physicochemical |
| kGut | Oral 1st order absorption rate constant | | 1/h | Physicochemical |
| Cinh | Inhalation | | | Other |
| Tinh | Inhalation duration | | | Other |
| OralDose | | | mmol | Other |
| DermalDose | | | mmol | Other |
| fSA_exposed | Fraction of skin surface area actually exposed | | | Physicochemical |
| FBlood | Blood flow | | | Other |
| FFat | Scaled parameters, blood flow to the fat | | | Other |
| FPoor | Scaled parameters, blood flow to poorly perfused tissues | | | Other |
| FRich | Scaled parameters, blood flow to richly perfused tissues | | | Other |
| FLiver | Scaled parameters, blood flow to the liver | | | Other |
| FSkin | Scaled parameters, blood flow to the skin | | | Other |
| VFat | Scaled parameters | | | Other |
| VRich | Scaled parameters, richly perfused tissue volume | | | Other |
| VLiver | Scaled parameters, liver volume | | | Other |
| VSkin_e | Scaled parameters, exposed skin volume | | | Other |
| VSkin_u | Scaled parameters, unexposed skin volume | | | Other |
| VSkin_sc_e | Scaled parameters, stratum corneum exposed skin volume | | | Other |
| VSkin_sc_u | Scaled parameters, stratum corneum unexposed skin volume | | | Other |
| VBlood | Scaled parameters, blood volume | | | Other |
| VPoor | Scaled parameters, poorly perfused tissue volume | | | Other |

continues on next page

Table 3.438 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| VArt | Scaled parameters, arterial blood volume | | | Other |
| VVen | Scaled parameters, venous blood volume | | | Other |
| FSkin_e | Scaled parameters, blood flow to exposed skin | | | Other |
| FSkin_u | Scaled parameters, blood flow to unexposed skin | | | Other |
| PCFat | Partition coefficient: fat over blood | | | PartitionCoefficient |
| PCPoor | Partition coefficient: muscle over blood (poorly perfused tissue) | | | PartitionCoefficient |
| PCRich | Partition coefficient: viscera over blood (richly perfused tissue) | | | PartitionCoefficient |
| PCLiver | Partition coefficient: liver over blood | | | PartitionCoefficient |
| PCSkin | Partition coefficient: viable skin over blood | | | PartitionCoefficient |
| PCSkin_sc | Partition coefficient: viable skin / stratum corneum | | | PartitionCoefficient |
| ResampledPC-Fat | Resampled value PCFat | | | PartitionCoefficient |

Model aliases: EuroMix_Generic_PBTK_model_V6, CosmosV6.

### PBK model chlorpyrifos (v1)

PBK model chlorpyrifos (v1)

Table 3.439: Exposure routes (forcings)

| Id | Description | Unit |
|---|---|---|
| Oral | Oral exposure | umoles |

Table 3.440: Model outputs

| Id | Description | ScalingFactor | Multiplication-Factor | Unit |
|---|---|---|---|---|
| O_CV_P | Concentration in venous blood (parent) | VVc | | uM |
| O_CV_M1 | Concentration in venous blood (metabolite 1) | VVc | | uM |

continues on next page

Table 3.440 – continued from previous page

| Id | Description | ScalingFactor | Multiplication-Factor | Unit |
|---|---|---|---|---|
| O_CV_M2 | Concentration in venous blood (metabolite 2) | VVc | | uM |
| O_CP_P | Concentration in plasma from whole blood (parent) | VVc | 0.6 | uM |
| O_CP_M1 | Concentration in plasma from whole blood (metabolite 1) | VVc | 0.6 | uM |
| O_CP_M2 | Concentration in plasma from whole blood (metabolite 2) | VVc | 0.6 | uM |
| O_CU_P | Concentration in uterus tissue (parent) | VUc | | uM |
| O_CU_M1 | Concentration in uterus tissue (metabolite 1) | VUc | | uM |
| O_CU_M2 | Concentration in uterus tissue (metabolite 2) | VUc | | uM |
| O_ACL_P | Concentration in cleared renally (parent) | | 0.03 | umoles |
| O_ACL_M1 | Concentration in cleared renally (metabolite 1) | | 0.03 | umoles |
| O_ACL_M2 | Concentration in cleared renally (metabolite 2) | | 0.03 | umoles |
| O_CS_P | Concentration in slowly perfused tissue (parent) | | | umoles |
| O_CS_M1 | Concentration in slowly perfused tissue (metabolite 1) | | | umoles |
| O_CS_M2 | Concentration in slowly perfused tissue (metabolite 2) | | | umoles |
| O_CR_P | Concentration in richly perfused tissue (parent) | | | umoles |
| O_CR_M1 | Concentration in richly perfused tissue (metabolite 1) | | | umoles |
| O_CR_M2 | Concentration in richly perfused tissue (metabolite 2) | | | umoles |
| O_CF_P | Concentration in fat (parent) | VFc | | umoles |
| O_CF_M1 | Concentration in fat (metabolite 1) | VFc | | umoles |
| O_CF_M2 | Concentration in fat (metabolite 2) | VFc | | umoles |

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Table 3.440 – continued from previous page

| Id | Description | ScalingFactor | Multiplication-Factor | Unit |
|---|---|---|---|---|
| O_CL_P | Concentration in liver (parent) | VLc | | umoles |
| O_CL_M1 | Concentration in liver (metabolite 1) | VLc | | umoles |
| O_CL_M2 | Concentration in liver (metabolite 2) | VLc | | umoles |
| O_CK_P | Concentration in kidney (parent) | VKc | | umoles |
| O_CK_M1 | Concentration in kidney (metabolite 1) | VKc | | umoles |
| O_CK_M2 | Concentration in kidney (metabolite 2) | VKc | | umoles |
| O_CM_P | Concentration in muscle (parent) | VMc | | umoles |
| O_CM_M1 | Concentration in muscle (metabolite 1) | VMc | | umoles |
| O_CM_M2 | Concentration in muscle (metabolite 2) | VMc | | umoles |
| O_CH_P | Concentration in heart (parent) | VHc | | umoles |
| O_CH_M1 | Concentration in heart (metabolite 1) | VHc | | umoles |
| O_CH_M2 | Concentration in heart (metabolite 2) | VHc | | umoles |
| O_CLu_P | Concentration in lung (parent) | VLuc | | umoles |
| O_CLu_M1 | Concentration in lung (metabolite 1) | VLuc | | umoles |
| O_CLu_M2 | Concentration in lung (metabolite 2) | VLuc | | umoles |
| O_CBrb_P | Concentration in brain blood (parent) | VBrc | 0.05 | umoles |
| O_CBrb_M1 | Concentration in brain blood (metabolite 1) | VBrc | 0.05 | umoles |
| O_CBrb_M2 | Concentration in brain blood (metabolite 2) | VBrc | 0.05 | umoles |
| O_CBrbt_P | Concentration in brain tissue (parent) | VBrc | 0.95 | umoles |
| O_CBrbt_M1 | Concentration in brain tissue (metabolite 1) | VBrc | 0.95 | umoles |
| O_CBrbt_M2 | Concentration in brain tissue (metabolite 2) | VBrc | 0.95 | umoles |
| O_CBr_P | Concentration in brain total (parent) | VBrc | | umoles |

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Table 3.440 – continued from previous page

| Id | Description | ScalingFactor | Multiplication-Factor | Unit |
|---|---|---|---|---|
| O_CBr_M1 | Concentration in brain total (metabolite 1) | VBrc | | umoles |
| O_CBr_M2 | Concentration in brain total (metabolite 2) | VBrc | | umoles |
| O_CA_P | Concentration in arterial blood (parent) | VAc | | umoles |
| O_CA_M1 | Concentration in arterial blood (metabolite 1) | VAc | | umoles |
| O_CA_M2 | Concentration in arterial blood (metabolite 2) | VAc | | umoles |

Table 3.441: Model parameters

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| VLc | Fraction liver tissue of BW | 0.0257 | | Physiological |
| VFc | Fraction fat tissue of BW | 0.2142 | | Physiological |
| VLuc | Fraction lung tissue of BW | 0.0076 | | Physiological |
| VAc | Fraction arterial blood of BW (0.074*1/4) | 0.0198 | | Physiological |
| VVc | Fraction venous blood of BW (0.074*3/4) | 0.0593 | | Physiological |
| VKc | Fraction kidney tissue of BW | 0.004 | | Physiological |
| VMc | Fraction muscle tissue of BW | 0.04 | | Physiological |
| VUc | Fraction uterus tissue of BW | 0.0018 | | Physiological |
| VBrc | Fraction brain tissue of BW | 0.02 | | Physiological |
| VHc | Fraction heart tissue of BW | 0.0047 | | Physiological |
| QLc | Fraction of blood flow to liver | 0.227 | | Physiological |
| QFc | Fraction of blood flow to fat | 0.052 | | Physiological |
| QKc | Fraction of blood flow to kidneys | 0.175 | | Physiological |
| QMc | Fraction of blood flow to muscle | 0.12 | | Physiological |
| QUc | Fraction of blood flow to uterus | 0.2 | | Physiological |

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Table 3.441 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| QBrc | Fraction of blood flow to brain | 0.114 | | Physiological |
| QHc | Fraction of blood flow to heart | 0.04 | | Physiological |
| MWP | Molecular weight parent | 350.59 | g/mol | Physicochemical |
| MWM1 | Molecular weight metabolite 1 | 334.52 | g/mol | Physicochemical |
| MWM2 | Molecular weight metabolite 2 | 198.43 | g/mol | Physicochemical |
| LogPP | Octanol/water partition coefficient parent | 4.784 | | PartitionCoefficient |
| LogPM1 | Octanol/water partition coefficient metabolite 1 | 3.894 | | PartitionCoefficient |
| LogPM2 | Octanol/water partition coefficient metabolite 2 | 1.856 | | PartitionCoefficient |
| Fa | Fraction absorbed. Obtained from Nolan 1984 | 0.7 | | Physicochemical |
| KaS | Absorption constant stomach. Obtained from Timchalk et al. 2002 (stomach; /h) | 0.00000733 | /h | Physicochemical |
| KaI | Absorption constant intestine. Obtained from Timchalk et al. 2002 (intestine; /h) | 1.00033 | /h | Physicochemical |
| KsI | Absorption constant (transfer stomach to intestine). Obtained from Timchalk et al. 2002 (transfer stomach to intestine; /h) | 0.967749 | /h | Physicochemical |
| fuP | Unbound fraction in plasma (parent) | 0.021 | | Physicochemical |
| fuM1 | Unbound fraction in plasma (metabolite 1) | 0.15 | | Physicochemical |
| fuM2 | Unbound fraction in plasma (metabolite 2) | 0.082 | | Physicochemical |
| BPP | B/P ratio (parent) | 1.3 | | Physicochemical |
| BPM1 | B/P (metabolite 1) | 2.7 | | Physicochemical |
| BPM2 | B/P (metabolite 2) | 1 | | Physicochemical |
| KurineP | Urinary excretion rate constant parent | 0 | /h | Physicochemical |
| KurineM1 | Urinary excretion rate constant metabolite 1 | 0 | /h | Physicochemical |

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Table 3.441 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| KurineM2 | Urinary excretion rate constant metabolite 2 | 0.026 | /h | Physicochemical |
| CYPabundance-CYP1A2 | CYP1A2 abundance (pmolCYP/mg protein) | 52 | | Physicochemical |
| CYPabundance-CYP2B6 | CYP2B6 abundance (pmolCYP/mg protein) | 15.8 | | Physicochemical |
| CYPabundance-CYP2C19 | CYP2C19 abundance (pmolCYP/mg protein) | 5.4 | | Physicochemical |
| CYPabundance-CYP3A4 | CYP3A4 abundance (pmolCYP/mg protein) | 137 | | Physicochemical |
| ISEFCYP1A2 | Scaling factor CYP1A2 ISEF (Vmax) (non compound-specific) | 0.072 | | Physicochemical |
| ISEFCYP2B6 | Scaling factor CYP2B6 ISEF (Vmax) (non compound-specific) | 0.476 | | Physicochemical |
| ISEFCYP2C19 | Scaling factor CYP2C19 ISEF (Vmax) (non compound-specific) | 0.209 | | Physicochemical |
| ISEFCYP3A4 | Scaling factor CYP3A4 ISEF (Vmax) (non compound-specific) | 0.107 | | Physicochemical |
| MPL | Scaling factor of human liver microsome in mg to gram liver (mg microsomal protein /g liver) (Al-Malahmeh, A. J et al., 2017) (Barter et al., 2007) | 32 | mg/g | Physicochemical |
| VMaxCYP1-A2mP1 | Vmax of CYP1A2 at supersome level (pmol/min/pmol CYP) (Experimentally determined using supersomes, Chen et al., 2022) | 3.963 | | Physicochemical |

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Table 3.441 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| VMaxCYP2-B6mP1 | Vmax of CYP2B6 at supersome level (pmol/min/pmol CYP) (Experimentally determined using supersomes, Chen et al., 2022) | 7.755 | | Physicochemical |
| VMaxCYP2-C19mP1 | Vmax of CYP2C19 at supersome level (pmol/min/pmol CYP) (Experimentally determined using supersomes, Chen et al., 2022) | 2.744 | | Physicochemical |
| VMaxCYP3-A4mP1 | Vmax of CYP3A4 at supersome level (pmol/min/pmol CYP) (Experimentally determined using supersomes, Chen et al., 2022) | 17.78 | | Physicochemical |
| KmCYP1A2P1 | Affinity constant of CYP1A2 (umoles/L) (Experimentally determined using supersomes, Chen et al., 2022) | 0.61 | umoles/L | Physicochemical |
| KmCYP2B6P1 | Affinity constant of CYP2B6 (umoles/L) (Experimentally determined using supersomes, Chen et al., 2022) | 0.14 | umoles/L | Physicochemical |
| KmCYP2C19-P1 | Affinity constant of CYP2C19 (umoles/L) (Experimentally determined using supersomes, Chen et al., 2022) | 1.89 | umoles/L | Physicochemical |
| KmCYP3A4P1 | Affinity constant of CYP3A4 (umoles/L) (Experimentally determined using supersomes, Chen et al., 2022) | 29.77 | umoles/L | Physicochemical |

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Table 3.441 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| VMaxCYP1-A2mP2 | Vmax of CYP1A2 at supersome level (pmol/min/pmol CYP) (Experimentally determined using supersomes, Chen et al., 2022) | 2.957 | | Physicochemical |
| VMaxCYP2-B6mP2 | Vmax of CYP2B6 at supersome level (pmol/min/pmol CYP) (Experimentally determined using supersomes, Chen et al., 2022) | 5.492 | | Physicochemical |
| VMaxCYP2-C19mP2 | Vmax of CYP2C19 at supersome level (pmol/min/pmol CYP) (Experimentally determined using supersomes, Chen et al., 2022) | 17.51 | | Physicochemical |
| VMaxCYP3-A4mP2 | Vmax of CYP3A4 at supersome level (pmol/min/pmol CYP) (Experimentally determined using supersomes, Chen et al., 2022) | 23.86 | | Physicochemical |
| KmCYP1A2P2 | Affinity constant of CYP1A2 (umoles/L) (Experimentally determined using supersomes, Chen et al., 2022) | 1.25 | umoles/L | Physicochemical |
| KmCYP2B6P2 | Affinity constant of CYP2B6 (umoles/L) (Experimentally determined using supersomes, Chen et al., 2022) | 1.28 | umoles/L | Physicochemical |
| KmCYP2C19-P2 | Affinity constant of CYP2C19 (umoles/L) (Experimentally determined using supersomes, Chen et al., 2022) | 1.37 | umoles/L | Physicochemical |

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Table 3.441 – continued from previous page

| Id | Description | Default | Unit | Type |
|---|---|---|---|---|
| KmCYP3A4P2 | Affinity constant of CYP3A4 (umoles/L) (Experimentally determined using supersomes, Chen et al., 2022) | 18.13 | umoles/L | Physicochemical |
| VMax3c | Maximum velocity constant (nmol/min/ml plasma) (Experimentally determined using microsomes, Chen et al., 2022) | 37.98 | nmoles/min/ml | Physicochemical |
| Km3 | Affinity constant (umoles/L) (Experimentally determined) | 627.9 | | Physicochemical |
| VMax4c | Maximum velocity constant (nmol/min/ml plasma) (Experimentally determined using microsomes, Chen et al., 2022) | 1844 | nmoles/min/ml | Physicochemical |
| Km4 | Affinity constant (umoles/L) (Experimentally determined) | 289.8 | umoles/L | Physicochemical |
| BW | | 70 | kg | BodyWeight |

Model aliases: PBK_Chlorpyrifos_V1.

### 3.7.4 PBK model parametrisations

External exposure can be from one or more exposure routes: oral (dietary or non-dietary), dermal or inhalation. Internal exposures are related to a specific *biological matrix*, in a kinetic model.

Use one of the PBK models specified in the *PBK models module*, with instances for specific substances defined in data table *kinetic model instances* and model parameters specified in data table *kinetic model instance parameters*.

Given a PBK model the calculation will fall back to a lower tier, see *kinetic conversion factors module*, in case of missing data.

This module has as primary entities: *Substances*

Output of this module is used by: *Internal exposures HBM analysis Kinetic conversion factors Hazard characterisations*

#### PBK model parametrisations from data

To simulate the fate of a substance in a compartment, the *PBK* models in MCRA are run using different dosing patterns. In general, the length of the simulation period is specified in days.

The *Exposure events and dose generation* setting specifies how repeated dose patterns are applied.

- *Use usual (average) exposures per route* to specify a single dose per day, repeated over the entire simulation length. The dose applied is for an acute exposure assessment equal to a daily dose, for a chronic assessment equal to the average of all daily exposures of an individual (e.g. *OIM*).

- *Use (randomly selected) daily exposures per route* to specify more complex dosing patterns. The daily exposures (in a chronic context) are randomly allocated to the events, so for one event per day, the entire sequence of doses is a random sequence of the daily doses of one individual and, in case of a two 24hour recall, two different doses are sampled. When the specified number of events is > 1, the daily doses are divided by the specified number of events in a day and randomly allocated to the events. Note that for PBK models with a resolution in hours, the number of events should be equal to 1, 2, 3, 4, 6, 8 and 12.

For irregular dosing patterns use setting *Specify event timings*. Allowed numbers are 1, 2, 3,…,24 separated by spaces (e.g. 1 2 7 12).

Currently, option *Specify event timings* is only implemented for the oral route and for PBK models with resolution in hours.

### PBK model parametrisations data formats

**Data tables:**

- Kinetic model instances
- Kinetic model instance parameters

PBK model parametrisations are specifications of parameter values of for PBK model definitions.

### PBK model data format

The PBK model parametrisations data format specifies parameter values of for PBK model definitions.

Download empty dataset template: Zipped CSV Excel

### PBK model instances

PBK model instances/parametrisations.

Table 3.442: Table definition for PBK model instances.

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idModel-Instance | AlphaNumeric (50) | Unique identification code of the PBK model instance/parametrisation. | idModel-Instance, Id, Code | Yes |
| idModel-Definition | AlphaNumeric | Identifier of the PBK model definition of which this is an instance/parametrisation. | idModel-Definition, ModelDefinition | Yes |
| Species | AlphaNumeric (50) | The species to which this instance/parametrisation applies. | Species, System, TestSystem | Yes |
| Substances | AlphaNumeric (150) | Code or comma separated list of the codes of the substances. Only applies for substance-specific parameters. | idSubstance, idSubstances, SubstanceId, SubstanceCode, SubstanceCodes, Substance, Substances | No |
| Reference | AlphaNumeric (100) | Reference or author. | References | No |
| Name | AlphaNumeric (100) | Name of the kinetic model instance/parametrisation. | Name | No |
| Description | AlphaNumeric (200) | Additional description of the model instance/parametrisation. | Description | No |

Accepted table names: PbkModelInstances, PbkModelParametrisations, KineticModelInstances, KineticModelInstance.

### PBK model instance parameters

PBK model instance/parametrisation parameter values.

Table 3.443: Table definition for PBK model instance parameters .

| Name | Type | Description | Aliases | Required |
|---|---|---|---|---|
| idModel-Instance | AlphaNumeric (50) | Unique identification code of the kinetic model instance to which this parameter belongs | Id, Code | Yes |
| Parameter | AlphaNumeric (50) | Identifier of the parameter in the PBK model. | | Yes |
| Description | AlphaNumeric (200) | Description of or reference for the parameter values in the model. | | No |
| Value | Numeric | Nominal parameter value of the distribution. | Mean | Yes |
| Distribution-Type | *PbkModelParameter-DistributionType* | Parameter distribution type. | Distribution-Type, Distribution | No |
| CvVariability | Numeric | Variability of the parameter expressed as a coefficient of variation (CV). | | No |
| CvUncertainty | Numeric | Uncertainty of the parameter expressed as a coefficient of variation (CV). | | No |

Accepted table names: PbkModelInstanceParameters, PbkModelInstanceParameterValues, KineticModelInstanceParameters, KineticModelInstanceParameter.

### PBK model parametrisations settings

### Calculation settings

Table 3.444: Calculation settings for module PBK model parametrisations.

| Name | Type | Description |
|---|---|---|
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Exposure routes | ExposureRoutes | Exposure routes included in assessment. |
| Restrict active substances to substances with available hazard characterisations | Boolean | Restrict assessment group membership based on presence/abser of hazard characterisations. |
| Number of simulated days | Numeric | The total duration (in days) of the PBK model simulations. |
| Number of initial days skipped | Numeric | The initial period (or burn-in period, specified in days) that nee to be skipped when calculating the steady-state or peak internal exposures from the simulated time series. |
| Use PBK model parameter variability | Boolean | When specified, use parameter variability. |
| Number of events per day for the DERMAL dose | Numeric | The daily dose is administered in equal portions (dose / number events) per event. |
| Number of events per day for the INHALATION dose | Numeric | The daily dose is administered in equal portions (dose / number events) per event. |
| Number of events per day for the ORAL dose | Numeric | The daily dose is administered in equal portions (dose / number events) per event. |
| Specify the hours (events). | Numeric | Specify the hours on which exposure events are simulated. Allowed numbers are 1, 2, 3, 4,…, 24 separated by spaces. |
| Specify event timings | Boolean | If checked, a specific sequence of hours on a day can be specifi on which exposure events are simulated. Otherwise the events a derived based on the number of exposure events per day. |
| Exposure events and dose generation method | *ExposureEventsGeneration-Method* | Generates doses and events for PBK model |
| PBK simulation method | *PbkSimulationMethod* | Specifies in which mode to run the PBK model |
| Lifetime start age in years | Numeric | The starting age (in years) for lifetime range simulation. |
| Lifetime end age in years | Numeric | The ending age (in years) for lifetime range simulation. |
| Lifetime window size in years | Numeric | The size of the time window (in years) for the lifetime window simulation. |
| Use bodyweight adjusted exposures | Boolean | Use bodyweight adjusted exposures in PBK model simulations. |

### Uncertainty settings

Table 3.445: Uncertainty settings for module PBK model parametrisations.

| Name | Type | Description |
|---|---|---|
| Resample PBK model parameter values | Boolean | Specifies whether PBK model parameter values are resampled. |

### PBK model parametrisations as data

Specify kinetic instances of PBK models and their parametrisations as data.

- *PBK model parametrisations data formats*
- *PBK model parametrisations from data*

Inputs used: *Active substances PBK model definitions*

Settings used

- *Calculation Settings*

## 3.8 Risk modules

Risk metrics compare *exposure* and *hazard characterisation*. When both are defined by single values, risk metrics - such as the traditional risk characterisation ratio (hazard/exposure) or hazard quotient (exposure/hazard) - can be calculated via the Single value risks module. For more complex analyses, the Risks module enables probabilistic calculations. In both modules a threshold can be set to assist in interpretation. The threshold value should align with the assessment factors used, for instance a *MOE* threshold of 100 (or *HI* = 0.01) is common when no assessment factors are present, while a threshold of 1 is appropriate if assessment factors have already been integrated to address relevant uncertainties.

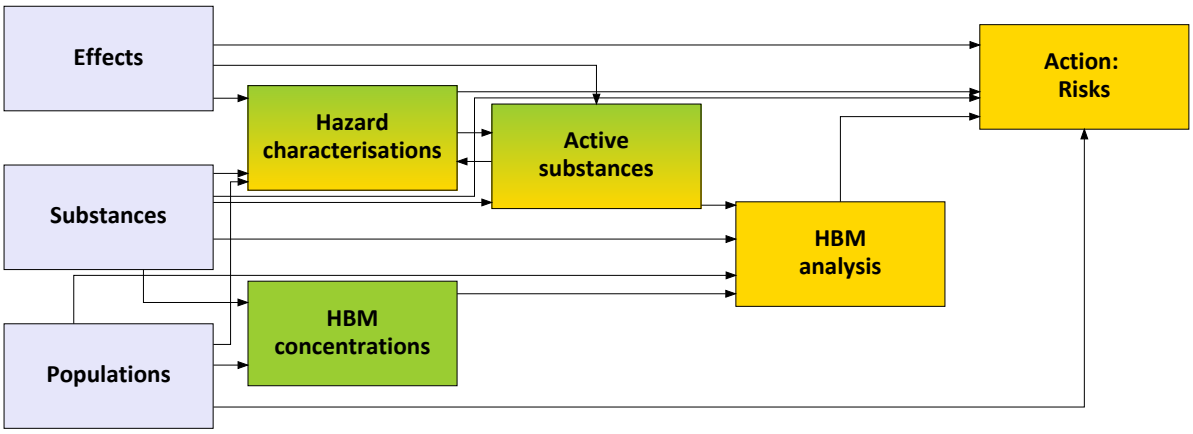


Figure 3.84: Risks module.

The environmental burden of disease (*EBD*) quantifies the amount of mortality and morbidity (illness) within a population that is attributable to environmental risk factors, such as air pollution, poor water quality, or chemical exposures. It measures the health impact of modifiable, non-genetic factors, enabling policymakers to prioritize prevention, with measurements often expressed in Deaths, Disability-Adjusted Life Years (*DALY* s), Cases (the number of specific, attributable health outcomes or illness). On the basis of EBD studies it is also possible to estimate the level of health-related Costs (medical expense for treatment, loss of productivity or, in general, economic impact).

### 3.8.1 Environmental burden of disease

Environmental Burden of Disease (EBD) assessment.

This module has as primary entities: *Populations Substances*

#### Environmental burden of disease calculation

See also: Environmental burden of disease methodology, (*EBD*) Plass et al. (2024).

In Figure 3.86, the attributable burden (in *DALY* s) with uncertainty bounds are displayed together with the cumulative percentage (right axis). On the x-axis, the exposure is displayed according to the specified bin boundaries, *see settings*. Specify custom bins or exposure response function ( *ERF*) defined bins (i.c. 5, 10, 25, 50, 75, 90, 95%).

In Figure 3.87, the attributable burden is standardised by the population size (*see primary entity populations data format*) and expressed per 100,000 individuals. Population size can be expressed with uncertainty that is propagated through the calculations.

Figure 3.88 shows the exposure response function, here an odds-ratio. Note that a confidence interval for the effect metric *OR* (odds ratio) is provided with a lower bound below 1, suggesting a health benefit. This is undesirable and

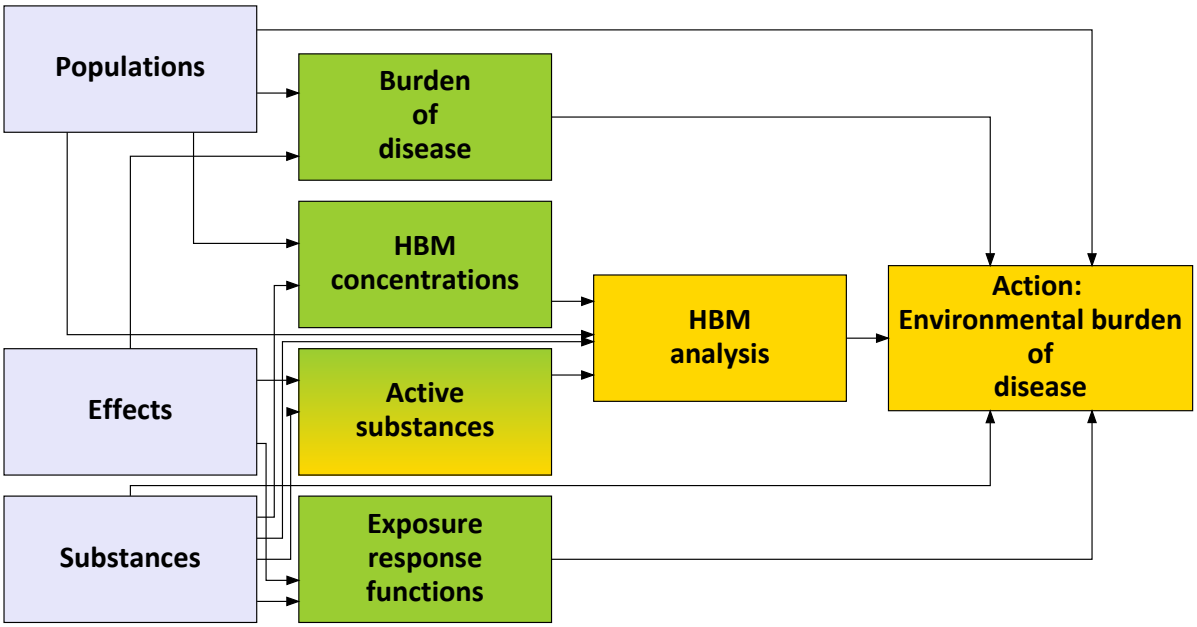


Figure 3.85: Environmental burden of disease module.

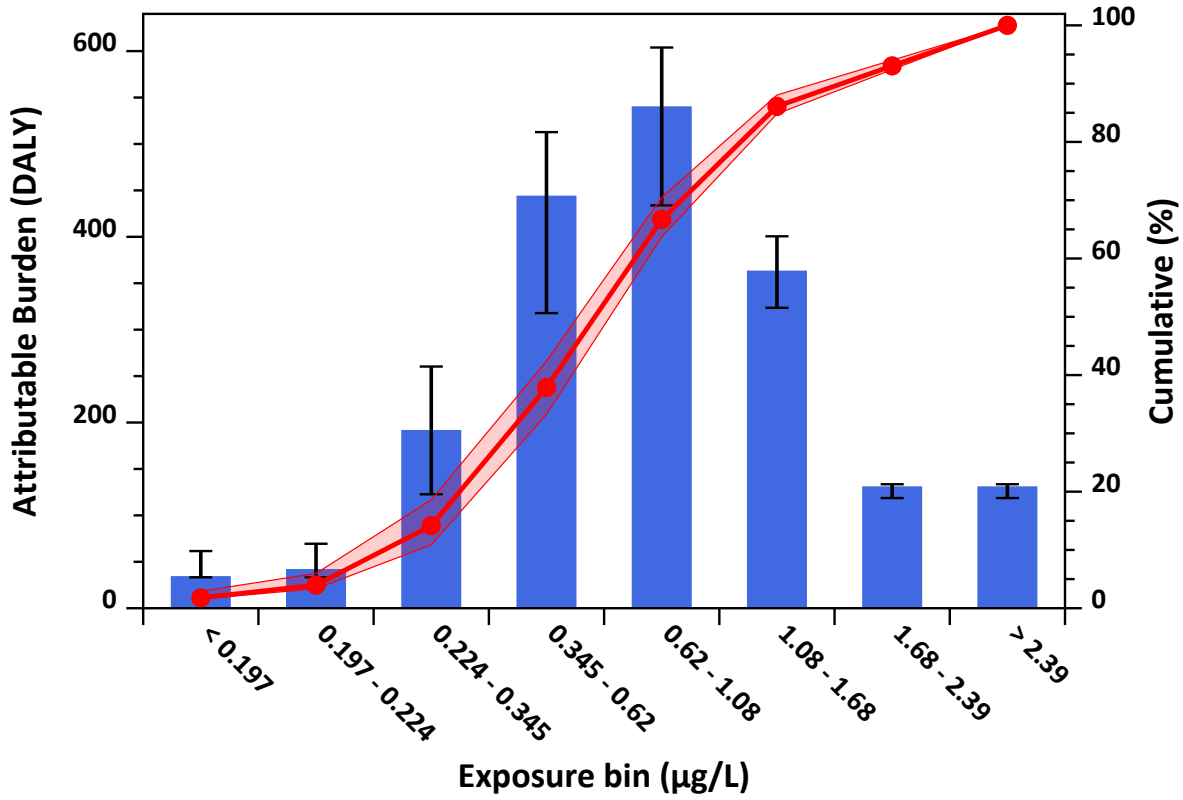


Figure 3.86: Attributable burden & cumulative percentage with ERF defined bins

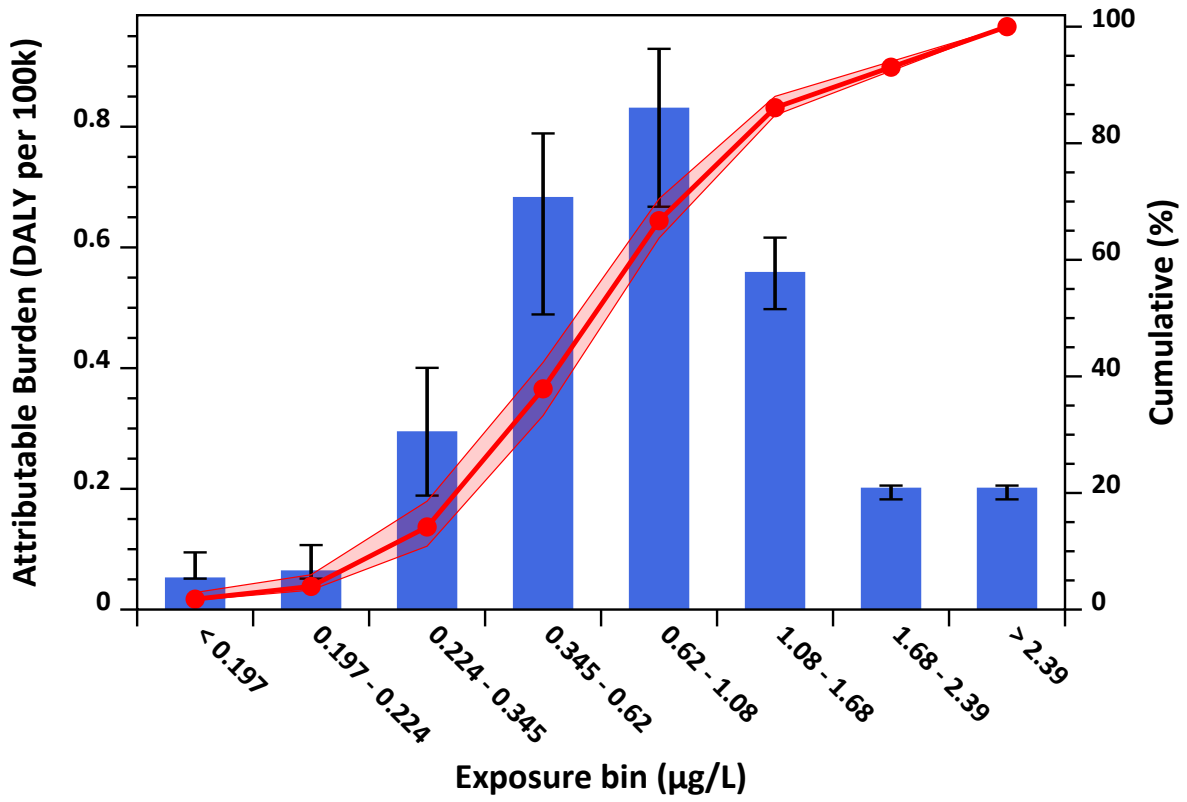


Figure 3.87: EBD per 100,000 individuals & cumulative percentage with ERF defined bins

the user should be able to force *PAF* values to have a lower limit of 0. Use setting *'Forces PAF values to a minimum of 0'* to force the $PAF > 0$ (only in a top down approach). The vertical red line indicates the counterfactual value of the ERF at 0.5.

## Environmental burden of disease settings

### Selection settings

Table 3.446: Selection settings for module Environmental burden of disease.

| Name | Type | Description |
|---|---|---|
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |

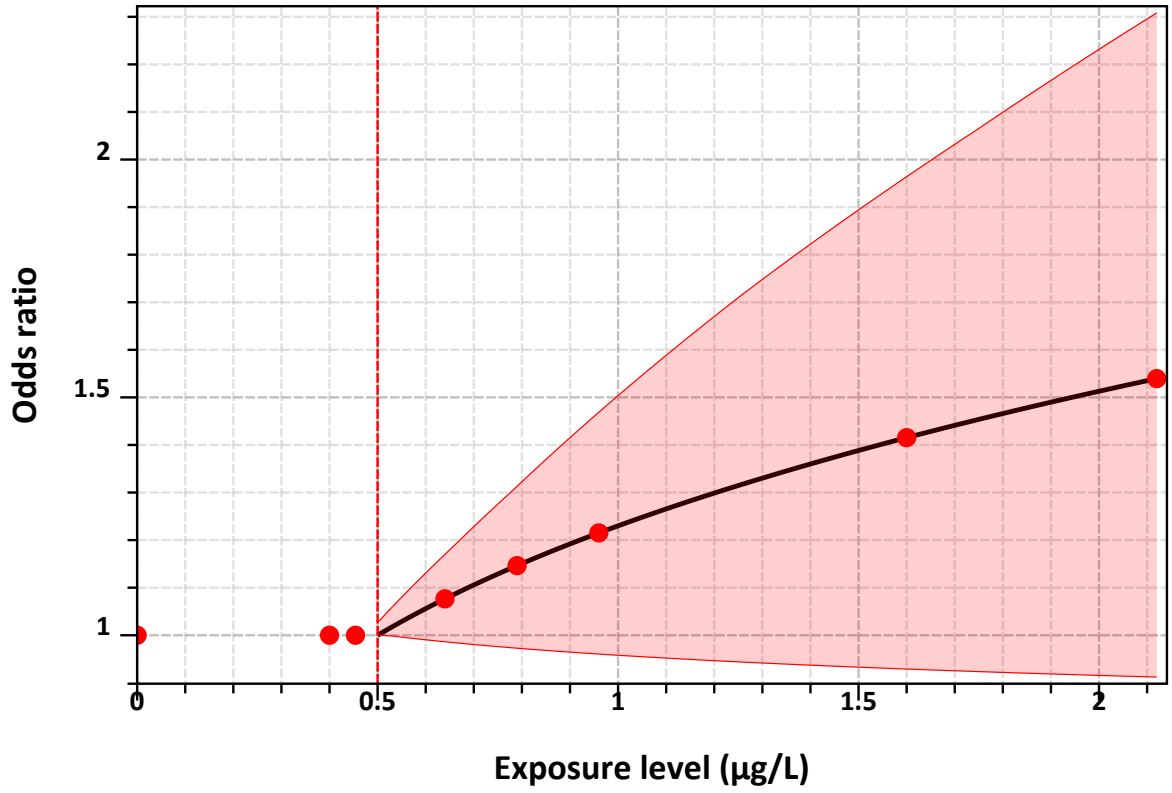


Figure 3.88: Exposure response function, effect metric is odds-ratio

### Calculation settings

Table 3.447: Calculation settings for module Environmental burden of disease.

| Name | Type | Description |
|---|---|---|
| Target level | *TargetLevelType* | Select whether the assessment is at the level of external dose, internal (target) concentration or internal (systemic) dose. For a aggregate assessment, combining dietary and nondietary exposures, the target level is always internal concentration or internal (systemic) dose. When only dietary exposures are available, the target level is optional and may be an external (administered) dose, an internal (tissue) concentration or an internal (absorbed) dose. |
| Exposure calculation method | *ExposureCalculationMethod* | Method for obtaining exposure estimates. These can be modell exposures (e.g., external (dietary) exposures or internal exposur estimates obtained by aggregating dietary and non-dietary exposures) or exposure estimates derived from human (bio)monitoring data. |
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Compute for cumulative exposures | Boolean | Specifies whether to compute EBDs based on cumulative exposures. |
| Burden of disease indicators | *BodIndicator* | Burden of disease indicators. |
| Bod approach | *BodApproach* | Specify the approach used for estimating the attributable burde of disease. |
| Exposure grouping method | *ExposureGroupingMethod* | Specify the method by which the exposures are grouped in bins For 'Custom bins', the specified bins are used for all exposure response functions. For 'ERF-defined bins', the bins defined for subgroups are used and for exposure response functions withou subgroups, the specified custom bins are used. |
| Bin boundaries | Numeric | Specify the boundaries (%) of the bins by which the exposures grouped. For 'Custom bins', the specified bins are used for all exposure response functions. For 'ERF-defined bins', the bins defined for subgroups are used and for exposure response |

#### Uncertainty settings

Table 3.448: Uncertainty settings for module Environmental burden of disease.

| Name | Type | Description |
|---|---|---|
| Lower uncertainty limit (%) | Numeric | Percentage lower bound, e.g. 2.5%. |
| Upper uncertainty limit (%) | Numeric | Percentage upper bound, e.g. 97.5%. |

#### Calculation of environmental burden of disease

EBDs are calculated from human monitoring data.

- *Environmental burden of disease calculation*

Inputs used: *Dietary exposures Internal exposures HBM analysis Exposure response functions Burden of disease HBM single value exposures Relative potency factors*

Settings used

- *Calculation Settings*

### 3.8.2 Risks

Risks (health impacts) are defined as a function of exposure and hazard characterisation at a chosen biological level (external or internal). Risk metrics are either based on the ratio hazard/exposure (e.g., MOE(T)) or exposure/hazard (e.g., HI, HQ, and RPI).

This module has as primary entities: *Substances Effects Populations*

Output of this module is used by: *Single value risks*

#### Risks calculation

A (cumulative) risk assessment aims to characterise the health impact due to exposure to one or multiple substances causing common adverse health effects. The health impact is characterised by a distribution of individual risks, expressed by a *risk metric* i.e., a risk characterisation ratio (hazard/exposure) (*H/E*); or a risk characterisation ratio (exposure/hazard) (*E/H*), comparing exposures and hazard characterisations at the chosen level (external or internal). Hazard characterisations are included as single values or in a probabilistic way.

The aim is to specify the probability that a random individual from a defined (sub)population will have an exposure high enough to cause a particular health effect of a predefined magnitude, the critical effect size. The exposure level that results in exactly that critical effect in a particular person is that person's individual critical hazard dose (*ICED*). Individuals in a population typically show variation, both in their individual exposure and in their hazard characterisation. Both the variation in exposure and the variation in hazard characterisation are quantified in the form of probability distributions. Assuming independence between both distributions, they are combined by Monte Carlo methods. The proportion of the $H/E$ ratio distribution below the (safety/uncertainty) threshold (or the proportion of the $E/H$ ratio distribution above e.g. 0.01 (in general 1) is the probability of critical effect (*POCE*), here 13%, in the particular (sub)population. Uncertainties involved in the overall risk assessment (i.e., both regarding exposure and hazard characterisation) are quantified using Monte Carlo and bootstrap methods. This results in an uncertainty distribution for any statistic of interest.

In Figure 3.91, the risk characterisation ratios (exposure/hazard) for a number of substances are shown. As shown, the distinction between variability (grey bars, 90% probability) and uncertainty (whiskers) is retained. This is discussed in van der Voet and Slob (2007) and van der Voet et al. (2009).

In Figure 3.92, hazards versus exposures are plotted for the same substances.

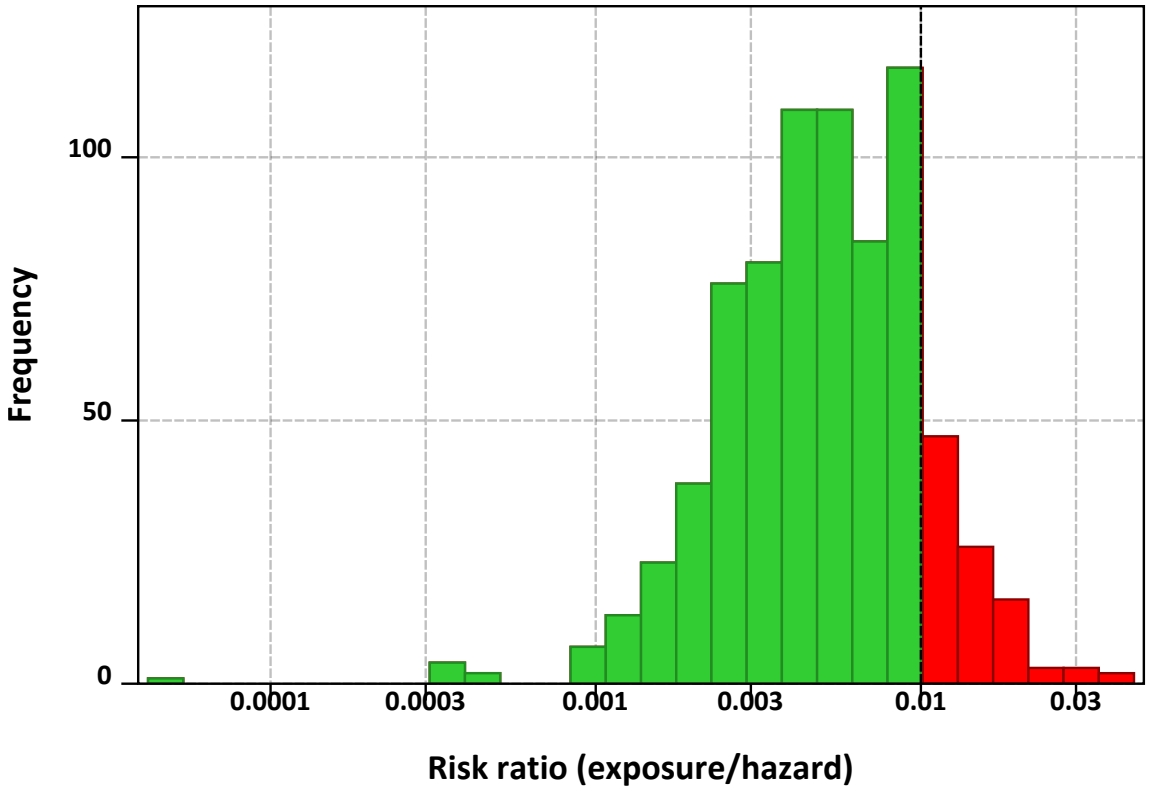


Figure 3.89: Risk characterisation ratio (exposure/hazard) total distribution (triazoles) with a threshold of 0.01.

### Risk metric calculation type

Currently, two types of risk metric calculation types are available. Both for the risk characterisation ratio (hazard/exposure) (ratio *H/E*) and (exposure/hazard) (ratio *E/H*):

- exposures are cumulated over substances using RPFs and the risk distribution is estimated based on the hazard characterisation of the reference substance and the cumulative exposure. All RPFs should be supplied. See also *cumulative RPF weighted risk distribution*.
- risk is calculated per substance as a ratio of each hazard characterisation and the exposure. Then, the risk is estimated as the cumulated *sum of ratios* over all substances. All hazard characterisations should be supplied. In formula:
- risk is calculated per substance as a ratio of each hazard characterisation and the exposure. Then, the risk is estimated as the cumulated *sum of ratios* over all substances. All hazard characterisations should be supplied. In formula:

For the risk characterisation ratio $E/H$:

$$E/H = HI = \sum_{s=1}^{S} HQ_s$$

where summation is over the number of substances per individual(day).

For the risk characterisation ratio $H/E$:

$$H/E = MOET = \frac{1}{\sum_{s=1}^{S} \frac{1}{H/Es}}$$

where summation is over the number of substances per individual(day).

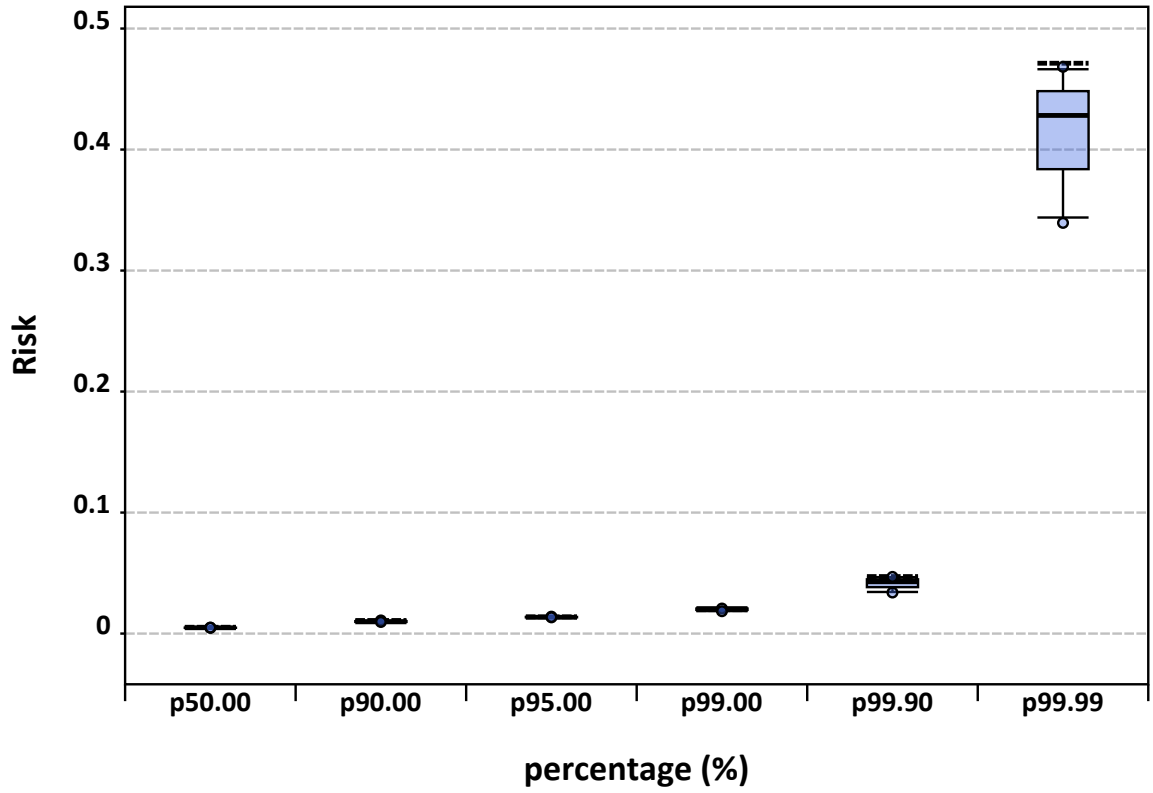


Figure 3.90: Uncertainty of percentiles.The boxplots for uncertainty show the p25 and p75 as edges of the box, and p2.5 and p97.5 as edges of the whiskers. The reference (nominal) value is indicated with the dashed black line, the median with the solid black line within the box. Outliers are displayed as dots outside the wiskers. Risk is specified as the characterisation ratio (exposure/hazard) (triazoles).

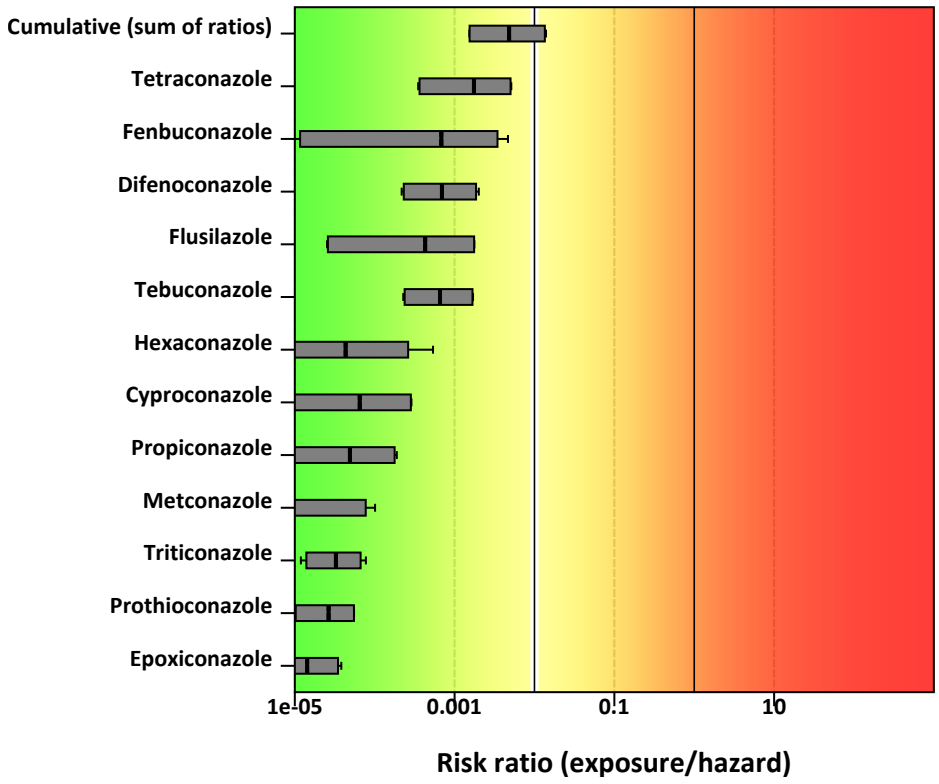


Figure 3.91: Risk characterisation ratio (exposure/hazard) plot for multiple substances (triazoles). The threshold of 0.01 is indicated with the left vertical line, the vertical black line on the right indicates a threshold of 1.

The blue line indicates the median value of the cumulative risks in the population. Note that the cumulative sum of the medians of the risk characterisation ratios of the contributing substances, here metals (red areas) does not necessarily add up to the cumulative risk (blue line). Simulations with multivariate lognormal distributions without correlation suggest that for moderate percentiles like the median the cumulative risk is higher than the risk calculated as sum of ratios.

### Inverse distribution

Risk can be calculated as a distribution of either a risk characterisation ratio hazard/exposure ($H/E$) or exposure/hazard ($E/H$), if at least one of the inputs exposure and hazard characterisation is a distribution. The risk distribution is characterised by percentiles. To accommodate for matching results of $H/E$ and $E/H$ in the case of percentiles, there is an option to calculate percentiles via the complementary percentile of the *inverse distribution* in order to handle numerical differences when calculating percentiles for a left or right tail. The option is especially useful for small data sets where percentile calculation is asymmetric in both tails. When set, the percentile is calculated as the inverse of the complementary percentage of the inverse distribution. E.g., the $p_1$ of the $H/E$ distribution is calculated as 1/($p_{99}$ of $1/H/E$ distribution); the $p_{99}$ of the $E/H$ distribution is calculated as 1/($p_1$ of $1/E/H$ distribution).

### Risk by food

The option *calculate risks by modelled foods* is available when the target dose level is external. Dietary exposures preserving all the information of exposures of modelled foods are used to calculate risks statistics for modelled foods and to calculate the percentages at risk of modelled foods in the background and foreground based on the specified *threshold* in the safety plot.

For co-exposure of substances, see *maximum cumulative ratio (MCR)* and the *exposure mixtures module*.

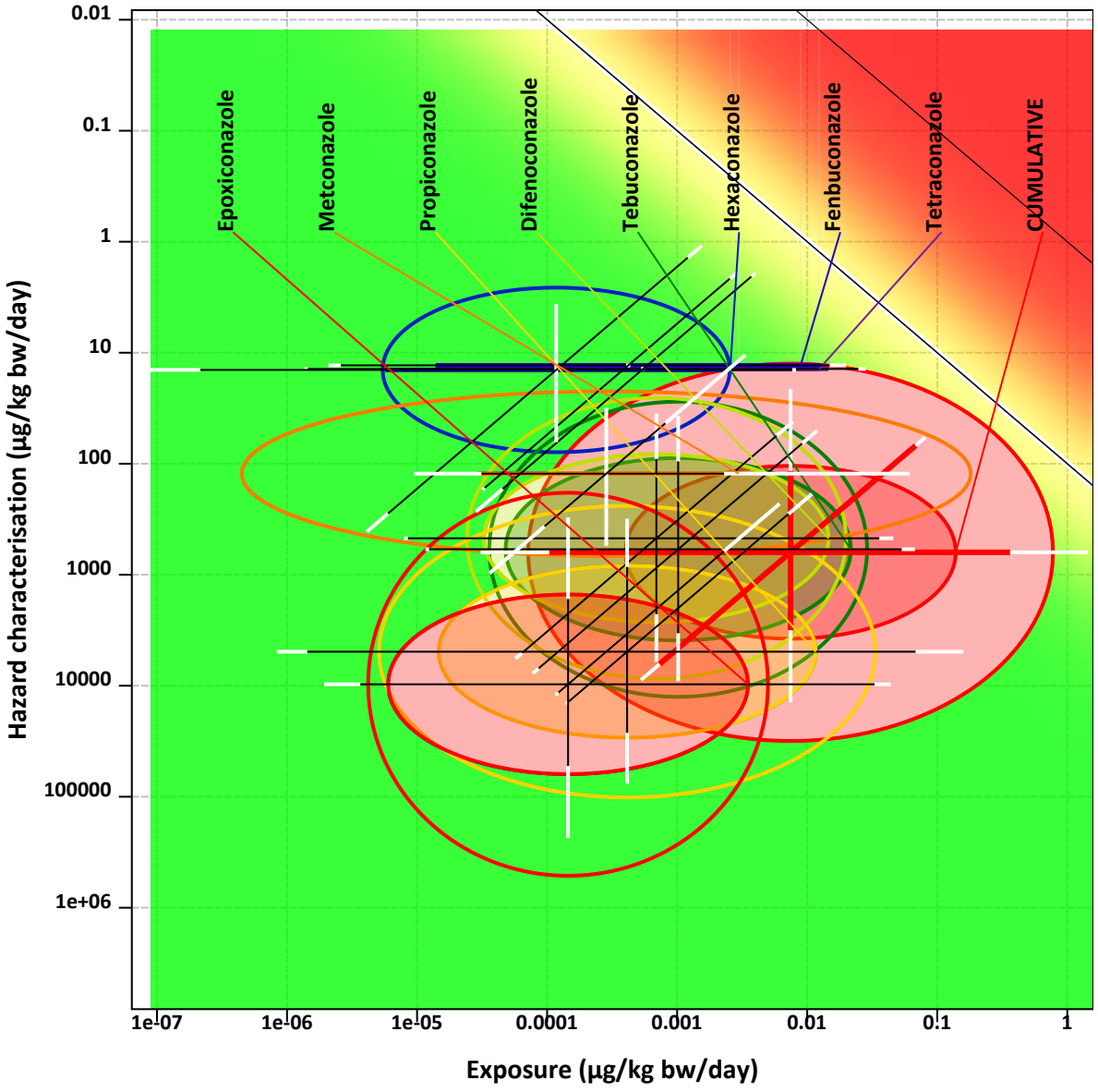


Figure 3.92: Hazard vs. exposure plot for multiple substances. 95% bivariate confidence areas for target hazard dose distribution and exposure distribution. Inner ellipses express variability, outer ellipses uncertainty.

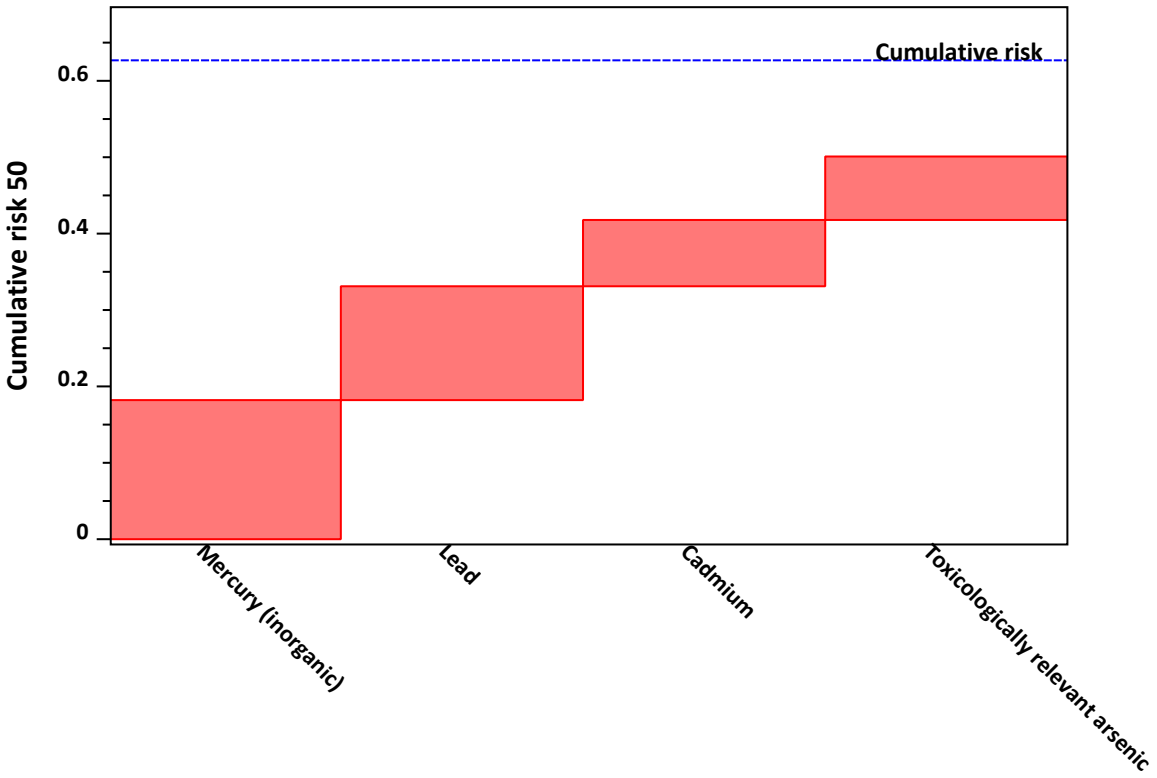


Figure 3.93: Cumulative risk characterisation ratios exposure/hazard (median) in the population (metals).

### Risks settings

### Calculation settings

Table 3.449: Calculation settings for module Risks.

| Name | Type | Description |
|---|---|---|
| Selected tier | SettingsTemplateType | Specifies all module settings should be set according to a pre-defined tier or using custom settings. |
| Seed for pseudo-random number generator | Numeric | A value of 0 will use a pseudo-random seed in each run, a valu 0 will provide the same results in a repeated run. |
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Compute cumulative risks | Boolean | Specifies whether to compute the combined/cumulative risk ov all substances. |
| Health effect type | *HealthEffectType* | Specifies whether the health effect is a risk (negative) or benefit (positive). |
| Risk characterisation ratio | *RiskMetricType* | Report risks in terms of the ratio exposure/hazard (e.g., HI, HQ RPI) or as hazard/exposure (e.g., MOE(T)). |
| Show equivalent animal dose output | Boolean | Specifies whether equivalent animal doses should be reported i the output. |
| Risk threshold | Numeric | Threshold for interpretation of the risk metric. For instance, fo the Margin of Exposure (MOE) a threshold of 100 is commonl used and for the Hazard Index (HI) the threshold is usually 1. |
| Use inverse distribution to calculate percentile | Boolean | Calculate percentile via the complementary percentage of the inverse distribution (default: no). Description: E.g., P0.1 of MOE(T) distribution is calculated via P99.9 of 1/MOE(T) distribution. Note: This option is provided because percentile calculation in small data sets is asymmetric in both tails. |
| Exposure routes | ExposureRoutes | Exposure routes included in assessment. |
| Target level | *TargetLevelType* | Select whether the assessment is at the level of external dose, internal (target) concentration or internal (systemic) dose. For a aggregate assessment, combining dietary and nondietary exposures, the target level is always internal concentration or internal (systemic) dose. When only dietary exposures are available, the target level is optional and may be an external (administered) dose, an internal (tissue) concentration or an internal (absorbed) dose. |
| Calculate risks by modelled foods, substances or a combination of the two | Boolean | When the dose target level is external, dietary exposures are directly used as input to risks. Dietary exposures preserve the information of exposure by modelled foods, substances or the combination. Summarizing this information may time consumi |
| Exposure calculation method | *ExposureCalculationMethod* | Method for obtaining exposure estimates. These can be modell exposures (e.g., external (dietary) exposures or internal exposur estimates obtained by aggregating dietary and non-dietary exposures) or exposure estimates derived from human (bio)monitoring data. |
| Cumulation setting | *RiskMetricCalculationType* | Specify method for computing cumulative risks of multiple substances (e.g., via RPF weighted exposures or as a sum of ratios). |
| Perform MCR analysis | Boolean | Perform a Maximum Cumulative Ratio (MCR) analysis to determine co-exposure between substances. |
| Substance weighting in mixtures | *ExposureApproachType* | Risk based: exposures in equivalents of the reference substance standardised: standardised exposures per substance have varian 1; or unweighted exposures: RPFs are equal to 1. |
| Cutoff MCR | Numeric | For selection of individual(day) exposures with maximum cumulative ratio (MCR = total exposure/maximum) above the cutoff. |
| Cutoff percentage in population ranked on total exposure | Numeric | For selection of individual(day) exposures above the cutoff percentage in the set of individual(day)s ranked on total exposu |
| Display ratio total exposure/ maximum (in MCR plot) | Numeric | For MCR plot: specify ratio total exposure/ maximum for individual(day) exposures . |
| Show tail percentiles (MCR plot) for: | Numeric | Give specific percentiles of exposure distribution (%), e.g. 97.5 99 (space separated). |

### Output settings

Table 3.450: Output settings for module Risks.

| Name | Type | Description |
|---|---|---|
| Left margin safety plot | Numeric | Left margin of the risk value in risk characterisation plots / safe charts. |
| Right margin safety plot | Numeric | Right margin of the risk value in risk characterisation plots / safety charts. |
| Number of plot labels | Numeric | Maximum number of labels to plot in hazard versus exposure pl |
| Number of substances in hazard vs. exposure plot | Numeric | Maximum number of substances to plot in hazard vs exposure plot. |
| Inclusion percentage variability interval | Numeric | The central percentage of the variability distribution to include intervals for exposure, hazard and MOE (e.g. 90 means p5-p95 |
| Exclude privacy sensitive data from outputs | Boolean | Use this setting to not report the parts of the results (i.e., figures tables, or sections) that are marked as (potentially) privacy sensitive. |
| Include drill-down on 9 individuals around specified percentile | Boolean | Specifies whether drilldown on 9 individuals is to be included in the output. |
| Show percentiles for | Numeric | Give specific percentiles of exposure distribution (%), e.g. 50 9 95 97.5 99 (space separated). |
| Percentage for drilldown | Numeric | Gives detailed output for nine individuals near this percentile of the exposure distribution. |
| Percentage for upper tail | Numeric | Gives detailed output for this upper percentage of the exposure distribution. |
| Number of levels of covariable to predict exposure | Numeric | Specify the number of levels, e.g. 20. The range of the covariat is divided by the number of levels: range = (max - min)/levels. For these covariable levels exposures are predicted. |
| Predict exposure at extra covariable levels | Numeric | Specify specific prediction levels in addition to the automaticall generated prediction levels (space separated). |
| Lower percentage for variability (%) | Numeric | The default value of 25% may be overruled. |
| Upper percentage for variability (%) | Numeric | The default value of 75% may be overruled. |
| Report consumptions and exposures per individual instead of per kg body weight | Boolean | Specifies whether body weights should be ignored and consumptions and exposures should be expressed per individual Otherwise, the consumptions and exposures are per kg body weight. |
| Stratify outputs | Boolean | This setting is used to get more details e.g. how exposures are distributed among males or females. |
| Stratification variable | *OutputStratificationVariable* | The variable used to categorise individuals into distinct subgrou for presentation of stratified outputs. |
| Age stratification boundaries | Numeric | Give specific age boundaries (years), e.g. 18 40 65 (space separated). |

### Uncertainty settings

Table 3.451: Uncertainty settings for module Risks.

| Name | Type | Description |
|---|---|---|
| Lower uncertainty limit (%) | Numeric | Percentage lower bound, e.g. 2.5%. |
| Upper uncertainty limit (%) | Numeric | Percentage upper bound, e.g. 97.5%. |
| Iterations uncertainty analysis | Numeric | Specifies the number of uncertainty cycles (default 100). |

## Risks tiers

### Overview

Table 3.452: Tier overview for module Risks.

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| C p cu m la ti ri | true | true | true | true | true | true | true | true | true | true |
| H ef fe ty | Risk | Risk | Risk | Risk | Risk | Risk | Risk | Risk | Risk | Risk |
| R ch ac te i- sa ti ra ti | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Haza Expo eRat |
| R th ol | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| U in ve di tr bu ti to ca cu la p ce | true | true | true | true | true | true | true | true | true | true |
| E p su ca cu la ti m | Modelled-Concen-tration | Modelled-Concen-tration | Modelled-Concen-tration | Modelled-Concen-tration | Modelled-Concen-tration | Modelled-Concen-tration | Modelled-Concen-tration | Modelled-Concen-tration | Modelled-Concen-tration | Mod Conc tratio |

Table 3.452 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| In cl si pe ce ag va al it in te va | 99.8 | 99.8 | 99.8 | 99.8 | 99.8 | 99.8 | 99.8 | 99.8 | 99.8 | 99.8 |
| C su ti or th sa da co fr th sa sa pl | false | false | false | false | false | true | true | false | false | false |
| U un va al it | true | | true | | false | true | | true | | true |
| M th ac | false | false | false | false | false | | false | false | false | false |
| C va at m el | false | false | false | false | false | false | false | false | false | false |
| It er at su ve | false | false | false | false | false | false | false | false | false | false |

Table 3.452 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| R p c s t a e p s p i d v u i s o p k b w | false | false | false | false | false | false | false | false | false | false |
| I n s p w | true | true | true | true | | | | true | true | true |
| E c i d v u a w l t N d | false | true | false | true | | | | false | true | false |
| T t d s c c t d | false | false | false | false | false | | false | false | false | false |

Table 3.452 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| F te sa pl ex ce in th co ce tr ti li it | false | false | false | false | | false | false | false | false | false |
| U su st co ve si ru | true | true | true | true | | | | true | true | true |
| S st co ve si m | UseMost-Toxic | UseMost-Toxic | DrawRandom | DrawRandom | | | | UseMost-Toxic | UseMost-Toxic | Draw dom |
| R ta al al lo ca su st af te ac ti su st al lo ca ti | true | true | true | true | | | | true | true | true |

Table 3.452 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| A co fo su st au th ri sa ti in su st co ve si | false | false | true | true | | | | false | false | true |
| F du pl ca su st al lo ca ti in co si te ci | false | false | false | false | | | | false | false | false |
| U ex tr o- la ti ru | true | true | true | true | | | | false | false | false |
| T ol fo ex tr o- la ti | 10 | 10 | 10 | 10 | | | | | | |

Table 3.452 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| R st ex tr o- la ti to ec M | true | true | true | true | | | | | | |
| R st ex tr o- la ti to au th ri us | true | true | true | true | | | | | | |
| In pr w te co ce tr ti | true | true | true | true | | | | true | true | true |
| W te co ce tr ti va (µ | 0.1 | 0.1 | 0.05 | 0.05 | | | | 0.1 | 0.1 | 0.05 |

Table 3.452 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| R st w te in pr ta ti to th fi m to su st | true | true | true | true | | | | true | true | true |
| R st w te in pr ta ti to au th ri us | false | false | false | false | | | | false | false | false |
| R st w te in pr ta ti to ap pr su st | false | false | false | false | | | | true | true | true |
| A pl pr ce in fa to | true | true | true | true | true | true | true | true | true | true |

Table 3.452 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| U di tr bu ti | false | false | false | false | false | false | false | false | false | false |
| Ig no pr ce in fa to le th 1 | false | false | false | false | false | true | true | false | false | false |
| D fa co ce tr ti m | Empirical | Empirical | Empirical | Empirical | Empirical | NonDetectSpikeLogNormal | NonDetectSpikeLogNormal | Empirical | Empirical | Emp |
| In cl M fa ba m | false | false | false | false | false | true | true | false | false | false |
| R st L in pu ta ti to au th ri us | false | false | false | false | | false | false | false | false | false |
| C sc va ue re pl m | ReplaceByLOR | ReplaceByLOR | ReplaceByLOR | ReplaceByLOR | ReplaceByZero | ReplaceByLOR | ReplaceByLOR | ReplaceByLOR | ReplaceByLOR | Repl ByL |

Table 3.452 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| F tc f (f x L or f x L or L + f x (I - L | 0.5 | 0.5 | 0.5 | 0.5 | | 1 | 1 | 0.5 | 0.5 | 0.5 |
| S pl ba | true | true | true | true | true | true | true | true | true | true |
| Ir pr m in va ue fr av al va ue (i ur m in va ue ar in pr w 0 | true | true | true | true | false | true | true | true | true | true |

Table 3.452 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| C re la in pr va ue w sa pl pe te | true | true | false | false | false | true | true | true | true | false |
| U oc cu re fr qu ci fo in pu ta ti | true | true | true | true | false | | | true | true | true |
| P m ri ur ce ta | false | false | false | false | false | true | false | false | false | false |
| A pl oc cu re pa te pe ce ag | false | false | true | true | | | | false | false | true |
| T ge le | External | External | External | External | External | External | External | External | External | Exte |
| U va ab it m | BetaDistribution | | BetaDistribution | | | BetaDistribution | | BetaDistribution | | Beta tribu |

Table 3.452 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| E ti m na tu | Realistic | | Realistic | | | Realistic | | Realistic | | Real |
| U va al it pa ra e- te | Variabili-tyFactor | | Variabili-tyFactor | | | Variabili-tyFactor | | Variabili-tyFactor | | Vari tyFa |
| C pu sh th li ti ex pe su | | false | | false | false | | false | | false | |
| M ty | | OIM | | OIM | OIM | | OIM | | OIM | |
| N (r bo of da in su ve | | 2 | | 2 | | | | | 2 | |
| S up us fr qu to 1( | | | true | true | | | | | | true |

Table 3.452 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| R st us pe ce ag up sc to at th ri us | | | true | true | | | | | | true |
| M Fa to (f x M | | | | | | 1 | 1 | | | |
| C m la ti se ti | | | | | | | | | | |
| C ce tr ti li fi te ex ce fa to | | | | | | | | | | |
| In cl fo ca co m it co ce tr ti | | | | | | | | | | |

Table 3.452 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| F ca co m it su st oc cu re p c ag | | | | | | | | | | |
| A ju m fa to fo th fo ca fo co c tr ti | | | | | | | | | | |
| U de te m is ti su st co ve si fo fo ca co m it | | | | | | | | | | |

Table 3.452 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2012 Optimistic | EFSA 2012 Acute Pessimistic | EFSA 2012 Chronic Pessimistic | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFS 202 Acu Tier |
|---|---|---|---|---|---|---|---|---|---|---|
| In cl pr ce de ti of th fo ca fo in m su m re pl m | | | | | | | | | | |

### Retrospective dietary CRA (EC 2018) - Acute / Tier I

Table 3.453: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | | |
| Health effect type | Risk | | |
| Risk characterisation ratio | Hazard-ExposureRatio | | |
| Risk threshold | 100 | | |
| Use inverse distribution to calculate percentile | true | | |
| Exposure calculation method | Modelled-Concentration | | |
| Inclusion percentage variability interval | 99.8 | | |
| Consumptions on the same day come from the same sample | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Dietary exposures* |

continues on next page

Table 3.453 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use unit variability | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Dietary exposures* |
| Covariate modelling | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Dietary exposures* |
| Iterate survey | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Dietary exposures* |
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Consumptions* |

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Table 3.453 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Total diet study concentration data | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |

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Table 3.453 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Restrict extrapolations to equal MRLs | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Restrict extrapolations to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.1 | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |

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Table 3.453 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to approved substances | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Processing factors* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |

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Table 3.453 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Correlate imputed values with sample potency | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |

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Table 3.453 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Parametric uncertainty | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Apply occurrence pattern percentages | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Hazard characterisations* |
| Unit variability model | BetaDistribution | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Unit variability factors* |
| Estimates nature | Realistic | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Unit variability factors* |
| Unit variability parameter | VariabilityFactor | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Unit variability factors* |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier I

Table 3.454: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | | |
| Health effect type | Risk | | |

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Table 3.454 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Risk characterisation ratio | Hazard-Exposur-eRatio | | |
| Risk threshold | 100 | | |
| Use inverse distribution to calculate percentile | true | | |
| Exposure calculation method | Modelled-Concen-tration | | |
| Inclusion percentage variability interval | 99.8 | | |
| Compute shorter than lifetime exposures | false | *Retrospec-tive dietary CRA (EC 2018) - Chronic / Tier I* | *Dietary exposures* |
| Consumptions on the same day come from the same sample | false | *Retrospec-tive dietary CRA (EC 2018) - Chronic / Tier I* | *Dietary exposures* |
| Model type | OIM | *Retrospec-tive dietary CRA (EC 2018) - Chronic / Tier I* | *Dietary exposures* |
| Model-then-add | false | *Retrospec-tive dietary CRA (EC 2018) - Chronic / Tier I* | *Dietary exposures* |
| Covariate modelling | false | *Retrospec-tive dietary CRA (EC 2018) - Chronic / Tier I* | *Dietary exposures* |
| Iterate survey | false | *Retrospec-tive dietary CRA (EC 2018) - Chronic / Tier I* | *Dietary exposures* |

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Table 3.454 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Dietary exposures* |
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Consumptions* |
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |

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Table 3.454 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Restrict extrapolations to equal MRLs | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |

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Table 3.454 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict extrapolations to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.1 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to approved substances | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Processing factors* |

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Table 3.454 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use distribution | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Processing factors* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |

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Table 3.454 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Sample based | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Correlate imputed values with sample potency | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Apply occurrence pattern percentages | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Hazard characterisations* |

### Retrospective dietary CRA (EC 2018) - Acute / Tier II

Table 3.455: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | | |
| Health effect type | Risk | | |
| Risk characterisation ratio | HazardExposureRatio | | |
| Risk threshold | 100 | | |
| Use inverse distribution to calculate percentile | true | | |
| Exposure calculation method | ModelledConcentration | | |
| Inclusion percentage variability interval | 99.8 | | |
| Consumptions on the same day come from the same sample | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Dietary exposures* |
| Use unit variability | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Dietary exposures* |
| Covariate modelling | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Dietary exposures* |
| Iterate survey | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Dietary exposures* |

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Table 3.455 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Dietary exposures* |
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |

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Table 3.455 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Restrict extrapolations to equal MRLs | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Restrict extrapolations to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |

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Table 3.455 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Impute water concentrations | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Processing factors* |

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Table 3.455 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Processing factors* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |

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Table 3.455 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Apply occurrence pattern percentages | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Occurrence patterns* |

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Table 3.455 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Target level | External | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Hazard characterisations* |
| Unit variability model | BetaDistribution | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Unit variability factors* |
| Estimates nature | Realistic | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Unit variability factors* |
| Unit variability parameter | VariabilityFactor | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Unit variability factors* |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier II

Table 3.456: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | | |
| Health effect type | Risk | | |
| Risk characterisation ratio | HazardExposureRatio | | |
| Risk threshold | 100 | | |
| Use inverse distribution to calculate percentile | true | | |
| Exposure calculation method | ModelledConcentration | | |
| Inclusion percentage variability interval | 99.8 | | |

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Table 3.456 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute shorter than lifetime exposures | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Dietary exposures* |
| Consumptions on the same day come from the same sample | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Dietary exposures* |
| Model type | OIM | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Dietary exposures* |
| Covariate modelling | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Dietary exposures* |
| Iterate survey | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Dietary exposures* |

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Table 3.456 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Consumptions* |
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |

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Table 3.456 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Restrict extrapolations to equal MRLs | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Restrict extrapolations to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |

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Table 3.456 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Impute water concentrations | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Processing factors* |

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Table 3.456 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Processing factors* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Censored values replacement | Replace-ByLOR | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |

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Table 3.456 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Apply occurrence pattern percentages | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Occurrence patterns* |

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Table 3.456 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Target level | External | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Hazard characterisations* |

### Retrospective dietary CRA (EFSA 2012) - Optimistic

Use the optimistic model settings according to the EFSA Guidance 2012. Concentration values are sampled using a sample-based empirical distribution. Available processing factors are applied. No unit variability model should be applied.

Table 3.457: Tier definition for Retrospective dietary CRA (EFSA 2012) - Optimistic.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | | |
| Health effect type | Risk | | |
| Risk characterisation ratio | Hazard-Exposur-eRatio | | |
| Risk threshold | 100 | | |
| Use inverse distribution to calculate percentile | true | | |
| Exposure calculation method | Modelled-Concen-tration | | |
| Inclusion percentage variability interval | 99.8 | | |
| Compute shorter than lifetime exposures | false | *Retrospec-tive dietary CRA (EFSA 2012) - Optimistic* | *Dietary exposures* |
| Consumptions on the same day come from the same sample | false | *Retrospec-tive dietary CRA (EFSA 2012) - Optimistic* | *Dietary exposures* |
| Use unit variability | false | *Retrospec-tive dietary CRA (EFSA 2012) - Optimistic* | *Dietary exposures* |
| Model type | OIM | *Retrospec-tive dietary CRA (EFSA 2012) - Optimistic* | *Dietary exposures* |
| Model-then-add | false | *Retrospec-tive dietary CRA (EFSA 2012) - Optimistic* | *Dietary exposures* |
| Covariate modelling | false | *Retrospec-tive dietary CRA (EFSA 2012) - Optimistic* | *Dietary exposures* |
| Iterate survey | false | *Retrospec-tive dietary CRA* | *Dietary exposures* |

### Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic

Acute probabilistic exposure assessment using the pessimistic model settings according to the EFSA Guidance 2012. Only processing factors > 1 are applied. For unit variability, the Beta distribution is applied.

Table 3.458: Tier definition for Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | | |
| Health effect type | Risk | | |
| Risk characterisation ratio | HazardExposureRatio | | |
| Risk threshold | 100 | | |
| Use inverse distribution to calculate percentile | true | | |
| Exposure calculation method | ModelledConcentration | | |
| Inclusion percentage variability interval | 99.8 | | |
| Consumptions on the same day come from the same sample | true | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Dietary exposures* |
| Use unit variability | true | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Dietary exposures* |
| Covariate modelling | false | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Dietary exposures* |
| Iterate survey | false | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Dietary exposures* |

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Table 3.458 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Dietary exposures* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Processing factors* |
| Ignore processing factors less than 1 | true | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Processing factors* |
| Default concentration model | NonDetect-SpikeLogNormal | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Food concentration models* |

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Table 3.458 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Include MRL fallback model | true | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 1 | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Food concentration models* |
| MRL Factor (f x MRL) | 1 | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Food concentration models* |

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Table 3.458 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Food concentration models* |
| Correlate imputed values with sample potency | true | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Food concentration models* |
| Parametric uncertainty | true | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Food concentration models* |
| Target level | External | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Hazard characterisations* |
| Unit variability model | BetaDistribution | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Unit variability factors* |
| Estimates nature | Realistic | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Unit variability factors* |

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Table 3.458 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Unit variability parameter | VariabilityFactor | *Retrospective dietary CRA (EFSA 2012) - Acute / Pessimistic* | *Unit variability factors* |

### Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic

Chronic probabilistic exposure assessment using the pessimistic model settings according to the EFSA Guidance 2012. Only processing factors > 1 are applied.

Table 3.459: Tier definition for Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | | |
| Health effect type | Risk | | |
| Risk characterisation ratio | HazardExposureRatio | | |
| Risk threshold | 100 | | |
| Use inverse distribution to calculate percentile | true | | |
| Exposure calculation method | ModelledConcentration | | |
| Inclusion percentage variability interval | 99.8 | | |
| Compute shorter than lifetime exposures | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Dietary exposures* |
| Consumptions on the same day come from the same sample | true | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Dietary exposures* |

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Table 3.459 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Model type | OIM | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Dietary exposures* |
| Covariate modelling | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Dietary exposures* |
| Iterate survey | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Dietary exposures* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food conversions* |

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Table 3.459 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Processing factors* |
| Ignore processing factors less than 1 | true | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Processing factors* |
| Default concentration model | NonDetect-SpikeLog-Normal | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food concentration models* |
| Include MRL fallback model | true | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food concentration models* |

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Table 3.459 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 1 | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food concentration models* |
| MRL Factor (f x MRL) | 1 | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food concentration models* |

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Table 3.459 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Correlate imputed values with sample potency | true | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Food concentration models* |
| Target level | External | *Retrospective dietary CRA (EFSA 2012) - Chronic / Pessimistic* | *Hazard characterisations* |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier I

Table 3.460: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | | |
| Health effect type | Risk | | |
| Risk characterisation ratio | HazardExposureRatio | | |
| Risk threshold | 100 | | |
| Use inverse distribution to calculate percentile | true | | |
| Exposure calculation method | ModelledConcentration | | |
| Inclusion percentage variability interval | 99.8 | | |

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Table 3.460 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Consumptions on the same day come from the same sample | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Dietary exposures* |
| Use unit variability | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Dietary exposures* |
| Covariate modelling | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Dietary exposures* |
| Iterate survey | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Dietary exposures* |

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Table 3.460 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |

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Table 3.460 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.1 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |

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Table 3.460 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Processing factors* |

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Table 3.460 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |

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Table 3.460 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Correlate imputed values with sample potency | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Apply occurrence pattern percentages | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Hazard characterisations* |

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Table 3.460 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Unit variability model | BetaDistribution | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Unit variability factors* |
| Estimates nature | Realistic | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Unit variability factors* |
| Unit variability parameter | VariabilityFactor | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Unit variability factors* |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I

Table 3.461: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | | |
| Health effect type | Risk | | |
| Risk characterisation ratio | HazardExposureRatio | | |
| Risk threshold | 100 | | |
| Use inverse distribution to calculate percentile | true | | |
| Exposure calculation method | ModelledConcentration | | |
| Inclusion percentage variability interval | 99.8 | | |

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Table 3.461 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute shorter than lifetime exposures | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Dietary exposures* |
| Consumptions on the same day come from the same sample | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Dietary exposures* |
| Model type | OIM | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Dietary exposures* |
| Covariate modelling | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Dietary exposures* |
| Iterate survey | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Dietary exposures* |

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Table 3.461 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Dietary exposures* |
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Consumptions* |
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |

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Table 3.461 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |

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Table 3.461 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Impute water concentrations | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.1 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Processing factors* |

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Table 3.461 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use distribution | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Processing factors* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |

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Table 3.461 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Correlate imputed values with sample potency | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |

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Table 3.461 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Hazard characterisations* |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier II

Table 3.462: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | | |
| Health effect type | Risk | | |
| Risk characterisation ratio | HazardExposureRatio | | |
| Risk threshold | 100 | | |
| Use inverse distribution to calculate percentile | true | | |
| Exposure calculation method | ModelledConcentration | | |
| Inclusion percentage variability interval | 99.8 | | |
| Consumptions on the same day come from the same sample | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Dietary exposures* |

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Table 3.462 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use unit variability | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Dietary exposures* |
| Covariate modelling | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Dietary exposures* |
| Iterate survey | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Dietary exposures* |
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Consumptions* |

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Table 3.462 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |

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Table 3.462 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |

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Table 3.462 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Processing factors* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |

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Table 3.462 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Include MRL fallback model | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |

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Table 3.462 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Correlate imputed values with sample potency | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Apply occurrence pattern percentages | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Occurrence patterns* |

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Table 3.462 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Target level | External | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Hazard characterisations* |
| Unit variability model | BetaDistribution | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Unit variability factors* |
| Estimates nature | Realistic | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Unit variability factors* |
| Unit variability parameter | VariabilityFactor | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Unit variability factors* |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II

Table 3.463: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | | |
| Health effect type | Risk | | |
| Risk characterisation ratio | HazardExposureRatio | | |
| Risk threshold | 100 | | |
| Use inverse distribution to calculate percentile | true | | |
| Exposure calculation method | ModelledConcentration | | |

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Table 3.463 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Inclusion percentage variability interval | 99.8 | | |
| Compute shorter than lifetime exposures | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Dietary exposures* |
| Consumptions on the same day come from the same sample | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Dietary exposures* |
| Model type | OIM | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Dietary exposures* |
| Covariate modelling | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Dietary exposures* |
| Iterate survey | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Dietary exposures* |

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Table 3.463 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Dietary exposures* |
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Consumptions* |
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |

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Table 3.463 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |

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Table 3.463 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Impute water concentrations | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Processing factors* |

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Table 3.463 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use distribution | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Processing factors* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |

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Table 3.463 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |

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Table 3.463 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Hazard characterisations* |

### Prospective dietary CRA (EFSA 2023) - Acute / Tier II

Table 3.464: Tier definition for Prospective dietary CRA (EFSA 2023) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | | |
| Health effect type | Risk | | |
| Risk characterisation ratio | HazardExposureRatio | | |
| Risk threshold | 100 | | |
| Use inverse distribution to calculate percentile | true | | |
| Exposure calculation method | ModelledConcentration | | |
| Cumulation setting | RPFWeighte | | |

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Table 3.464 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Inclusion percentage variability interval | 99.8 | | |
| Consumptions on the same day come from the same sample | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Dietary exposures* |
| Use unit variability | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Dietary exposures* |
| Covariate modelling | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Dietary exposures* |
| Iterate survey | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Dietary exposures* |

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Table 3.464 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |

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Table 3.464 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |

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Table 3.464 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |

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Table 3.464 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Processing factors* |
| Use distribution | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Processing factors* |
| Default concentration model | Empirical | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |

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Table 3.464 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Include MRL fallback model | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Sample based | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |

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Table 3.464 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Correlate imputed values with sample potency | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Occurrence patterns* |

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Table 3.464 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Target level | External | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Hazard characterisations* |
| Unit variability model | BetaDistribution | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Unit variability factors* |
| Estimates nature | Realistic | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Unit variability factors* |
| Unit variability parameter | VariabilityFactor | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Unit variability factors* |

### Prospective dietary CRA (EFSA 2023) - Chronic / Tier II

Table 3.465: Tier definition for Prospective dietary CRA (EFSA 2023) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | | |
| Health effect type | Risk | | |
| Risk characterisation ratio | HazardExposureRatio | | |
| Risk threshold | 100 | | |
| Use inverse distribution to calculate percentile | true | | |
| Exposure calculation method | ModelledConcentration | | |
| Cumulation setting | RPFWeighte | | |

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Table 3.465 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Inclusion percentage variability interval | 99.8 | | |
| Compute shorter than lifetime exposures | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Dietary exposures* |
| Consumptions on the same day come from the same sample | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Dietary exposures* |
| Model type | OIM | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Dietary exposures* |
| Covariate modelling | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Dietary exposures* |
| Iterate survey | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Dietary exposures* |

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Table 3.465 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Report consumptions and exposures per individual instead of per kg body weight | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Dietary exposures* |
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Consumptions* |
| N (number of days in survey) | 2 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |

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Table 3.465 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |

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Table 3.465 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |

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Table 3.465 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Processing factors* |
| Use distribution | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Processing factors* |

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Table 3.465 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Ignore processing factors less than 1 | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Processing factors* |
| Default concentration model | Empirical | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |

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Table 3.465 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Sample based | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Occurrence patterns* |

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Table 3.465 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Occurrence patterns* |
| Target level | External | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Hazard characterisations* |

### Prospective dietary CRA (EFSA 2024) - Acute / Tier II

Table 3.466: Tier definition for Prospective dietary CRA (EFSA 2024) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | | |
| Health effect type | Risk | | |
| Risk characterisation ratio | HazardExposureRatio | | |
| Risk threshold | 100 | | |
| Use inverse distribution to calculate percentile | true | | |
| Exposure calculation method | ModelledConcentration | | |
| Cumulation setting | RPFWeighte | | |
| Inclusion percentage variability interval | 99.8 | | |

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Table 3.466 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Consumptions on the same day come from the same sample | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Dietary exposures* |
| Use unit variability | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Dietary exposures* |
| Covariate modelling | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Dietary exposures* |
| Iterate survey | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Dietary exposures* |

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Table 3.466 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |

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Table 3.466 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |

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Table 3.466 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |

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Table 3.466 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Include processed derivatives of the focal food in measurement replacement | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Processing factors* |
| Use distribution | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Processing factors* |

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Table 3.466 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Sample based | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |

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Table 3.466 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Occurrence patterns* |

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Table 3.466 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Occurrence patterns* |
| Target level | External | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Hazard characterisations* |
| Unit variability model | BetaDistribution | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Unit variability factors* |
| Estimates nature | Realistic | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Unit variability factors* |
| Unit variability parameter | VariabilityFactor | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Unit variability factors* |

### Prospective dietary CRA (EFSA 2024) - Chronic / Tier II

Table 3.467: Tier definition for Prospective dietary CRA (EFSA 2024) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | | |
| Health effect type | Risk | | |

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Table 3.467 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Risk characterisation ratio | Hazard-Exposur-eRatio | | |
| Risk threshold | 100 | | |
| Use inverse distribution to calculate percentile | true | | |
| Exposure calculation method | Modelled-Concen-tration | | |
| Cumulation setting | RPFWeighte | | |
| Inclusion percentage variability interval | 99.8 | | |
| Compute shorter than lifetime exposures | false | *Prospec-tive dietary CRA (EFSA 2024) - Chronic / Tier II* | *Dietary exposures* |
| Consumptions on the same day come from the same sample | false | *Prospec-tive dietary CRA (EFSA 2024) - Chronic / Tier II* | *Dietary exposures* |
| Model type | OIM | *Prospec-tive dietary CRA (EFSA 2024) - Chronic / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Prospec-tive dietary CRA (EFSA 2024) - Chronic / Tier II* | *Dietary exposures* |
| Covariate modelling | false | *Prospec-tive dietary CRA (EFSA 2024) - Chronic / Tier II* | *Dietary exposures* |

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Table 3.467 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Iterate survey | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Dietary exposures* |
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Consumptions* |
| N (number of days in survey) | 2 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food conversions* |

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Table 3.467 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |

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Table 3.467 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |

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Table 3.467 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Include processed derivatives of the focal food in measurement replacement | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |

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Table 3.467 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply processing factors | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Processing factors* |
| Use distribution | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Processing factors* |
| Default concentration model | Empirical | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |

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Table 3.467 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Censored values replacement | ReplaceByLOR | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Sample based | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |

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Table 3.467 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Parametric uncertainty | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Occurrence patterns* |
| Target level | External | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Hazard characterisations* |

### Calculation of risks

Risk (health impact) is quantified as exposure relative to hazard characterisation. Exposures or hazards can be single values or distributions, the risk metric is a distribution if at least one of the inputs is a distribution (if both are single values, see the module single value risks). Risk metrics are valid for a specific biological level (external or internal at a specific biological matrix).

- *Risks calculation*

Inputs used: *Dietary exposures Internal exposures Hazard characterisations HBM analysis Relative potency factors*

Settings used

- *Calculation Settings*

Risks are expressed as distribution of risk characterisation ratios (hazard/exposure) or )exposure/hazard). The distribution is summarised by percentiles, and by the probability to exceed the specified threshold value (e.g. 1 or 100). The hazard vs. exposure plot compares the exposures and the hazard characterisation for individuals or individual-days in a population. Exposures, hazard characterisations and risks can be acute or chronic. The default unit for exposures and hazard characterisations is $\mu g/kgBW/day$, but this can be changed by choosing non-default units for consumptions, concentrations and/or body weight.

By using probabilistic tiers for both exposure and hazard characterisation, the calculated risk distribution is equal to the Integrated hazard/exposure (IMOE) distribution, as described for the Integrated Probabilistic Risk Assessment (IPRA) approach in van der Voet and Slob (2007) and van der Voet et al. (2009).

### 3.8.3 Single value risks

Single value risks are risk estimates obtained from combining single value exposures with single value hazard characterisations or as a percentile from a risk distribution.

This module has as primary entities: *Substances Effects Populations*

#### Single value risks calculation

Single value risks can be calculated in two ways.

1. **From single value risks:** *single value exposures* are combined with (single value) *hazard characterisations*.
2. **As percentile from risks distribution:** a percentile can be selected from a *risks* distribution.

See below for a more detailed explanation.

#### Combining single value exposures and hazard characterisations

Single value risks are computed by combining *single value exposures* by route/source and substance with (single value) *hazard characterisations* by substance. They are computed as risk characterisation ratios hazard/exposure, hazard quotient or risk characterisation ratios exposure/hazard, or as a percentage of the reference dose (100 * exposure/hazard characterisation).

#### Single value risks from individual risks

In this option, a percentage point can be specified for the chosen risk metric, e.g. the risk characterisation ratio hazard/exposure ($H/E$) or exposure/hazard ($E/H$). The corresponding percentile is calculated from the distribution of individual *risks*. The default percentiles are a risk characterisation ratio hazard/exposure at 0.1% or a ratio exposure/hazard at 99.9%. Specify whether the risk metric is calculated using the inverse distribution or not. This option is provided because percentile calculation in small data sets is asymmetric in both tails. When this option is set, the percentile is calculated as the inverse of the complementary percentage of the inverse distribution. E.g., the $p_{0.1}$ of the $H/E$ distribution is calculated as 1/($p_{99.9}$ of 1/$H/E$ distribution); the $p_{99.9}$ of the $E/H$ distribution is calculated as 1/($p_{0.1}$ of 1/$E/H$ distribution).

#### Adjustment factors and uncertainty specification

Many sources of uncertainty that may affect input data, model assumptions and assessment methodology do not enter the assessment. In EFSA (2020a) and EFSA (2020b), thirty-four sources of uncertainty were identified and the impact of each source on the ratio $H/E$ was quantified. Some uncertainties tend to overestimate the ratio $H/E$, others tend to underestimate it. Following the guidance of the EFSA Scientific Committee, specific ratio $E/H$ and/or ratio $H/E$ percentiles are adjusted using adjustment factors for exposure and hazard, e.g. from expert elicitation. They may be available as fixed values or as parametric uncertainty distributions. In the nominal run, the percentile is adjusted with the median of the uncertainty distribution. In each uncertainty run, adjustment factors are sampled from the uncertainty distribution. In the MCRA interface, for both exposure and hazard distribution separately, a fixed value or a parametric uncertainty distribution is specified. The available parametric uncertainty distributions are the same as available in the SHELF package that was used by EFSA. The SHeffield ELicitation Framework (SHELF)

is a package of documents, templates and software to carry out elicitation of probability distributions for uncertain quantities from a group of experts (http://www.tonyohagan.co.uk/shelf/).

To summarize, in the nominal run, the median of the uncertainty distribution is taken as adjustment factor. In each uncertainty run, the adjustment factor value is sampled from the uncertainty distribution. The adjustment factors for exposure and hazard are multiplied yielding the overall adjustment factor.

**Options for specifying uncertainty distributions are:**

- Gamma(a, b) with offset c, with shape and rate parameters a and b > 0.
- Beta(a, b) scaled to the interval [$c$, d], with shape parameters a and b > 0.
- Lognormal($\mu$, $s$) with offset $c$. Parameters $\mu$ and $s$ specify the mean and standard deviation of the underlying normal.
- Log Student t($\mu$, $s$, $\nu$) with offset d. Parameters $\mu$ and $s$ specify the mean and standard deviation of the underlying normal, $\nu$ the degrees of freedom, $\nu > 0$.

In the figures below, the consensus distributions of the experts for the combined impact of the quantified uncertainties affecting exposure are shown. When the larger part of the distribution is above 1, it is more likely that resolving the uncertainties will increase the median estimate. The vertical red line marks f = 1, where resolving the uncertainties would not change the calculated estimate.

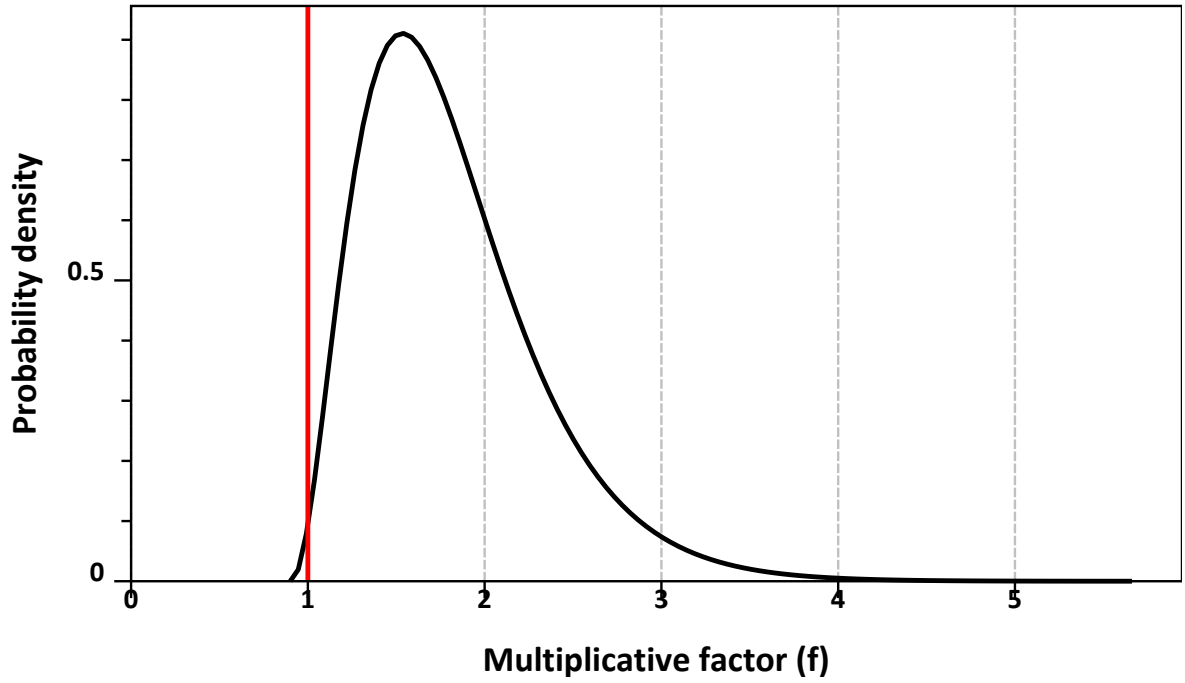


Figure 3.94: Scaled gamma (a=3.26, b=3.56, offset=0.9), table 6, EFSA (2020a).

### Background-only adjustment factor

When exposures are calculated by *combining focal food/substance concentrations with background concentrations*, it may be appropriate to have a separate adjustment for the foreground and background. A pragmatic solution agreed with EFSA is to estimate the contribution of the foreground in the tail above the selected percentile. Suppose this contribution is $c$. Note that $c$ will vary in uncertainty runs. Then, the adjustment factor should be multiplied by $(1 - c)$, i.e. no adjustment for the focal part.

The calculation proceeds as follows:

$$
\begin{aligned}
p_{H/E,\texttt{adjusted}} &= p_{H/E} \cdot (c + (1-c) \cdot \texttt{AdjustmentFactor}_{\texttt{exposure}} \cdot \texttt{AdjustmentFactor}_{\texttt{hazard}}) \\
p_{E/H,\texttt{adjusted}} &= \frac{p_{E/H}}{c + (1-c) \cdot \texttt{AdjustmentFactor}_{\texttt{exposure}} \cdot \texttt{AdjustmentFactor}_{\texttt{hazard}}}
\end{aligned}
$$

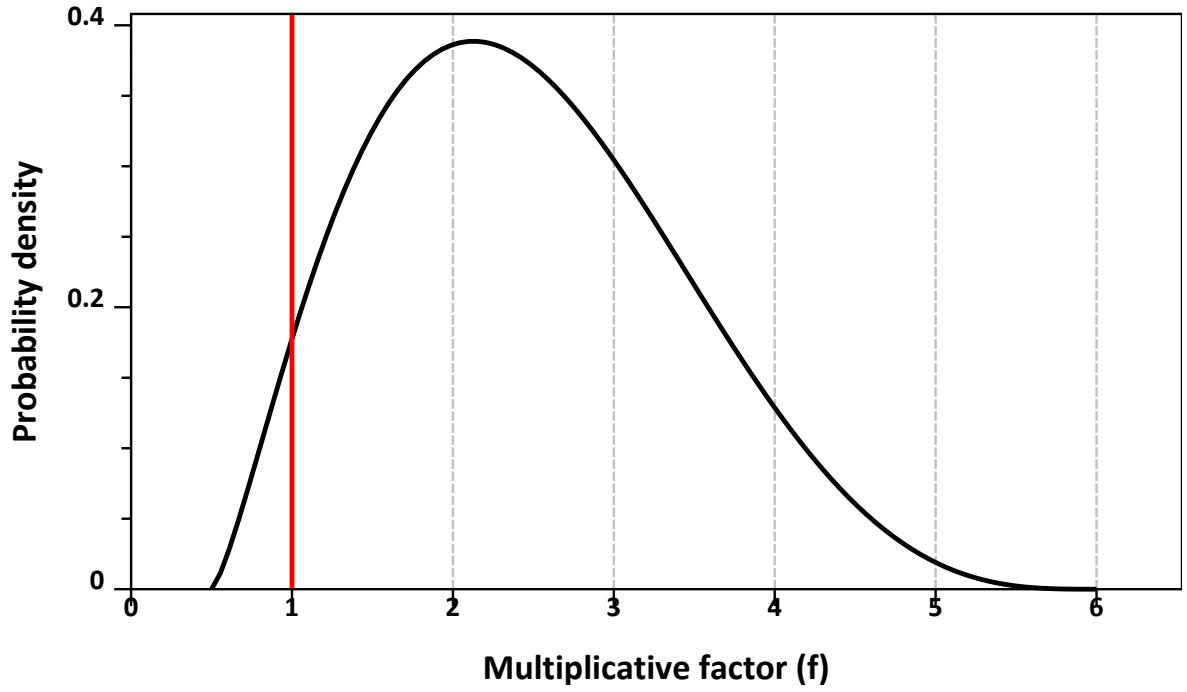


Figure 3.95: Scaled beta (a=2.37, b=4.26, lowerbound=0.5, upperbound=6), table 7, EFSA (2020a).

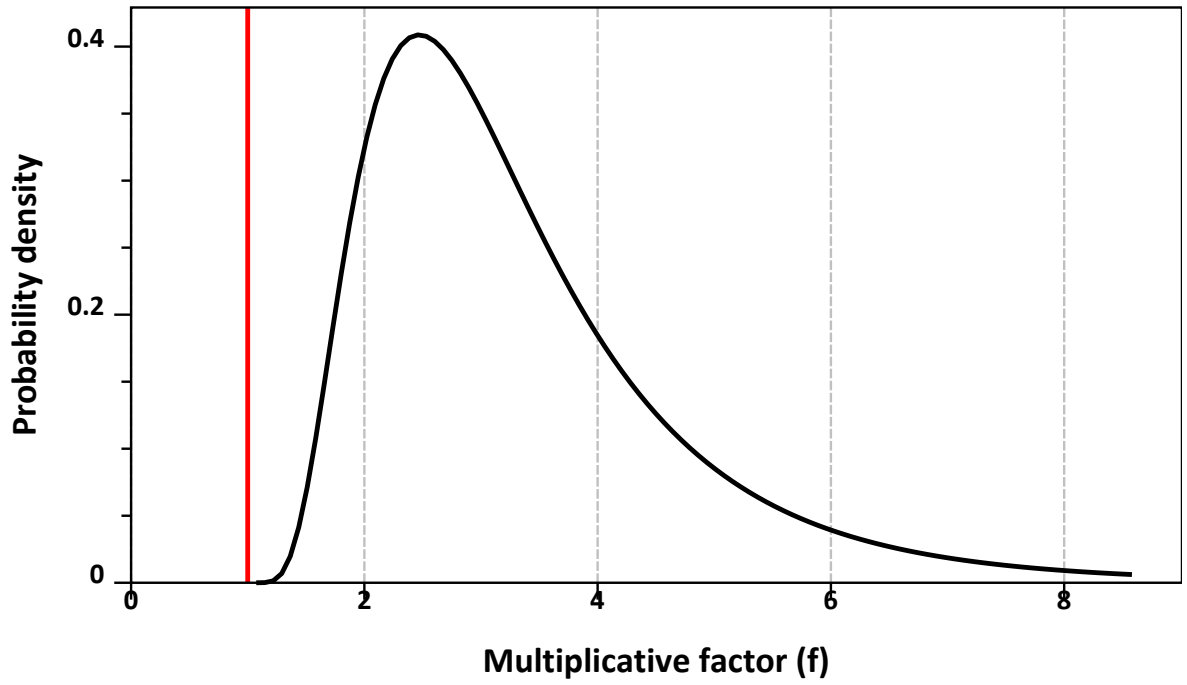


Figure 3.96: Scaled lognormal ($\mu = 0.705$, $s = 0.566$, offset=1), table 8, EFSA (2020b).

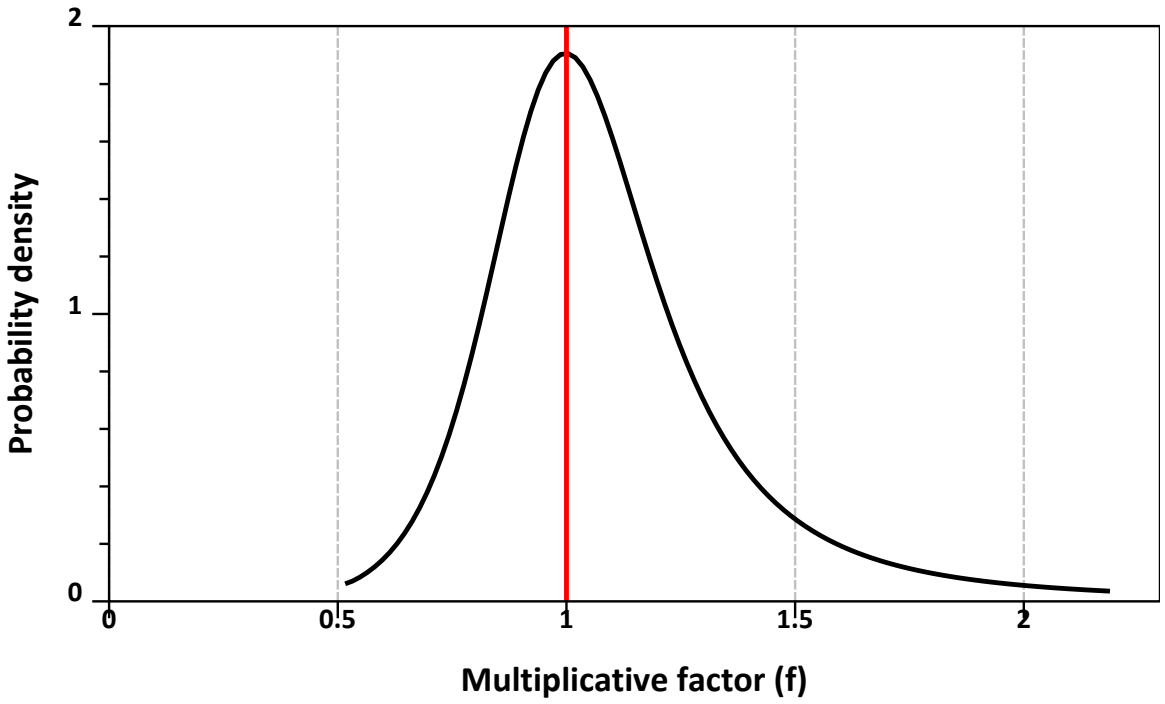


Figure 3.97: Scaled logstudents t ($\mu = -0.593$, $s = 0.367$, $\nu = 3$, offset=0.5), table 9, EFSA (2020b).

Note that when the focal substance measurements are converted to active substances using *substance conversions* or *deterministic substance conversions*, then $c$ is the sum of the contributions of the focal food in and all active substances to which the substance translates.

In Figure 3.98, an example is shown where the risk characterisation ratio (hazard/exposure) is adjusted for the exposure and hazard distribution based on expert elicitation. The median adjustment factors for exposure and hazard are respectively, 1.77 and 3.01. The overall adjustment factor is 5.33.

### Single value risks settings

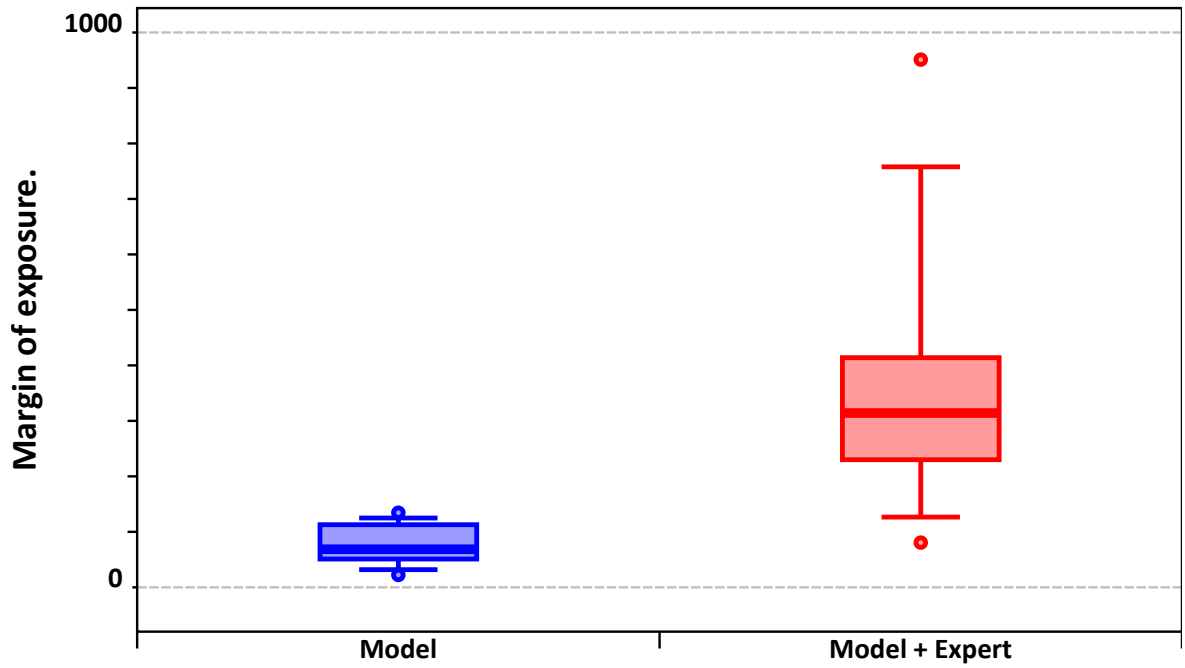


Figure 3.98: Risk characterisation ratio H/E (model) and adjusted ratio H/E (model + expert) with uncertainty bounds.

### Calculation settings

Table 3.468: Calculation settings for module Single value risks.

| Name | Type | Description |
|---|---|---|
| Selected tier | SettingsTemplateType | Specifies all module settings should be set according to a pre-defined tier or using custom settings. |
| Single value risk calculation method | *SingleValueRiskCalculationMethod* | Calculate single value from exposures and hazard or from an individual risks distribution. |
| Exposure type | *ExposureType* | The type of exposure considered in the assessment; acute (short term) or chronic (long-term). |
| Multiple substances analysis | Boolean | Specifies whether the assessment involves multiple substances. |
| Compute cumulative exposures | Boolean | Specifies whether the assessment involves multiple substances a results should be cumulated over all substances. |
| Health effect type | *HealthEffectType* | Specifies whether the health effect is a risk (negative) or benefit (positive). |
| Risk characterisation ratio | *RiskMetricType* | Report risks in terms of the ratio exposure/hazard (e.g., HI, HQ RPI) or as hazard/exposure (e.g., MOE(T)). |
| Percentage for percentile | Numeric | Percentage for percentile (default 0.1 for MOE(T) or 99.9 for H HQ, RPI). |
| Use inverse distribution to calculate percentile | Boolean | Calculate percentile via the complementary percentage of the inverse distribution (default: no). Description: E.g., P0.1 of MOE(T) distribution is calculated via P99.9 of 1/MOE(T) distribution. Note: This option is provided because percentile calculation in small data sets is asymmetric in both tails. |
| Apply adjustment factors to the specified risk percentile | Boolean | Specify adjustment factors, e.g. based on expert knowledge elicitation, to a specified MOE(T) percentile (default 0.1%). If selected risk metric is HI, HQ, RPI, the adjustment factors shou still be specified for the complementary percentile of MOE(T) (e.g. P0.1 of MOE(T) if P99.9 of HI, HQ, RPI is selected). |
| Adjustment type related to exposure | *AdjustmentFactorDistributionMethod* | Specify the factor and/or distribution of the adjustment factor f the MOE(T) percentile. Default is no adjustment. Alternatives a fixed factor or an uncertainty distribution. If distributions are selected, default values are set based on EFSA cumulative risk reports 2020. |
| Parameter A (Fixed factor, mean Lognormal or LogStudent-t, or shape | Numeric | This parameter can be: 1) the fixed adjustment factor; 2) for Lognormal or LogStudent-t, the mean of the underlying normal distribution; 3) For Beta or Gamma, the shape parameter. |

### Uncertainty settings

Table 3.469: Uncertainty settings for module Single value risks.

| Name | Type | Description |
|---|---|---|
| Lower uncertainty limit (%) | Numeric | Percentage lower bound, e.g. 2.5%. |
| Upper uncertainty limit (%) | Numeric | Percentage upper bound, e.g. 97.5%. |

### Single value risks tiers

#### Overview

Table 3.470: Tier overview for module Single value risks.

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec-tive Tier II | EFS 2023 Chro Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| S gl va ri ca cu la ti m | FromIndi-vidual-Risks | FromIndi-vidual-Risks | FromIndi-vidual-Risks | FromIndi-vidual-Risks | FromIndi-vidual-Risks | FromIndi-vidual-Risks | FromIndi-vidual-Risks | FromIndi-vidual-Risks | FromIndi-vidual-Risks | From vidu Risk |
| P ce ag fo pe ce | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Ig no sa pl w | true | true | true | true | true | true | true | true | true | true |
| E cl in di vi u- al w le th N da | false | true | false | true | false | true | false | true | false | true |

Table 3.470 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec-tive Tier II | EFS 2023 Chro Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| T ta di st co ce tr ti da | false | false | false | false | false | false | false | false | false | false |
| F te sa pl ex co in th co ce tr ti li it | false | false | false | false | false | false | false | false | true | true |
| U su st co ve si ru | true | true | true | true | true | true | true | true | true | true |
| S st co ve si m | UseMost-Toxic | UseMost-Toxic | DrawRan-dom | DrawRan-dom | UseMost-Toxic | UseMost-Toxic | DrawRan-dom | DrawRan-dom | DrawRan-dom | Draw dom |

Table 3.470 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec-tive Tier II | EFS 202 Chr Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| R ta al al lc ca su st af te ac ti su st al lc ca ti | true | true | true | true | true | true | true | true | true | true |
| A co fo su st au th ri sa ti in su st co ve si | false | false | true | true | false | false | true | true | true | true |
| F du pl ca su st al lc ca ti in co si te ci | false | false | false | false | false | false | false | false | false | false |

Table 3.470 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec-tive Tier II | EFS 2023 Chro Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| U ex tr o- la ti ru | true | true | true | true | false | false | false | false | false | false |
| T ol fc ex tr o- la ti | 10 | 10 | 10 | 10 | | | | | | |
| R st ex tr o- la ti tc ec M | true | true | true | true | | | | | | |
| R st ex tr o- la ti tc au th ri us | true | true | true | true | | | | | | |
| Ir pr w te co co tr ti | true | true | true | true | true | true | true | true | true | true |

Table 3.470 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec-tive Tier II | EFS 2023 Chro Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| W te co ce tr ti va (μ | 0.1 | 0.1 | 0.05 | 0.05 | 0.1 | 0.1 | 0.05 | 0.05 | 0.05 | 0.05 |
| R st w te ir pu ta ti to th fi m to su st | true | true | true | true | true | true | true | true | true | true |
| R st w te ir pu ta ti to au th ri us | false | false | false | false | false | false | false | false | false | false |
| R st w te ir pu ta ti to ap pr su st | false | false | false | false | true | true | true | true | true | true |

Table 3.470 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec-tive Tier II | EFS 2023 Chro Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| A pl pr ce in fa to | true | true | true | true | true | true | true | true | true | true |
| U di tr bu ti | false | false | false | false | false | false | false | false | false | false |
| Ig no pr ce in fa to le th 1 | false | false | false | false | false | false | false | false | false | false |
| U va al it m | BetaDis-tribution | | BetaDis-tribution | | BetaDis-tribution | | BetaDis-tribution | | BetaDis-tribution | |
| E ti m na tu | Realistic | | Realistic | | Realistic | | Realistic | | Realistic | |
| U va al it pa ra e- te | Variabili-tyFactor | | Variabili-tyFactor | | Variabili-tyFactor | | Variabili-tyFactor | | Variabili-tyFactor | |
| A pl oc cu re pa te pe ce ag | false | false | true | true | false | false | true | true | true | true |

Table 3.470 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec-tive Tier II | EFS 2023 Chro Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| T ge le | External | External | External | External | External | External | External | External | External | Exte |
| C pt cu m la ti ri | true | true | true | true | true | true | true | true | true | true |
| H ef fe ty | Risk | Risk | Risk | Risk | Risk | Risk | Risk | Risk | Risk | Risk |
| R cl ac te i-sa ti ra ti | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Hazard-Exposur-eRatio | Haza Expo eRat |
| R th ol | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| U in ve di tr bu ti to ca cu la pe ce | true | true | true | true | true | true | true | true | true | true |
| E pe su ca cu la ti m | Modelled-Concen-tration | Modelled-Concen-tration | Modelled-Concen-tration | Modelled-Concen-tration | Modelled-Concen-tration | Modelled-Concen-tration | Modelled-Concen-tration | Modelled-Concen-tration | Modelled-Concen-tration | Mod Conc tratio |

Table 3.470 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec-tive Tier II | EFS 2023 Chro Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| Ir cl si pe ce ag va al it in te va | 99.8 | 99.8 | 99.8 | 99.8 | 99.8 | 99.8 | 99.8 | 99.8 | 99.8 | 99.8 |
| C su ti or th sa da co fr th sa sa pl | false | false | false | false | false | false | false | false | false | false |
| U us va al it | true | | true | | true | | true | | true | |
| M th ac | false | false | false | false | false | false | false | false | false | false |
| C va at m el | false | false | false | false | false | false | false | false | false | false |
| It er at su ve | false | false | false | false | false | false | false | false | false | false |

Table 3.470 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec-tive Tier II | EFS 202 Chr Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| R p c s t a e p s p i d v u i s o p k b w | false | false | false | false | false | false | false | false | false | false |
| D f c c t t m | Empirical | Empirical | Empirical | Empirical | Empirical | Empirical | Empirical | Empirical | Empirical | Emp |
| I c M f b m | false | false | false | false | false | false | false | false | false | false |
| R s L i p t t t a t r u | false | false | false | false | false | false | false | false | false | false |

Table 3.470 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec-tive Tier II | EFS 2023 Chro Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| C sc va ue re pl m | Replace-ByLOR | Replace-ByLOR | Replace-ByLOR | Replace-ByLOR | Replace-ByLOR | Replace-ByLOR | Replace-ByLOR | Replace-ByLOR | Replace-ByLOR | Repl ByL |
| F to f (f x L or f x L or L + f x (I - L | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| S pl ba | true | true | true | true | true | true | true | true | true | true |

Table 3.470 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec- tive Tier II | EFS 202 Chr Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| In pr m in va uc fr av al va uc (i ur m in va uc ar in pr w 0) | true | true | true | true | true | true | true | true | true | true |
| C re la in pr va uc w sa pl pc te | true | true | false | false | true | true | false | false | false | false |
| U oc cu re fr qu ci fc in pu ta ti | true | true | true | true | true | true | true | true | true | true |

Table 3.470 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec-tive Tier II | EFS 2023 Chro Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| P m ri u ce ta | false | false | false | false | false | false | false | false | false | false |
| N (r b o d in su v | | 2 | | 2 | | 2 | | 2 | | 2 |
| C p sh th li ti ex p su | | false | | false | | false | | false | | false |
| M ty | | OIM | | OIM | | OIM | | OIM | | OIM |
| S u us fr q to 1 | | | true | true | | | true | true | true | true |
| R st us p ce ag u sc to au th ri us | | | true | true | | | true | true | true | true |

Table 3.470 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec-tive Tier II | EFS 2023 Chro Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| C ce tr ti li fi te ex ce fa to | | | | | | | | | 2 | 2 |
| Ir cl fo ca co m it co ce tr ti | | | | | | | | | true | true |
| F ca co m it su st oc cu re po ce ag | | | | | | | | | 20 | 20 |
| A ju m fa to fo th fo ca fo co ce tr ti | | | | | | | | | 1 | 1 |

Table 3.470 – continued from previous page

| N | EC 2018 Acute Tier I | EC 2018 Chronic - Tier I | EC 2018 Acute Tier II | EC 2018 Chronic Tier II | EFSA 2022 Acute Tier I | EFSA 2022 Chronic Tier I | EFSA 2022 Acute Tier II | EFSA 2022 Chronic Tier II | EFSA 2023 Acute Prospec-tive Tier II | EFS 2023 Chro Pros tive II |
|---|---|---|---|---|---|---|---|---|---|---|
| U de te m is ti su st co ve si fo fo ca co m it | | | | | | | | | true | true |
| C m la ti se ti | | | | | | | | | RPFWeighte | RPF |
| Ir cl pr ce de ti of th fo ca fo in m su m re pl m | | | | | | | | | | |

### Retrospective dietary CRA (EC 2018) - Acute / Tier I

Table 3.471: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Single value risk calculation method | FromIndividualRisks | | |
| Percentage for percentile | 0.1 | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |

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Table 3.471 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Restrict extrapolations to equal MRLs | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Restrict extrapolations to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |

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Table 3.471 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Impute water concentrations | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.1 | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to approved substances | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Processing factors* |

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Table 3.471 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Processing factors* |
| Unit variability model | BetaDistribution | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Unit variability factors* |
| Estimates nature | Realistic | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Unit variability factors* |
| Unit variability parameter | VariabilityFactor | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Unit variability factors* |
| Apply occurrence pattern percentages | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Hazard characterisations* |
| Compute cumulative risks | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Risks* |

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Table 3.471 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Health effect type | Risk | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Risks* |
| Risk characterisation ratio | HazardExposureRatio | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Risks* |
| Risk threshold | 100 | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Risks* |
| Use inverse distribution to calculate percentile | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Risks* |
| Exposure calculation method | ModelledConcentration | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Risks* |
| Inclusion percentage variability interval | 99.8 | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Risks* |
| Consumptions on the same day come from the same sample | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Dietary exposures* |

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Table 3.471 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use unit variability | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Dietary exposures* |
| Covariate modelling | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Dietary exposures* |
| Iterate survey | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Dietary exposures* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |

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Table 3.471 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Correlate imputed values with sample potency | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |

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Table 3.471 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Parametric uncertainty | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier I* | *Food concentration models* |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier I

Table 3.472: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Single value risk calculation method | FromIndividualRisks | | |
| Percentage for percentile | 0.1 | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Consumptions* |
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food conversions* |

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Table 3.472 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |

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Table 3.472 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Restrict extrapolations to equal MRLs | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Restrict extrapolations to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.1 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |

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Table 3.472 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to approved substances | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Processing factors* |
| Apply occurrence pattern percentages | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Hazard characterisations* |
| Compute cumulative risks | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Risks* |

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Table 3.472 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Health effect type | Risk | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Risks* |
| Risk characterisation ratio | HazardExposureRatio | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Risks* |
| Risk threshold | 100 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Risks* |
| Use inverse distribution to calculate percentile | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Risks* |
| Exposure calculation method | ModelledConcentration | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Risks* |
| Inclusion percentage variability interval | 99.8 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Risks* |
| Compute shorter than lifetime exposures | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Dietary exposures* |

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Table 3.472 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Consumptions on the same day come from the same sample | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Dietary exposures* |
| Model type | OIM | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Dietary exposures* |
| Covariate modelling | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Dietary exposures* |
| Iterate survey | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Dietary exposures* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |

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Table 3.472 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Include MRL fallback model | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Correlate imputed values with sample potency | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |

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Table 3.472 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier I* | *Food concentration models* |

### Retrospective dietary CRA (EC 2018) - Acute / Tier II

Table 3.473: Tier definition for Retrospective dietary CRA (EC 2018) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Single value risk calculation method | FromIndividualRisks | | |
| Percentage for percentile | 0.1 | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food conversions* |

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Table 3.473 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |

continues on next page

Table 3.473 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Restrict extrapolations to equal MRLs | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Restrict extrapolations to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |

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Table 3.473 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to approved substances | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Processing factors* |
| Unit variability model | BetaDistribution | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Unit variability factors* |
| Estimates nature | Realistic | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Unit variability factors* |
| Unit variability parameter | VariabilityFactor | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Unit variability factors* |

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Table 3.473 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Hazard characterisations* |
| Compute cumulative risks | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Risks* |
| Health effect type | Risk | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Risks* |
| Risk characterisation ratio | HazardExposureRatio | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Risks* |

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Table 3.473 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Risk threshold | 100 | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Risks* |
| Use inverse distribution to calculate percentile | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Risks* |
| Exposure calculation method | Modelled-Concentration | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Risks* |
| Inclusion percentage variability interval | 99.8 | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Risks* |
| Consumptions on the same day come from the same sample | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Dietary exposures* |
| Use unit variability | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Dietary exposures* |

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Table 3.473 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Covariate modelling | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Dietary exposures* |
| Iterate survey | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Dietary exposures* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |

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Table 3.473 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EC 2018) - Acute / Tier II* | *Food concentration models* |

### Retrospective dietary CRA (EC 2018) - Chronic / Tier II

Table 3.474: Tier definition for Retrospective dietary CRA (EC 2018) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Single value risk calculation method | FromIndividualRisks | | |
| Percentage for percentile | 0.1 | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Consumptions* |
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |

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Table 3.474 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Use extrapolation rules | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Threshold for extrapolation | 10 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Restrict extrapolations to equal MRLs | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |

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Table 3.474 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict extrapolations to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Processing factors* |

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Table 3.474 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use distribution | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Processing factors* |
| Apply occurrence pattern percentages | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Hazard characterisations* |
| Compute cumulative risks | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Risks* |

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Table 3.474 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Health effect type | Risk | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Risks* |
| Risk characterisation ratio | HazardExposureRatio | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Risks* |
| Risk threshold | 100 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Risks* |
| Use inverse distribution to calculate percentile | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Risks* |
| Exposure calculation method | ModelledConcentration | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Risks* |
| Inclusion percentage variability interval | 99.8 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Risks* |
| Compute shorter than lifetime exposures | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Dietary exposures* |

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Table 3.474 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Consumptions on the same day come from the same sample | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Dietary exposures* |
| Model type | OIM | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Dietary exposures* |
| Covariate modelling | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Dietary exposures* |
| Iterate survey | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Dietary exposures* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |

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Table 3.474 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Include MRL fallback model | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |

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Table 3.474 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EC 2018) - Chronic / Tier II* | *Food concentration models* |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier I

Table 3.475: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Single value risk calculation method | FromIndividualRisks | | |
| Percentage for percentile | 0.1 | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food conversions* |

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Table 3.475 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |

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Table 3.475 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.1 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentrations* |

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Table 3.475 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Processing factors* |
| Unit variability model | BetaDistribution | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Unit variability factors* |
| Estimates nature | Realistic | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Unit variability factors* |
| Unit variability parameter | VariabilityFactor | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Unit variability factors* |

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Table 3.475 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply occurrence pattern percentages | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Hazard characterisations* |
| Compute cumulative risks | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Risks* |
| Health effect type | Risk | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Risks* |
| Risk characterisation ratio | HazardExposureRatio | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Risks* |
| Risk threshold | 100 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Risks* |

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Table 3.475 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use inverse distribution to calculate percentile | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Risks* |
| Exposure calculation method | Modelled-Concentration | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Risks* |
| Inclusion percentage variability interval | 99.8 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Risks* |
| Consumptions on the same day come from the same sample | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Dietary exposures* |
| Use unit variability | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Dietary exposures* |

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Table 3.475 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Covariate modelling | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Dietary exposures* |
| Iterate survey | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Dietary exposures* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |

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Table 3.475 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Correlate imputed values with sample potency | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |

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Table 3.475 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Parametric uncertainty | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier I* | *Food concentration models* |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I

Table 3.476: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Single value risk calculation method | FromIndividualRisks | | |
| Percentage for percentile | 0.1 | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Consumptions* |
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food conversions* |

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Table 3.476 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Substance conversion method | UseMostToxic | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Account for substance authorisations in substance conversions | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |

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Table 3.476 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.1 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentrations* |

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Table 3.476 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Processing factors* |
| Apply occurrence pattern percentages | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Hazard characterisations* |
| Compute cumulative risks | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Risks* |

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Table 3.476 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Health effect type | Risk | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Risks* |
| Risk characterisation ratio | HazardExposureRatio | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Risks* |
| Risk threshold | 100 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Risks* |
| Use inverse distribution to calculate percentile | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Risks* |
| Exposure calculation method | ModelledConcentration | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Risks* |
| Inclusion percentage variability interval | 99.8 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Risks* |

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Table 3.476 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute shorter than lifetime exposures | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Dietary exposures* |
| Consumptions on the same day come from the same sample | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Dietary exposures* |
| Model type | OIM | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Dietary exposures* |
| Covariate modelling | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Dietary exposures* |
| Iterate survey | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Dietary exposures* |

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Table 3.476 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Dietary exposures* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |

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Table 3.476 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Sample based | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Correlate imputed values with sample potency | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier I* | *Food concentration models* |

### Retrospective dietary CRA (EFSA 2022) - Acute / Tier II

Table 3.477: Tier definition for Retrospective dietary CRA (EFSA 2022) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Single value risk calculation method | FromIndividualRisks | | |
| Percentage for percentile | 0.1 | | |

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Table 3.477 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |

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Table 3.477 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |

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Table 3.477 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Processing factors* |
| Use distribution | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Processing factors* |

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Table 3.477 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Unit variability model | BetaDistribution | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Unit variability factors* |
| Estimates nature | Realistic | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Unit variability factors* |
| Unit variability parameter | VariabilityFactor | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Unit variability factors* |
| Apply occurrence pattern percentages | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Occurrence patterns* |

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Table 3.477 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Target level | External | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Hazard characterisations* |
| Compute cumulative risks | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Risks* |
| Health effect type | Risk | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Risks* |
| Risk characterisation ratio | HazardExposureRatio | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Risks* |
| Risk threshold | 100 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Risks* |
| Use inverse distribution to calculate percentile | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Risks* |

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Table 3.477 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Exposure calculation method | Modelled-Concentration | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Risks* |
| Inclusion percentage variability interval | 99.8 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Risks* |
| Consumptions on the same day come from the same sample | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Dietary exposures* |
| Use unit variability | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Dietary exposures* |
| Covariate modelling | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Dietary exposures* |

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Table 3.477 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Iterate survey | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Dietary exposures* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |

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Table 3.477 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EFSA 2022) - Acute / Tier II* | *Food concentration models* |

### Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II

Table 3.478: Tier definition for Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Single value risk calculation method | FromIndividualRisks | | |
| Percentage for percentile | 0.1 | | |
| Ignore sampling weights | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Consumptions* |
| N (number of days in survey) | 2 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |

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Table 3.478 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use substance conversion rules | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |

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Table 3.478 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Impute water concentrations | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Processing factors* |

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Table 3.478 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use distribution | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Processing factors* |
| Apply occurrence pattern percentages | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Occurrence patterns* |
| Target level | External | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Hazard characterisations* |

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Table 3.478 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Risks* |
| Health effect type | Risk | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Risks* |
| Risk characterisation ratio | HazardExposureRatio | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Risks* |
| Risk threshold | 100 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Risks* |
| Use inverse distribution to calculate percentile | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Risks* |
| Exposure calculation method | ModelledConcentration | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Risks* |

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Table 3.478 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Inclusion percentage variability interval | 99.8 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Risks* |
| Compute shorter than lifetime exposures | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Dietary exposures* |
| Consumptions on the same day come from the same sample | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Dietary exposures* |
| Model type | OIM | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Dietary exposures* |
| Covariate modelling | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Dietary exposures* |

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Table 3.478 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Iterate survey | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Dietary exposures* |
| Default concentration model | Empirical | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |

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Table 3.478 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Sample based | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Retrospective dietary CRA (EFSA 2022) - Chronic / Tier II* | *Food concentration models* |

### Prospective dietary CRA (EFSA 2023) - Acute / Tier II

Table 3.479: Tier definition for Prospective dietary CRA (EFSA 2023) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Single value risk calculation method | FromIndividualRisks | | |
| Percentage for percentile | 0.1 | | |
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |

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Table 3.479 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |

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Table 3.479 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |

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Table 3.479 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Processing factors* |
| Use distribution | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Processing factors* |

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Table 3.479 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Unit variability model | BetaDistribution | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Unit variability factors* |
| Estimates nature | Realistic | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Unit variability factors* |
| Unit variability parameter | VariabilityFactor | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Unit variability factors* |
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Occurrence patterns* |

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Table 3.479 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Target level | External | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Hazard characterisations* |
| Compute cumulative risks | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Risks* |
| Health effect type | Risk | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Risks* |
| Risk characterisation ratio | HazardExposureRatio | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Risks* |
| Risk threshold | 100 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Risks* |
| Use inverse distribution to calculate percentile | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Risks* |

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Table 3.479 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Exposure calculation method | Modelled-Concentration | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Risks* |
| Cumulation setting | RPFWeighte | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Risks* |
| Inclusion percentage variability interval | 99.8 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Risks* |
| Consumptions on the same day come from the same sample | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Dietary exposures* |
| Use unit variability | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Dietary exposures* |

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Table 3.479 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Covariate modelling | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Dietary exposures* |
| Iterate survey | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Dietary exposures* |
| Default concentration model | Empirical | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |

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Table 3.479 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Censored values replacement | ReplaceByLOR | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Sample based | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |

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Table 3.479 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Parametric uncertainty | false | *Prospective dietary CRA (EFSA 2023) - Acute / Tier II* | *Food concentration models* |

### Prospective dietary CRA (EFSA 2023) - Chronic / Tier II

Table 3.480: Tier definition for Prospective dietary CRA (EFSA 2023) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Single value risk calculation method | FromIndividualRisks | | |
| Percentage for percentile | 0.1 | | |
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Consumptions* |
| N (number of days in survey) | 2 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food conversions* |

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Table 3.480 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |

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Table 3.480 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |

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Table 3.480 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Processing factors* |

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Table 3.480 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use distribution | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Processing factors* |
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Occurrence patterns* |
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Occurrence patterns* |
| Target level | External | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Hazard characterisations* |

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Table 3.480 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Compute cumulative risks | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Risks* |
| Health effect type | Risk | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Risks* |
| Risk characterisation ratio | HazardExposureRatio | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Risks* |
| Risk threshold | 100 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Risks* |
| Use inverse distribution to calculate percentile | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Risks* |
| Exposure calculation method | ModelledConcentration | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Risks* |

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Table 3.480 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Cumulation setting | RPFWeighte | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Risks* |
| Inclusion percentage variability interval | 99.8 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Risks* |
| Compute shorter than lifetime exposures | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Dietary exposures* |
| Consumptions on the same day come from the same sample | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Dietary exposures* |
| Model type | OIM | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Dietary exposures* |

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Table 3.480 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Covariate modelling | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Dietary exposures* |
| Iterate survey | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Dietary exposures* |
| Default concentration model | Empirical | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |

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Table 3.480 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Censored values replacement | ReplaceByLOR | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Sample based | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |

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Table 3.480 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Parametric uncertainty | false | *Prospective dietary CRA (EFSA 2023) - Chronic / Tier II* | *Food concentration models* |

### Prospective dietary CRA (EFSA 2024) - Acute / Tier II

Table 3.481: Tier definition for Prospective dietary CRA (EFSA 2024) - Acute / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Single value risk calculation method | FromIndividualRisks | | |
| Percentage for percentile | 0.1 | | |
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |

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Table 3.481 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |

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Table 3.481 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |

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Table 3.481 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Include processed derivatives of the focal food in measurement replacement | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Processing factors* |

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Table 3.481 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use distribution | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Processing factors* |
| Unit variability model | BetaDistribution | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Unit variability factors* |
| Estimates nature | Realistic | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Unit variability factors* |
| Unit variability parameter | VariabilityFactor | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Unit variability factors* |
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Occurrence patterns* |

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Table 3.481 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Occurrence patterns* |
| Target level | External | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Hazard characterisations* |
| Compute cumulative risks | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Risks* |
| Health effect type | Risk | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Risks* |
| Risk characterisation ratio | HazardExposureRatio | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Risks* |

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Table 3.481 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Risk threshold | 100 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Risks* |
| Use inverse distribution to calculate percentile | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Risks* |
| Exposure calculation method | Modelled-Concentration | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Risks* |
| Cumulation setting | RPFWeighte | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Risks* |
| Inclusion percentage variability interval | 99.8 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Risks* |
| Consumptions on the same day come from the same sample | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Dietary exposures* |

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Table 3.481 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use unit variability | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Dietary exposures* |
| Covariate modelling | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Dietary exposures* |
| Iterate survey | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Dietary exposures* |
| Default concentration model | Empirical | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |

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Table 3.481 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Include MRL fallback model | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Sample based | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |

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Table 3.481 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Correlate imputed values with sample potency | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Prospective dietary CRA (EFSA 2024) - Acute / Tier II* | *Food concentration models* |

### Prospective dietary CRA (EFSA 2024) - Chronic / Tier II

Table 3.482: Tier definition for Prospective dietary CRA (EFSA 2024) - Chronic / Tier II.

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Single value risk calculation method | FromIndividualRisks | | |
| Percentage for percentile | 0.1 | | |
| Ignore sampling weights | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Consumptions* |
| Exclude individuals with less than N days | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Consumptions* |

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Table 3.482 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| N (number of days in survey) | 2 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Consumptions* |
| Total diet study concentration data | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food conversions* |
| Filter samples exceeding the concentration limits | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Concentration limit filter exceedance factor | 2 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Use substance conversion rules | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Substance conversion method | DrawRandom | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |

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Table 3.482 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Retain all allocated substances after active substance allocation | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Account for substance authorisations in substance conversions | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Fix duplicate substance allocation inconsistencies | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Use extrapolation rules | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Impute water concentrations | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Water concentration value (µg/kg) | 0.05 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |

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Table 3.482 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Restrict water imputation to the five most toxic substances | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Restrict water imputation to approved substances | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Include focal commodity concentrations | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Focal commodity substance occurrence percentage | 20 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Adjustment factor for the focal food/substance concentration | 1 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |

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Table 3.482 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Use deterministic substance conversions for focal commodity | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Include processed derivatives of the focal food in measurement replacement | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentrations* |
| Apply processing factors | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Processing factors* |
| Use distribution | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Processing factors* |
| Ignore processing factors less than 1 | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Processing factors* |
| Apply occurrence pattern percentages | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Occurrence patterns* |

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Table 3.482 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Scale up use frequency to 100% | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Occurrence patterns* |
| Restrict use percentage up-scaling to authorised uses | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Occurrence patterns* |
| Target level | External | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Hazard characterisations* |
| Compute cumulative risks | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Risks* |
| Health effect type | Risk | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Risks* |
| Risk characterisation ratio | HazardExposureRatio | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Risks* |

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Table 3.482 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Risk threshold | 100 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Risks* |
| Use inverse distribution to calculate percentile | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Risks* |
| Exposure calculation method | Modelled-Concentration | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Risks* |
| Cumulation setting | RPFWeighte | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Risks* |
| Inclusion percentage variability interval | 99.8 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Risks* |
| Compute shorter than lifetime exposures | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Dietary exposures* |

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Table 3.482 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Consumptions on the same day come from the same sample | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Dietary exposures* |
| Model type | OIM | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Dietary exposures* |
| Model-then-add | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Dietary exposures* |
| Covariate modelling | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Dietary exposures* |
| Iterate survey | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Dietary exposures* |
| Report consumptions and exposures per individual instead of per kg body weight | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Dietary exposures* |

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Table 3.482 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Default concentration model | Empirical | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Include MRL fallback model | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Restrict LOR imputation to authorised uses | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Censored values replacement | ReplaceByLOR | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Factor f (f x LOR or f x LOD or LOD + f x (LOQ - LOD) | 0.5 | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Sample based | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |

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Table 3.482 – continued from previous page

| Name | Setting | From input tier | In module |
|---|---|---|---|
| Impute missing values from available values (if unchecked, missing values are imputed with 0) | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Correlate imputed values with sample potency | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Use occurrence frequencies for imputation | true | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |
| Parametric uncertainty | false | *Prospective dietary CRA (EFSA 2024) - Chronic / Tier II* | *Food concentration models* |

### Calculation of single value risks

Single value risk can be computed by route and substance in the form of the risk characterisation ratio hazard/exposure or exposure/hazard. Single value risks are risk estimates obtained from combining single value exposures with single value hazard characterisations or as a percentile from a risk distribution. Optionally, the exposure and hazard behind the percentile calculation can be adjusted with fixed adjustment factors or factors drawn from parametric uncertainty distributions.

- *Single value risks calculation*

Inputs used: *Single value dietary exposures Hazard characterisations Risks*

Settings used

- *Calculation Settings*

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|

Table 3.483: Overview of MCRA modules.

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| *Primary entity* | *Foods* | | *Consumptions*, *Single value consumptions*, *Market shares*, *Food recipes*, *Food concentrations*, *Food concentration distributions*, *Single value concentrations*, *Processing factors*, *Unit variability factors*, *Occurrence patterns*, *Occurrence frequencies*, *Substance authorisations*, *Deterministic substance conversion factors*, *Concentration limits*, *Food concentration models*, *Modelled foods*, *Focal food concentrations*, *Total diet study sample compositions*, *Food extrapolations*, *Food conversions*, *Consumptions by modelled food*, *High exposure food-substance combinations*, *Dietary exposures*, *Single value dietary exposures*, | Foods are uniquely defined sources of dietary exposure to chemical substances. Foods may refer to 1) foods as eaten, foods as coded in food consumption data (e.g. pizza); 2) modelled foods, foods as coded in concentration data (e.g. wheat, tomato); 3) any other type of food (e.g. ingredients like flour, tomato sauce). |

Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Non-dietary exposure sources* | | | Non-dietary exposure sources are the sources containing chemical substances to which individuals in a population are exposed via any of three non-dietary routes: dermal, inhalation or oral, per day. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Substances* | | *Dust exposure determinants*, *Soil exposure determinants*, *Air exposure determinants*, *Consumer product exposure determinants*, *Food concentrations*, *Food concentration distributions*, *Dust concentrations*, *Dust concentration distributions*, *Soil concentrations*, *Soil concentration distributions*, *Air concentration distributions*, *Indoor air concentrations*, *Outdoor air concentrations*, *Single value concentrations*, *Processing factors*, *Unit variability factors*, *Occurrence patterns*, *Occurrence frequencies*, *Substance authorisations*, *Substance approvals*, *Substance conversions*, *Deterministic substance conversion factors*, *Concentration limits*, *Food concentration models*, *Modelled* | Substances are chemical entities that can refer to: 1) active substances such as investigated in toxicology; 2) measured substances such as defined in specific analytical methods. MCRA assessments can have one or more substances as the scope. When more than one substance is specified, there is an option to perform a cumulative assessment. In that case one of the substances has to be indicated as the index/reference substance, and results will be expressed in equivalents of the index substance. |

Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Effects* | | *Food concentration models*, *High exposure food-substance combinations*, *Dietary exposures*, *Exposure mixtures*, *QSAR membership models*, *Molecular docking models*, *Active substances*, *Relative potency factors*, *Hazard characterisations*, *Points of departure*, *Effect representations*, *Inter-species conversions*, *Intra species factors*, *AOP networks*, *Exposure response functions*, *Burden of disease*, *Risks*, *Single value risks*. | Effects are biological or toxicological consequences for human health, that may result from chemical exposure and are the focus of hazard or risk assessment. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Populations* | | *Consumptions*, *Single value consumptions*, *Consumer product use frequencies*, *Food concentrations*, *Consumptions by modelled food*, *Dietary exposures*, *Single value dietary exposures*, *Single value non-dietary exposures*, *Non-dietary exposures*, *Internal exposures*, *HBM concentrations*, *HBM analysis*, *Exposure comparisons*, *Dust exposures*, *Soil exposures*, *Air exposures*, *Individuals*, *Consumer product exposures*, *HBM single value exposures*, *Hazard characterisations*, *Burden of disease*, *Risks*, *Single value risks*, *Environmental burden of disease*. | Populations are groups of human individuals that are the scope of exposure or risk assessments. Optional descriptors of populations are location (e.g. a country), time period (with a start and end date), age range (with a minimum and maximum age) and gender. Example: the French population in 2005-2007 (= time period) of women (= gender) of child-bearing age 18-45 yr (= age range). |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Test systems* | | *Responses*, *Dose response models*, *Dose response data*. | Test systems are biological or artificial systems used for assessing hazard in relation to chemical exposure from substances in varying doses. Test systems may refer to 1) in-vivo test systems (e.g. a rat 90-day study, a human biomonitoring study); 2) in-vitro test systems (e.g. HepaRG cells). |
| | *Responses* | *Test systems*. | *Dose response models*, *Dose response data*, *Effect representations*. | Responses are measurable entities in test systems. Responses are used to represent effects (see effect representations) and their measured values are collected in dose response data. |
| | *Consumer products* | | *Consumer product exposure determinants*, *Consumer product use frequencies*, *Consumer product concentrations*, *Consumer product concentration distributions*, *Consumer product exposure estimates*, *Consumer product exposures*. | Consumer products are uniquely defined sources of (personal care) products. |
| *Consumption* | *Consumptions* | *Populations*, *Foods*. | *Food conversions*, *Consumptions by modelled food*. | Consumptions data are the amounts of foods consumed on specific days by individuals in a food consumption survey. For acute exposure assessments, the interest is in a population of person-days, so one day per individual may be sufficient. For chronic exposure assessments, the interest is in a population of persons, so preferably two or more days per individual are needed. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Single value consumptions* | *Consumptions by modelled food*. | *Single value dietary exposures*. | Single value consumption data are the single value amounts (Large Portion, Mean Consumption, p97.5Consumption) of modelled foods (foods-as-measured) consumed in a population. |
| | *Market shares* | *Foods*. | *Food conversions*. | Market shares data specify for a given food, percentages of more specific foods (subfoods, e.g. brands) representing their share in a market. Market shares are used when consumption data are available at a more generalised level than concentration data. |
| | *Food recipes* | *Foods*. | *Food conversions*. | Food recipes data specify the composition of specific foods (typically: foods-as-eaten) in terms of other foods (intermediate foods or modelled foods) by specifying proportions in the form of a percentage. |
| | *Dust exposure determinants* | *Substances*. | *Dust exposures*. | Dust exposure determinants specify the factors that determine the exposure of individuals to dust. |
| | *Soil exposure determinants* | *Substances*. | *Soil exposures*. | Soil exposure determinants specify the factors that determine the exposure of individuals to soil. |
| | *Air exposure determinants* | *Substances*. | *Air exposures*. | Air exposure determinant data are distributions of chemical substances occurring in air samples. The distributions can differ per age group. |
| | *Consumer product exposure determinants* | *Substances*, *Consumer products*. | *Consumer product exposures*. | Consumer product exposure determinant data are distributions of chemical substances occurring in consumer products. The distributions can differ per age group. |
| | *Consumer product use frequencies* | *Populations*, *Consumer products*. | *Consumer product exposures*. | Consumer product use frequencies specify the frequency of use for a consumer product (personal care, do-it-yourself, cleaning product) per day. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| *Occurrence* | *Food concentrations* | *Foods*, *Substances*, *Populations*, *Focal food concentrations*, *Food extrapolations*, *Substance conversions*, *Deterministic substance conversion factors*, *Relative potency factors*, *Substance authorisations*, *Active substances*, *Concentration limits*, *Substance approvals*, *Processing factors*. | *Single value concentrations*, *Occurrence patterns*, *Food concentration models*, *Modelled foods*. | Food concentrations data are analytical measurements of chemical substances occurring in food samples. In their simplest form, food concentration data can just be used as provided by datasets. Optionally, food concentrations data can be manipulated for active substances, extrapolated to other foods, and/or default values can be added for water. |
| | *Food concentration distributions* | *Foods*, *Substances*. | *Food concentration models*, *Dietary exposures*. | Food concentration distributions describe substance concentrations on foods in the form of summary statistics. |
| | *Dust concentrations* | *Substances*. | *Dust concentration distributions*. | Dust concentrations are analytical measurements of chemical substances occurring in dust samples. In their simplest form, concentration data can just be used as provided by datasets. |
| | *Dust concentration distributions* | *Dust concentrations*. | *Dust exposures*. | Dust concentration distributions are specified by a mean, cv and distribution type (lognormal). Specify the occurrence percentage as the percentage of samples that has positive concentrations. |
| | *Soil concentrations* | *Substances*. | *Soil concentration distributions*. | Soil concentrations data are analytical measurements of chemical substances occurring in soil samples. In their simplest form, concentration data can just be used as provided by datasets. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Soil concentration distributions* | *Soil concentrations*. | *Soil exposures*. | Soil concentration distributions are specified by a mean, cv and distribution type (lognormal). Specify the occurrence percentage as the percentage of samples that has positive concentrations. |
| | *Air concentration distributions* | *Indoor air concentrations*, *Outdoor air concentrations*. | *Air exposures*. | Air (indoor, outdoor) concentration distributions are specified by a mean, cv and distribution type (lognormal). Specify the occurrence percentage as the percentage of samples that has positive concentrations. |
| | *Indoor air concentrations* | *Substances*. | *Air concentration distributions*. | Indoor air concentrations data are analytical measurements of chemical substances occurring in indoor air samples. In their simplest form, concentration data can just be used as provided by datasets. |
| | *Outdoor air concentrations* | *Substances*. | *Air concentration distributions*. | Outdoor air concentrations data are analytical measurements of chemical substances occurring in outdoor air samples. In their simplest form, concentration data can just be used as provided by datasets. |
| | *Single value concentrations* | *Active substances*, *Food concentrations*, *Concentration limits*, *Deterministic substance conversion factors*. | *Modelled foods*, *Single value dietary exposures*. | Single value concentrations data are the single value estimates (High Residue, Maximum Residue Limit, Supervised Trials Median Residue) of residue concentrations on modelled foods. |
| | *Processing factors* | *Foods*, *Substances*. | *Food concentrations*, *Food conversions*, *Dietary exposures*, *Single value dietary exposures*. | Processing factors are multiplication factors to derive the concentration in a processed food from the concentration in an unprocessed food and can be specified for identified processing types (e.g., cooking, washing, drying). Processing factors are primarily used in dietary exposure assessments to correct for the effect of processing on substance concentrations in dietary exposure calculations. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Unit variability factors* | *Foods*, *Substances*. | *Dietary exposures*, *Single value dietary exposures*. | Unit variability factors specify the variation in concentrations between single units of the same food, which have been put together in a mixture sample on which the concentration measurements have been made. Unit variability factors are used to account for the fact that concentration data often relate to composite samples, whereas an acute risk may result from single food units. |
| | *Occurrence patterns* | *Substance authorisations*, *Active substances*, *Food concentrations*. | *Occurrence frequencies*, *Dietary exposures*. | Occurrence patterns (OPs) are the combinations (or mixtures) of substances that occur together on foods and the frequencies of these mixtures occurring per food, expressed in percentages. In the context of pesticides, occurrence patterns are associated with agricultural use percentages. Occurrence patterns are relevant to account for co-occurrence of active substances in exposed individuals. Occurrence patterns may be specified as data or modelled based on observed patterns of positive concentrations. |
| | *Occurrence frequencies* | *Active substances*, *Occurrence patterns*. | *Food concentration models*, *Single value dietary exposures*. | Occurrence frequencies specify how often substances occur on foods. Frequencies are expressed as percentages. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Substance authorisations* | *Foods*, *Substances*. | *Food concentrations*, *Occurrence patterns*, *Food concentration models*. | Substance authorisations specify which food/substance combinations are authorised for (agricultural) use. If substance authorisations are used, then only the food/substance combinations that are specified in the data are assumed to be authorised and all other combinations are assumed to be not authorised. This information may, for instance, be used to determine whether concentration measurements below the LOQ or LOD could be assumed true zeros. I.e., if a food/substance combinations is assumed to be unauthorised, then the LOQ, LOD may be assumed to be a zero. |
| | *Substance approvals* | *Substances*. | *Food concentrations*. | Substance approvals specify which substances are approved within the definition under regulation (EC) No 1107/2009. This information may, for instance, be used to to restrict water imputation to approved substances only. |
| | *Substance conversions* | *Substances*, *Active substances*. | *Food concentrations*. | Substance conversions specify how measured substances are converted into active substances, which are the substances assumed to cause health effects. In pesticide legislation such measured substances and the substance conversion rules are known as residue definitions. |
| | *Deterministic substance conversion factors* | *Substances*, *Foods*. | *Food concentrations*, *Single value concentrations*. | Data module for deterministic substance conversion factors. These are (possibly food specific) conversion factors for expressing measured substance concentrations to equivalent active substance concentrations. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Concentration limits* | *Foods*, *Substances*. | *Food concentrations*, *Single value concentrations*, *Food concentration models*, *Modelled foods*. | Concentration limits specify (legal) limit values for substance concentrations on foods and are sometimes used as conservative values for concentration data. In the framework of pesticides the legal Maximum Residue Limit (MRL) is the best known example. |
| | *Food concentration models* | *Food concentrations*, *Concentration limits*, *Active substances*, *Modelled foods*, *Substance authorisations*, *Occurrence frequencies*, *Relative potency factors*, *Food concentration distributions*, *Total diet study sample compositions*. | *High exposure food-substance combinations*, *Dietary exposures*. | Food concentration models are distributional models of substance concentrations on foods. They describe both the substance presence (yes/no, with no representing an absolute zero concentration) and the substance concentrations. Food concentration models are specified per food/substance combination. |
| | *Modelled foods* | *Food concentrations*, *Single value concentrations*, *Concentration limits*. | *Food concentration models*, *Food conversions*. | Modelled foods are foods within the foods scope for which concentration data or MRLs of substances are available (or expected). |
| | *Focal food concentrations* | *Foods*, *Substances*. | *Food concentrations*. | In some cases the attention in an assessment is on a specific food (focal food), against the background of other foods. Focal food concentrations are separate concentration data for one or more focal food commodities, that will take the place of any other concentration data for the focal food in the ordinary concentration data. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Total diet study sample compositions* | *Foods*. | *Food concentration models*, *Food conversions*. | Total diet study sample compositions specify the composition of mixed food samples, such as used in a total diet study (TDS), in terms of their constituting foods. |
| | *Food extrapolations* | *Foods*. | *Food concentrations*, *Food conversions*. | Food extrapolations data specify which foods (data rich foods) can be used to impute concentration data for other foods with insufficient data (data poor foods). |
| | *Consumer product concentrations* | *Substances*, *Consumer products*. | *Consumer product concentration distributions*. | Consumer product concentration (distributions) data are analytical measurements of chemical substances occurring in PCPs. In their simplest form, concentration data can just be used as provided by datasets. |
| | *Consumer product concentration distributions* | *Consumer product concentrations*. | *Consumer product exposures*. | Consumer product concentration distributions are specified by a mean, cv and distribution type (lognormal). Specify the occurrence percentage i.c. the percentage of the consumer product with positive concentrations. |
| *Exposure* | *Food conversions* | *Consumptions*, *Modelled foods*, *Processing factors*, *Food recipes*, *Market shares*, *Food extrapolations*, *Total diet study sample compositions*, *Active substances*. | *Consumptions by modelled food*, *Dietary exposures*. | Food conversions relate foods-as-eaten, as found in the consumption data, to modelled foods (foods-as-measured), which are the foods for which concentration data are available. A food-as-eaten can be linked to one, or multiple modelled foods using various conversion steps (e.g., using food recipes to translate a composite food into its ingredients). There are several types of conversion steps, and a conversion path may comprise multiple conversion steps between a food-as-eaten and a modelled food. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Consumptions by modelled food* | *Consumptions*, *Food conversions*. | *Single value consumptions*, *High exposure food-substance combinations*, *Dietary exposures*. | Consumptions by modelled food are consumptions of individuals expressed on the level of the foods for which concentration data are available (i.e., the modelled-foods). These are calculated from consumptions of foods-as-eaten and food conversions that link the foods-as-eaten amounts to modelled-foods amounts. |
| | *High exposure food-substance combinations* | *Consumptions by modelled food*, *Food concentration models*, *Active substances*, *Relative potency factors*. | *Dietary exposures*. | Identification of food-as-eaten/modelled food/substance combinations that have the highest expected contribution to exposure based on a simple screening model. |
| | *Dietary exposures* | *Consumptions by modelled food*, *Food concentration models*, *Processing factors*, *Unit variability factors*, *High exposure food-substance combinations*, *Active substances*, *Occurrence patterns*, *Relative potency factors*, *Food conversions*, *Food concentration distributions*. | *Internal exposures*, *Exposure mixtures*, *Dust exposures*, *Soil exposures*, *Air exposures*, *Risks*, *Environmental burden of disease*. | Dietary exposures are the amounts of substances, expressed per kg bodyweight or per individual, to which individuals in a population are exposed from their diet per day. Depending on the exposure type, dietary exposures can be short-term/acute exposures and then contain exposures for individual-days, or they can be long-term/chronic exposures, in which case they represent the average exposure per day over an unspecified longer time period. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Single value dietary exposures* | *Single value consumptions*, *Single value concentrations*, *Processing factors*, *Unit variability factors*, *Occurrence frequencies*. | *Single value risks*. | Single value dietary exposures are based on the single value concentrations of substances, expressed per standard (kg) bodyweight and/or single value amounts of consumed modelled food. Depending on the exposure type, dietary exposures can be short-term/acute exposures. |
| | *Single value non-dietary exposures* | | | Single value non-dietary exposures are based on the single value concentrations or amounts of substances, as opposed to the distribution-based exposures of individuals in the non-dietary exposure module. Exposures are via any of the non-dietary routes: dermal, inhalation, or oral. Depending on the exposure type, single value non-dietary exposures can be short-term/acute or long term/chronic exposures. The exposures can be modelled as external exposures or internal exposures. |
| | *Non-dietary exposures* | *Populations*, *Substances*, *Active substances*. | *Internal exposures*. | Non-dietary exposures are the amounts of substances to which individuals in a population are exposed via any of three non-dietary routes: dermal, inhalation or oral, per day. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Internal exposures* | *Active substances*, *Dietary exposures*, *Consumer product exposures*, *Air exposures*, *Dust exposures*, *Soil exposures*, *Non-dietary exposures*, *Occupational scenarios*, *Occupational exposures*, *Individuals*, *Absorption factors*, *Kinetic conversion factors*, *PBK model parametrisations*, *Relative potency factors*. | *Exposure mixtures*, *Exposure comparisons*, *Risks*, *Environmental burden of disease*. | Internal doses and concentrations are amounts of substances, typically expressed per mass unit and per day, to which individuals in a population are exposed at the chosen target level. This target level is an internal dose or an internal concentration (expressed per unit [organ] weight). Internal exposures may be aggregated from dietary and non-dietary exposures using either absorption factors for systemic doses or kinetic conversion factors or PBK models to translate the external exposures to internal concentrations at the specific target or tissue. Internal exposures can be short-term/acute exposures and then contain exposures for individual-days, or they can be long-term/chronic exposures, in which case they represent the average exposure per day over an unspecified longer time period. |
| | *Exposure mixtures* | *Dietary exposures*, *Internal exposures*, *Relative potency factors*, *HBM analysis*. | | Exposure mixtures will select sets of co-occurring substances (one or more) that contribute most to the overall exposure patterns. |
| | *HBM concentrations* | *Populations*, *Substances*. | *HBM analysis*. | Human (bio)monitoring data quantify substance concentrations found in humans collected in human monitoring surveys. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Consumer product exposure estimates* | *Substances*, *Consumer products*. | *Consumer product exposures*. | Consumer product exposure estimates describing metadata and the distribution of chemical substances in consumer products for exposure assessments from the Probabilistic Aggregate Consumer Exposure Model (PACEM). |
| | *HBM analysis* | *HBM concentrations*, *Active substances*, *Relative potency factors*, *Kinetic conversion factors*, *Exposure biomarker conversions*, *PBK model parametrisations*, *Occupational scenarios*. | *Exposure mixtures*, *Exposure comparisons*, *Risks*, *Environmental burden of disease*. | Human biomonitoring concentrations are substance concentration estimates for a biological matrix (e.g., urine or blood) derived from data obtained from human monitoring studies. |
| | *Exposure comparisons* | *HBM analysis*, *Internal exposures*. | | Substances in the human body are absorbed, excreted without transformation, excreted after metabolization or stored in various tissues, bones or body fluids. The term biological matrix refers to all human specimens where concentratrions of a chemical can be measured like bodily fluids, such as blood, urine, saliva, breast milk, sweat, and other specimens, such as faeces, hair, teeth, and nails. Exposure comparisons compares observed human monitoring data with predictions made for the same population of individuals from dietary survey data, concentration data and (optionally) non-dietary exposure data. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Dust exposures* | *Active substances*, *Dietary exposures*, *Dust concentration distributions*, *Dust exposure determinants*, *Individuals*. | *Internal exposures*. | Dust exposures are the amounts of substances, expressed per kg bodyweight, to which individuals in a population are exposed from dust per day. Dust exposures are long-term/chronic exposures, they represent the average exposure per day over an unspecified longer time period. |
| | *Soil exposures* | *Active substances*, *Dietary exposures*, *Soil concentration distributions*, *Soil exposure determinants*, *Individuals*. | *Internal exposures*. | Soil exposures are the amounts of substances, expressed per kg bodyweight, to which individuals in a population are exposed from soil per day. Soil exposures are long-term/chronic exposures, they represent the average exposure per day over an unspecified longer time period. |
| | *Air exposures* | *Active substances*, *Dietary exposures*, *Air concentration distributions*, *Air exposure determinants*, *Individuals*. | *Internal exposures*. | Air exposures are the amounts of substances, expressed per kg bodyweight, to which individuals in a population are exposed from air per m3. Air exposures are long-term/chronic exposures, they represent the average exposure per m3 over an unspecified longer time period. |
| | *Individuals* | *Populations*. | *Occupational exposures*, *Internal exposures*, *Dust exposures*, *Soil exposures*, *Air exposures*, *Consumer product exposures*. | Simulates individuals with properties like age, body weight, sex, and body surface area. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Consumer product exposures* | *Active substances*, *Consumer product concentration distributions*, *Consumer product use frequencies*, *Consumer product exposure determinants*, *Individuals*, *Consumer product exposure estimates*. | *Internal exposures*. | Consumer product exposures are the amounts of substances, expressed per kg bodyweight, to which individuals in a population are exposed from average consumer product usage per individual. Consumer product exposures are long-term/chronic exposures, they represent the average exposure per day over an unspecified longer time period. |
| | *HBM single value exposures* | *Populations*, *Substances*. | *Environmental burden of disease*. | Human (bio)monitoring (HBM) population exposure estimates specified as (single value) percentile points of the exposure distribution. |
| | *Occupational task exposures* | *Substances*, *Occupational scenarios*. | *Occupational exposures*. | Occupational task exposures are exposures associated with specific job tasks performed by workers. |
| | *Occupational exposures* | *Active substances*, *Individuals*, *Occupational task exposures*, *Occupational scenarios*. | *Internal exposures*. | Occupational exposures are the amounts of substances to which individuals are exposed while performing job tasks. Occupational exposures are long-term/chronic exposures, they represent the average exposure per day over an unspecified longer time period. |
| | *Occupational scenarios* | | *Occupational task exposures*, *Internal exposures*, *HBM analysis*, *Occupational exposures*. | Occupational scenarios are scenarios, tasks and scenario tasks associated with specific job tasks performed by workers. |
| | *Exposure biomarker conversions* | *Substances*. | *HBM analysis*. | Occasionally, the biomarker of interest (substance) is not measured. Exposure biomarker conversions specify how measured biomarkers are converted to the relevant biomarkers (substances). This type of conversion is within biological matrices. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| *In-silico* | *QSAR membership models* | *Substances*, *Effects*, *AOP networks*. | *Active substances*. | QSAR membership models specify assessment group memberships for active substances related to a specific health effect (adverse outcome). Memberships should be derived externally from Quantitative Structure-Activity Relationship (QSAR) models. |
| | *Molecular docking models* | *Substances*, *Effects*, *AOP networks*. | *Active substances*. | Molecular docking models specify binding energies for substances in specific molecular docking models related to a specific health effect (adverse outcome). |
| *Kinetic* | *Absorption factors* | *Substances*, *Active substances*. | *Internal exposures*, *Hazard characterisations*. | Absorption factors are chemical- and route-specific values representing the fraction of external exposures passing the absorption barrier. They are used to derive internal systemic exposures from external exposures for some specified exposure route. The corresponding exposure is referred to as internal dose. |
| | *PBK model parametrisations* | *Substances*, *Active substances*, *PBK model definitions*. | *Internal exposures*, *HBM analysis*, *Kinetic conversion factors*, *Hazard characterisations*. | The parametrisation of PBK models are specified as data. PBK models relate exposures or hazard characterisations from one or more external routes (oral, dermal, inhalation) to an internal target or biological matrix. PBK models are based on differential-equation. MCRA currently includes the EuroMix generic PBK model and the bisphenol model of ETHZ. The corresponding exposure in the biological matrix is referred to as internal concentration. |
| | *Kinetic conversion factors* | *Active substances*, *PBK model parametrisations*. | *Internal exposures*, *HBM analysis*, *Hazard characterisations*. | Kinetic conversion factors relate exposures or hazard characterisations from one or more external routes (dietary, non-dietary oral, dermal, inhalation) to an internal target or biological matrix. The corresponding exposure is referred to as internal concentration. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *PBK model definitions* | | *PBK model parametrisations*. | Physiologically based kinetic (PBK) models are mathematical representations of biological organisms designed to describe and predict the time-dependent processes of absorption, distribution, metabolism, and excretion (ADME) of chemicals across tissues and organs. PBK model definitions establish the structural framework of these models - specifying compartments, chemical species, and their interconnections - without prescribing specific parameter values. When combined with parameter values, these definitions enable the estimation of internal chemical concentrations from external exposures, and vice versa. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| *Hazard* | *Active substances* | *AOP networks*, *Points of departure*, *Hazard characterisations*, *Molecular docking models*, *QSAR membership models*. | *Food concentrations*, *Single value concentrations*, *Occurrence patterns*, *Occurrence frequencies*, *Substance conversions*, *Non-dietary exposures*, *Dust exposures*, *Soil exposures*, *Air exposures*, *Consumer product exposures*, *Occupational exposures*, *Absorption factors*, *PBK model parametrisations*, *Kinetic conversion factors*, *Relative potency factors*, *Hazard characterisations*, *Inter-species conversions*, *Intra species factors*, *Food concentration models*, *Food conversions*, *High exposure food-substance combinations*, *Dietary exposures*, *Internal exposures*, *HBM analysis*. | Active substances are substances that may lead (P>0) to a specific health effect (adverse outcome). Active substances are specified directly as data or calculated from POD presence, QSAR models or Molecular docking models. Active substances can have an assessment group membership 1 (crisp), or values in the range (0,1] (probabilistic). |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Relative potency factors* | *Active substances*, *AOP networks*, *Hazard characterisations*. | *Food concentrations*, *Food concentration models*, *High exposure food-substance combinations*, *Dietary exposures*, *Internal exposures*, *Exposure mixtures*, *HBM analysis*, *Risks*, *Environmental burden of disease*. | Relative potency factors (RPFs) quantify potencies of substances with respect to a defined effect, relative to the potency of a chosen index substance. RPFs can be used to express combined exposures of multiple substances in terms of a the exposure value of the chosen index substance (i.e., in index substance equivalents). In MCRA, hazard characterisations, and therefore also RPFs are based on mass units (e.g., µg), and not on mol units. RPFs can be different for different levels of the human organism (external, internal, specific compartment). RPFs can be given as data or computed from hazard characterisations. RPFs can be specified with uncertainty. Computation from uncertain hazard characterisations allows to include correlations between uncertain RPFs which originate from using the same index substance. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Hazard characterisations* | *AOP networks*, *Active substances*, *Points of departure*, *Dose response models*, *Effect representations*, *Inter-species conversions*, *Intra species factors*, *Absorption factors*, *Kinetic conversion factors*, *PBK model parametrisations*. | *Active substances*, *Relative potency factors*, *Risks*, *Single value risks*. | Hazard characterisations are reference exposure values for active substances at the chosen biological target level (external or internal). Hazard characterisations may be specified for specific effects or for the critical effect as defined in hazard characterisation. Hazard characterisations are specified as external values (e.g. human based guidance values, such as ADI or ARfD) or are based on points of departure, such as BMD(L)s from dose-response models or externally specified points of departure (NOAEL, LOAEL, MDS). The computation may involve assessment factors, e.g. for inter-species conversion, intra-species variation or additional sources of uncertainty. The calculation may also use kinetic conversion factors, PBK models or absorption factors to convert external doses to internal concentration/doses or vice versa. |
| | *Points of departure* | *Substances*, *Effects*, *AOP networks*. | *Active substances*, *Hazard characterisations*. | Externally specified points of departure can be used as an alternative to calculated BMDs from dose response models. Points of departure can be of various types, such as NOAEL, LOAEL or BMD. They can be used to construct the list of active substances, to derive relative potency factors, and to perform health impact assessments. |
| | *Dose response models* | *Dose response data*, *Effect representations*. | *Hazard characterisations*. | Dose response models are models fitted to dose response data and can be provided as data or calculated using a local or remote version of PROAST. The main results for hazard and risk assessment are benchmark doses (BMDs, BMDLs), related to a specified substance, response, optionally covariate value, and the benchmark response (BMR). |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Dose response data* | *Substances*, *Test systems*, *Responses*. | *Dose response models*. | Dose response data are data on response values of test systems at specified doses of substances (or mixtures of substances) from dose response experiments. |
| | *Effect representations* | *Effects*, *Responses*, *AOP networks*. | *Hazard characterisations*, *Dose response models*. | Effect representations specify the responses that can be used to measure specified effects and which response levels, the benchmark response (BMR), define the hazard limits for the effects. |
| | *Inter-species conversions* | *Substances*, *Effects*, *Active substances*. | *Hazard characterisations*. | Inter-species conversions specify how to convert a hazard characterisation for a given species to a hazard characterisation for humans. In the simplest approach, this specifies a fixed inter-species factor. In a higher tier, this specifies a geometric mean (GM) and geometric standard deviation (GSD) for a lognormal uncertainty distribution of the interspecies factor. Inter-species conversion are specified per effect and can be general or substance-specific. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Intra species factors* | *Substances*, *Effects*, *Active substances*. | *Hazard characterisations*. | Intra-species factors describe variation between individuals concerning their individual sensitivities to experience well-defined health effects. Traditionally the intraspecies factor is a fixed value, but the true distribution might be (very) uncertain. There is some support for assuming a lognormal distribution to describe the variability between individuals. In MCRA, intraspecies factors are sampled from a lognormal distribution, characterised by a geometric mean (GM) equal to 1 and a geometric standard deviation (GSD) thats needs to be given a value representing the intraspecies variability. GM is 1 by definition (50% of the population is assumed to be less sensitive than the average, 50% is mor sensitive) and has no uncertainty. On the other hand, there is uncertainty about the GSD. In MCRA it is assumed that this uncertainty is described by a Chi-square distribution with df degrees of freedom. By specifying a lower and upper bound for the p95 sensitive individual e.g. a lower value 2 and upper value 10 (meaning, the p95 individuals are between 2 and 10 times more sensible than the average human), a Chi-square distribution can be estimated where 1) the GSD specifies the variability and 2) the degrees of freedom specifies the uncertainty around the GSD. |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *AOP networks* | *Effects*. | *QSAR membership models*, *Molecular docking models*, *Active substances*, *Relative potency factors*, *Hazard characterisations*, *Points of departure*, *Effect representations*. | Effects are related to each other using the toxicological concept of adverse outcome pathways (AOPs) and adverse outcome pathway networks (see https://aopwiki.org). Adverse Outcome Pathway (AOP) Networks specify how biological events (effects) can lead to an adverse outcome (AO) in a qualitative way through relations of upstream and downstream key events (KEs), starting from molecular initiating events (MIEs). Using AOPs, the adverse outcome (AO), e.g., liver steatosis, is linked to key events (KEs), e.g., triglyceride accumulation in the liver, and to molecular initiating events (MIEs), e.g., PPAR-alpha receptor antagonism. In general, multiple AOPs may lead to the same AO, and therefore AOP networks can be identified. |
| | *Exposure response functions* | *Substances*, *Effects*. | *Environmental burden of disease*. | Exposure response functions define the relation between percentiles and percentile specific ratios for exposure effect related to environmental burden of disease. |
| | *Burden of disease* | *Populations*, *Effects*. | *Environmental burden of disease*. | Burden of disease data specify the burden of disease information related to specific effects and burden of disease indicators in specific populations. |
| *Risk* | *Risks* | *Dietary exposures*, *Internal exposures*, *Hazard characterisations*, *HBM analysis*, *Relative potency factors*. | *Single value risks*. | Risks (health impacts) are defined as a function of exposure and hazard characterisation at a chosen biological level (external or internal). Risk metrics are either based on the ratio hazard/exposure (e.g., MOE(T)) or exposure/hazard (e.g., HI, HQ, and RPI). |

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Table 3.483 – continued from previous page

| Category | Module | Inputs | Used by | Description |
|---|---|---|---|---|
| | *Single value risks* | *Single value dietary exposures*, *Hazard characterisations*, *Risks*. | | Single value risks are risk estimates obtained from combining single value exposures with single value hazard characterisations or as a percentile from a risk distribution. |
| | *Environmental burden of disease* | *Dietary exposures*, *Internal exposures*, *HBM analysis*, *Exposure response functions*, *Burden of disease*, *HBM single value exposures*, *Relative potency factors*. | | Environmental Burden of Disease (EBD) assessment. |

CHAPTER

FOUR

# STANDARD ACTIONS

A standard action is a user friendly way to perform a complex probabilistic calculation. By using a standard action predefined settings are used and the user can set only a limited number of selections. All settings (pre-defined and set by the user) are visible in the output. As a result a short output is presented. More detailed output is still available.

## 4.1 Acute single substance dietary exposure assessment of carbofuran or chlorpyrifos

This standard action is of type: *Dietary exposures*

This standard action allows you to perform probabilistic acute dietary exposure assessments of single substances in food. This standard actions contains examples for the two pesticides carbofuran and chlorpyrifos. The assessment is based on consumption data for two-years-old from the Dutch National Food Consumption Survey (DNFCS)-Young children (Ocké et al. (2008)). The consumption data are coded according to EFSAs coding system raw primary commodity (RPC) (EFSA (2019)). The 2014 concentration data of carbofuran and chlorpyrifos were extracted from EFSAs Data Warehouse and are organised according to the SSD data format. The standard action is developed for training purposes and results should not be regarded as representative outcomes of full dietary exposure assessments of carbofuran or chlorpyrifos.

In this standard action you can:

- Select the substance; carbofuran or chlorpyrifos,
- Choose the method for handling left-censored concentration measurements (lower bound or upper bound approach),
- Choose whether to include *correction for processing*,
- Choose whether to account for *unit-to-unit variation* using the Beta model,
- Run with or without uncertainty.

Table 4.1: Datasources for Acute single substance dietary exposure assessment of carbofuran or chlorpyrifos.

| Table Group | Name | Repository | Type |
|---|---|---|---|
| Compounds | Catalogues_WHO_Training_Acu NL2.xlsx | Standard Actions/Acute single substance dietary exposure assessment of carbofuran or chlorpyrifos | Fixed |
| FoodTranslations | Catalogues_WHO_Training_Acu NL2.xlsx | Standard Actions/Acute single substance dietary exposure assessment of carbofuran or chlorpyrifos | Fixed |
| Foods | Catalogues_WHO_Training_Acu NL2.xlsx | Standard Actions/Acute single substance dietary exposure assessment of carbofuran or chlorpyrifos | Fixed |
| Populations | Catalogues_WHO_Training_Acu NL2.xlsx | Standard Actions/Acute single substance dietary exposure assessment of carbofuran or chlorpyrifos | Fixed |
| Processing | Catalogues_WHO_Training_Acu NL2.xlsx | Standard Actions/Acute single substance dietary exposure assessment of carbofuran or chlorpyrifos | Fixed |
| UnitVariability | Catalogues_WHO_Training_Acu NL2.xlsx | Standard Actions/Acute single substance dietary exposure assessment of carbofuran or chlorpyrifos | Fixed |
| Concentrations | Concentrations_WHO_Carbofuran_Chlorp | Standard Actions/Acute single substance dietary exposure assessment of carbofuran or chlorpyrifos | Fixed |
| Survey | Consumptions_NL_2yr_VCP-2002-2006_RPC.xlsx | Standard Actions/Acute single substance dietary exposure assessment of carbofuran or chlorpyrifos | Fixed |

## 4.2 Chronic cumulative exposure assessment PA

This standard action is of type: *Risks*

In 2017 EFSA published a statement *Risks for human health related to the presence of pyrrolizidine alkaloids in honey, tea, herbal infusions and food supplements*, see EFSA (2017b). Occurrence data used in this opinion was published in 2015 in the external scientific report *Occurrence of Pyrrolizidine Alkaloids in food*, see Mulder et al. (2015). The occurrence data in tea and herbal infusions is linked to the Consumption of 6 different population groups of the DNFCS 2012-2016. An lower bound (LB) and upper bound (UB) chronic cumulative exposure assessment can be calculated for different PAs. One scenario is assuming equipotency, another scenario is using provisional RPFs (Merz and Schrenk (2016)).

## 4.3 Chronic cumulative exposure assessment PFAS

This standard action is of type: *Risks*

This standard action can be used to calculate a chronic cumulative exposure for four PFAS. Assuming equipotency, and using proposed RPFs.

Table 4.2: Datasources for Chronic cumulative exposure assessment PFAS.

| Table Group | Name | Repository | Type |
|---|---|---|---|
| Survey | ConsumptionData-1-2yr.mdb | Standard Actions/Chronic cumulative exposure assessment PFAS | Fixed |
| Survey | ConsumptionData-10-17yr.mdb | Standard Actions/Chronic cumulative exposure assessment PFAS | Fixed |
| Survey | ConsumptionData-18-64yr.mdb | Standard Actions/Chronic cumulative exposure assessment PFAS | Fixed |
| Survey | ConsumptionData-3-9yr.mdb | Standard Actions/Chronic cumulative exposure assessment PFAS | Fixed |
| Survey | ConsumptionData-65-74yr.mdb | Standard Actions/Chronic cumulative exposure assessment PFAS | Fixed |
| Survey | ConsumptionData-75plusyr.mdb | Standard Actions/Chronic cumulative exposure assessment PFAS | Fixed |
| Concentrations | PFAS-Occurrencedata-EFSA-LB.mdb | Standard Actions/Chronic cumulative exposure assessment PFAS | Fixed |
| AssessmentGroupMemberships | PFAS-OtherData.mdb | Standard Actions/Chronic cumulative exposure assessment PFAS | Fixed |
| Compounds | PFAS-OtherData.mdb | Standard Actions/Chronic cumulative exposure assessment PFAS | Fixed |
| Effects | PFAS-OtherData.mdb | Standard Actions/Chronic cumulative exposure assessment PFAS | Fixed |
| Foods | PFAS-OtherData.mdb | Standard Actions/Chronic cumulative exposure assessment PFAS | Fixed |
| HazardCharacterisations | PFAS-OtherData.mdb | Standard Actions/Chronic cumulative exposure assessment PFAS | Fixed |
| RelativePotencyFactors | PFAS-RelativePotencyFactorsEquipotenc | Standard Actions/Chronic cumulative exposure assessment PFAS | Fixed |

## 4.4 Chronic mixture risk assessment of metals

This standard action is of type: *Risks*

In the context of the European projects HBM4EU and PARC, the National Institute for Public Health and the Environment of the Netherlands (RIVM) performed a case study on the risk assessment of the combined exposure of four metals relevant for chronic kidney disease, i.e. cadmium, lead, in-organic arsenic and inorganic mercury. The exposure assessment used chemical concentration in foods of 14 European countries over the years 2014-2018, obtained from the EFSA data warehouse and individual Dutch food consumption data. Since chronic kidney disease is relevant for the adult population, adults in the age of 18-64 years were selected in the standard action. Exposure estimates were obtained using the observed individual means (OIM) model implemented in MCRA. Using relative potency factors, the exposure to the metals was expressed as equivalents of cadmium and summed per individual in the food consumption database, yielding a distribution of summed cadmium-equivalents. The summed cadmium-equivalents per individual were divided by the reference point of cadmium, which resulted in a distribution of risk characterisation ratios (exposure/hazard) $E/H$ (or better modified reference point indexes) from which the mean, P50 and P95 are obtained. A ratio E/H or modified reference point index > 1 means either a risk cannot be excluded or refinement of the assessment is needed, depending on the assesses uncertainties. The standard action is meant for training and demonstration purposes, to demonstrate assessment of the impact of setting (new) maximum limits concentrations (MLs).

Table 4.3: Datasources for Chronic mixture risk assessment of metals.

| Table Group | Name | Repository | Type |
|---|---|---|---|
| AssessmentGroupMemberships | Catalogues_DNT_NEF-metals.xlsx | Standard Actions/Chronic mixture risk assessment of metals | Fixed |
| Compounds | Catalogues_DNT_NEF-metals.xlsx | Standard Actions/Chronic mixture risk assessment of metals | Fixed |
| Effects | Catalogues_DNT_NEF-metals.xlsx | Standard Actions/Chronic mixture risk assessment of metals | Fixed |
| FoodTranslations | Catalogues_DNT_NEF-metals.xlsx | Standard Actions/Chronic mixture risk assessment of metals | Fixed |
| Foods | Catalogues_DNT_NEF-metals.xlsx | Standard Actions/Chronic mixture risk assessment of metals | Fixed |
| HazardCharacterisations | Catalogues_DNT_NEF-metals.xlsx | Standard Actions/Chronic mixture risk assessment of metals | Fixed |
| Populations | Catalogues_DNT_NEF-metals.xlsx | Standard Actions/Chronic mixture risk assessment of metals | Fixed |
| RelativePotencyFactors | Catalogues_DNT_NEF-metals.xlsx | Standard Actions/Chronic mixture risk assessment of metals | Fixed |
| Concentrations | DNT-NEF-SSD-metals.xlsx | Standard Actions/Chronic mixture risk assessment of metals | Fixed |
| MaximumResidueLimits | NEF-MLs-metals.xlsx | Standard Actions/Chronic mixture risk assessment of metals | Fixed |
| Survey | NL-FE1-FCS2016_Core_1-79y.accdb | Standard Actions/Chronic mixture risk assessment of metals | Fixed |

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## 4.5 Chronic single substance dietary exposure assessment of lead or atropine

This standard action is of type: *Dietary exposures*

This standard action enables you to perform probabilistic chronic dietary exposure assessments of single substances in food (Boon et al. (2017), Boon et al. (2022)). The assessment is based on consumption data of women aged 15-44 years from the FAO-WHO Gift survey of Bangladesh, coded according to EFSA's FoodEx2 classification. The atropine concentration data were extracted from the GEMS database. The lead concentration data for foods are artificial, manually generated around the means reported by EFSA in 2012 (EFSA 2012). The concentration data are organised according the SSD data format. The standard action is developed for training purposes and results should not be seen as a full dietary exposure assessment of atropine or lead

This example allows you to:

- Select the substance atropine or lead,
- Choose the method for handling left-censored concentration measurements (lower bound or upper bound approach),
- Select a method for modelling long term intakes (OIM/LNN),
- Run with or without uncertainty

Table 4.4: Datasources for Chronic single substance dietary exposure assessment of lead or atropine.

| Table Group | Name | Repository | Type |
|---|---|---|---|
| Compounds | Catalogues_WHO_Training_chBD.xlsx | Standard Actions/Chronic single substance dietary exposure assessment lead or atropine | Fixed |
| FoodTranslations | Catalogues_WHO_Training_chBD.xlsx | Standard Actions/Chronic single substance dietary exposure assessment lead or atropine | Fixed |
| Foods | Catalogues_WHO_Training_chBD.xlsx | Standard Actions/Chronic single substance dietary exposure assessment lead or atropine | Fixed |
| Populations | Catalogues_WHO_Training_chBD.xlsx | Standard Actions/Chronic single substance dietary exposure assessment lead or atropine | Fixed |
| Concentrations | Concentrations_WHO_Training_Pb_At.x | Standard Actions/Chronic single substance dietary exposure assessment lead or atropine | Fixed |
| Survey | Consumptions_BD_GIFT_2022.xlsx | Standard Actions/Chronic single substance dietary exposure assessment lead or atropine | Fixed |

## 4.6 Demo Human Monitoring Analysis bisphenols

This standard action is of type: *Exposure comparisons*

Human BioMonitoring (HBM) is a primary instrument to measure real-life exposure to chemicals. Because of the associated high costs, chemical levels in body fluids such as blood or urine would ideally be predictable from estimated external exposure levels, such as in the diet and/or from other non-dietary sources. It is needed to convert external exposures to internal concentrations by use of a kinetic (PBK) model or the application of a simple kinetic conversion factor.

This standard action provides a simple demonstration of this approach. It is based on the EuroMix biomonitoring study (Husøy et al. (2019), Karrer et al. (2019)) and considers three of the investigated chemical substances in this study, i.e. the bisphenols BPA, BPS and BPF, which could have adverse estrogenic effects and therefore require risk assessment. These substances were measured in the urine of 144 adult individuals on two days (in this demo, we only use the data of a single day). The study subjects also kept detailed diaries on their food consumption and use of personal care products.

In this demonstrator standard action, the dietary exposure and optionally the non-dietary exposure from personal care products and thermal paper is modelled. HBM measurement values below the limit of detection are imputed. The specific gravity of the urine samples was measured as well, which is used in the calculation to calculate adjusted urine concentrations as decribed in Husøy et al. (Husøy et al. (2019)). The dietary exposure is predicted from the consumption data for 226 modelled foods derived from the food diaries and food monitoring concentration data for BPA, BPS and BPF in these foods. Additionally, non-dietary exposure from personal care products and from handling thermal paper was modelled separately by Karrer et al. (Karrer et al. (2020)) and these exposures are available as data for three non-dietary routes, i.e. dermal, oral and inhalation. These non-dietary exposures can be aggregated with the dietary exposures at the individual level. In this demonstrator the conversion from external exposures to urine concentration can be done using a simple kinetic conversion factor approach or using a PBK model developed by Karrer et al., which is also available in MCRA (Karrer et al. (2018), Karrer et al. (2019), Karrer et al. (2020)).

In this demonstrator standard action several choices can be made:

- **Exposure type:** Select acute or chronic exposure. For acute, HBM data are taken per day and modelled exposures are obtained from 1000 simulated dietary exposures obtained from Monte Carlo integration of individual day consumption patterns and food concentrations and possibly combined/aggregated with matching non-dietary exposures of the simulated individual days. For chronic, HBM data and non-dietary exposure data are averaged per individual and dietary exposures are modelled using the observed individual means model.
- **Exposure route:** Derive modelled concentrations from dietary exposure only or aggregate with non-dietary exposure sources.
- **Censored valude handling method:** For the modelled concentrations, assume censored values in the food concentration data (measurements below the limit of reporting LOR) to be zero or impute them with a value 0.5 x LOR.
- **Kinetic conversion model:** Choose from two example data files with substance-specific absorption factors or use the PBK model developed by Karrer et al.

Table 4.5: Datasources for Demo Human Monitoring Analysis bisphenols.

| Table Group | Name | Repository | Type |
|---|---|---|---|
| Compounds | Demo_HBM_CataloguesAndSecondaryData | Standard Actions/Demo Human Monitoring Analysis | Fixed |
| Effects | Demo_HBM_CataloguesAndSecondaryData | Standard Actions/Demo Human Monitoring Analysis | Fixed |
| FoodTranslations | Demo_HBM_CataloguesAndSecondaryData | Standard Actions/Demo Human Monitoring Analysis | Fixed |
| Foods | Demo_HBM_CataloguesAndSecondaryData | Standard Actions/Demo Human Monitoring Analysis | Fixed |
| RelativePotencyFactors | Demo_HBM_CataloguesAndSecondaryData | Standard Actions/Demo Human Monitoring Analysis | Fixed |
| Concentrations | Demo_HBM_ConcentrationsSSD.xlsx | Standard Actions/Demo Human Monitoring Analysis | Fixed |
| Survey | Demo_HBM_Consumptions.xlsx | Standard Actions/Demo Human Monitoring Analysis | Fixed |
| KineticConversionFactors | Demo_HBM_KineticConversionFactorsBisp | Standard Actions/Demo Human Monitoring Analysis | Fixed |
| PbkModels | Demo_HBM_KineticModelsBisphenols_KM | Standard Actions/Demo Human Monitoring Analysis | Fixed |
| NonDietary | Demo_HBM_NonDietaryExposures.xlsx | Standard Actions/Demo Human Monitoring Analysis | Fixed |
| HumanMonitoringData | Demo_HBM_PhenolsUrinePooledOneDay.x | Standard Actions/Demo Human Monitoring Analysis | Fixed |

## 4.7 Demo acute cumulative risk assessment

This standard action is of type: *Risks*

In this demo with fictitious data, acute cumulative risk assessments can be performed following various calculation methods (EFSA 2012 Optimistic and Pessimistic, EC 2018 Tier 1 and Tier 2). Here, also the effect of applying processing factors can be assessed.

Table 4.6: Datasources for Demo acute cumulative risk assessment.

| Table Group | Name | Repository | Type |
|---|---|---|---|
| MaximumResidueLimits | DemoConcentrationLimits.mdb | Standard Actions/Demo Acute Cumulative Risk Assessment | Fixed |
| Concentrations | DemoConcentrations.mdb | Standard Actions/Demo Acute Cumulative Risk Assessment | Fixed |
| Survey | DemoConsumptions.mdb | Standard Actions/Demo Acute Cumulative Risk Assessment | Fixed |
| Effects | DemoEffects.mdb | Standard Actions/Demo Acute Cumulative Risk Assessment | Fixed |
| FoodExtrapolations | DemoFoodExtrapolations.mdb | Standard Actions/Demo Acute Cumulative Risk Assessment | Fixed |
| FoodTranslations | DemoFoodRecipes.mdb | Standard Actions/Demo Acute Cumulative Risk Assessment | Fixed |
| Foods | DemoFoods.mdb | Standard Actions/Demo Acute Cumulative Risk Assessment | Fixed |
| HazardDoses | DemoPointsOfDeparture.mdb | Standard Actions/Demo Acute Cumulative Risk Assessment | Fixed |
| Processing | DemoProcessingfactorOri.mdb | Standard Actions/Demo Acute Cumulative Risk Assessment | Fixed |
| AuthorisedUses | DemoSubstanceAuthorisations.mdb | Standard Actions/Demo Acute Cumulative Risk Assessment | Fixed |
| ResidueDefinitions | DemoSubstanceConversions.mdb | Standard Actions/Demo Acute Cumulative Risk Assessment | Fixed |
| Compounds | DemoSubstances.mdb | Standard Actions/Demo Acute Cumulative Risk Assessment | Fixed |
| UnitVariability | DemoUnitVar36.mdb | Standard Actions/Demo Acute Cumulative Risk Assessment | Fixed |
| UnitVariability | DemoUnitVarPRIMo.mdb | Standard Actions/Demo Acute Cumulative Risk Assessment | Fixed |

## 4.8 Long-term dietary exposure and risk of nickel for the Belgian population

This standard action is of type: *Risks*

The risk assessment originally conducted by the European Food Safety Authority stated some concerns regarding the chronic exposure of the European population to nickel due to food intake. This study aimed to evaluate the extent of the Belgian population's exposure to nickel via intake of different foods/drinks available in their market.

This standard actions is using nickel concentration data and Belgian consumption data-2014 data, for training and demonstration purposes and is meant to demonstrate the average nickel exposure for total Belgian consumers, for differences Belgian sub-populations and specifying the exposure for different foods (LB and UB).

This standard action demonstrates the aggregated exposure assessment of the effects of nickel occurrence in food of Belgian population. It uses 2017 Nickel contamination data in foods available in Belgian market and Belgian

consumption data 2014.

Table 4.7: Datasources for Long-term dietary exposure and risk of nickel for the Belgian population.

| Table Group | Name | Repository | Type |
|---|---|---|---|
| Survey | 2021-09-17_BelgianConsumptions.xlsx | Standard Actions/Long-term dietary exposure and risk of nickel for Belgian age groups | Fixed |
| Compounds | Catalogues_FNS_Case_Study_BE_Ni_M | Standard Actions/Long-term dietary exposure and risk of nickel for Belgian age groups | Fixed |
| Effects | Catalogues_FNS_Case_Study_BE_Ni_M | Standard Actions/Long-term dietary exposure and risk of nickel for Belgian age groups | Fixed |
| Foods | Catalogues_FNS_Case_Study_BE_Ni_M | Standard Actions/Long-term dietary exposure and risk of nickel for Belgian age groups | Fixed |
| HazardCharacterisations | Catalogues_FNS_Case_Study_BE_Ni_M | Standard Actions/Long-term dietary exposure and risk of nickel for Belgian age groups | Fixed |
| Populations | Catalogues_FNS_Case_Study_BE_Ni_M | Standard Actions/Long-term dietary exposure and risk of nickel for Belgian age groups | Fixed |
| Concentrations | Contaminants_BE_2017-2019_INNIBEL_Ni_MCRA_FE2.xlsx | Standard Actions/Long-term dietary exposure and risk of nickel for Belgian age groups | Fixed |
| FoodTranslations | FoodTranslations_INNIBEL_Ni.xlsx | Standard Actions/Long-term dietary exposure and risk of nickel for Belgian age groups | Fixed |

## 4.9 Risk steatosis from imazalil

This standard action is of type: *Risks*

Traditional risk assessment often uses animal data to evaluate toxicological limit values, such as the acceptable daily intake (ADI). However, in-vitro tests may help to reduce the use of test animals. In the standard action described here such a traditional risk calculation can be compared to a similar calculation based on in-vitro data. For example, a risk calculation of steatosis as health effect and imazalil as chemical substance can be compared to the toxicological hazard characterisation based on in-vitro data from AdipoRed measurements in human liver cells. In-vitro concentrations are assumed to represent internal liver concentrations. A human physiologically based kinetic model for imazalil is used to extrapolate from in-vitro to in-vivo doses.

In this standard action, risk for steatosis from exposure to imazalil is estimated from in-vivo or in-vitro based hazard characterisations.

**Two parameter sets are available:**

1. estimates based on QSAR models only, and
2. estimates based on QSAR models and in-vitro experiments.

The latter parameter set shows that in the long term concentration levels of imazalil in the liver are stationary.

Table 4.8: Datasources for Risk steatosis from imazalil.

| Table Group | Name | Repository | Type |
|---|---|---|---|
| AdverseOutcomePathwayNetworks | AOPN-Effects-EffectRelations-181017.xlsx | Standard Actions/Risk steatosis from imazalil | Fixed |
| Effects | AOPN-Effects-EffectRelations-181017.xlsx | Standard Actions/Risk steatosis from imazalil | Fixed |
| DoseResponseData | BfR-HepaRG-AdipoRed-Single.xlsx | Standard Actions/Risk steatosis from imazalil | Fixed |
| Concentrations | ConcentrationsSSD_20190129.zip | Standard Actions/Risk steatosis from imazalil | Fixed |
| Compounds | EuroMix Substances Inventory (v8) (PPPs).zip | Standard Actions/Risk steatosis from imazalil | Fixed |
| PbkModels | Euromix-Cosmos_Tebby et al ParamB_QSAR_vitro.xlsx | Standard Actions/Risk steatosis from imazalil | Fixed |
| UnitVariability | Foods coded in FoodEx1.mdb | Standard Actions/Risk steatosis from imazalil | Fixed |
| HazardCharacterisations | HazardCharacterisation Imazalil.xlsx | Standard Actions/Risk steatosis from imazalil | Fixed |
| Survey | NL-VCP-RPC 2005-2006 2-6yr.mdb | Standard Actions/Risk steatosis from imazalil | Fixed |
| Survey | NL-VCP-RPC 2007-2010 7-69yr.mdb | Standard Actions/Risk steatosis from imazalil | Fixed |
| Survey | NL-VCP-RPC 2010-2012 70+yr.mdb | Standard Actions/Risk steatosis from imazalil | Fixed |
| FoodTranslations | NL-VCP-RPC Foods.mdb | Standard Actions/Risk steatosis from imazalil | Fixed |
| Foods | NL-VCP-RPC Foods.mdb | Standard Actions/Risk steatosis from imazalil | Fixed |
| EffectRepresentations | TestSystems-Responses-EffectRepresentations-181026.xlsx | Standard Actions/Risk steatosis from imazalil | Fixed |
| Responses | TestSystems-Responses-EffectRepresentations-181026.xlsx | Standard Actions/Risk steatosis from imazalil | Fixed |
| TestSystems | TestSystems-Responses-EffectRepresentations-181026.xlsx | Standard Actions/Risk steatosis from imazalil | Fixed |

## 4.10 TDS-based long term dietary exposure and risk assessment

This standard action is of type: *Risks*

This standard action provides an overview about probabilistic long-term dietary exposure assessments with TDS data in MCRA. Possibilities to calculate exposure for population (sub-)groups from different countries and for different substances are provided. In addition, options for regional, seasonal or production type specific exposure are demonstrated along with options to select for consumers of different foods. In order to highlight options of the MCRA TDS module, the standard actions provide a simple and condensed overview about possible settings in MCRA. Consult the documentation pages on *TDS-based exposure and risk assessment* if you want to learn more about running these types of assessments in MCRA.

## 4.11 TDS-based long-term exposure and risk assessment of methylmercury for German children

This standard action is of type: *Risks*

**Note**

This standard action was developed within the FNS-Cloud project (https://www.fns-cloud.eu). Related consumption data and example conversion scripts for uploading data will be made available in the FNS Cloud (status 05/2022: in progress).

### 4.11.1 Introduction

This standard action performs *a TDS-based probabilistic risk assessment* regarding the exposure of German children to methylmercury. Total Diet Study (TDS) data are combined with food consumption data, and stratification of the calculations regarding region, season and production type (organic or conventional) can be considered. Total Diet Studies (TDS) are an appropriate method to representatively reflect background occurrence levels of substances in food in a population's diet. More than 90 % of the diet are covered, the foods are prepared as consumed and pooled to composite samples prior to chemical analysis. Next to the representation of almost the total diet in Germany, the German TDS (BfR MEAL Study) also allows to elaborate potential differences in occurrence of substances in different stratifications. The stratifications consider four different regions (North, East, South and West Germany), two different seasons (which are in this demo fictitious summer and winter season), and the production type (i.e. organic versus conventional production).

In this example, consumption data for children in Germany and fictive TDS occurrence data for methylmercury are used. The commonly used lower bound (LB) or upper bound (UB) scenarios are used for treatment of censored data. Exposure is calculated applying the Observed Individual Means model. The exposure is expressed as µg per kg body weight and day for the mean, and the 50th, 90th, 95th, 97.5th, 99th and 99.9th percentiles of the exposure distribution and the relative contributions from modelled foods or main food groups to total exposure is displayed. For risk assessment, the exposure distribution is compared to the tolerable weekly intake (TWI) of 1.3 µg per kg body weight and day set for methylmercury set by EFSA. The risk in indicated by the risk characterisation ratio exposure/hazard $E/H$ quantified by exposure relative to the TWI.

### 4.11.2 Standard action options

In this standard action, potential differences between stratification related exposure assessments are demonstrated. The user is able to select and combine the above-mentioned stratifications and compare exposure outcomes and risks.

- By selection of a certain region the occurrence data from this region will be combined with the respective consumptions data from children living in this region.
- By selection of a certain season the occurrence data from this season will be combined with consumption events during this season. Summer season is defined from April to September and Winter season from October till March.
- By selection of a type of production occurrence data from organically or conventionally produced foods will be combined with the overall consumption, since information on consumption of organically or conventionally produced foods is not included in the consumption data.
- Exposure from foods that are not stratified according to the above-mentioned characteristics is included on an unspecific basis into the assessments (e.g., the item "pasta" is not sampled in different regions, therefore regional exposure will be calculated by combining regional consumption with the concentration of the unspecified sample).
- The assessments can be done either for all individuals included in the consumption survey or can be restricted to consumers only. The restriction will consider consumers of one or more selected TDS (modelled) foods but includes all consumptions of these individuals.
- The option to calculate uncertainties analysis results in 95 % confidence intervals (CIs) by resampling the individuals.

### 4.11.3 Standard action data

Table 4.9: Datasources for TDS-based long-term exposure and risk assessment of methylmercury for German children.

| Table Group | Name | Repository | Type |
|---|---|---|---|
| Compounds | Catalogues_FNS_DE_MeHg | Standard Actions/TDS-based long-term exposure and risk assessment of methylmercury for German children | Fixed |
| Effects | Catalogues_FNS_DE_MeHg | Standard Actions/TDS-based long-term exposure and risk assessment of methylmercury for German children | Fixed |
| Foods | Catalogues_FNS_DE_MeHg | Standard Actions/TDS-based long-term exposure and risk assessment of methylmercury for German children | Fixed |
| HazardCharacterisations | Catalogues_FNS_DE_MeHg | Standard Actions/TDS-based long-term exposure and risk assessment of methylmercury for German children | Fixed |
| TotalDietStudy | Catalogues_FNS_DE_MeHg | Standard Actions/TDS-based long-term exposure and risk assessment of methylmercury for German children | Fixed |
| Concentrations | Concentrations_FNS_DE_MeHg_ | Standard Actions/TDS-based long-term exposure and risk assessment of methylmercury for German children | Fixed |
| Survey | Consumptions_DE_VEI 2002 | Standard Actions/TDS-based long-term exposure and risk assessment of methylmercury for German children | Fixed |

## 4.12 Training prospective risk assessment acute Tier II

This standard action is of type: *Single value risks*

This standard action allows you to run and compare the background and different Tier II approaches to probabilistic prospective risk assessment for a newly proposed use (focal substance/food) as defined by the EC working group. This is an acute risk assessment of a neurological effect (functional alternations of the motor division) for the Dutch toddlers, the Dutch other children, the Bulgarian other children and Italian adults populations. The focal food and substance combination that can be selected are emamectin with peach, acrinathrin with wheat (fictitious data) or pirimicarb with lettuces (fictitious data). The focal exposure can be based on a MRL, a GAP or an actual exposure scenario as defined by the working group, or it can be omitted (for comparison) so that only the background exposure is calculated. The 99.9th percentile of the exposure has been adjusted using uncertain adjustment factors from the EFSA cumulative risk assessment report 2020. The exposure is calculated probabilistically and the risk is expressed as margin of exposure (MOE) and is compared to a threshold value of 100.

Table 4.10: Datasources for Training prospective risk assessment acute Tier II.

| Table Group | Name | Repository | Type |
|---|---|---|---|
| FocalFoods | FocalConcentrations-MrlScenario.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| AssessmentGroupMemberships | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| AuthorisedUses | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| Compounds | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| Effects | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| FoodExtrapolations | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| FoodTranslations | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| Foods | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| HazardDoses | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| MaximumResidueLimits | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| Processing | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| ResidueDefinitions | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| DeterministicSubstanceConversionFactors | SingleValueCalculations.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| UnitVariability | UnitVar36.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| Concentrations | a_ConcentrationsSSD_NA | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| Survey | a_ConsumptionsBU.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| Survey | a_ConsumptionsIT.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| Survey | a_ConsumptionsNL2.mdb | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |
| Survey | a_ConsumptionsNL3_6.mc | Standard Actions/Training Acute Prospective Risk Assessment Tier II | Fixed |

## 4.13 Training prospective risk assessment chronic Tier II

This standard action is of type: *Single value risks*

This standard action allows you to run and compare the background and different Tier II approaches to probabilistic chronic prospective risk assessment for a newly proposed use (focal substance/food) as defined by the EC working group. This is a chronic risk assessment of an effect (hypothyroidism) for the Dutch toddlers, Dutch other children and German adults populations. The focal food and substance combination that can be selected are cyprodinil with apples (fictitious data), valifenalate with lettuce or valifenalate with aubergines. The focal exposure can be based on a GAP or actual exposure scenario as defined by the working group, or it can be omitted (for comparison) so that only the background exposure is calculated. The 99.9th percentile of the exposure has been adjusted using uncertain adjustment factors from the EFSA cumulative risk assessment report 2020. The exposure is calculated

probabilistically and. the risk is expressed as margin of exposure (MOE) and is compared to a threshold value of 100.

Table 4.11: Datasources for Training prospective risk assessment chronic Tier II.

| Table Group | Name | Repository | Type |
|---|---|---|---|
| FocalFoods | FocalConcentrations-GAPScenario.mdb | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| AssessmentGroupMemberships | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| AuthorisedUses | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| Compounds | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| Effects | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| FoodExtrapolations | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| FoodTranslations | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| Foods | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| HazardDoses | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| MaximumResidueLimits | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| Processing | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| ResidueDefinitions | SecondaryInput-DataMRL2016.mdb | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| DeterministicSubstanceConversionFactors | SingleValueCalculations.mdb | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| Concentrations | c_ConcentrationsSSD_TCF | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| Survey | c_ConsumptionsDE.mdb | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| Survey | c_ConsumptionsNL2.mdb | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |
| Survey | c_ConsumptionsNL3_6.md | Standard Actions/Training Chronic Prospective Risk Assessment Tier II | Fixed |

## 4.14 Training substance prioritisation acute neuro

This standard action is of type: *Risks*

This standard action allows to prioritise substances to be included in a cumulative risk assessment by inspecting a list of (semi-)probabilistic hazard quotients, ranked from high to low. This is a risk assessment for either all neurotoxicological effects in the Dutch toddler population (level 1), or one of the effect subgroups (NAM or NAN) (level 2). The hazard quotient (termed hazard index in MCRA) compares a percentile from the dietary exposure distribution (P99 or P99.9 can be selected) to the ARfD, which a fixed value for the hazard characterisation (hence the designation as semi-probabilistic).

Table 4.12: Datasources for Training substance prioritisation acute neuro.

| Table Group | Name | Repository | Type |
|---|---|---|---|
| AssessmentGroupMemberships | ActiveSubstances.xlsx | Standard Actions/Training Substance Prioritisation Acute Neuro | Fixed |
| MaximumResidueLimits | ConcentrationLimits.xlsx | Standard Actions/Training Substance Prioritisation Acute Neuro | Fixed |
| Effects | Effects.xlsx | Standard Actions/Training Substance Prioritisation Acute Neuro | Fixed |
| FoodExtrapolations | FoodExtrapolations.xlsx | Standard Actions/Training Substance Prioritisation Acute Neuro | Fixed |
| FoodTranslations | FoodRecipes.xlsx | Standard Actions/Training Substance Prioritisation Acute Neuro | Fixed |
| Foods | Foods.xlsx | Standard Actions/Training Substance Prioritisation Acute Neuro | Fixed |
| HazardCharacterisations | HazardCharacterisations.xlsx | Standard Actions/Training Substance Prioritisation Acute Neuro | Fixed |
| Processing | ProcessingFactors.xlsx | Standard Actions/Training Substance Prioritisation Acute Neuro | Fixed |
| AuthorisedUses | SubstanceAuthorisations.xlsx | Standard Actions/Training Substance Prioritisation Acute Neuro | Fixed |
| ResidueDefinitions | SubstanceConversions.xlsx | Standard Actions/Training Substance Prioritisation Acute Neuro | Fixed |
| Compounds | Substances.xlsx | Standard Actions/Training Substance Prioritisation Acute Neuro | Fixed |
| UnitVariability | UnitVarPrimo.xlsx | Standard Actions/Training Substance Prioritisation Acute Neuro | Fixed |
| Concentrations | a_ConcentrationsSSD_Neu | Standard Actions/Training Substance Prioritisation Acute Neuro | Fixed |
| Survey | a_ConsumptionsNL2.mdb | Standard Actions/Training Substance Prioritisation Acute Neuro | Fixed |
| Survey | a_ConsumptionsNL3_6.md | Standard Actions/Training Substance Prioritisation Acute Neuro | Fixed |

- *Acute single substance dietary exposure assessment of carbofuran or chlorpyrifos*
- *Chronic cumulative exposure assessment PA*
- *Chronic cumulative exposure assessment PFAS*
- *Chronic mixture risk assessment of metals*
- *Chronic single substance dietary exposure assessment of lead or atropine*
- *Demo Human Monitoring Analysis bisphenols*
- *Demo acute cumulative risk assessment*
- *Long-term dietary exposure and risk of nickel for the Belgian population*
- *Risk steatosis from imazalil*
- *TDS-based long term dietary exposure and risk assessment*
- *TDS-based long-term exposure and risk assessment of methylmercury for German children*
- *Training prospective risk assessment acute Tier II*
- *Training prospective risk assessment chronic Tier II*
- *Training substance prioritisation acute neuro*

CHAPTER

FIVE

# STANDARD REGULATORY ACTIONS

Standard regulatory actions (SRAs) are user-friendly and easy-to-use actions in MCRA for regulators to perform assessments compliant with agreed methodologies for regulatory risk assessment (see Kruisselbrink et al. (2023)). At present, MCRA contains SRAs for retrospective and prospective dietary cumulative risk assessment of pesticides, jointly developed with EFSA. These are listed below. Previous (versions of the) SRAs remain also available in MCRA for traceability. These are kept in the archive of *old SRA versions*.

## 5.1 SRA: EU Prospective Dietary Cumulative Risk Assessment (2026)

This standard action is of type: *Single value risks*

Standard regulatory action (SRA) for running the probabilistic Tier II scenarios for prospective cumulative dietary risk assessment of pesticide residues for a new use of a focal substance/food requiring a new MRL, in accordance with EC working group on cumulative risk assessment definitions. This standard action is an update of the *SRA for prospective dietary CRA 2025*. Detailed information on the regulatory methodology and guidance on the use of this SRA is included in the cookbook on performing prospective cumulative risk assessment (EFSA (2025)).

This SRA uses data collected and prepared by EFSA which were uploaded to MCRA (see Kruisselbrink et al. (2025)). It includes consumption data for population sub-groups of different EU countries and cumulative assessment groups (CAGs) for four acute effects (NAN, NAM, DAC, DAH) and three chronic effects (NCN, TCF and TCP). For calculation of the background exposure, combined occurrence data from all member states based on 3-year monitoring cycles are used. Occurrence data from the cycles 2019-2021, 2020-2022, 2021-2023 and 2022-2024 are included in this SRA.

For a selected combination of focal food, focal substance, and effect/CAG, the SRA supports assessments for three prospective scenarios: safety of MRL, safety of GAP with 100% use frequency, and safety of GAP with 20% use frequency. These assessments can be performed either on the entire population, or on the sub-group of only the consumers of the focal food. For running the safety of GAP scenarios, users should supply their own focal occurrence data (from field trials) for the selected focal food/substance. In addition, users should supply specific substance conversion factors for allocation of active substance concentrations from the measured concentrations for the focal substance. Data templates for both the deterministic substance conversion factors and the focal food concentrations can be downloaded using the download data template button. When focal substance and focal food are selected, the template will be partly prefilled.

The regulatory methodology prescribes to quantify sampling uncertainty in consumption data and occurrence data by performing a full uncertainty analysis of 100 bootstrap cycles (see EFSA (2022), EFSA (2021), and Kruisselbrink et al. (2023)). The options to run without uncertainty analysis or with limited uncertainty analysis can be used for testing. For assessment of other sources of uncertainties, this SRA includes sensitivity analyses for four uncertainties described in the cookbook (EFSA (2025)):

- **U02:** risk drivers included in the CAG with low CAG-membership probability,
- **U04:** assumption of dose-addition for substances with dissimilar mode of action,
- **U08:** unspecific residue definitions,
- **U09:** missing processing factors,

- **U10:** washing of commodities and peeling of edible peels.

## 5.2 SRA: EU Retrospective Dietary Cumulative Risk Assessment (2026)

This standard action is of type: *Single value risks*

Standard regulatory action for running retrospective cumulative dietary risk assessment of pesticide residues, in accordance with EC regulatory methodology. This standard action is an update of the *SRA for retrospective dietary CRA 2025*.

This SRA uses data collected and prepared by EFSA which were uploaded to MCRA (Kruisselbrink et al. (2025)). It includes consumption data for population sub-groups of different EU countries and cumulative assessment groups for four acute effects (NAN, NAM, DAC, DAH) and three chronic effects (NCN, TCF and TCP). Occurrence data from all member states based on 3-year monitoring cycles are used. Occurrence data from the cycles 2019-2021, 2020-2022, 2021-2023 and 2022-2024 are included in this SRA.

The exposure is calculated using a probabilistic approach. The risk is characterised using the Margin of Exposure Total (MOET) and assessed by comparing the MOET at the 99.9th percentile of the exposure distribution against the regulatory threshold value of 100. For more information on the (regulatory) methodology see EFSA (2022), EFSA (2021), and Kruisselbrink et al. (2023).

The regulatory methodology prescribes to quantify sampling uncertainty in consumption data and occurrence data by performing a full uncertainty analysis of 100 bootstrap cycles. The options to run without uncertainty analysis or with limited uncertainty analysis can be used for testing.

## 5.3 EU Prospective Dietary Cumulative Risk Assessment (2025)

This standard action is of type: *Single value risks*

Standard regulatory action (SRA) for running the probabilistic Tier II scenarios for prospective cumulative dietary risk assessment of pesticide residues for a new use of a focal substance/food requiring a new MRL, in accordance with EC working group on cumulative risk assessment definitions. This standard action is an update of the *SRA for prospective dietary CRA 2024*. Detailed information on the regulatory methodology and guidance on the use of this SRA is included in the cookbook on performing prospective cumulative risk assessment (EFSA (2025)).

This SRA uses data collected and prepared by EFSA which were uploaded to MCRA (see Kruisselbrink et al. (2025)). It includes consumption data for population sub-groups of different EU countries and cumulative assessment groups (CAGs) for four acute effects (NAN, NAM, DAC, DAH) and three chronic effects (NCN, TCF and TCP). For calculation of the background exposure, combined occurrence data from all member states based on 3-year monitoring cycles are used. Occurrence data from the cycles 2019-2021, 2020-2022, and 2021-2023 are included in this SRA.

For a selected combination of focal food, focal substance, and effect/CAG, the SRA supports assessments for three prospective scenarios: safety of MRL, safety of GAP with 100% use frequency, and safety of GAP with 20% use frequency. These assessments can be performed either on the entire population, or on the sub-group of only the consumers of the focal food. For running the safety of GAP scenarios, users should supply their own focal occurrence data (from field trials) for the selected focal food/substance. In addition, users should supply specific substance conversion factors for allocation of active substance concentrations from the measured concentrations for the focal substance. Data templates for both the deterministic substance conversion factors and the focal food concentrations can be downloaded using the download data template button. When focal substance and focal food are selected, the template will be partly prefilled.

The regulatory methodology prescribes to quantify sampling uncertainty in consumption data and occurrence data by performing a full uncertainty analysis of 100 bootstrap cycles (see EFSA (2022), EFSA (2021), and Kruisselbrink et al. (2023)). The options to run without uncertainty analysis or with limited uncertainty analysis can be used for testing. For assessment of other sources of uncertainties, this SRA includes sensitivity analyses for four uncertainties described in the cookbook (EFSA (2025)):

- **U02:** risk drivers included in the CAG with low CAG-membership probability,
- **U08:** unspecific residue definitions,

- **U09:** missing processing factors,
- **U10:** washing of commodities and peeling of edible peels.

## 5.4 EU Retrospective Dietary Cumulative Risk Assessment (2025)

This standard action is of type: *Single value risks*

Standard regulatory action for running retrospective cumulative dietary risk assessment of pesticide residues, in accordance with EC regulatory methodology. This standard action is an update of the *SRA for retrospective dietary CRA 2024*.

This SRA uses data collected and prepared by EFSA which were uploaded to MCRA (Kruisselbrink et al. (2025)). It includes consumption data for population sub-groups of different EU countries and cumulative assessment groups for four acute effects (NAN, NAM, DAC, DAH) and three chronic effects (NCN, TCF and TCP). Occurrence data from all member states based on 3-year monitoring cycles are used. Occurrence data from the cycles 2019-2021, 2020-2022, and 2021-2023 are included in this SRA.

The exposure is calculated using a probabilistic approach. The risk is characterised using the Margin of Exposure Total (MOET) and assessed by comparing the MOET at the 99.9th percentile of the exposure distribution against the regulatory threshold value of 100. For more information on the (regulatory) methodology see EFSA (2022), EFSA (2021), and Kruisselbrink et al. (2023).

The regulatory methodology prescribes to quantify sampling uncertainty in consumption data and occurrence data by performing a full uncertainty analysis of 100 bootstrap cycles. The options to run without uncertainty analysis or with limited uncertainty analysis can be used for testing.

- *SRA: EU Prospective Dietary Cumulative Risk Assessment (2026)*
- *SRA: EU Retrospective Dietary Cumulative Risk Assessment (2026)*
- *EU Prospective Dietary Cumulative Risk Assessment (2025)*
- *EU Retrospective Dietary Cumulative Risk Assessment (2025)*

## 5.5 Old SRA versions

The SRAs listed below are previous (versions of) standard regulatory actions in MCRA. These remain available in MCRA for traceability.

### 5.5.1 EU Prospective Dietary Cumulative Risk Assessment (2024)

This standard action is of type: *Single value risks*

Standard regulatory action (SRA) for running the probabilistic Tier II scenarios for prospective cumulative dietary risk assessment of pesticide residues for a new use of a focal substance/food requiring a new MRL, in accordance with EC working group on cumulative risk assessment definitions. For detailed information on the regulatory methodology and guidance on the use of this SRA see Kruisselbrink et al. (2025).

This SRA uses data collected and prepared by EFSA which were uploaded to MCRA (see Kruisselbrink et al. (2025)). It includes consumption data for population sub-groups of different EU countries and cumulative assessment groups (CAGs) for four acute effects (NAN, NAM, DAC, DAH) and three chronic effects (NCN, TCF and TCP). For calculation of the background exposure, combined occurrence data from all member states based on 3-year monitoring cycles are used. Occurrence data from the cycles 2019-2021 and 2020-2022 are included in this SRA.

For a selected combination of focal food, focal substance, and effect/CAG, the SRA supports assessments for three prospective scenarios: safety of MRL, safety of GAP with 100% use frequency, and safety of GAP with 20% use frequency. These assessments can be performed either on the entire population, or on the sub-group of only the consumers of the focal food. For running the safety of GAP scenarios, users should supply their own focal occurrence data (from field trials) for the selected focal food/substance. In addition, users should supply specific substance conversion factors for allocation of active substance concentrations from the measured concentrations for the focal substance. Data templates for both the deterministic substance conversion factors and the focal food concentrations

can be downloaded using the download data template button. When focal substance and focal food are selected, the template will be partly prefilled.

The regulatory methodology prescribes to quantify sampling uncertainty in consumption data and occurrence data by performing a full uncertainty analysis of 100 bootstrap cycles (see EFSA (2022), EFSA (2021), and Kruisselbrink et al. (2023)). The options to run without uncertainty analysis or with limited uncertainty analysis can be used for testing. For assessment of other sources of uncertainties, this SRA includes a sensitivity analyses for assessing the impact of missing processing factors.

### 5.5.2 EU Retrospective Dietary Cumulative Risk Assessment (2024)

This standard action is of type: *Single value risks*

Standard regulatory action for running retrospective cumulative dietary risk assessment of pesticide residues, in accordance with EC regulatory methodology.

This SRA uses data collected and prepared by EFSA (Kruisselbrink et al. (2025)). It includes consumption data for population sub-groups of different EU countries and cumulative assessment groups for four acute effects (NAN, NAM, DAC, DAH) and three chronic effects (NCN, TCF and TCP). Occurrence data from all member states based on 3-year monitoring cycles are used. Occurrence data from the cycles 2019-2021 and 2020-2022 are included in this SRA.

The exposure is calculated using a probabilistic approach. The risk is characterised using the Margin of Exposure Total (MOET) and assessed by comparing the MOET at the 99.9th percentile of the exposure distribution against the regulatory threshold value of 100. For more information on the (regulatory) methodology see EFSA (2022), EFSA (2021), and Kruisselbrink et al. (2023).

The regulatory methodology prescribes to quantify sampling uncertainty in consumption data and occurrence data by performing a full uncertainty analysis of 100 bootstrap cycles. The options to run without uncertainty analysis or with limited uncertainty analysis can be used for testing.

### 5.5.3 EU Prospective Dietary Cumulative Risk Assessment (2023)

This standard action is of type: *Single value risks*

In the context of the third framework partnership agreement between the National Institute for Public Health and the Environment of the Netherlands (RIVM) and the European Food Safety Authority (EFSA) Standard Regulatory Actions are provided to allow users to perform prospective acute and chroniccumulative dietary exposure assessments.

A user can choose for different effects. For two cumulative assessment groups (CAGs) of pesticides that affect the nervous system: pesticides causing brain and/or erythrocyte AChE inhibition (CAG-NAN, 47 pesticides) and pesticides causing functional alterations of the motor division (CAG-NAM, 100 pesticides).

For two cumulative assessment groups (CAGs) of pesticides that affect craniofacial alterations: pesticides causing craniofacial alterations due abnormal skeletal development (CAG-DAC, 41 pesticides) and pesticides causing head abnormalities not due to abnormal skeletal (CAG-DAH, 41 pesticides).

For chronic an assessment group of pesticides that affect the nervous system: pesticides causing brain and/or erythrocyte AChE inhibition (CAG-NCN, 47 pesticides. And the group a group of pesticides having an effect on the parafollicular (C-) cells or the calcitonin system (CAG-TCP, 18 substances) and pesticide residues affecting follicular cells and/or thyroid hormone (T3/T4) system (CAG TCF, 124 substances).

Occurrence datasets for the background are different 3-year cycle datasets containing occurrence data of all member states in the 3-year cycle, or it can be omitted (for comparison) so that only the background exposure is calculated. MRL exceedances can be removed taking into account measurement uncertainty. As an advanced option it is possible to adjust the 99.9th percentile of the exposure using uncertain adjustment factors from the EFSA cumulative risk assessment report 2020. The exposure is calculated probabilistically and the risk is expressed as margin of exposure (MOE) and is compared to a threshold value of 100. The user can upload own focal commodity/focal substance data (+ processing factors/conversion factors).

### 5.5.4 EU Retrospective Dietary Cumulative Risk Assessment (2023)

This standard action is of type: *Single value risks*

Standard regulatory action for running retrospective cumulative dietary risk assessment of pesticide residues, in accordance with EC regulatory methodology.

This SRA uses data collected and prepared by EFSA which were uploaded to MCRA (Engel et al. (2024)). It includes consumption data for population sub-groups of different EU countries and cumulative assessment groups for four acute effects (NAN, NAM, DAC, DAH) and three chronic effects (NCN, TCF and TCP). Occurrence data from all member states based on the 3-year monitoring cycle 2019-2021 are used.

The exposure is calculated using a probabilistic approach. The risk is characterised using the Margin of Exposure Total (MOET) and assessed by comparing the MOET at the 99.9th percentile of the exposure distribution against the regulatory threshold value of 100. For more information on the (regulatory) methodology see EFSA (2022), EFSA (2021), and Kruisselbrink et al. (2023).

The regulatory methodology prescribes to quantify sampling uncertainty in consumption data and occurrence data by performing a full uncertainty analysis of 100 bootstrap cycles. The options to run without uncertainty analysis or with limited uncertainty analysis can be used for testing.

### 5.5.5 Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)

This standard action is of type: *Single value risks*

This standard action will enable you to run acute cumulative dietary risk assessment of craniofacial alterations by pesticide residues using the same methods and data as used by EFSA in 2022.

Table 5.1: Datasources for Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022).

| Table Group | Name | Repository | Type |
|---|---|---|---|
| Compounds | Catalogues.xlsx | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Other data | Fixed |
| Effects | Catalogues.xlsx | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Other data | Fixed |
| Foods | Catalogues.xlsx | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Other data | Fixed |
| Concentrations | ConcentrationsSSD_DAC.md | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Concentrations | Fixed |
| Survey | ConsumptionsBE.mdb | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Consumptions | Fixed |
| Survey | ConsumptionsCZ.mdb | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Consumptions | Fixed |
| Survey | ConsumptionsDE.mdb | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Consumptions | Fixed |
| Survey | ConsumptionsDK.mdb | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Consumptions | Fixed |
| Survey | ConsumptionsES.mdb | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Consumptions | Fixed |
| Survey | ConsumptionsFI.mdb | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Consumptions | Fixed |
| Survey | ConsumptionsFR.mdb | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Consumptions | Fixed |
| Survey | ConsumptionsHU.mdb | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Consumptions | Fixed |
| Survey | ConsumptionsIE.mdb | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Consumptions | Fixed |
| Survey | ConsumptionsIT.mdb | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Consumptions | Fixed |
| Survey | ConsumptionsLT.mdb | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Consumptions | Fixed |
| Survey | ConsumptionsNL.mdb | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Consumptions | Fixed |
| Survey | ConsumptionsRO.mdb | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Consumptions | Fixed |
| Survey | ConsumptionsSE.mdb | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Consumptions | Fixed |
| AssessmentGroupMemberships | SecondaryData.xlsx | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Other data | Fixed |
| AuthorisedUses | SecondaryData.xlsx | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Other data | Fixed |
| FoodTranslations | SecondaryData.xlsx | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Other data | Fixed |
| HazardDoses | SecondaryData.xlsx | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Other data | Fixed |
| MaximumResidueLimits | SecondaryData.xlsx | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Other data | Fixed |
| Processing | SecondaryData.xlsx | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Other data | Fixed |
| ResidueDefinitions | SecondaryData.xlsx | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Other data | Fixed |
| SubstanceApprovals | SecondaryData.xlsx | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Other data | Fixed |
| UnitVariability | UnitVar36.xlsx | Standard Actions/Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)/Other data | Fixed |

### 5.5.6 EU acute cumulative exposure assessment (2018) Tier I and Tier II

This standard action is of type: *Single value risks*

This standard action is based on work done in 2018 (van Klaveren et al. (2019a)). In the context of the second framework partnership agreement between the National Institute for Public Health and the Environment of the Netherlands (RIVM) and the European Food Safety Authority (EFSA) acute cumulative dietary exposure assessments were performed for two cumulative assessment groups (CAGs) of pesticides that affect the nervous system: pesticides causing brain and/or erythrocyte AChE inhibition (CAG-NAN, 47 pesticides) and pesticides causing functional alterations of the motor division (CAG-NAM, 100 pesticides). The exposure assessments used monitoring data collected by the Netherlands under their official monitoring programmes in 2014, 2015 and 2016 and individual Dutch food consumption data. Exposure estimates were obtained for each group of pesticides using the MCRA software. The Standing Committee on Plants, Animals, Food and Feed (SC PAFF) discussed the scope of the assessment in 2018 and agreed on the parameters to be used for the cumulative exposure assessment. Based on that discussion, a very conservative tier I modelling approach and a refined, but still conservative tier II modelling approach were used. In these assessments, common risk assessment practice was followed and the cumulative exposure was expressed as the total riskcharacterisation ratio hazard/exposure at the 50th, 90th, 95th, 99th and 99.9th percentile of the exposure distribution.

### 5.5.7 EU chronic cumulative exposure assessment (2018) Tier I and Tier II

This standard action is of type: *Risks*

This standard action is based on research done in 2018 van Klaveren et al. (2019b).

This standard action will enable you to reproduce the exposure assessment of chronic cumulative effects of pesticide residues in food affecting the thyroid. These are retrospective exposure assessments of the cumulative exposure for the thyroid using monitoring data from 2014, 2015 and 2016. In this standard action Dutch monitoring and consumption data are used. The results, data used and methodology are reported in a scientific report following published on the EFSA website in September 2019. The methodology fulfils the requirements set by the European Commission.

Table 5.2: Datasources for EU chronic cumulative exposure assessment (2018) Tier I and Tier II.

| Table Group | Name | Repository | Type |
|---|---|---|---|
| AssessmentGroupMemberships | LeanCAGsAssessmentGroupMembership10%p999.xlsx | Standard Actions/EU 2018 Chronic Cumulative Exposure Assessment | Fixed |
| AuthorisedUses | SecondaryInputData.mdb | Standard Actions/EU 2018 Chronic Cumulative Exposure Assessment | Fixed |
| Compounds | SecondaryInputData.mdb | Standard Actions/EU 2018 Chronic Cumulative Exposure Assessment | Fixed |
| Effects | SecondaryInputData.mdb | Standard Actions/EU 2018 Chronic Cumulative Exposure Assessment | Fixed |
| FoodExtrapolations | SecondaryInputData.mdb | Standard Actions/EU 2018 Chronic Cumulative Exposure Assessment | Fixed |
| FoodTranslations | SecondaryInputData.mdb | Standard Actions/EU 2018 Chronic Cumulative Exposure Assessment | Fixed |
| Foods | SecondaryInputData.mdb | Standard Actions/EU 2018 Chronic Cumulative Exposure Assessment | Fixed |
| HazardDoses | SecondaryInputData.mdb | Standard Actions/EU 2018 Chronic Cumulative Exposure Assessment | Fixed |
| MaximumResidueLimits | SecondaryInputData.mdb | Standard Actions/EU 2018 Chronic Cumulative Exposure Assessment | Fixed |
| Processing | SecondaryInputData.mdb | Standard Actions/EU 2018 Chronic Cumulative Exposure Assessment | Fixed |
| ResidueDefinitions | SecondaryInputData.mdb | Standard Actions/EU 2018 Chronic Cumulative Exposure Assessment | Fixed |
| Survey | c_ConsumptionsNL2.mdb | Standard Actions/EU 2018 Chronic Cumulative Exposure Assessment | Fixed |
| Survey | c_ConsumptionsNL3_6.mdb | Standard Actions/EU 2018 Chronic Cumulative Exposure Assessment | Fixed |

- *EU Prospective Dietary Cumulative Risk Assessment (2024)*
- *EU Retrospective Dietary Cumulative Risk Assessment (2024)*
- *EU Prospective Dietary Cumulative Risk Assessment (2023)*
- *EU Retrospective Dietary Cumulative Risk Assessment (2023)*
- *Acute Cumulative Risk Assessment Craniofacial Alterations (EFSA 2022)*
- *EU acute cumulative exposure assessment (2018) Tier I and Tier II*
- *EU chronic cumulative exposure assessment (2018) Tier I and Tier II*

CHAPTER

SIX

# TYPE AND UNIT DEFINITIONS

## 6.1 Adjustment factor distribution method types

Accepted justment factor distribution method types.

Table 6.1: Unit definition for Adjustment factor distribution method types.

| Name | Accepted names | Description |
|---|---|---|
| No adjustment factor | None | No adjustment factor. |
| Fixed adjustment factor | Fixed | Fixed adjustment factor. |
| LogNormal | LogNormal | Lognormal distribution with parameters a and b and offset c (default c = 0). |
| LogStudents_t | LogStudents_t | Log Students-t distribution with parameters a, b and c and offset d (default d = 0). |
| Beta | Beta | Beta distribution with shape parameters a and b on interval [c, d], (default = 0, 1). |
| Gamma | Gamma | Gamma distribution with shape parameter a and rate parameter b with offset = c (default = 0). |

## 6.2 Age alignment method

Age alignment method used for the selected exposure source.

Table 6.2: Unit definition for Age alignment method.

| Name | Accepted names | Description |
|---|---|---|
| Fit to closest available age | FitClosest | Fit to closest available age. |
| User defined bins (in years) | AgeBins | User defined bins. |

## 6.3 Air body exposure fraction uncertainty distribution types.

Air body exposure fraction uncertainty distribution types.

Table 6.3: Unit definition for Air body exposure fraction uncertainty distribution types..

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and a coefficient of variation. |
| Uniform | Uniform | Uniform distribution specified by a mean/median and a coefficient of variation. |

## 6.4 Air concentration distribution types.

Air concentration distribution types.

Table 6.4: Unit definition for Air concentration distribution types..

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and a coefficient of variation. |

## 6.5 Air concentration unit

Accepted units for substance concentration volumes.

Table 6.5: Unit definition for Air concentration unit.

| Name | Accepted names |
|---|---|
| microgram/cubimeter | ugPerm3, ug/m3, ugram/m3, ugr/m3 |
| microgram/liter | ugPerL, ug/L, ugram/L, ugr/L |

## 6.6 Application amount unit

Accepted units for consumer product application amounts.

Table 6.6: Unit definition for Application amount unit.

| Name | Accepted names |
|---|---|
| kilogram | kg, kilograms, kilogr, G167A |
| gram | g, gram, grams, gr, G148A |
| milligram | mg, milligrams, milligram |
| liter | L, liter, liters |
| deciliter | dL, deciliter, deciliters |
| centiliter | cL, centiliter, centiliters |
| milliliter | mL, milliliter, milliliters |
| microliter | uL, microliter, microliters |
| nanoliter | nL, nanoliter, nanoliters |

## 6.7 Assessment group membership calculation methods

Accepted Assessment group membership calculation methods.

Table 6.7: Unit definition for Assessment group membership calculation methods.

| Name | Accepted names | Description |
|---|---|---|
| Any (crisp) | CrispMax | Assign the highest membership value as membership. For crisp memberships, assign positive substance membership if any model indicates positive membership, and negative membership otherwise. |
| Majority (crisp) | CrispMajority | Assign positive substance membership if the majority of the membership models indicates positive membership, otherwise, the substance is considered not to be in the assessment group. |
| Ratio (probabilistic) | ProbabilisticRatio | Express substance membership as a probability ranging from zero (certainly out) to one (certainly in), computed as the average membership score. |
| Bayesian (probabilistic) | ProbabilisticBayesian | Express substance memberships as a probability with values ranging from zero (certainly out) to one (certainly in) computed using a Bayesian approach. |

## 6.8 Benchmark response type

Accepted benchmark response types.

Table 6.8: Unit definition for Benchmark response type.

| Name | Accepted names | Description |
|---|---|---|
| Fraction change | FractionChange, FactorChange | The benchmark response is defined as a fraction change of the background response (i.e., defined for both increase and decrease). E.g., for a factor of 0.1, the benchmark response is at +/- 10% of background response. |
| Percentage change | PercentageChange | The benchmark response is defined as a percentage change of the background response (i.e., defined for both increase and decrease). E.g., for a percentage of 10, the benchmark response is at +/- 10% of background response. |
| Fraction of background response | Factor, Fraction, FactorOfBackground | The benchmark response is defined as a fraction of the background response. E.g., for a factor of 0.9, the benchmark response is at 0.9 times the background response (i.e., a decrease). |
| Percentage of background response | Percentage, PercentageOfBackground | The benchmark response is defined as a percentage of the background response. E.g., for a percentage of 90, the benchmark response is at 90% of the background response (i.e., a decrease). |
| Extra risk | ExtraRisk | For quantal response types. The benchmark dose is defined as the dose that corresponding with an extra risk of a factor times the background risk. A factor of 0.05 corresponds with 5% extra risk. |
| Additional risk | AdditionalRisk | For quantal response types. The benchmark dose is defined as the dose that corresponding with an additional risk of a factor times the background risk. A factor of 0.05 corresponds with 5% additional risk. |
| ED50 | ED50, Ed50 | For quantal response types. The benchmark dose is defined as the dose that corresponds with an estimated risk of 50% (ED50). |
| Absolute threshold value | Absolute | The benchmark dose is defined as an absolute threshold value. |
| Absolute difference | Difference | The benchmark dose is defined an absolute difference with the background risk. |

## 6.9 Biological matrix

Accepted types of biological matrices.

Table 6.9: Unit definition for Biological matrix.

| Name | Accepted names | Description |
|---|---|---|
| Whole body | WholeBody, Body, Whole body, CTotal | Use whole body when the results apply to the whole body. |
| Blood | Blood, Whole blood, WholeBlood, Full blood, FullBlood, BWB, CPlasmaOut | The complete blood from a standard blood donation. |
| Blood serum | BloodSerum, Serum, Blood serum, BS | The portion of blood plasma that excludes clotting factors. |
| Blood plasma | BloodPlasma, Plasma, Blood plasma, O_CP, BP | The liquid component of blood, in which erythrocytes are suspended. |
| Cord blood | CordBlood, Cord blood, CBWB | Blood that remains in the placenta and in the attached umbilical cord after childbirth. |
| Cord blood serum | CordBlood-Serum, Cord blood serum, CBS | The portion of cord blood plasma that excludes clotting factors. |
| Cord blood plasma | CordBlood-Plasma, Cord blood plasma, CBP | The liquid component of cord blood, in which erythrocytes are suspended. |
| Venous blood | VenousBlood, Venous blood, O_CV, CVen | The deoxygenated blood which travels from the peripheral blood vessels. |
| Venous plasma | VenousPlasma | Plasma of the deoxygenated blood which travels from the peripheral blood vessels. |
| Arterial blood | ArterialBlood, Arterial blood, CArt, O_CA | The oxygenated blood in the circulatory system found in the pulmonary vein. |
| Arterial plasma | ArterialPlasma | Plasma of the oxygenated blood in the circulatory system found in the pulmonary vein. |
| Brain blood | BrainBlood, Brain blood, O_CBrb | The blood present in the brain. |
| Urine | Urine, AurinebpaOut, AurinegOut, AurineTotalOut | A non-invasive matrix definition for urine. |
| Excreta | Excreta | Human waste (i.e., both urine and feces). |

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Table 6.9 – continued from previous page

| Name | Accepted names | Description |
|---|---|---|
| Saliva | Saliva | The extracellular fluid produced and secreted by salivary glands in the mouth. |
| Semen | Semen | The fluid that is emitted from the male reproductive tract and that contains sperm cells. |
| Breath | Breath | The condensate of exhaled breath. |
| Red blood cells | RedBloodCells | The red blood cells. |
| Breast milk | BreastMilk | The human milk as a biological system. |
| Fat (adipose) tissue | BodyFat, AdiposeTissue, Adipose Tissue, Body fat, FatTissue, Fat, CFat, O_CF | Adipose tissue, body fat, or simply fat is the main reservoir of fat in the body beneath the skin. |
| Hair | Hair | The human hair as a non-invasive matrix for biomarkers of exposure. |
| Toenails | ToeNails | The layer of cells situated at the base of the fingernail or the toenail. |
| Big toenails | BigToeNails | The layer of cells situated at the base of the big fingernail or the big toenail. |
| Outer skin | OuterSkin | The extracellular connective tissue matrix of the skin. |
| Amniotic fluid | AmnioticFluid | The amniotic fluid is the protective liquid contained by the amniotic sac, serves as a cushion for the growing fetus. |
| Placenta tissue | PlacentaTissue, Placenta | The tissues which support fetal development. |
| Uterus tissue | UterusTissue, O_CU | The uterus or womb is the organ in the reproductive system that accommodates the fetal development until birth. |
| Uterus | Uterus | The uterus or womb (organ) as biological matrix. |
| Liver | Liver, CLiver, O_CL | The liver as biological matrix. |
| Muscle tissue | MuscleTissue, Muscle, Muscles, CPoor, O_CM | Perfused (muscle) tissue. |
| Viscera tissue | Viscera, CRich | Perfused tissue of the viscera, the soft internal organs of the body, especially the intestines. |
| Skin | Skin | Skin of the body. |
| Viable epidermis exposed skin | ViableEpidermisExposedSkin, SkinViableExposed, ViableSkinExposed, CSkin_e | Viable epidermis of skin exposed to air. |

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Table 6.9 – continued from previous page

| Name | Accepted names | Description |
|---|---|---|
| Viable epidermis unexposed skin | ViableEpidermisUnexposedSkin, SkinViableUnexposed, ViableSkinUnexposed, CSkin_u | Viable epidermis of skin not exposed to air. |
| Stratum corneum of exposed skin | StratumCorneumExposedSkin, StratumCorneumExposed, CSkin_sc_e | The outermost layer of the epidermis, exposed to the open air. |
| Stratum corneum of unexposed skin | StratumCorneumUnexposedSkin, StratumCorneumUnexposed, CSkin_sc_u | The outermost layer of the epidermis, not exposed to the open air. |
| Kidney | Kidney, Kidneys | The kidney organ as biological matix. |
| Adrenal gland | Adrenal, Adrenal gland, Adrenal glands | The adrenal gland as biological matix. |
| Thyroid gland | Thyroid, Thyroid gland | The thyroid gland as biological matix. |
| Heart | Heart, O_CH | The heart as biological matix. |
| Lung | Lung, Lungs, O_CLu | The lung as biological matix. |
| Brain tissue | BrainTissue | Brain tissue. |
| Brain | Brain | The brain (organ) as biological matix. |
| Eyes | Eyes, Eye, Ocular | The eyes as biological matix. |
| Gonad tissue | Gonad, Gonads, GonadTissue, CGonadOut, O_CBr | The biological matrix of the reproductive system that produces and releases eggs (ovary) or sperm (testicle/testis). |
| Slowly perfused tissue | SlowlyPerfusedTissue, PoorlyPerfusedTissue, Slowly perfused tissue, O_CS | The biological matrix of poorly perfused tissue include skin and subcutaneous tissue, and resting muscle. |
| Richly perfused tissue | RichlyPerfusedTissue, Richly perfused tissue, O_CR | The biological matrix of richly perfused tissue include liver, heart, lungs, kidneys, and brain. |
| Feces | Feces, Excrement, Poop | Bodily waste discharged through the anus. |
| Air | Air | Inhaled or alveolar air. |

## 6.10 Biological organisation type

Accepted biological organisation types.

Table 6.10: Unit definition for Biological organisation type.

| Name | Accepted names | Description |
|---|---|---|
| Molecular | Molecular | Molecular level |
| Cellular | Cellular | Cellular level |
| Tissue | Tissue | Tissue level |
| Organ | Organ, Organelle | Organ level |
| Individual | Individual | Whole body level |
| Population | Population | Population level |

## 6.11 Biomarker conversion distribution type

Biomarker conversion distribution types.

Table 6.11: Unit definition for Biomarker conversion distribution type.

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and upper p95 percentile. |
| Uniform | Uniform | Uniform distribution specified by a mean/median and an upper boundary. |
| Beta | Beta | Beta distribution parameterised by a mean and a variance. |

## 6.12 BoD Indicator

Different metrics in which burden of disease can be expressed.

Table 6.12: Unit definition for BoD Indicator.

| Name | Accepted names | Description |
|---|---|---|
| DALY | DALY, DALYs | Disability-adjusted life year. |
| Deaths | Deaths | Number of deaths. |
| Cases | Cases | Number of cases. |
| Costs | Costs | Costs. |
| Prevalence | Prevalence, Prevalences | Prevalence. |

## 6.13 Body weight unit

Accepted units for person body weights.

Table 6.13: Unit definition for Body weight unit.

| Name | Accepted names |
|---|---|
| kilogram | kg, kilograms, kilogr, 3, G167A |
| gram | g, grams, gr, 0, G148A |

## 6.14 Boolean type

Accepted boolean types.

Table 6.14: Unit definition for Boolean type.

| Name | Accepted names |
|---|---|
| True | True, Yes, T, Y |
| False | False, F, No, N |

## 6.15 Burden of disease approach

Methodologial approach used for estimating the burden of disease attributable to a chemical exposure.

Table 6.15: Unit definition for Burden of disease approach.

| Name | Accepted names | Description |
|---|---|---|
| Top-down | TopDown | Top-down approach starting with an estimate of the total burden in the population. A population attributable fraction (PAF) is calculated by applying an exposure response function (ERF) along with observed exposures, thereby estimating the proportion of the overall burden attributable to the chemical exposure. The attributable burden follows from multiplication of the total burden by the PAF. |
| Bottom-up | BottomUp | Bottom-up approach starting either by estimating the number of new or excess cases based on observed exposures and the exposure response function (ERF), or by evaluating the expected shift in individual responses (e.g. changes in IQ) resulting from exposure. These are translated into a burden measure – often by multiplying by factors such as duration and disability weight (or a monetary value) to calculate the attributable BoD for indicators like DALYs. |

## 6.16 Burden of disease indicator uncertainty distribution types.

Burden of disease indicator uncertainty distribution types.

Table 6.16: Unit definition for Burden of disease indicator uncertainty distribution types..

| Name | Accepted names | Description |
|---|---|---|
| Normal | Normal | Normal distribution parameterised by a mean and upper p95 percentile. |
| LogNormal | LogNormal | LogNormal distribution parameterised by a mean and upper p95 percentile. |
| Triangular | Triangular | Triangular distribution specified by a mode and a lower and upper boundary. |

## 6.17 Case control types.

Case control types.

Table 6.17: Unit definition for Case control types..

| Name | Accepted names | Description |
|---|---|---|
| Control | Control | Control. |
| Case | Case | Case. |

## 6.18 Cluster method type

Accepted cluster method types.

Table 6.18: Unit definition for Cluster method type.

| Name | Accepted names | Description |
|---|---|---|
| Component selection (SNMU) | NoClustering | Only component selection is performed. |
| Component selection and population subgrouping (SNMU + k-means clustering) | Kmeans | Component selection followed by K-Means clustering of individuals based on their component exposure. K-means classifies individuals in multiple groups (i.e., clusters), such that individuals within the same cluster are as similar as possible (i.e., high intra-class similarity), whereas individuals from different clusters are as dissimilar as possible (i.e., low inter-class similarity). In k-means clustering, each cluster is represented by its center (i.e, centroid) which corresponds to the mean of points assigned to the cluster. |
| Component selection and population subgrouping (SNMU + hierarchical clustering) | Hierarchical | Component selection followed by hierarchical (Ward's) clustering of individuals based on their component exposure. Hierachical clustering builds a hierarchy from the bottom-up, and doesn't require to specify the number of clusters beforehand. Hierarchical clustering produces a tree-based representation of the observations known as a dendrogram. |

## 6.19 Combination method membership info and PoD presence types

Accepted Combination method membership info and PoD presence types.

Table 6.19: Unit definition for Combination method membership info and PoD presence types.

| Name | Accepted names | Description |
|---|---|---|
| Consider active if POD/HC AND (in-silico) memberships indicate active | Intersection | Consider active if POD/HC AND (in-silico) memberships indicate active. |
| Consider active if POD/HC OR (in-silico) memberships indicates active | Union | Consider active if POD/HC OR (in-silico) memberships indicates active. |

## 6.20 Concentration limit value type

Accepted concentration limit value types.

Table 6.20: Unit definition for Concentration limit value type.

| Name | Accepted names |
|---|---|
| Maximum residue limit | MaximumResidueLimit, MRL |
| Proposed maximum residue limit | ProposedMaximumResidueLimit, ProposedMrl |

## 6.21 Concentration model types

Accepted Concentration model types.

Table 6.21: Unit definition for Concentration model types.

| Name | Accepted names | Description |
|---|---|---|
| Empirical | Empirical | Residues are sampled from the empirical distribution. Fallback: zero. |
| Censored value Spike LogNormal | NonDetectSpikeLogNormal | A lognormal model (logarithmic transformed values, with parameters mu and sigma^2) is fitted to the positive residues values. LOR information is not used. Fallback (if number of positives less than 2): Empirical, but Maximum Residu Limit for pessimistic assessments. |
| Censored Spike Truncated LogNormal | NonDetectSpikeTruncatedLogNormal | A truncated lognormal model (with parameters mu and sigma^2) is fitted to the positive residues values. The LOR is used to estimate the truncated left tail of the distribution. Fallback: Lognormal non-detect spike. |
| Censored LogNormal | CensoredLogNormal | Advanced. A censored lognormal model (with parameters mu and sigma^2) is fitted to the censored and positives residue values. Note, this model is not available when agricultural use information is used. Fallback: Lognormal non-detect spike. |
| Zero Spike Censored LogNormal | ZeroSpikeCensoredLogNormal | Advanced. A mixture model with zero spike (p0) and censored lognormal model (with parameters mu and sigma^2) is fitted to the censored and positives residue values. Note, this model is not available when agricultural use information is used. Fallback: Censored lognormal. |
| Censored Spike Maximum Residue Limit | MaximumResidueLimit | Censored Spike Maximum Residue Limit. |
| Summary statistics | SummaryStatistics | Summary statistics. |
| LogNormal | LogNormal | Lognormal model. |
| Constant | Constant | A degenerate propability distribution with a single possible value. |

## 6.22 Concentration unit

Accepted units for substance concentrations.

Table 6.22: Unit definition for Concentration unit.

| Name | Accepted names |
|---|---|
| milligram/kilogram | mgPerKg, mg/kg, milligram/kilogram, milligram/kg, milligr/kg, -6, G049A, G061A |
| kilogram/kilogram | kgPerKg, kg/kg, kilogram/kilogram, kilogram/kg, 0, G063A |
| gram/kilogram | gPerKg, g/kg, gram/kilogram, gram/kg, gr/kg, -3, G015A, G060A, G191A |
| microgram/kilogram | ugPerKg, µg/kg, ug/kg, microgram/kilogram, microgram/kg, microgr/kg, -9, G050A, G076A |
| nanogram/kilogram | ngPerKg, ng/kg, nanogram/kilogram, nanogram/kg, nanogr/kg, -12, G077A, G080A |
| picogram/kilogram | pgPerKg, pg/kg, picogram/kilogram, picogram/kg, picogr/kg, -15, G081A |
| kilogram/liter | kgPerL, kg/l, kg/L, kilogram/liter, kilogram/litre, G017A |
| gram/liter | gPerL, g/l, g/L, gram/liter, gram/litre, gr/l, gr/L, G016A |
| milligram/liter | mgPerL, mg/l, mg/L, milligram/liter, milligram/litre, milligr/l, milligr/L, G052A, G062A |
| microgram/liter | ugPerL, µg/l, ug/L, microgram/liter, microgram/litre, microgr/l, microgr/L, G051A, G079A |
| nanogram/liter | ngPerL, ng/l, ng/L, nanogram/liter, nanogram/litre, nanogr/l, nanogr/L, G078A |
| picogram/liter | pgPerL, pg/l, pg/L, picogram/liter, picogram/litre, picogr/l, picogr/L |
| microgram/milliliter | ugPermL, µg/ml, ug/mL, microgram/milliliter, microgram/millilitre, microgr/ml, microgr/mL |
| nanogram/milliliter | ngPermL, ng/ml, ng/mL, nanogram/milliliter, nanogram/millilitre, nanogr/ml, nanogr/mL |
| milligram/deciliter | mgPerdL, mg/dl, milligram/deciliter, milligr/dL, milligr/dl |
| microgram/gram | ugPerg, µg/g, µgram/gram, µg/gr, ug/g, ugram/gram, ug/gr |
| nanogram/gram | ngPerg, ng/g, ngram/gram, ngr/gr |

## 6.23 Concentration value type

Accepted concentration value type.

Table 6.23: Unit definition for Concentration value type.

| Name | Accepted names | Description |
|---|---|---|
| Mean concentration | MeanConcentration, ConcentrationMean, MC | Mean value from the residue trials. |
| Median concentration | MedianConcentration, MR, STMR, SupervisedTrialMedianResidue | Median concentration / residue value of the positive measurements of the residue trials. |
| Highest concentration | HighestConcentration, HighestResidue, HR | Highest measured residue / concentration value. |
| Concentration percentile | Percentile | |
| Limit of quantification | LOQ | |
| Maximum residue limit | MRL | |

## 6.24 Consumer product application amount distribution types.

Consumer product application amount uncertainty distribution types.

Table 6.24: Unit definition for Consumer product application amount distribution types..

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and a coefficient of variation. |
| Uniform | Uniform | Uniform distribution specified by a mean/median and a coefficient of variation. |

## 6.25 Consumer product assessment matching method

Method types for consumer product assessment matching based on gender and age ranges.

Table 6.25: Unit definition for Consumer product assessment matching method.

| Name | Accepted names | Description |
|---|---|---|
| At random | AtRandom | Match at random. |
| Match on gender | MatchOnGender | Match individuals to assessments based on gender. |
| Match on age | MatchOnAge | Match individuals to assessments based on age ranges. |
| Match on gender and age | MatchOnAgeAndGender | Match individuals to assessments based on gender and age ranges. |

## 6.26 Consumer product concentration uncertainty distribution types.

Consumer product concentration uncertainty distribution types.

Table 6.26: Unit definition for Consumer product concentration uncertainty distribution types..

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and a coefficient of variation. |
| Uniform | Uniform | Uniform distribution specified by a mean/median and a coefficient of variation. |

## 6.27 Consumer product concentration unit

Accepted units for substance concentrations in consumer products.

Table 6.27: Unit definition for Consumer product concentration unit.

| Name | Accepted names |
|---|---|
| microgram/gram | ugPerg, µg/g, µgram/gram, µg/gr, ug/g, ugram/gram, ug/gr |
| nanogram/gram | ngPerg, ng/g, ngram/gram, ngr/gr |
| gram/kilogram | gPerKg, g/kg, gram/kilogram, gram/kg, gr/kg, -3, G015A, G060A, G191A |
| milligram/kilogram | mgPerKg, mg/kg, milligram/kilogram, milligram/kg, milligr/kg, -6, G049A, G061A |
| microgram/kilogram | ugPerKg, µg/kg, ug/kg, microgram/kilogram, microgram/kg, microgr/kg, -9, G050A, G076A |
| nanogram/kilogram | ngPerKg, ng/kg, nanogram/kilogram, nanogram/kg, nanogr/kg, -12, G077A, G080A |
| picogram/kilogram | pgPerKg, pg/kg, picogram/kilogram, picogram/kg, picogr/kg, -15, G081A |
| gram/liter | gPerL, g/l, g/L, gram/liter, gram/litre, gr/l, gr/L, G016A |
| milligram/liter | mgPerL, mg/l, mg/L, milligram/liter, milligram/litre, milligr/l, milligr/L, G052A, G062A |
| microgram/liter | ugPerL, µg/l, ug/L, microgram/liter, microgram/litre, microgr/l, microgr/L, G051A, G079A |
| nanogram/liter | ngPerL, ng/l, ng/L, nanogram/liter, nanogram/litre, nanogr/l, nanogr/L, G078A |
| picogram/liter | pgPerL, pg/l, pg/L, picogram/liter, picogram/litre, picogr/l, picogr/L |
| microgram/milliliter | ugPermL, µg/ml, ug/mL, microgram/milliliter, microgram/millilitre, microgr/ml, microgr/mL |
| nanogram/milliliter | ngPermL, ng/ml, ng/mL, nanogram/milliliter, nanogram/millilitre, nanogr/ml, nanogr/mL |
| milligram/deciliter | mgPerdL, mg/dl, milligram/deciliter, milligr/dL, milligr/dl |
| gram per unit | gPerUnit, g/unit, gram/unit, gr/unit, g, gram, gr |
| milligram per unit | mgPerUnit, mg/unit, milligram/unit, milligr/unit, mg, milligram, milligr |
| microgram per unit | ugPerUnit, µg/unit, ug/unit, microgram/unit, microgr/unit, µg, ug, microgram, microgr |
| nanogram per unit | ngPerUnit, ng/unit, ngram/unit, ngr/unit, ng, ngram, ngr |

## 6.28 Consumer product exposure calculation method

Method types for consumer product exposure calculation.

Table 6.28: Unit definition for Consumer product exposure calculation method.

| Name | Accepted names | Description |
|---|---|---|
| Use consumer product uses and concentration data | FromUsesAndConcentrations | Compute exposure based on combining consumer product use data with product concentration data. |
| Use consumer product exposure estimates | FromExposureEstimates | Compute exposure based on exposure estimates data. |

## 6.29 Consumer product exposure estimate type

Accepted estimate types for consumer product exposure.

Table 6.29: Unit definition for Consumer product exposure estimate type.

| Name | Accepted names | Description |
|---|---|---|
| Internal (systemic) dose | Systemic, InternalDose | The absorbed dose is the amount of chemical that is systemically available and can be regarded as the fraction of the external dose that is absorbed and enters the general circulation. |
| DermalLoad | DermalLoad | The quantitative amount of a chemical substance in direct contact with a specific area of the skin (measured as mass per unit area. |

## 6.30 Consumer product exposure estimate unit

Accepted units for job exposure activities.

Table 6.30: Unit definition for Consumer product exposure estimate unit.

| Name | Accepted names | Description |
|---|---|---|
| µg/cm2/day | ugPerCm2PerDay, µg/cm2/day, ug/cm2/day | Exposure expressed in micrograms per square centimeter (µg/cm2) per day. |
| mg/cm2/day | mgPerCm2PerDay, mg/cm2/day | Exposure expressed in milligrams per square centimeter (mg/cm2) per day. |
| milligram/kilogram bodyweight/day | mgPerKgBWPerDay, mg/kg bw/day, mg/kg/day, milligram/kg bw/day, milligr/kg bw/day, G211A | |
| microgram/kilogram bodyweight/day | ugPerKgBWPerDay, µg/kg bw/day, µg/kg/day, microgram/kg bw/day, microgr/kg bw/day, G210A | |
| nanogram/kilogr bodyweight/day | ngPerKgBWPerDay, ng/kg bw/day, ng/kg/day, nanogram/kg bw/day, nanogr/kg bw/day, G214A | |

## 6.31 Consumption intake unit

Accepted units for consumption intake amounts.

Table 6.31: Unit definition for Consumption intake unit.

| Name | Accepted names |
|---|---|
| gram/kilogram bodyweight/day | gPerKgBWPerDay, g/kg bw, gram/kg bw, g/kg bw/day, gram/kg bw/day, gr/kg bw/day, G212A |
| gram/day | gPerDay, gram, grams, g/day, gram/day, gr/day |

## 6.32 Consumption unit

Accepted units for consumption amounts.

Table 6.32: Unit definition for Consumption unit.

| Name | Accepted names |
|---|---|
| kilogram | kg, kilograms, kilogr, 3, G167A |
| gram | g, grams, gr, 0, G148A |

## 6.33 Consumption value type

Accepted consumption value types.

Table 6.33: Unit definition for Consumption value type.

| Name | Accepted names |
|---|---|
| Large portion | LargePortion, LP |
| Mean consumption | MeanConsumption, MC |
| Percentile | Percentile, P |

## 6.34 Counter factual value uncertainty distribution types.

Counter factual value uncertainty distribution types.

Table 6.34: Unit definition for Counter factual value uncertainty distribution types..

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and upper p95 percentile. |
| Uniform | Uniform | Uniform distribution specified by a mean/median and an upper boundary. |
| Triangular | Triangular | Triangular distribution specified by a mode and a lower and upper boundary. |

## 6.35 Covariate model types

Accepted Covariate model types.

Table 6.35: Unit definition for Covariate model types.

| Name | Accepted names | Description |
|---|---|---|
| Only constant | Constant | No relation between exposure and e.g. age or gender. |
| Only covariable | Covariable | Exposure depends on the covariable, e.g. age. |
| Only cofactor | Cofactor | Exposure depends on the level of the cofactor, e.g. gender. |
| Both covariable and cofactor | CovariableCofactor | Exposure depends on both covariable and cofactor (additive model). |
| Both covariable and cofactor and interaction | CovariableCofactorInteraction | Exposure depends on both covariable and cofactor and the effect of the covariable differs for different levels of the cofactor (multiplicative model). |

## 6.36 Dietary exposures details level types

Accepted ietary exposures details level types.

Table 6.36: Unit definition for Dietary exposures details level types.

| Name | Accepted names | Description |
|---|---|---|
| Full | Full | Show all details. |
| Restrict to risk-drivers (dietary exposures screening) | OnlyRiskDrivers | Restrict to detailed output for risk-drivers identified by dietary exposures screening. |
| Omit foods-as-eaten details | OmitFoodsAsEaten | Restrict to detailed output for modelled foods and substances. Omit foods-as-eaten details. |

## 6.37 Dose response model type

Accepted dose response model types.

Table 6.37: Unit definition for Dose response model type.

| Name | Accepted names | Description |
|---|---|---|
| Exp-m1 | Expm1 | Exponential model 1 |
| Exp-m2 | Expm2 | Exponential model 2 |
| Exp-m3 | Expm3 | Exponential model 3 |
| Exp-m4 | Expm4 | Exponential model 4 |
| Exp-m5 | Expm5 | Exponential model 5 |
| Hill-m1 | Hillm1 | Hill model 1 |
| Hill-m2 | Hillm2 | Hill model 2 |
| Hill-m3 | Hillm3 | Hill model 3 |
| Hill-m4 | Hillm4 | Hill model 4 |
| Hill-m5 | Hillm5 | Hill model 5 |
| TwoStage | TwoStage | |
| LogLogist | LogLogist | |
| Weibull | Weibull | |
| LogProb | LogProb | |
| Gamma | Gamma | |
| Logistic | Logistic | |
| Probit | Probit | |
| LVM Exp m2 | LVM_Exp_M2, LVM Exp m2 | |
| LVM Exp m3 | LVM_Exp_M3, LVM Exp M3 | |
| LVM Exp m4 | LVM_Exp_M4, LVM Exp M4 | |
| LVM Exp m5 | LVM_Exp_M5, LVM Exp M5 | |
| LVM Hill m2 | LVM_Hill_M2, LVM Hill m2 | |
| LVM Hill m3 | LVM_Hill_M3, LVM Hill M3 | |
| LVM Hill m4 | LVM_Hill_M4, LVM Hill M4 | |
| LVM Hill m5 | LVM_Hill_M5, LVM Hill m5 | |

## 6.38 Dose unit

Accepted units for substance doses.

Table 6.38: Unit definition for Dose unit.

| Name | Accepted names |
|---|---|
| gram/kilogram bodyweight/day | gPerKgBWPerDay, g/kg bw/day, g/kg/day, gram/kg bw/day, gram/kg/day, gr/kg bw/day, G212A |
| milligram/kilogram bodyweight/day | mgPerKgBWPerDay, mg/kg bw/day, mg/kg/day, milligram/kg bw/day, milligr/kg bw/day, G211A |
| microgram/kilogram bodyweight/day | ugPerKgBWPerDay, µg/kg bw/day, µg/kg/day, microgram/kg bw/day, microgram/kg/day, microgr/kg bw/day, microgr/kg/day, G210A |
| nanogram/kilogram bodyweight/day | ngPerKgBWPerDay, ng/kg bw/day, ng/kg/day, nanogram/kg bw/day, nanogram/kg/day, nanogr/kg bw/day, nanogr/kg/day, G214A |
| picogram/kilogram bodyweight/day | pgPerKgBWPerDay, pg/kg bw/day, pg/kg/day, picogram/kg bw/day, picogram/kg/day, picogr/kg bw/day, picogr/kg/day |
| femtogram/kilogram bodyweight/day | fgPerKgBWPerDay, fg/kg bw/day, fg/kg/day, femtogram/kg bw/day, femtogram/kg/day, femtogr/kg bw/day, femtogr/kg/day |
| gram/gram bodyweight/day | gPerGBWPerDay, g/g bw/day, g/g/day, gram/g bw/day, gram/g/day, gr/g bw/day, gr/g/day |
| milligram/gram bodyweight/day | mgPerGBWPerDay, mg/g bw/day, mg/g/day, milligram/g bw/day, milligram/g/day, milligr/g bw/day, milligr/g/day |
| microgram/gram bodyweight/day | ugPerGBWPerDay, µg/g bw/day, µg/g/day, microgram/g bw/day, microgram/g/day, microgr/g bw/day, microgr/g/day |
| nanogram/gram bodyweight/day | ngPerGBWPerDay, ng/g bw/day, ng/g/day, nanogram/g bw/day, nanogram/g/day, nanogr/g bw/day, nanogr/g/day |
| picogram/gram bodyweight/day | pgPerGBWPerDay, pg/g bw/day, pg/g/day, picogram/g bw/day, picogram/g/day, picogr/g bw/day, picogr/g/day |
| femtogram/gram bodyweight/day | fgPerGBWPerDay, fg/g bw/day, fg/g/day, femtogram/g bw/day, femtogram/g/day, femtogr/g bw/day, femtogr/g/day |
| kilogram/day | kgPerDay, kg/day, kilogram/day, kilogr/day |
| gram/day | gPerDay, g/day, gram/day, gr/day |
| milligram/day | mgPerDay, mg/day, milligram/day, milligr/day |
| microgram/day | ugPerDay, µg/day, microgram/day, microgr/day |
| nanogram/day | ngPerDay, ng/day, nanogram/day, nanogr/day |
| picogram/day | pgPerDay, pg/day, picogram/day, picogr/day |
| femtogram/day | fgPerDay, fg/day, femtogram/day, femtogr/day |
| kilogram/kilogram | kgPerKg, kg/kg, kilogram/kilogram, kilogram/kg, kg/kg bw |
| gram/kilogram | gPerKg, g/kg, gram/kilogram, gram/kg, gr/kg, g/kg bw |
| milligram/kilogram | mgPerKg, mg/kg, milligram/kilogram, milligram/kg, milligr/kg, mg/kg bw, G225A |
| microgram/kilogram | ugPerKg, µg/kg, microgram/kilogram, microgram/kg, microgr/kg, µg/kg bw |
| nanogram/kilogram | ngPerKg, ng/kg, nanogram/kilogram, nanogram/kg, nanogr/kg, ng/kg bw |
| picogram/kilogram | pgPerKg, pg/kg, picogram/kilogram, picogram/kg, picogr/kg, pg/kg bw |

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Table 6.38 – continued from previous page

| Name | Accepted names |
|---|---|
| molar | M, mol/L |
| millimolar | mM, mmol/L |
| micromolar | uM, µM, umol/L |
| nanomolar | nM, nmol/L |
| moles | moles, Moles |
| millimoles | mmoles, mMoles |
| micromoles | umoles, uMoles |
| nanomoles | nmoles, nmol, nMoles |
| gram/kilogram bodyweight/week | gPerKgBWPerWeek, g/kg bw/week, gram/kg bw/week, gr/kg bw/week, G218A |
| milligram/kilogram bodyweight/week | mgPerKgBWPerWeek, mg/kg bw/week, milligram/kg bw/week, milligr/kg bw/week, G217A |
| microgram/kilogram bodyweight/week | ugPerKgBWPerWeek, µg/kg bw/week, microgram/kg bw/week, microgr/kg bw/week, G216A |
| nanogram/kilogram bodyweight/week | ngPerKgBWPerWeek, ng/kg bw/week, nanogram/kg bw/week, nanogr/kg bw/week, G215A |
| picogram/kilogram bodyweight/week | pgPerKgBWPerWeek, pg/kg bw/week, picogram/kg bw/week, picogr/kg bw/week |
| femtogram/kilogram bodyweight/week | fgPerKgBWPerWeek, fg/kg bw/week, femtogram/kg bw/week, femtogr/kg bw/week |
| gram/gram bodyweight/week | gPerGBWPerWeek, g/g bw/week, gram/g bw/week, gr/g bw/week |
| milligram/gram bodyweight/week | mgPerGBWPerWeek, mg/g bw/week, milligram/g bw/week, milligr/g bw/week |
| microgram/gram bodyweight/week | ugPerGBWPerWeek, µg/g bw/week, microgram/g bw/week, microgr/g bw/week |
| nanogram/gram bodyweight/week | ngPerGBWPerWeek, ng/g bw/week, nanogram/g bw/week, nanogr/g bw/week |
| picogram/gram bodyweight/week | pgPerGBWPerWeek, pg/g bw/week, picogram/g bw/week, picogr/g bw/week |
| femtogram/gram bodyweight/week | fgPerGBWPerWeek, fg/g bw/week, femtogram/g bw/week, femtogr/g bw/week |
| kilogram/week | kgPerWeek, kg/week, kilogram/week, kilogr/week |
| gram/week | gPerWeek, g/week, gram/week, gr/week |
| milligram/week | mgPerWeek, mg/week, milligram/week, milligr/week |
| microgram/week | ugPerWeek, µg/week, microgram/week, microgr/week |
| nanogram/week | ngPerWeek, ng/week, nanogram/week, nanogr/week |
| picogram/week | pgPerWeek, pg/week, picogram/week, picogr/week |
| femtogram/week | fgPerWeek, fg/week, femtogram/week, femtogr/week |
| kilogram/liter | kgPerL, kg/l, kg/L, kilogram/liter, kilogram/litre, G017A |
| gram/liter | gPerL, g/l, g/L, gram/liter, gram/litre, gr/l, gr/L, G016A |
| milligram/liter | mgPerL, mg/l, mg/L, milligram/liter, milligram/litre, milligr/l, milligr/L, G052A, G062A |
| microgram/liter | ugPerL, µg/l, ug/L, microgram/liter, microgram/litre, microgr/l, microgr/L, G051A, G079A |
| nanogram/liter | ngPerL, ng/l, ng/L, nanogram/liter, nanogram/litre, nanogr/l, nanogr/L, G078A |
| picogram/liter | pgPerL, pg/l, pg/L, picogram/liter, picogram/litre, picogr/l, picogr/L |
| milligram/gram | mgPerg, mg/g, milligram/gram |
| microgram/gram | ugPerg, µg/g, microgram/gram |
| nanogram/gram | ngPerg, ng/g, nanogram/gram |

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Table 6.38 – continued from previous page

| Name | Accepted names |
|---|---|
| picogram/gram | pgPerg, pg/g, picogram/gram |

## 6.39 Dust adherence amount uncertainty distribution types.

Dust adherence amount uncertainty distribution types.

Table 6.39: Unit definition for Dust adherence amount uncertainty distribution types..

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and a coefficient of variation. |
| Uniform | Uniform | Uniform distribution specified by a mean/median and a coefficient of variation. |

## 6.40 Dust availability fraction uncertainty distribution types.

Dust availability fraction uncertainty distribution types.

Table 6.40: Unit definition for Dust availability fraction uncertainty distribution types..

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and a coefficient of variation. |
| Uniform | Uniform | Uniform distribution specified by a mean/median and a coefficient of variation. |

## 6.41 Dust body exposure fraction uncertainty distribution types.

Dust body exposure fraction uncertainty distribution types.

Table 6.41: Unit definition for Dust body exposure fraction uncertainty distribution types..

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and a coefficient of variation. |
| Uniform | Uniform | Uniform distribution specified by a mean/median and a coefficient of variation. |

## 6.42 Dust concentration uncertainty distribution types.

Dust concentration uncertainty distribution types.

Table 6.42: Unit definition for Dust concentration uncertainty distribution types..

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and a coefficient of variation. |

## 6.43 Dustingestion uncertainty distribution types.

Dust ingestion uncertainty distribution types.

Table 6.43: Unit definition for Dustingestion uncertainty distribution types..

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and a coefficient of variation. |
| Uniform | Uniform | Uniform distribution specified by a mean/median and a coefficient of variation. |

## 6.44 Effect metric

Accepted types of effect metrics.

Table 6.44: Unit definition for Effect metric.

| Name | Accepted names | Description |
|---|---|---|
| Relative risk | RelativeRisk, Relative, RR, Relative Risk | Use relative risk when the risk is expressed as a relative risk. |
| Odds ratio | OddsRatio, Odds, OR, Odds Ratio | Use odds ratio when the risk is expressed as an odds ratio. |
| Negative shift | NegativeShift, Negative Shift | Use negative shift when the risk is expressed as a negative shift in a continuous variable. |
| Positive shift | PositiveShift, Positive Shift | Use positive shift when the risk is expressed as a positive shift in a continuous variable. |

## 6.45 Environmental burden of disease standardisation method

Accepted environmental burden of disease standardisation types.

Table 6.45: Unit definition for Environmental burden of disease standardisation method.

| Name | Accepted names | Description |
|---|---|---|
| per 10,000 | PER10K | EBD standardised per 10,000. |
| per 100,000 | PER100K | EBD standardised per 100,000. |
| per 1,000,000 | PER1M | EBD standardised per 1,000,000. |

## 6.46 Estimates nature types

Accepted Estimates nature types.

Table 6.46: Unit definition for Estimates nature types.

| Name | Accepted names | Description |
|---|---|---|
| Realistic | Realistic | For lognormal: no censoring at the value of the composite sample concentration, no upper limit to the unit concentration. For Beta: no censoring at the value of the composite sample concentration, unit values are never higher than the number of units in composite sample * value of composite sample concentration. |
| Conservative | Conservative | For lognormal: unit values will be left-censored at the value of the composite sample concentration, no upper limit to the unit concentration. For Beta: unit values will be left-censored at the value of the value of composite sample concentration, unit are values never higher than the number of units in composite sample * value of composite sample concentration. |

## 6.47 Exposure approach method

Accepted Exposure approach method types.

Table 6.47: Unit definition for Exposure approach method.

| Name | Accepted names | Description |
|---|---|---|
| Modelled exposures | Modelled | A parametric model is fitted to the data. |
| Measured exposures | Measured | Data are taken as such. |

## 6.48 Exposure approach types

Accepted Exposure approach types.

Table 6.48: Unit definition for Exposure approach types.

| Name | Accepted names | Description |
|---|---|---|
| Risk based (RPFs) | RiskBased | Exposures are multiplied by the RPF and thus exposures to different substances are on the same and comparable scale. |
| Standardised | ExposureBased | All substances are standardised to equal variance (selection of the components will work on patterns of correlation only). |
| Unstandardised (RPFs = 1) | UnweightedExposures | Exposures as such are taken (unstandardised). This is equivalent to RPFs equal to 1. Thus exposures to different substances are not on the same and comparable scale anymore. |

## 6.49 Exposure calculation method

Method types for obtaining exposure estimates.

Table 6.49: Unit definition for Exposure calculation method.

| Name | Accepted names | Description |
|---|---|---|
| Modelled exposures | ModelledConcentration | Compute risks from dietary and/or non-dietary routes, aggregated. |
| Human biomonitoring concentrations | MonitoringConcentration | Compute risks based on exposure estimates obtained from human biomonitoring concentrations. |

## 6.50 Exposure events and dose generation

Exposure events generation methods for PBK model simulations.

Table 6.50: Unit definition for Exposure events and dose generation.

| Name | Accepted names | Description |
|---|---|---|
| Use usual (average) exposures per route | DailyAverageEvents | Use usual (average) exposures per route, only one event per day. |
| Use (randomly selected) daily exposures per route | RandomDailyEvents | Use (randomly selected) daily exposures per route and specify events. |

## 6.51 Exposure grouping method

Method used for grouping exposures in bins.

Table 6.51: Unit definition for Exposure grouping method.

| Name | Accepted names | Description |
|---|---|---|
| Custom bins | CustomBins | Define custom bins by providing bin boundaries. |
| ERF-defined bins | ErfDefinedBins | Use bins defined by categories in the exposure response function. |

## 6.52 Exposure method types

Accepted Exposure method types.

Table 6.52: Unit definition for Exposure method types.

| Name | Accepted names | Description |
|---|---|---|
| Manual | Manual | Exposure levels are determined by explicit specification. |
| Automatic | Automatic | Exposure levels are generated automatically based on the estimated exposure distribution. |

## 6.53 Exposure path type

Accepted paths of exposure to chemicals. A path is a combination of a route and the class of exposure sources (i.e., dietary or non-dietary).

Table 6.53: Unit definition for Exposure path type.

| Name | Accepted names | Description |
|---|---|---|
| Dietary exposure | Dietary | Dietary exposure. |
| Oral exposure | Oral | Oral exposure (both from dietary and non-dietary sources). |
| Dermal exposure | Dermal | Dermal exposure. |
| Inhalation exposure | Inhalation | Inhalation exposure. |
| At target | AtTarget | Exposures directly at the target (organ). |

## 6.54 Exposure response specification uncertainty distribution types.

Exposure response specification uncertainty distribution types.

Table 6.54: Unit definition for Exposure response specification uncertainty distribution types..

| Name | Accepted names | Description |
|---|---|---|
| Normal | Normal | Normal distribution parameterised by a mean and upper p95 percentile. |
| LogNormal | LogNormal | LogNormal distribution parameterised by a mean and upper p95 percentile. |
| Triangular | Triangular | Triangular distribution specified by a mode and a lower and upper boundary. |
| Uniform | Uniform | Uniform distribution specified by a mean and upper boundary. |

## 6.55 Exposure response type

Accepted exposure response types.

Table 6.55: Unit definition for Exposure response type.

| Name | Accepted names | Description |
|---|---|---|
| Function | Function | Exposure response expressed as function. |
| PerDoubling | PerDoubling, Doubling | Exposure response expressed as increase per doubling of exposure. |
| PerUnit | PerUnit, Unit | Exposure response expressed as increase per increase of 1 unit of exposure. |
| Constant | Constant | Exposure response expressed as constant value. |

## 6.56 Exposure route

Accepted routes of exposure to chemicals (i.e., oral, dermal, or inhalation).

Table 6.56: Unit definition for Exposure route.

| Name | Accepted names | Description |
|---|---|---|
| Oral | Oral, Dietary | Contact to a chemical via ingestion. |
| Dermal | Dermal | Exposure via contact between a chemical and the skin. |
| Inhalation | Inhalation | Exposure via contact between a chemical and the respiratory system. |

## 6.57 Exposure source

Accepted types of exposure sources, i.e., the origin of the substance(s) for the purpose of an exposure or risk assessment.

Table 6.57: Unit definition for Exposure source.

| Name | Accepted names | Description |
|---|---|---|
| Diet | Diet | Dietary exposure sources. |
| Air | Air | Air exposure sources. |
| Dust | Dust | Dust exposure sources. |
| Soil | Soil | Soil exposure sources. |
| Consumer products | ConsumerProducts | Consumer product exposure sources. |
| Other (non-diet) | OtherNonDiet, Other non-dietary | Other non-dietary exposure sources. |
| Occupational | Occupational | Occupational exposure sources. |

## 6.58 Exposure type

Accepted exposure types.

Table 6.58: Unit definition for Exposure type.

| Name | Accepted names | Description |
|---|---|---|
| Acute | Acute | Acute exposure. |
| Chronic | Chronic | Chronic exposure. |

## 6.59 Expression type

Expression types define the way in which a substance amount may be standardised, or possible other way expressed. For example, a substance in urine may be expressed in terms of a creatinine standardisation.

Table 6.59: Unit definition for Expression type.

| Name | Accepted names | Description |
|---|---|---|
| None | None | No expression type. |
| Lipids | Lipids | Standardise lipid-soluble substances by total lipid content. |
| Creatinine | Creatinine | Standardise substance concentrations by creatinine content. |
| Specific gravity | SpecificGravity, SpecificGravityNormalised, Specific gravity, Specific gravity normalised, SG, SGNormalised, SG normalised | Normalise substance concentrations to specific gravity. |

## 6.60 External exposure unit

Accepted units for external exposures.

Table 6.60: Unit definition for External exposure unit.

| Name | Accepted names |
|---|---|
| gram/kilogram bodyweight/day | gPerKgBWPerDay, g/kg bw/day, g/kg/day, gram/kg bw/day, gr/kg bw/day, G212A |
| milligram/kilogram bodyweight/day | mgPerKgBWPerDay, mg/kg bw/day, mg/kg/day, milligram/kg bw/day, milligr/kg bw/day, G211A |
| microgram/kilogram bodyweight/day | ugPerKgBWPerDay, µg/kg bw/day, µg/kg/day, microgram/kg bw/day, microgr/kg bw/day, G210A |
| nanogram/kilogram bodyweight/day | ngPerKgBWPerDay, ng/kg bw/day, ng/kg/day, nanogram/kg bw/day, nanogr/kg bw/day, G214A |
| picogram/kilogram bodyweight/day | pgPerKgBWPerDay, pg/kg bw/day, picogram/kg bw/day, picogr/kg bw/day |
| femtogram/kilogram bodyweight/day | fgPerKgBWPerDay, fg/kg bw/day, fg/kg/day, femtogram/kg bw/day, femtogr/kg bw/day |
| gram/gram bodyweight/day | gPerGBWPerDay, g/g bw/day, g/g/day, gram/g bw/day, gr/g bw/day |
| milligram/gram bodyweight/day | mgPerGBWPerDay, mg/g bw/day, mg/g/day, milligram/g bw/day, milligr/g bw/day |
| microgram/gram bodyweight/day | ugPerGBWPerDay, µg/g bw/day, µg/g/day, microgram/g bw/day, microgr/g bw/day |
| nanogram/gram bodyweight/day | ngPerGBWPerDay, ng/g bw/day, nanogram/g bw/day, nanogr/g bw/day |
| picogram/gram bodyweight/day | pgPerGBWPerDay, pg/g bw/day, pg/g/day, picogram/g bw/day, picogr/g bw/day |
| femtogram/gram bodyweight/day | fgPerGBWPerDay, fg/g bw/day, fg/g/day, femtogram/g bw/day, femtogr/g bw/day |
| kilogram/day | kgPerDay, kg/day, kilogram/day, kilogr/day |
| gram/day | gPerDay, g/day, gram/day, gr/day, g/d |
| milligram/day | mgPerDay, mg/day, milligram/day, milligr/day, mg/d |
| microgram/day | ugPerDay, µg/day, ug/day, microgram/day, microgr/day, µg/d, ug/d |
| nanogram/day | ngPerDay, ng/day, nanogram/day, nanogr/day, ng/d |
| picogram/day | pgPerDay, pg/day, picogram/day, picogr/day, pg/d |
| femtogram/day | fgPerDay, fg/day, femtogram/day, femtogr/day, fg/d |
| gram/kilogram | gPerKg, g/kg, gram/kg, gr/kg, G015A |
| milligram/kilogram | mgPerKg, mg/kg, milligram/kg, milligr/kg, G061A |
| microgram/kilogram | ugPerKg, µg/kg, microgram/kg, microgr/kg, G050A |
| nanogram/kilogram | ngPerKg, ng/kg, nanogram/kg, nanogr/kg, G077A |
| picogram/kilogram | pgPerKg, pg/kg, picogram/kg, picogr/kg, G081A |
| femtogram/kilogram | fgPerKg, fg/kg, femtogram/kg, femtogr/kg |

## 6.61 Focal commodity replacement method types

Accepted Focal commodity replacement method types.

Table 6.61: Unit definition for Focal commodity replacement method types.

| Name | Accepted names | Description |
|---|---|---|
| Replace samples with focal commodity samples | ReplaceSamples | Replace all samples of the selected focal commodity/commodities. |
| Append focal commodity samples | AppendSamples | Add the samples of the focal commodity/commodities to the background concentration data. |
| Replace measurements of focal food/substance combinations with measurements from focal commodity samples | ReplaceSubstances | Replace the substance concentrations of the background concentrations by substance concentrations from the focal commodity concentration data. |
| Remove measurements of focal food/substance combinations | MeasurementRemoval | Remove substance measurements for the selected focal food/substance combinations. |
| Replace measurements of focal food/substance combinations with proposed concentration limit value from data | ReplaceSubstanceConcentrationsByLimitValue | Replace the substance concentrations of the background concentrations with a proposed concentration limit value from data. |
| Replace measurements of focal food/substance combinations with proposed concentration limit value | ReplaceSubstanceConcentrationsByProposedLimitValue | Replace the substance concentrations of the background concentrations with a proposed concentration limit value (in mg/kg). |

## 6.62 Frequency resolution type

Controlled terminology for specification of frequency resolution.

Table 6.62: Unit definition for Frequency resolution type.

| Name | Accepted names | Description |
|---|---|---|
| Per day | PerDay, Day | Frequency specified in times per day. |
| Per week | PerWeek, Week | Frequency specified in times per week. |
| Per month | PerMonth, Month | Frequency specified in times per month. |

## 6.63 Function types

Accepted Function types.

Table 6.63: Unit definition for Function types.

| Name | Accepted names | Description |
|---|---|---|
| Polynomial | Polynomial | A polynomial regression fits a nonlinear relationship between the value of the independent variable (e.g. age) and the corresponding conditional mean of y (here the exposure). A polynomial with a degree of 0 is simply a constant function; with a degree of 1 is a line; with a degree of 2 is a quadratic; with a degree of 3 is a cubic, and so on. |
| Spline | Spline | A spline fits a nonlinear relationship between the value of the independent variable (e.g. age) and the corresponding conditional mean of y (here the exposure). A spline with a degree of 0 is simply a constant function; with a degree of 1 is a line; with a degree of 2 is a quadratic; with a degree of 3 is a cubic, and so on. |

## 6.64 Hand protection type

Controlled terminology for type of hand protection.

Table 6.64: Unit definition for Hand protection type.

| Name | Accepted names | Description |
|---|---|---|
| None | None | None |
| Gloves | Gloves | Gloves with unspecified protection level. |

## 6.65 Harvest application type

Accepted harvest application types.

Table 6.65: Unit definition for Harvest application type.

| Name | Accepted names | Description |
|---|---|---|
| Pre-harvest application | PreHarvest | Pre-harvest application |
| Post-harvest application | PostHarvest | Post-harvest application |

## 6.66 Hazard characterisation type

Accepted hazard characterisation types.

Table 6.66: Unit definition for Hazard characterisation type.

| Name | Accepted names |
|---|---|
| Benchmark dose | Bmd, BMD |
| No observed adverse effect level | Noael, NOAEL |
| Lowest observed adverse effect level | Loael, LOAEL |
| Acceptable daily intake | Adi, ADI |
| Acute reference dose | Arfd, ARfD, ARfD (from ADI) |
| No observed effect level | Noel, NOEL |
| Tolerable daily intake | Tdi, TDI |
| Tolerable weekly intake | Twi, TWI |
| Benchmark dose lower confidence limit of 1% | Bmdl01, BMDL01 |
| Benchmark dose lower confidence limit of 10% | Bmdl10, BMDL10 |
| Human biomonitoring guidance values | Hbmgv, HBMGV |
| Other | Other |

## 6.67 Hazard characterisations calculation method types

Calculation method types for computing hazard characterisations.

Table 6.67: Unit definition for Hazard characterisations calculation method types.

| Name | Accepted names | Description |
|---|---|---|
| Compute from points of departure | InVivoPods | Compute from points of departure. |
| Compute from dose response models | InVitroBmds | Compute from dose response models. |
| Combine point of departure from index substance with RPFs from dose response models | CombineInVivoPodInVitroDrms | In-vivo Points of Departures for index substance, others using RPFs from in-vitro dose response models |

## 6.68 Hazard dose imputation method types

Accepted Hazard dose imputation method types.

Table 6.68: Unit definition for Hazard dose imputation method types.

| Name | Accepted names | Description |
|---|---|---|
| Munro P5 (TTC approach) | MunroP5 | Use the P5 of the Munro NOEL collection. |
| Munro central value | MunroUnbiased | Use an unbiased nominal value from the Munro NOEL collection; draw randomly from this collection in the uncertainty runs. |
| Available hazard characterisations distribution P5 | HazardDosesP5 | Use the P5 of the available points of departure. |
| Available hazard characterisations distribution central value | HazardDosesUnbiased | Use an unbiased nominal value from the collection of available points of departure; draw randomly from this collection in the uncertainty runs. |

## 6.69 Health effect types

Accepted Health effect types.

Table 6.69: Unit definition for Health effect types.

| Name | Accepted names | Description |
|---|---|---|
| Risk | Risk | Health effect is negative (risk). |
| Benefit | Benefit | Health effect is positive (benefit). |

## 6.70 Individual property type

Accepted individual property types.

Table 6.70: Unit definition for Individual property type.

| Name | Accepted names | Description |
|---|---|---|
| Categorical | Categorical | Categorical e.g. blood type A, B, AB, O or region East, West, North, South. |
| Boolean | Boolean | Boolean e.g. yes, no, true, false. See Boolean types unit definitions. |
| Numeric | Numeric | Numeric, real numbers. |
| Nonnegative | Nonnegative | Nonnegative real numbers, positive or zero. |
| Integer | Integer | Integer, integer numbers. |
| NonnegativeInteger | NonnegativeInteger | NonnegativeInteger integer numbers, positive or zero. |
| Month | Month | Month. See Month types unit definitions. |
| DateTime | DateTime | DateTime, period. |
| Gender | Gender, Sex | Gender or sex. At present, these terms are used interchangeably when making selections on individual properties. See Gender types unit definitions. |
| Location | Location | Location, country. |
| Isced | Isced, Education | ISCED, education level. See Isced types unit definitions. |
| JobTask | JobTask, WorkTask | Job task. See JobTask types unit definitions. |

## 6.71 Individual reference set

Methods for obtaining individuals for calculating air exposures.

Table 6.71: Unit definition for Individual reference set.

| Name | Accepted names | Description |
|---|---|---|
| Use individuals from individuals module | Simulate | Use individuals from individuals module. |
| Use individuals from dietary exposures | UseDietaryExposures | Use individuals from dietary exposures module. |

## 6.72 Individual reference set

Methods for obtaining individuals for calculating dust exposures.

Table 6.72: Unit definition for Individual reference set.

| Name | Accepted names | Description |
|---|---|---|
| Use from individuals module | Simulate | Use individuals from individuals module. |
| Use individuals from dietary exposures module | UseDietaryExposures | Use individuals from dietary exposures module. |

## 6.73 Individual reference set

Methods for obtaining individuals for calculating soil exposures.

Table 6.73: Unit definition for Individual reference set.

| Name | Accepted names | Description |
|---|---|---|
| Use individuals from individuals module | Simulate | Use individuals from individuals module. |
| Use individuals from dietary exposures | UseDietaryExposures | Use individuals from dietary exposures module. |

## 6.74 Individual subset types

Methods for selecting/matching survey individuals with a specified/scoped population.

Table 6.74: Unit definition for Individual subset types.

| Name | Accepted names | Description |
|---|---|---|
| Match individuals selection to population definition | MatchToPopulationDefinition | Match individuals selection to population definition. |
| Ignore population definition (use all individuals in survey) | IgnorePopulationDefinition | Ignore population definition (use all individuals in survey). |
| Match individuals selection to population definition using selected properties only | MatchToPopulationDefinitionUsingSelectedProperties | Match individuals selection to population definition using selected properties only. |

## 6.75 Intake model types

Accepted Intake model types.

Table 6.75: Unit definition for Intake model types.

| Name | Accepted names | Description |
|---|---|---|
| Observed Individual Means | OIM | Observed Individual Means: just the empirical means over the observed days. |
| BetaBinomial Normal | BBN | BetaBinomial distribution for frequency of exposure + (transformed) Normal distribution for amounts (de Boer et al. 2009). |
| Logistic-Normal Normal | LNN0 | Logistic-Normal distribution for frequency of exposure + (transformed) Normal distribution for amounts. |
| Logistic-Normal Normal with correlation | LNN | Logistic-Normal distribution for frequency of exposure + (transformed) Normal distribution for amounts. Both models are estimated taking into account the correlation between exposure frequency and amounts. |
| Iowa State University Foods model | ISUF | Iowa State University Foods model: semiparametric distribution for frequency of exposure + (transformed) Normal distribution for amounts (de Boer et al. 2009, Dodd (1996)). |

## 6.76 Internal model type

Methods for translating between different (internal/external) exposure targets.

Table 6.76: Unit definition for Internal model type.

| Name | Accepted names | Description |
|---|---|---|
| Use kinetic conversion factors | ConversionFactorModel, ConversionFactor | Use (low-tier) kinetic conversion factor models. |
| Use PBK models with fallback on kinetic conversion factors | PBKModel, PBK | Use (high-tier) PBK models with fallback on (low-tier) kinetic conversion factors. |
| Use PBK models | PBKModelOnly, PBKOnly | Use (high-tier) PBK models. |

## 6.77 Isced type

Accepted International Standard Classification of Education (ISCED) types.

Table 6.77: Unit definition for Isced type.

| Name | Accepted names | Description |
|---|---|---|
| EarlyChildhoodEducation | ECE, EarlyChildhoodEducation | Early childhood education |
| PrimaryEducation | PE, PrimaryEducation | Primary education |
| LowerSecondaryEducation | LSE, LowerSecondaryEducation | Lower secondary education |
| UpperSecondaryEducation | USE, UpperSecondaryEducation | Upper secondary education |
| PostSecondaryNonTertiaryEducation | PSNTE, PostSecondaryNonTertiaryEducation | Post-secondary non-tertiary education |
| ShortCycleTertiaryEducation | SCTE, ShortCycleTertiaryEducation | Short-cycle tertiary education |
| BachelorsOrEquivalentLevel | BOEL, BachelorsOrEquivalentLevel | Bachelor's or equivalent level |
| MastersOrEquivalentLevel | MOEL, MastersOrEquivalentLevel | Master's or equivalent level |
| DocteralOrEquivalentLevel | DOEL, DocteralOrEquivalentLevel | Docteral or equivalent level |

## 6.78 Job task exposure estimate type

Accepted job exposure estimate types.

Table 6.78: Unit definition for Job task exposure estimate type.

| Name | Accepted names | Description |
|---|---|---|
| 8h TWA | TWA8h, 8hTWA, 8h TWA | Exposure estimate is an 8-hour time-weighted average (TWA). |
| LTA | LTA | Long-term average exposure estimate. |

## 6.79 Job task exposure unit

Accepted units for job exposure activities.

Table 6.79: Unit definition for Job task exposure unit.

| Name | Accepted names | Description |
|---|---|---|
| µg/cm2/day | ugPerCm2PerDay, µg/cm2/day, ug/cm2/day | Exposure expressed in micrograms per square centimeter (µg/cm2) per day. |
| mg/cm2/day | mgPerCm2PerDay, mg/cm2/day | Exposure expressed in milligrams per square centimeter (mg/cm2) per day. |
| µg/m3 | ugPerM3, µg/m3 | Exposure expressed in micrograms per cubic meters (µg/m3). |
| mg/m3 | mgPerM3, mg/m3 | Exposure expressed in milligrams per cubic meters (mg/m3). |
| µg/day | ugPerDay, µg/day, ug/day, µg/d, ug/d | Exposure expressed in micrograms per day (µg/day). |
| mg/day | mgPerDay, mg/day, mg/d | Exposure expressed in milligrams per day (mg/day). |

## 6.80 Job task type

Accepted Job Task types.

Table 6.80: Unit definition for Job task type.

| Name | Accepted names | Description |
|---|---|---|
| BathPlating | BP, BathPlating | Bath plating |
| ChromePaintApplications | CPA, ChromePaintApplications | Chrome paint applications |
| Machining | MA, Machining | Machining |
| Welding | WE, Welding | Welding |
| ThermalSpraying | TS, ThermalSpraying | Thermal spraying |
| SteelProduction | SP, SteelProduction | Steel production |
| MaintenanceAndLaboratoryWorkers | MALW, MaintenanceAndLaboratoryWorkers | Maintenance and laboratory workers |

## 6.81 Kinetic conversion factor uncertainty distribution types.

Kinetic conversion factor uncertainty distribution types.

Table 6.81: Unit definition for Kinetic conversion factor uncertainty distribution types..

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and upper p95 percentile. |
| Uniform | Uniform | Uniform distribution specified by a mean/median and an upper boundary. |
| InverseUniform | InverseUniform | Inverse uniform distribution specified by a median and an upper boundary. |

## 6.82 Kinetic conversion method type

Methods for translating between different (internal/external) exposure targets.

Table 6.82: Unit definition for Kinetic conversion method type.

| Name | Accepted names | Description |
|---|---|---|
| Use kinetic conversion factors | ConversionFactorModel, ConversionFactor | Use (low-tier) kinetic conversion factor models. |
| Use PBK models | PbkModel, PBKModelOnly, PBKOnly | Use (high-tier) PBK models. |
| Use PBK models with fallback on kinetic conversion factors | PbkWithFallback, PBKModel, PBK | Use (high-tier) PBK models with fallback on (low-tier) kinetic conversion factors. |

## 6.83 Left-censored data handling methods

Methods for handling left-censored data (i.e., imputation/substitution).

Table 6.83: Unit definition for Left-censored data handling methods.

| Name | Accepted names | Description |
|---|---|---|
| Replace all left-censored values by zero | ReplaceByZero | All left-censored measurements are assumed to be zero's (set to 0). |
| Replace all left-censored values by f * LOR | ReplaceByLOR | All left-censored measurements are substituted by f * LOR where f is a constant. Here, the term LOR (limit-of-reporting) is a generic term for LOD and LOQ. If both LOD and LOQ are available, then LOQ is used, also for non-detects (i.e., measurements reported as <LOD). |
| Replace non-detects by f * LOD and non-quantifications by LOD + f * (LOQ - LOD) | ReplaceByLODLOQSystem | Non-detects are replaced by f * LOD; non-quantifications are replaced by LOD + f * (LOQ - LOD), where f is a constant. |
| Replace non-detects by 0 and non-quantifications by f * LOQ | ReplaceByZeroLOQSystem | Non-detects are replaced by 0; non-quantifications are replaced by f * LOQ, where f is a constant. |

## 6.84 Mean value correction types

Accepted Mean value correction types.

Table 6.84: Unit definition for Mean value correction types.

| Name | Accepted names | Description |
|---|---|---|
| Unbiased | Unbiased | The mean of the lognormal is unbiased (bias correction). |
| Biased | Biased | The mean of the lognormal is biased (no bias correction). |

## 6.85 Measurement result type

Specifies the type of a measurement result. E.g., a positive value, a non-detect, or missing value.

Table 6.85: Unit definition for Measurement result type.

| Name | Accepted names | Description |
|---|---|---|
| VAL | VAL | Positive measurement greater than zero. |
| LOD | LOD | Measurement below the limit of detection (LOD). |
| LOQ | LOQ | Measurement below the limit of quantification (LOQ). |
| MV | MV | Missing value (MV). |

## 6.86 Missing value imputation method types

Missing value imputation method types.

Table 6.86: Unit definition for Missing value imputation method types.

| Name | Accepted names | Description |
|---|---|---|
| By zero | SetZero | Set missing values to zero. |
| Impute from data | ImputeFrom-Data | Replace missing measurements by random other measurements of the same substance, biological matrix and sampling type. |
| No missing value imputation | NoImputation | No missing value imputation, all missing values remain in the data set and samples with missing values will be removed before analysis. |

## 6.87 Modelled foods calculation source types

Accepted Modelled foods calculation source types.

Table 6.87: Unit definition for Modelled foods calculation source types.

| Name | Accepted names | Description |
|---|---|---|
| Derive modelled foods from concentrations | DeriveModelledFoodsFromSampleBasedConcentrations | Derive modelled foods from sample based concentration data. |
| Derive modelled foods from single value concentrations | DeriveModelledFoodsFromSingleValueConcentrations | Derive modelled foods from single value concentrations. |
| Derive modelled foods from concentration limits | UseWorstCaseValues | Derive modelled foods from concentration limits. |

## 6.88 Month type

Accepted months types.

Table 6.88: Unit definition for Month type.

| Name | Accepted names |
|---|---|
| January | January, Jan, Januari, 1 |
| February | February, Feb, Februari, 2 |
| March | March, Mar, 3 |
| April | April, Apr, 4 |
| May | May, 5 |
| June | June, Jun, 6 |
| July | July, Jul, 7 |
| August | August, Aug, 8 |
| September | September, Sep, Sept, 9 |
| October | October, Oct, 10 |
| November | November, Nov, 11 |
| December | December, Dec, 12 |

## 6.89 Multiple substance handling method types

Accepted Multiple substance handling method types.

Table 6.89: Unit definition for Multiple substance handling method types.

| Name | Accepted names | Description |
|---|---|---|
| Combined assessment of selected substances | Cumulate | Combined assessment of selected substances. |
| Loop over selected substances | LoopSubstances | Loop over selected substances. |

## 6.90 Network analysis type

Accepted Network analysis types.

Table 6.90: Unit definition for Network analysis type.

| Name | Accepted names | Description |
|---|---|---|
| No network analysis | NoNetwork-Analysis | No network analysis is applied. |
| Apply network analysis | NetworkAnaly-sis | Network analysis is applied on the substance x component (U) matrix. |

## 6.91 Nondetect imputation method types

Accepted nondetect imputation method types.

Table 6.91: Unit definition for Nondetect imputation method types.

| Name | Accepted names | Description |
|---|---|---|
| Replace by LOR/LOQ/LOD | Replace-ByLimit | Non-quantifications are replaced by f * LOR or f * LOD or by LOD + f * (LOQ - LOD) where f is a constant. |
| Impute from censored lognormal distribution | CensoredLog-Normal | Replace nondetect measurements by a random draw from the lower (left) tail of the censored lognormal distribution. |

## 6.92 Occupational exposure calculation method

Available methods for calculating modelled occupational exposures.

Table 6.92: Unit definition for Occupational exposure calculation method.

| Name | Accepted names | Description |
|---|---|---|
| Compute for single individual | SingleIndividual | Compute for single individual. |
| Compute for individual set | IndividualSet | Compute for a set of individuals. |

## 6.93 Occupational exposure model type

Exposure model types for occupational exposures.

Table 6.93: Unit definition for Occupational exposure model type.

| Name | Accepted names | Description |
|---|---|---|
| Use percentile point | Percentile | Constant model from selected distribution percentile. |
| Use distribution | Distribution | A parametric model is fitted on the provided distribution percentiles. |

## 6.94 Output stratification variable

Supported variables to categorise individuals into distinct subgroups for stratified presentation outputs.

Table 6.94: Unit definition for Output stratification variable.

| Name | Accepted names | Description |
|---|---|---|
| Sex | Sex | Stratify individuals by sex. |
| Occupational scenario | OccupationalScenario | Stratify by occupational scenario. |
| Case control | CaseControl | Stratify by occupational scenario case control. |
| Age | Age | Stratify individuals by age group. |

## 6.95 PBK model compartment type

PBK model compartment type definitions.

Table 6.95: Unit definition for PBK model compartment type.

| Name | Accepted names |
|---|---|
| Other | Other |
| alveolar air compartment | AlveolarAir |
| arterial blood compartment | ArterialBlood |
| arterial plasma compartment | ArterialPlasma |
| Blood compartment | Blood |
| blood plasma compartment | BloodPlasma |
| fat compartment | Fat |
| feces compartment | Feces |
| gut compartment | Gut |
| gonads compartment | Gonads |
| heart compartment | Heart |
| kidney compartment | Kidney |
| liver compartment | Liver |
| lung compartment | Lung |
| poorly perfused tissue compartment | PoorlyPerfusedTissue |
| rest-of-body compartment | RestOfBody |
| richly perfused tissue compartment | RichlyPerfusedTissue |
| skin compartment | Skin |
| exposed skin compartment | ExposedSkin |
| unexposed exposed skin compartment | UnexposedSkin |
| stratum corneum exposed skin compartment | StratumCorneumExposedSkin |
| stratum corneum unexposed skin compartment | StratumCorneumUnexposedSkin |
| urine compartment | Urine |
| uterus compartment | Uterus |
| venous blood compartment | VenousBlood |
| venous plasma compartment | VenousPlasma |
| viable epidermis exposed skin compartment | ViableEpidermisExposedSkin |
| viable epidermis unexposed skin compartment | ViableEpidermisUnexposedSkin |

## 6.96 PBK model parameter distribution types.

Probability distribution types for PBK model parameters.

Table 6.96: Unit definition for PBK model parameter distribution types..

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and two coefficients of variation (CVs), one representing variability around the mean and the other reprenting uncertainty of the mean. |
| Normal | Normal | Normal distribution parameterised by a mean and two standard deviations (SDs), one representing variability around the mean and the other reprenting uncertainty of the mean. |
| Logistic Normal | LogisticNormal | Logistic Normal distribution parameterised by a mean and two coefficients of variation (CVs), one representing variability around the mean and the other reprenting uncertainty of the mean. |
| Deterministic | Deterministic, Constant | Deterministic distribution. |

## 6.97 PBK model parameter type

PBK model parameter type definitions.

Table 6.97: Unit definition for PBK model parameter type.

| Name | Accepted names | Description |
|---|---|---|
| Other | Other | |
| physiological parameter | Physiological | |
| sex | Sex, Gender | |
| age | Age | Age of individual (during simulation). |
| age | AgeInit | (Initial) age of individual (i.e. at start of simulation). |
| reference age | AgeRef | Reference age of individual (e.g. age at time of measuring the reference body weight, see reference body weight). |
| Delta bodyweight | DeltaBody-Weight | Relative different of individual body weight compared to nominal population bodyweight. |
| body weight | BodyWeight, BW | |
| reference body weight | Body-WeightRef, BWRef | Reference body weight of individual measured at a certain age. |
| body surface area | Body-SurfaceArea, BSA | |
| body mass index | BodyMassIn-dex, BMI | |
| height | Height | |
| physicochemi-cal parameter | Physicochemi-cal | |
| molecular weight | Molecular-Weight, MW | |
| metabolic parameter | Metabolic | |
| partition coefficient | PartitionCoeffi-cient, PC | |

## 6.98 PBK model species type

PBK model species type definitions.

Table 6.98: Unit definition for PBK model species type.

| Name | Accepted names | Description |
|---|---|---|
| human | Human | Human |
| Mice | Mice | Mice |

## 6.99 PBK output resolution time unit

Time unit for specification of the evaluation/output resolution of PBK model simulations.

Table 6.99: Unit definition for PBK output resolution time unit.

| Name | Accepted names | Description |
|---|---|---|
| Use model time unit | ModelTimeUnit | Use model time resolution. |
| Minutes | Minutes | PBK simulation output resolution is specified in minutes. |
| Hours | Hours | PBK simulation output resolution is specified in hours. |
| Days | Days | PBK simulation output resolution is specified in days. |

## 6.100 PBK simulation methods

PBK simulation methods.

Table 6.100: Unit definition for PBK simulation methods.

| Name | Accepted names | Description |
|---|---|---|
| Standard PBK model simulation | Standard | Standard PBK model simulation, starting at current age and run simulation for specified time period. |
| Lifetime model simulation from birth to current age | LifetimeToCurrentAge | Run lifetime PBK model simulation from birth until current age. |
| Lifetime model simulation from birth to specified age | LifetimeToSpecifiedAge | Run lifetime PBK model simulation from birth until specified age. |
| Lifetime model simulation over a window until current age | LifetimeWindowToCurrent | Run lifetime PBK model simulation over a given window of years up to the current age. |
| Lifetime model simulation over a specified age range | LifetimeRange | Run lifetime PBK model simulation over a specified age range. |
| Lifetime model simulation from current to specified age | LifetimeCurrentToSpecifiedAge | Run lifetime PBK model simulation from current age until a specified end age. |
| Lifetime model simulation from current to specified years forward | LifetimeCurrentAgeForward | Run lifetime PBK model simulation from current age forward for a given number of years. |

## 6.101 Point of departure type

Accepted point of departure types.

Table 6.101: Unit definition for Point of departure type.

| Name | Accepted names |
|---|---|
| Benchmark dose | Bmd, BMD |
| No observed adverse effect level | Noael, NOAEL |
| Lowest observed adverse effect level | Loael, LOAEL |
| No observed effect level | Noel, NOEL |
| Median lethal dose | Ld50, LD50 |
| Benchmark dose lower confidence limit of 1% | Bmdl01, BMDL01 |
| Benchmark dose lower confidence limit of 10% | Bmdl10, BMDL10 |

## 6.102 Point of departure types

Accepted Point of departure types.

Table 6.102: Unit definition for Point of departure types.

| Name | Accepted names | Description |
|---|---|---|
| Unspecified (no conversion to common expression type) | FromReference | Do not convert non-standard point of departures. |
| BMD (convert all hazard characterisations as BMDs) | BMD | Convert all point of departures to bench mark doses. |
| NOAEL (convert all hazard characterisations as NOAELs) | NOAEL | Convert all point of departures to NOAELs. |

## 6.103 Population alignment method

The population alignment method used for the selected exposure source.

Table 6.103: Unit definition for Population alignment method.

| Name | Accepted names | Description |
|---|---|---|
| Match completely at random | MatchRandom | Match completely at random. |
| Match at individual level | MatchIndividualID, MatchIndividualId | Match at individual level (on individual ID). |
| Match at random based on cofactors (stratified at random) | MatchCofactors | Match at random based on cofactors (stratified at random). |

## 6.104 Population characteristic distribution types.

Distribution types used to described population characteristics.

Table 6.104: Unit definition for Population characteristic distribution types..

| Name | Accepted names | Description |
|---|---|---|
| Normal | Normal | Normal distribution parameterised by a mean and a coefficient of variation. |
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and a coefficient of variation. |
| Uniform | Uniform | Uniform distribution specified by a mean/median and a coefficient of variation. |

## 6.105 Population characteristic type

Different characteristic types that can be used to describe a population.

Table 6.105: Unit definition for Population characteristic type.

| Name | Accepted names | Description |
|---|---|---|
| IQ | IQ | Intelligence quotient. |
| BirthWeight | BirthWeight | Body weight of a baby at their birth. |

## 6.106 Population size uncertainty distribution types.

Population size uncertainty distribution types.

Table 6.106: Unit definition for Population size uncertainty distribution types..

| Name | Accepted names | Description |
|---|---|---|
| Normal | Normal | Normal distribution parameterised by a mean and and upper p95 percentile. |
| Triangular | Triangular | Triangular distribution specified by a mode and a lower and upper boundary. |

## 6.107 Processing distribution type

Accepted processing distribution types.

Table 6.107: Unit definition for Processing distribution type.

| Name | Accepted names | Description |
|---|---|---|
| Logistic Normal distribution | LogisticNormal, 1 | Logisticnormal distribution. |
| Log Normal distribution | LogNormal, 2 | Lognormal distribution. |

## 6.108 Property level type

Accepted property level types.

Table 6.108: Unit definition for Property level type.

| Name | Accepted names | Description |
|---|---|---|
| Individual | Individual | Individual level. |
| IndividualDay | IndividualDay | IndividualDay. |

## 6.109 Protective clothing type

Controlled terminology for type of protective clothing.

Table 6.109: Unit definition for Protective clothing type.

| Name | Accepted names | Description |
|---|---|---|
| None | None | No protective clothing |
| Protective clothing | Protective-Clothing, PC, PPC | Personal protective clothing with unspecified protection level. |

## 6.110 RPE type

Controlled terminology for type of RPE.

Table 6.110: Unit definition for RPE type.

| Name | Accepted names | Description |
|---|---|---|
| None | None | None |
| RPE | RPE | RPE |

## 6.111 Reference individual set

Reference individual set.

Table 6.111: Unit definition for Reference individual set.

| Name | Accepted names | Description |
|---|---|---|
| Diet | Diet | Individuals from the dietary exposures module. |
| Consumer products | ConsumerProducts | Individuals from the consumer product exposures module. |
| Air | Air | Individuals from the air exposures module. |
| Dust | Dust | Individuals from the dust exposures module. |
| Soil | Soil | Individuals from the soil exposures module. |
| Individuals | Individuals | Individuals collected/generated in the individuals module. |

## 6.112 Response type

Accepted response types.

Table 6.112: Unit definition for Response type.

| Name | Accepted names | Description |
|---|---|---|
| Continuous multiplicative | ContinuousMultiplicative | Response values are positive real numbers, e.g., weight, size. |
| Continuous additive | ContinuousAdditive | Response values are real numbers, e.g., weight change, temperature. |
| Binary | Binary | Response values have binary outcomes (yes/no, true/false, success/failure, 0/1, etc.). |
| Quantal | Quantal, Binomial | Response is measured in terms of number of successes out of N possible. |
| Quantal group | QuantalGroup | Individual responses are measured as binary values, which may be grouped to form a quantal response. |
| Count | Count | Number of items (cells, molecules, deaths, etc.) in given interval/area/volume. |
| Ordinal | Ordinal | Relative scores (or graded scores) useable only for ranking. |

## 6.113 Risk characterisation ratio

The form of the ratio for expressing risk based on an exposure estimate and a hazard threshold value. This can be either exposure/hazard or hazard/exposure.

Table 6.113: Unit definition for Risk characterisation ratio.

| Name | Accepted names | Description |
|---|---|---|
| hazard/exposure | HazardExposureRatio | Express risk as the ratio hazard/exposure (e.g., MOE(T)). |
| exposure/hazard | ExposureHazardRatio | Express risk as the ratio exposure/hazard (e.g., HI,HQ, RPI). |

## 6.114 Riskmetric calculation types

Accepted Riskmetric calculation types.

Table 6.114: Unit definition for Riskmetric calculation types.

| Name | Accepted names | Description |
|---|---|---|
| RPF weighted | RPFWeighted | Calculates risk as a single ratio involving cumulative RPF-weighted exposures. |
| Sum of risk characterisation ratios | SumRatios | Calculate risk as sum of ratios of exposure and hazard. |

## 6.115 Selected exposure routes

Selected exposure routes for inclusion in exposure calculations.

Table 6.115: Unit definition for Selected exposure routes.

| Name | Accepted names | Description |
|---|---|---|
| Dermal exposure | Dermal | Dermal exposure. |
| Inhalation exposure | Inhalation | Inhalation exposure. |

## 6.116 Sex type

Controlled vocabulary for biological sex (at birth).

Table 6.116: Unit definition for Sex type.

| Name | Accepted names | Description |
|---|---|---|
| Female | Female, F, Femme, Frau | Female |
| Male | Male, M, Homme, Mann | Male |

## 6.117 Shift types.

Controlled vocabulary for shift types.

Table 6.117: Unit definition for Shift types..

| Name | Accepted names | Description |
|---|---|---|
| Pre-shift | PreShift | Pre-shift. |
| Post-shift | PostShift | Post-shift. |

## 6.118 Shorter than lifetime residue generation method

Methods for generating residues for shorter than lifetime exposure calculations.

Table 6.118: Unit definition for Shorter than lifetime residue generation method.

| Name | Accepted names | Description |
|---|---|---|
| Use means | UseMeans | Use means as in chronic exposure calculations. |
| Random per consumption | RandomPer-Consumption | Use random values per consumption, as in acute exposure calculations. |

## 6.119 Single value dietary exposures calculation method types

Accepted Single value dietary exposures calculation method types.

Table 6.119: Unit definition for Single value dietary exposures calculation method types.

| Name | Accepted names | Description |
|---|---|---|
| IESTI | IESTI | IESTI. |
| IESTI new | IESTINew | IESTI new. |
| TMDI | TMDI | Theoretical Maximum Daily Intake. |
| IEDI | IEDI | International Estimated Daily Intake. |
| Rees–Day model (I) | NEDI1 | Rees–Day model (I). |
| Rees–Day model (II) | NEDI2 | Rees–Day model (II). |

## 6.120 Single value risk calculation method types

Accepted Single value risk calculation method types.

Table 6.120: Unit definition for Single value risk calculation method types.

| Name | Accepted names | Description |
|---|---|---|
| From single value dietary exposures | FromSingleValues | From single value dietary exposures and hazard characterisations. |
| As percentile from risks distribution | FromIndividualRisks | As percentile from risks distribution. |

## 6.121 Soil concentration uncertainty distribution types.

Soil concentration uncertainty distribution types.

Table 6.121: Unit definition for Soil concentration uncertainty distribution types..

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and a coefficient of variation. |

## 6.122 Soilingestion uncertainty distribution types.

Soil ingestion uncertainty distribution types.

Table 6.122: Unit definition for Soilingestion uncertainty distribution types..

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and a coefficient of variation. |
| Uniform | Uniform | Uniform distribution specified by a mean/median and a coefficient of variation. |

## 6.123 Standardise blood methods

Accepted Standardise blood methods.

Table 6.123: Unit definition for Standardise blood methods.

| Name | Accepted names | Description |
|---|---|---|
| Standardise by total lipid measured via gravimetric analysis | GravimetricAnalysis | Standardise by total lipid measured via gravimetric analysis. |
| Standardise by total lipid measured via enzymatic summation | EnzymaticSummation | Standardise by total lipid measured via enzymatic summation. |
| Standardise by derived total lipid content of Triglycerides/Cholesterc (Bernert et al. 2007) | BernertMethod | Standardise by derived total lipid content (Bernert et al. 2007). |

## 6.124 Standardise/normalise urine concentration method

Accepted Standardise urine concentration methods based on creatinine.

Table 6.124: Unit definition for Standardise/normalise urine concentration method.

| Name | Accepted names | Description |
|---|---|---|
| Normalise by specific gravity | SpecificGravity | Normalise by specific gravity. Levine and Fahy (1945). |
| Standardise by creatinine concentration | CreatinineStandardisation | Standardise by creatinine concentration. |
| Normalise by specific gravity derived from creatinine, adults (Carrieri et al. 2001) | SpecificGravityCreatinineAdjustment | A specific gravity adjustment is applied by multiplying a creatinine adjusted concentration with a factor (default 1.48 for adults 18 - 68 year). |
| Normalise by specific gravity derived from nonlinear modelling of creatinine, children 6 - 14 yr (Busgang et al. 2023, model 1) | SpecificGravityCreatinineNonlinearModelOne | A specific gravity adjustment is applied by nonlinear modelling of a creatinine adjusted concentration, using model 1 of table 3 of Busgang et al. 2023 (children 6 - 14 year). |
| Normalise by specific gravity derived from nonlinear modelling of creatinine, children 6 - 14 yr, age and gender dependent (Busgang et al. 2023, model 2) | SpecificGravityCreatinineNonlinearModelTwo | A specific gravity adjustment is applied by nonlinear modelling of a creatinine adjusted concentration, using the age and gender dependent model 2 of table 3 of Busgang et al. 2023 (children 6 - 14 year). |

## 6.125 Substance group selection method types

Accepted Substance group selection method types.

Table 6.125: Unit definition for Substance group selection method types.

| Name | Accepted names | Description |
|---|---|---|
| All substances | IncludeAll | Include all substances of the substances table and use hazard characterisation imputation for missing hazard data. |
| Restrict to available hazard data | RestrictHazardDoseRpf | Restrict to the substances with available hazard data (either in the form of dose response models or RPFs). |
| Restrict to available hazard data and possible membership | RestrictHazardDoseRpfAndProbableMembership | Consider only the substances with available hazard data and non-zero membership (i.e., P(AG) > 0). |
| Restrict to available hazard data and certain membership | RestrictHazardDoseRpfAndCertainMembership | Consider only substances with certain assessment group membership (i.e., P(AG) = 1) and for which a hazard characterisation is available. |
| Restrict to non-zero membership | RestrictProbableMembership | Consider all substances, use TTC based on the Cramer class for the substances for which no limit dose or RPF is defined. |
| Restrict to certain membership | RestrictCertainMembership | Consider only the substances with certain assessment group membership (i.e., P(AG) = 1). |

## 6.126 Substance translation allocation method types

Accepted Substance translation allocation method types.

Table 6.126: Unit definition for Substance translation allocation method types.

| Name | Accepted names | Description |
|---|---|---|
| Random allocation | DrawRandom | Random allocation. |
| Allocate most potent | UseMostToxic | Allocate most potent active substance. |
| Allocate least potent | UseLeastToxic | Allocate least potent active substance. |
| Nominal estimate | NominalEstimates | Allocate nominal estimate (weighted average allocation). |
| Allocate to all | AllocateToAll | Allocate for each active substance independently as if all concentrations were allocated to this active substance. |

## 6.127 Target dose selection method types

Accepted Target dose selection method types.

Table 6.127: Unit definition for Target dose selection method types.

| Name | Accepted names | Description |
|---|---|---|
| Select most toxic | MostToxic | Choose the most toxic (default). |
| Take aggregate | Aggregate | Choose an aggregated hazard characterisation when there there are multiple available candidates in nominal runs. |
| Random draw | Draw | Draw a random hazard characterisation. |

## 6.128 Target level type

The exposure target level indicates whether an exposure/dose is assumed to be an internal (target) concentration, an external dose, or an internal (systemic) dose.

Table 6.128: Unit definition for Target level type.

| Name | Accepted names | Description |
|---|---|---|
| External dose | External, ExternalDose | The administered or external dose, often referred to as exposure or intake. |
| Internal (systemic) dose | Systemic, InternalDose | The absorbed dose is the amount of chemical that is systemically available and can be regarded as the fraction of the external dose that is absorbed and enters the general circulation. |
| Internal (target) concentration | Internal, InternalConcentration | Internal dose or target dose (tissue dose) is the amount of chemical present in a specific target of interest, i.c. a concentration. |

## 6.129 Test system type

Accepted test system types.

Table 6.129: Unit definition for Test system type.

| Name | Accepted names | Description |
|---|---|---|
| In vivo | InVivo | In vivo |
| Cell line | CellLine | CellLine |
| Primary cells | PrimaryCells, StemCells, Embryo | PrimaryCells |
| Tissue | Tissue | Tissue |
| Organ | Organ | Organ |

## 6.130 Testing method types

Accepted testing method types.

Table 6.130: Unit definition for Testing method types.

| Name | Accepted names | Description |
|---|---|---|
| Backward | Backward | Backward selection starts with selecting a model with a function of the highest degree. Then, the degree of the function is decreased by one and the model is tested again. This process is repeated until decreasing the degree does not improve the model fit anymore. |
| Forward | Forward | Forward selections starts with selecting a model with a function of the lowest degree. Then, the degree of the function is increased by one and the model is tested again. This process is repeated until increasing the degree does not improve the model fit anymore. |

## 6.131 Time unit

Supported time units.

Table 6.131: Unit definition for Time unit.

| Name | Accepted names | Description |
|---|---|---|
| seconds | Seconds, sec | Seconds |
| minutes | Minutes, min | In minutes |
| hours | Hours, h | In hours |
| days | Days, d | days |

## 6.132 Transform types

Accepted Transform types.

Table 6.132: Unit definition for Transform types.

| Name | Accepted names | Description |
|---|---|---|
| Logarithmic | Logarithmic | Exposure amounts are transformed to normality using a logarithmic transformation. |
| No transformation | NoTransform | Exposure amounts are not transformed. |
| Power | Power | Exposure amounts are transformed to normality using a Box-Cox power transformation. |

## 6.133 Uncertainty types

Accepted Uncertainty types.

Table 6.133: Unit definition for Uncertainty types.

| Name | Accepted names | Description |
|---|---|---|
| Empirical | Empirical | Data are taken as such. |
| Parametric | Parametric | A parametric model is fitted to the data. |

## 6.134 Unit variability correlation types

Accepted Unit variability correlation types.

Table 6.134: Unit definition for Unit variability correlation types.

| Name | Accepted names | Description |
|---|---|---|
| No correlation | NoCorrelation | The unit residue values for unit portions (consumption amount/unitweight) are randomly drawn, explicitly ignoring any correlation between unit residues. |
| Full correlation | FullCorrelation | The unit residue values for unit portions (consumption amount/unitweight) are randomly drawn, explicitly introducing correlation between unit residues, e.g. high (small) values occur more frequently together. |

## 6.135 Unit variability model types

Accepted Unit variability model types.

Table 6.135: Unit definition for Unit variability model types.

| Name | Accepted names | Description |
|---|---|---|
| Beta distribution | BetaDistribution | Requires knowledge of the number of units in a composite sample, and of the variability between units (realistic or conservative estimates). Under the beta model, the simulated unit values are drawn from a bounded distribution on the interval. |
| Lognormal distribution | LogNormalDistribution | Requires only knowledge of the variability between units (realistic or conservative estimates). The lognormal distribution is considered as an appropriate model for many empirical positive concentration distributions (unbounded distribution). |
| Bernoulli distribution | BernoulliDistribution | Requires only knowledge of the number of units in a composite sample (results are always conservative). The bernoulli model is a limiting case of the beta model, which can be used if no information on unit variability is available, but only the number of units in a composite sample is known. |

## 6.136 Unit variability types

Accepted Unit variability types.

Table 6.136: Unit definition for Unit variability types.

| Name | Accepted names | Description |
|---|---|---|
| Variation coefficient | VariationCoefficient | Standard deviation divided by the mean. |
| Variability factor | VariabilityFactor | Defined as 97.5th percentile divided by the mean. |

## 6.137 Unit weight value type

Accepted unit weight types.

Table 6.137: Unit definition for Unit weight value type.

| Name | Accepted names | Description |
|---|---|---|
| Unit weight RAC | UnitWeightRac, UnitWeightRAC, RAC, UnitWeightRawAgriculturalCommodity | Unit weight raw agricultural commodity (RAC). |
| Unit Weight EP | UnitWeightEp, EP, UnitWeightEP, UnitWeightEdiblePortion | Unit weight edible portion (EP). |

## 6.138 Value qualifier

Supported value qualifiers.

Table 6.138: Unit definition for Value qualifier.

| Name | Accepted names |
|---|---|
| = | Equals, = |
| < | LessThan, lt, < |

## 6.139 Ventilatory flow rate variability distribution types.

Ventilatory flow rate variability distribution types.

Table 6.139: Unit definition for Ventilatory flow rate variability distribution types..

| Name | Accepted names | Description |
|---|---|---|
| LogNormal | LogNormal | Lognormal distribution parameterised by a mean and a coefficient of variation. |

## 6.140 Within bin exposure representation method

Method used for selecting the value within a bin that should represent the exposure for the bin.

Table 6.140: Unit definition for Within bin exposure representation method.

| Name | Accepted names | Description |
|---|---|---|
| Minimum in bin | MinimumInBin | Minimum exposure value within the bin. |
| Maximum in bin | MaximumInBin | Maximum exposure value within the bin. |
| Average in bin | AverageInBin | Average exposure value within the bin. |

CHAPTER

SEVEN

# APPLICATION PROGRAMMING INTERFACE (API)

The entire API interface is described using the Swagger application.

CHAPTER

EIGHT

# COMMAND LINE INTERFACE (CLI)

## 8.1 Introduction

The MCRA core library comes with a command line interface (CLI) utility to run MCRA actions using input files and producing output files. Data files and specification of sequences of modules and settings are supplied in an action template. An action template is a local disk folder with a defined structure which is described in *Action template structure*. A new empty action template can be created by the CLI as demonstrated in *Create a new action template*. Alternatively, the template can also be a compressed (zip) file format. Running an action via the CLI is described in *Run an action*. This generates results in local disk output files that can be accessed via, for instance, a web browser as described in *Action template structure*.

The latest release of the CLI utility of MCRA Core is available as a download from GitHub (https://github.com/rivm-syso/mcra-core/releases) or can be built from the sources.

## 8.2 Action template structure

The CLI can process either folders or zip files as input. This paragraph explains the structure of the files and subfolders inside the input folder or zip file which the CLI needs to run an MCRA action correctly. This structure is the same for both the contents of a zip file and the contents of a folder. The term base folder will be used to refer to either the zip file or the folder containing the settings and data of the action. The base folder must contain the following XML files:

- _ActionData.xml: contains the configuration of the input data for the action
- _ActionSettings.xml: contains the configuration for the action

The data for the action may be included as CSV files containing MCRA table data directly in the base folder together with the settings files. In this case the _ActionData.xml file is optional. The other option is to put the input data files in a subfolder named Data. In this case the following file formats are accepted:

- Excel files: files with an XLS or XLSX extension;
- Access files: files with an ACCDB or MDB extension;
- Zipped CSV: zip files containing the MCRA data in one CSV file per table.

The files mentioned above must adhere to the data formats of MCRA available in the documentation.

*Action settings XML file structure*

The model settings XML file must be named '_ActionSettings.xml' (with a leading underscore '_' character). A simple example, configuring a 'Foods' action, is:

```
<Project>
  <Name>ExampleFoodsAction</Name>
  <ActionType>Foods</ActionType>
</Project>
```

The Project tag is the root element of the XML file; it is named Project for historic reasons. This configuration file is an example of a minimalistic configuration in which all other settings have been omitted. By using the *Create a new*

*action template* option, a configuration file will be automatically generated that contains all possible options for the action.

*Data configuration*

As mentioned before, MCRA accepts Excel, Access and zipped CSV data files as input when they are included in the Data subfolder. For simple actions there is also the option to include CSV files directly in the root of the folder or zip file. In this case the folder or zip file itself becomes the single input file for the action. The next section lists all possible options. Data for running an action with the CLI is accepted in the following ways: 1. As CSV (comma separated values) files directly in the root of the folder or zip file. In this case, the zip file or folder is itself the single data file, containing the MCRA tables. A data configuration XML file is optional, but it can still be used to filter the table groups that are loaded during the run. 2. A Data subfolder containing one or more of the accepted MCRA file types. In this case a data configuration XML file is necessary to link the MCRA table groups and data files to use.

*Data configuration XML file structure*

The data configuration XML file must be named _ActionData.xml (with the leading underscore '_' character) and must be placed in the root of the zip file or folder. It describes the links between the modules and data. The link is made based on a so-called MCRA table group definition. A data file can contain data for one or more table groups. An example of a simple data configuration file is as follows:

```
<DataSourceConfiguration xmlns:xsd=http://www.w3.org/2001/XMLSchema
    xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance">
  <DataSourceMappingRecords>
    <DataSourceMappingRecord>
      <SourceTableGroup>Foods</SourceTableGroup>
      <Name>InputData.xls</Name>
    </DataSourceMappingRecord>
    <DataSourceMappingRecord>
      <SourceTableGroup>Compounds</SourceTableGroup>
      <Name>InputData.xls</Name>
    </DataSourceMappingRecord>
    <DataSourceMappingRecord>
      <SourceTableGroup>Survey</SourceTableGroup>
      <Name>Consumptions.mdb</Name>
    </DataSourceMappingRecord>
    <DataSourceMappingRecord>
      <SourceTableGroup>FoodConsumptions</SourceTableGroup>
      <Name>Consumptions.mdb</Name>
    </DataSourceMappingRecord>
  </DataSourceMappingRecords>
</DataSourceConfiguration>
```

The data source configuration contains one collection of DataSourceMappingRecords. Each DataSourceMappingRecord must contain at least the SourceTableGroup. The Name element refers to the file name in the Data subfolder when data files are used. If the zip file or folder contains CSV table files in the root itself, the name is optional. In this case the name of the zip file itself is used.

## 8.3 Create a new action template

The CLI can generate an empty action template for any type of action that is supported by MCRA. This generated template consists of the correct files and folder structure for the action, with all default settings, and Excel data files with empty tables as a starting point to fill in your own input data.

Use the following command to create a new action of a given type:

```
mcra.exe create '<name_of_new_action>' -a <action type>
```

where the option -a specifies the type of action to be created. For example, to create a basic skeleton for analysing your own single value risk estimate with the name MySingleValueRisk, run the command,

```
mcra.exe create MySingleValueRisk  -a SingleValueRisk
```

The name of the action type, SingleValueRisk in the example above, is a reserved keyword and must match with one of the supported action types. To get a list of all supported action types, run the command,

```
mcra.exe create -u
```

This will print out a list of reserved names of all action types. After creating this template, you can start filling in the input data in the Excel files and adjusting the calculation settings in the _ActionSettings.xml file.

## 8.4 Run an action

The most basic use of the CLI is to specify a folder name or a zip file containing the settings and data for the action that you want to run (see section *Action template structure* for a detailed description). In a terminal window. e.g. PowerShell or the command prompt, run the command:

```
mcra.exe run '<path to action folder>' [options]
or:
mcra.exe run '<name_of_action>.zip' [options]
```

As an example, assume that an action folder has been composed for doing a calculation on the retrospective Tier 2 of cumulative exposure to pesticides. This model can be run by the command:

```
mcra.exe run 'EU acute cumulative exposure assessment (2018) Tier 2'
```

The name of the action in this example is equal to the name of the folder that contains the data and settings as input for the CLI, so in this example there is a folder with the name 'EU acute cumulative exposure assessment (2018) Tier 2'. To get an overview of the available options for running the command line interface, run the following command:

```
mcra.exe help run
```

The output of this command lists the options for the run command as shown below (exact details maybe different, depending on the version of the CLI utility).

Table 8.1: command-line parameters for running an action

| Parameter | Description |
|---|---|
| task input name | (pos. 0, required) Name of the input zip file or base folder containing the simulation task to be processed. |
| -o, --output | Base folder for output. Project output will be written to a subfolder, using the project name. |
| --overwrite | (Default: false) Overwrite existing output. If set to false, the output will be written to a uniquely named folder, otherwise the project name is used as output folder |
| --skipreport | (Default: false) Don't render the full output report. |
| --skiptables | (Default: false) Don't generate CSV output tables. |
| --skipcharts | (Default: false) Don't generate SVG charts. |
| --keeptempfiles | (Default: false) Keep temporary (intermediate) files. |
| -r, --randomseed | Use this value as the Monte Carlo random seed for the project. |
| -i, --interactive | (Default: false) Set to true to run in interactive mode. |
| -s, --silent | (Default: false) Set to true to run in silent mode. |
| --dbType | (Default: Csv) Database type. Possible options: - csv: Intermediate data will be written to CSV files during the run |
| --help | Display this help screen. |
| --version | Display version information. |

*Output*

By default the CLI utility creates the output files in a subfolder in the location where the CLI command is run, use the '--output' command line option to specify a different output folder.

## 8.5 Output files and folder structure

The output of an action performed with the CLI is saved to a folder, which by default has the name of the action suffixed with date and time to create a unique folder name. The output of the action consists of metadata, data and image (chart) files. The CLI options '--skipreport', '--skiptables' and/or '--skipcharts' are available to limit the output if desired. The contents of the output folder are as follows.

Table 8.2: Output file and folders of an action run

| File | Description |
|---|---|
| Metadata files | |
| _CsvFileIndex.txt | Tab delimited text file containing lookup data for the output CSV data files. It contains the name of the file and the path to the file in the full MCRA output. |
| _MCRAVersion.txt | Contains detailed MCRA version information of the CLI that was used. |
| _TOC.txt | Contains a detailed internal table of contents of references to report sections. |
| _TOC-Charts.txt | Contains a detailed table of contents of the output charts (if any). |
| _TOC-CsvData.txt | Contains a detailed table of contents of the output CSV files. |
| _TOC-XmlData.txt | Contains a detailed table of contents of any output data in XML format. |
| ProjectOriginalSettings.xml | A copy of the original action settings file (_ActionSettings.xml) |
| ProjectSimulatedSettings.xml | A fully populated XML file containing all settings that were used in the run. This includes the defaults of all other settings that are available in MCRA. |
| Data files | |
| FoodsTable.csv | Foods output data table |
| SubstancesTable.csv | Substances output data table |
| Reports | |
| _Report.html | The MCRA report in HTML format. This report contains all output sections with tables and charts in one page. |
| Tables/charts | The tables and charts in the HTML file are included in this folder and are referenced from the HTML file. |

CHAPTER

NINE

# APPENDICES

## 9.1 NOEL collection of Munro et al.

This collection is from Munro et al. (1996) and can be downloaded here.

## 9.2 Box-Cox power transformation

The Box-Cox power transformation is a data transformation to achieve a better normality and to stabilize the variance. In MCRA, the transformation parameter $p$ in $(y^p - 1)/p$ is determined by maximizing the log-likelihood function

$$l(p) = -\frac{n}{s} \log \left[ \frac{1}{n} \sum_{i=1}^{n} (y_i^{(p)} - \overline{y^{(p)}})^2 \right] + (p-1) \sum_{i=1}^{n} \log y_i$$

where $i$ indexes the $n$ observations and

$$\overline{y^{(p)}} = \frac{1}{n} \sum_{i=1}^{n} y_i^{(p)}$$

is the average of the $y_i^{(p)}$, see Box and Cox (1964).

## 9.3 Gauss-Hermite Integration

### 9.3.1 One-dimensional Gauss-Hermite integration

Gauss-Hermite integration approximates a specific integral as follows

$$\int_{-\infty}^{\infty} f(x) \exp(-x^2) \mathrm{d}x \approx \sum_{j=1}^{N} w_j f(x_j)$$

in which $w_j$ and $x_j$ are weights and abscissas for N-point Gauss-Hermite integration, see Abramowitz and Stegun (1972). N-point integration is exact for all polynomials $f(x)$ of degree 2N-1, see Dahlquist and Bjorck (1974). This can for instance be used to approximate the mean of a function $F(Y)$ of a normally distributed random variable $Y$ with mean $\mu$ and variance $\sigma^2$:

$$\int_{-\infty}^{\infty} F(x) \frac{1}{\sqrt{2\pi}\sigma} \exp\left( -\frac{(y-\mu)^2}{2\sigma^2} \right) \mathrm{d}y$$

$$= \int_{-\infty}^{\infty} F(\mu + \sqrt{2}\sigma x) \frac{1}{\sqrt{\pi}} \exp(-x^2) \mathrm{d}x$$

$$= \frac{1}{\sqrt{\pi}} \sum_{j=1}^{N} w_j F(\mu + \sqrt{2}\sigma x_j)$$

### 9.3.2 Two-dimensional Gauss-Hermite integration

One-dimensional Gauss-Hermite integration can readily be extended to two dimensions. The following principal result in two dimensions is more or less given in Jäckel (2005) for the standard bivariate normal distribution $\phi(x, y; \rho)$ with correlation parameter $\rho$ :

$$\int_{-\infty}^{\infty}\int_{-\infty}^{\infty} F(x,y)\phi(x,y;\rho)\mathrm{d}x\mathrm{d}y \approx \frac{1}{\pi}\sum_{i=1}^{N}\sum_{j=1}^{N} w_i w_j F(\sqrt{2}[ax_i + bx_j], \sqrt{2}[bx_i + ax_j])$$

in which

$$a = \frac{\sqrt{1+\rho} + \sqrt{1-\rho}}{2}$$

and

$$b = \frac{\sqrt{1+\rho} - \sqrt{1-\rho}}{2}$$

as given in Jäckel (2005) .

Jäckel (2005) discusses other Gauss-Hermite approximations to the two-dimensional integral, but found that the approximation given above generally gives the most accurate results. For the general bivariate normal distribution with means $(\mu_x, \mu_y)$ and variances $(\sigma_x^2, \sigma_y^2)$ the integral can be approximated by means of

$$\frac{1}{\pi}\sum_{i=1}^{N}\sum_{j=1}^{N} w_i w_j F(\mu_x + \sigma_x\sqrt{2}[ax_i + bx_j], \mu_y + \sigma_y\sqrt{2}[bx_i + ax_j])$$

The product $w_i w_j$ can be very small, especially when many quadrature points are used, thus wasting possibly precious calculation time. This can be remedied by pruning, i.e. by dropping combinations of $(i, j)$ with very small values of the product $w_i w_j$.

### 9.3.3 Maximum likelihood for the LNN model with two-dimensional Gauss-Hermite integration

Denote non-consumption on day $j$ for individual $i$ as $Y_{ij} = 0$. The conditional likelihood, i.e. given random effects $b_i$ and $v_i$, of a non-consumption on day $j$ equals, with $H()$ the inverse of the logit function

$$P(Y_{ij} = 0|b_i, v_i) = 1\text{–}H(\lambda + v_i).$$

The conditional likelihood of a positive intake $Y_{ij} > 0$ equals, with $\phi$ the density of the normal distribution

$$f(Y_{ij} = y_{ij}|y_{ij} > 0, b_i, v_i) = H(\lambda + v_i)\phi(y_{ij} - \mu - b_i; 0, \sigma_w^2)$$

The conditional likelihood contribution for individual $i$ is the product of the individual contributions for each day. The marginal likelihood contribution for individual $i$ is obtained by integrating over the possible values of $b_i$ and $v_i$. Since the pair $(b_i, v_i)$ follows a bivariate normal distribution, the likelihood contribution for individual $i$ can be approximated by means of two-dimensional Gauss-Hermite integration. Individually based covariables, such as sex or age, imply that $\mu_i$ and $\lambda_i$ must be used instead of $\mu$ and $\lambda$. The likelihood must be optimized by means of some general optimization routine.

## 9.4 Distributions

### 9.4.1 Uniform distribution

The uniform distribution is defined on the interval $[a, b]$ where $a$ and $b$ are the minimum and maximum value and $a > 0, b > 0$.

The conversion factor is the nominal value of the uniform distribution, and

$$factor = \frac{a+b}{2}$$

For the variability upper value, $b$ = $upper$ and $a$ is calculated as:

$$a = 2 \cdot factor - b$$

See also module *exposure biomarker conversions*, *kinetic conversion factors*.

### 9.4.2 Lognormal distribution

The lognormal distribution is characterised by parameters $\mu$ and $\sigma$, which are the mean and standard deviation on log-scale.

The conversion factor is the nominal value of the lognormal distribution, $\mu = ln(factor)$. The variability upper value specifies the p95 of the standard lognormal. Parameter $\sigma$ is calculated as:

$$\sigma = \frac{ln(upper) - \mu}{1.645}$$

See also module *exposure biomarker conversions*, *kinetic conversion factors*.

### 9.4.3 Beta distribution

The standard beta distribution is defined on the interval (0, 1) and is usually characterised by two parameters $a$ and $b$, with $a > 0$, $b > 0$ (see e.g. Mood et al. (1974)). Alternatively, it can be parameterised by the mean (conversion factor)

$$\mu = a/(a + b) \in (0, 1)$$

and the variance

$$\sigma^2 = ab/(a + b + 1)^{-1}(a + b)^{-2}$$

Note that:

$$\frac{ab}{(a+b)^2(a+b+1)} = \frac{\mu(1-\mu)}{(a+b)^2(a+b+1)} < \frac{\mu(1-\mu)}{1} = \mu(1-\mu) \in (0.0.5^2)$$

The conversion factor is the nominal value of the beta distribution, here the mean. The variability upper value is the variance of the beta distribution. The equations solved for $a$ and $b$ show that:

$$a = \left(\frac{1-\mu}{\sigma^2} - \frac{1}{\mu}\right) \cdot \mu^2$$

and

$$b = a \cdot \left(\frac{1}{\mu} - 1\right)$$

See also module *exposure biomarker conversions*, *kinetic conversion factors*.

### 9.4.4 InverseUniform distribution

The inverse uniform distribution is defined on the interval [$a$, $b$] where $a$ and $b$ are the minimum and maximum value and $a > 0$, $b > 0$.

The conversion factor is the median (nominal) value of the inverse uniform distribution, and the median is equal to

$$factor = \frac{2}{a+b}$$

The variability upper value is equal to $\frac{1}{a}$, so

$$a = \frac{1}{upper}$$

and

$$b = \frac{2}{factor} - a$$

Uniform distributed values are drawn from the interval [$a$, $b$] and inverted. See e.g. Invers distribution and Inverse transform.

See also module *exposure biomarker conversions*, *kinetic conversion factors*.

CHAPTER

TEN

# GLOSSARY

**ADI**

Acceptable daily intake. The ADI is an estimate of the amount of a substance in food or drinking water that can be consumed daily over a lifetime without presenting an appreciable risk to health. It is usually expressed as milligrams of the substance per kilogram of body weight and day and applies to chemical substances such as food additives, pesticide residues and veterinary drugs.

**ADME**

An abbreviation for "absorption, distribution, metabolism and excretion", the four key processes which describe how drugs and chemicals get into the body, what happens to them while they are there, and how they are eliminated

**AF**

Assessment factor.

**AIC**

Akaike Information Criterion.

**ANSES**

Agence National de Securite Sanitaire. The French Agency for Food, Environmental and Occupational Health & Safety

**AOP**

Adverse Outcome Pathways. An AOP is a structured representation of biological events leading to adverse effects and is considered relevant to risk assessment.

**ARfD**

Acute reference dose. Estimate of the amount of a substance in food and/or drinking water, normally expressed on a body weight basis, that can be ingested in a period of 24 h or less without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation.

**AU**

Agricultural Use.

**BBN**

Beta binomial normal model.

**BMD**

Benchmark dose. A dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response or *BMR*) compared to background.

**BMDL**

Benchmark dose lower confidence limit.

**BMDU**

Benchmark dose upper confidence limit.

**BMI**

The body mass index is a measurement that expresses the relationship between an individual's weight and height. BMI is calculated by dividing weight in kilograms by height in metres squared (i.e. height x height). Used to assess whether someone's weight is appropriate.

**BMR**
Benchmark response.

**BoD**
Burden of disease.

**BREAM**
Bystander and resident exposure assessment model for plant protection products.

**BROWSE**
Bystanders, residents, operators and workers exposure models for plant protection products.

**BSA**
Body surface area.

**BW**
Body weight.

**CA**
Concentration Addition. This model is based on a dilution principle, and was designed for chemicals with a similar mechanism of action.

**CAG**
Cumulative assessment group. A group of chemicals that could plausibly act by a common mode of action, not all of which will necessarily do so. Membership of a CAG can usually be refined (reduced) by application of successively higher tiers of assessment.

**ConsExpo**
Consumer exposure model.

**CRA**
Cumulative risk assessment. Risk assessment for combined exposure to two or more chemicals by all relevant pathways and routes.

**DA**
Dose addition. A process to establish the response of organisms to a mixture of chemicals with similar toxicity. This involves adding up their individual effects to predict the likely impact of the overall mixture.

**DALY**
Disability-adjusted life year. One DALY represents the loss of the equivalent of one year of full health. DALYs for a disease or health condition are the sum of the years of life lost to due to premature mortality YLLs (*YLL*) and the years lived with a disability YLDs (*YLD*) due to prevalent cases of the disease or health condition in a population.

**DPIA**
Data Protection Impact Assessment.

**DR**
Dose response. The relationship between the amount of a substance to which an individual organism, population or ecosystem is exposed and the way in which it responds (e.g. in terms of toxicity).

**E/H**
Risk characterisation ratio (Exposure/Hazard).

**EBD**
Environmental burden of disease.

**EEA**
European Environment Agency.

**EFSA**
European Food Safety Authority.

**ERF**
Exposure response function.

**FA**
Food additive. A substance deliberately added to foods or beverages for beneficial technological reasons (e.g.

to preserve, flavour, colour or ensure a particular texture). Food additives are not normally consumed by themselves nor used as typical ingredients in food.

**FC**

Focal commodity. A commodity for which an *MRL* is to be set or for which a high residue event has been monitored, and which is therefore the focus of an exposure assessment.

**GAP**

Good agricultural practice. GAP is a certification system for agriculture, specifying procedures (and attendant documentation) that must be implemented to create food for consumers or further processing that is safe and wholesome, using sustainable methods.

**GDPR**

General Data Protection Regulation, a landmark European law that establishes strong rules for how organizations collect, process, and store the personal data of individuals within the European Union (EU) and European Economic Area (EEA).

**GM**

Geometric mean.

**GSD**

Geometric standard deviation.

**HBM**

Human biomonitoring. A direct measurement of the level of toxic chemical compounds present in the body. Often, these measurements are made using blood and urine.

**HBGV**

Health based guidance value. HBGV is a science-based recommendation for the maximum (oral) exposure to a substance that is not expected to result in an appreciable health risk, taking into account current safety data, uncertainties in these data, and the likely duration of consumption.

**HC**

Hazard characterisations is a generic term for any reference value for a substances at a chosen biological target level (external or internal) beyond which exposure is associated with potential adverse health effects. Hazard characterisations can be specified as external values (e.g., a human based guidance value, such as an *ADI* or *ARfD*) or are based on a point of departure (*POD*), such as BMDs from dose-response models or externally specified points of departure (*NOAEL*, *LOAEL*, MDS). The computation may involve assessment factors, e.g., for inter-species conversion, intra-species variation or additional sources of uncertainty. The calculation may also use kinetic models or absorption factors to convert external doses to internal doses or vice versa.

**HCPs**

House Cleaning Products.

**HI**

The hazard index is the sum of all hazard quotiens (*HQ*) of the substances that are associated with the same potential adverse health effect.

**HQ**

The hazard quotient is the ratio of the exposure to a substance and the reference level at which no adverse effects are expected (i.e., exposure divided by the reference level). A HQ smaller than 1 is associated with no expected adverse health effect and a HQ larger than 1 is associated with possible adverse health effects. The HQ is closely related to the *MOE*, which can be seen as the inverse metric.

**HR**

Highest residue. The HR is the highest residue level (expressed as mg/kg) in a composite sample of the edible portion of a food commodity when a pesticide has been used according to maximum *GAP* conditions. The HR is estimated as the highest of the residue values (one from each trial) from supervised trials conducted according to maximum GAP conditions, and includes residue components defined by the JMPR for estimation of dietary intake.

**H/E**

Risk characterisation ratio (Hazard/Exposure).

**ICED**
Individual critical effect dose.

**In-silico**
Research theoretical method, particularly involving computer models, to predict the likely toxicological, or other, effects of substances.

**In-vitro**
Research method which involves testing cells or tissues extracted from living organisms.

**In-vivo**
Research method which involves testing individual live animals or populations of live animals.

**IVIVE**
In vitro to in vivo extrapolation. Refers to the qualitative or quantitative transposition of experimental results or observations made in vitro to predict phenomena in vivo, biological organisms.

**JRC**
Joint Research Centre.

**Lipid**
Fat and fat-like substance.

**LNN**
Logistic normal normal model.

**LOAEL**
Lowest observed adverse effect level.

**LOD**
Limit of detection. Lowest concentration of a pesticide residue in a defined matrix where positive identification can be achieved using a specified method (IUPAC, 2006).

**LOQ**
Limit of quantification. Lowest concentration of a pesticide residue in a defined matrix where positive identification and quantification measurement can be achieved using a specified analytical method (IUPAC, 2006).

**LOR**
Limit of reporting. Practical limit of residue quantification at or above the *LOQ*. The conservative limit of quantification for a defined matrix and method which may vary between laboratories or within the one laboratory from time to time because of different equipment, techniques, and reagents. Commonly either the lower limit of the calibrated range of the method or the lowest level at which quantitative recovery of the analyse has been demonstrated (IUPAC, 2006).

**MCR**
Maximum cumulative ratio.

**MCRA**
Monte Carlo Risk Assessment.

**MIE**
Molecular initiating event.

**MoA**
Mode of Action.

**MOE**
The margin of exposure (MOE) is the ratio between the reference level at which no adverse effects are expected to the exposure to a substance (i.e., reference level divided by exposure). Commonly, the reference level is assumed to be a point of departure (*POD*) based on animal studies that does not incorporate all factors to translate to a human reference value. A MOE is therefore typically compared to a uncertainty/safety factor (UF) composed of the product of the uncertainty factors. An MOE is smaller than the UF is associated with risk. A MOE larger than the UF is associated with no expected adverse health effects.

**MOET**
The harmonic sum of all individual MOEs.

**MRA**
Mixture risk assessment.

**MRL**
Maximum residue level. Maximum concentration of a residue that is legally permitted or recognized as acceptable in,or on, a food, agricultural commodity, or animal feedstuff as set by Codex or a national regulatory authority(IUPAC, 2006).

**MV**
Missing value.

**NAMs**
New approach methodologies. The term NAM has been emerged as a descriptive reference to any non-animal-based approaches that can be used to provide information in the context of chemical hazard and risk assessment

**NMF**
Non-negative Matrix Factorization.

**NOAEL**
No observed adverse effect level is the greatest concentration or amount of a substance at which no detectable adverse effects occur in an exposed population.

**NOEC**
No observed effect concentration.

**NOEL**
No Observed Effect Level.

**OR**
Odds ratio is a statistical measure comparing the likelihood of an event occurring in one group versus another, commonly used to determine if an exposure increases or decreases the risk of an outcome.

**OIM**
Observed Individual Means approach. An approach for estimating longer term exposures by taking each individual's observed mean consumption over the duration of a dietary survey.

**OP**
Occurrence pattern.

**PACEM**
Probabilistic Aggregate Consumer Exposure Model. PACEM evaluates aggregate exposure in a population considering individual use and co-use patterns as well as variation in product composition. Product usage data is included on personal care products (*PCPs*) and household cleaning products (*HCPs*).

**PAF**
Population attributable fraction, the proportion of a total disease burden that is ascribed to a specific risk factor.

**PARC**
Partnership for the Assessment of the Risk of Chemicals.

**PBK**
Physiologically based kinetic models

**PBPK**
Physiologically based pharmacokinetic/toxicokinetic models

**PCPs**
Personal care products

**POCE**
The probability of critical exposure (PoCE) is the proportion of the *HI* distribution above the threshold (or of the generalised *MOE* below the threshold) is the probability of critical exposure in the particular (sub)population. The threshold value can be 1 if all assessment factors have already been accounted for in the calculation of HI or MOE.

**POD**
: A point of departure is defined as a point on a toxicological dose-response curve obtained from a dose dose-response experiment in the region at which the curve transitions from no effects to effects. It is used as the base value for deriving toxicological reference values, or hazard characterisations. Common PODs are the no-observed adverse effect level (*NOAEL*) and benchmark dose (*BMD*).

**PPE**
: Personal Protective Equipment

**PPP**
: Plant protection products. Products used to protect, preserve or influence the growth of desirable plants or to destroy or control the growth of unwanted plants or parts of plants.

**PRIMo**
: *EFSA* pesticide residue intake model.

**QSAR**
: Quantitative structure activity relationship. The quantitative/qualitative structure activity relationships are a set of methods by which the effects of different compounds are related to their molecular structures. It allows the likely adverse or beneficial effects of a particular chemical to be predicted by comparing it with others which have similar structures.

**RA**
: Response Addition. An approach to the risk assessment of mixtures of substances in which responses to each of the individual components are determined and added together in order to predict the response to the mixture as a whole. This approach is only valid if the individual components do not interact with each other, i.e. their effects are completely independent.

**RAC**
: Raw agricultural commodity. Part of a crop used as a food or feed commodity directly from the harvested crop without processing.

**RIVM**
: Rijksinstituut voor Volksgezondheid en Milieu (Dutch National Institute for Public Health and the Environment).

**RPC**
: Raw Primary Commodity.

**RPC derivatives**
: Single-component foods altered by processing.

**RPE**
: Respiratory Protective Equipment

**RPF**
: Relative potency factor. The ratio of the toxic potency of a given chemical to that of an index chemical in the Cumulative Assessment Group (*CAG*). Relative potency factors are used to convert exposures of all chemicals in the CAG into their exposure equivalents of the index chemical.

**RR**
: Relative risk.

**RSExpo**
: Modelling tool developed by *ANSES*, to estimate aggregate internal systemic exposures from multiple sources and routes using absorption factors

**SA**
: Standard action

**SBML**
: Systems Biology Markup Language

**SD**
: Standard deviation

**SG**
: Specific gravity of urine

**SNMU**
: Sparse Nonnegative Matrix Underapproximation

**SRA**
: Standard Regulatory Action

**SSC**
: Source/Substance Combination

**SSD**
: *EFSA* Standard sample description.

**TDI**
: Tolerable daily intake. Is an estimate of the amount of a substance in food or drinking water which is not added deliberately (e.g. contaminants) and which can be consumed over a lifetime without presenting an appreciable risk to health.

**TDS**
: Total diet study. A study designed to estimate the likely consumption of harmful or beneficial substances in the diet. When undertaking such a study, commonly-consumed foods are purchased from shops in a particular country before being analysed.

**TEF**
: Toxic equivalency factor.

**TK**
: Toxicokinetics. The study of the processes by which potentially toxic substances are handled in the body. This involves an understanding of the absorption, distribution, metabolism and excretion of such substances *ADME*.

**TP**
: Thermal paper.

**TTC**
: Threshold of toxicological concern. A screening tool that provides conservative exposure limits in the absence of sufficient chemical-specific toxicological data. It is a science-based approach for prioritising chemicals with low-level exposures that require more data over those that can be presumed to present no appreciable human health risk.

**TWI**
: The tolerable weekly intake is the maximum intake of substances in food, such as nutrients or contaminants, that can be consumed weekly over a lifetime without risking adverse health effects.

**YLD**
: Years of healthy life lost due to disability. One YLD represents the equivalent of one full year of healthy life lost due to disability or ill-health.

**YLL**
: Years of life lost from mortality. One YLL represents the loss of one year of life. YLLs are calculated from the number of deaths multiplied by a global standard life expectancy at the age at which death occurs.

# Part III

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CHAPTER

ELEVEN

# PUBLICATIONS USING MCRA

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CHAPTER

TWELVE

# COLOPHON

**WUR/Biometris, Wageningen University & Research**
**FERA, Food and Environmental Research Agency**
**RIVM, National Institute for Public Health and the Environment**

This manual was created for MCRA 10, version 10.3.2, build 10.3.2.0 for Prod-RIVM on Wednesday September 09, 2026, 12:59:58.

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CHAPTER

THIRTEEN

# CHANGE LOG

## 13.1 Version 10.3.2 (2026-09-09)

### 13.1.1 Added

- Implementation of module ConsumerProductExposureEstimates (upload PACEM exposure data) (#2481)
- Add column Age, Sex to table RawConsumerProductExposureFractions (#2509)
- Add AbsorptionFactor to Table ConsumerProductExposureSets (#2513)

### 13.1.2 Fixed

- Breadcrumb in action toolbar shows action id instead of name (#2499)

## 13.2 Version 10.3.1 (2026-08-14)

### 13.2.1 Fixed

- Wrong URL sent for password reset / email verification
- Short documentation tables not readable in dark mode (#2486)
- Multiple select of task outputs in Workspace tasks and sub tasks doens't work (#2486)
- Context menu button not visible in the rightmost column of admin tables (users, etc) (#2486)
- Updated 3rd party NuGet package dependencies
- Update front-end Angular version to 22

## 13.3 Version 10.3.0 (2026-07-17)

### 13.3.1 Added

- Main toolbar button for switching between light and dark mode for MCRA front-end
- EFSA SRAs for 2026 (Pro- and Retrospective) added next to existing SRAs for 2025

### 13.3.2 Changed

- Update PBK simulation settings form for lifetime scenarios
- Rename biological matrix comparisons module to "Exposure comparisons" (#2352)
- Update R version for MCRA to 4.6.1 (#2479)
- Update .NET target framework to .NET 10.0
- Update front-end Angular version to 21 and Material v3 (#2374)

### 13.3.3 Fixed

- Broken module links in documentation, check consistency with definition in MCRA Core during sphinx build (#2392)
- Uncertainty for exposure response functions is not applied correctly

## 13.4 Version 10.2.22 (2026-06-26)

### 13.4.1 Added

- Implement stratification on sex for HBM analysis module and internal exposures module (#2451)
- Implement stratification on age for HBM analysis and internal exposures module (#2452)

### 13.4.2 Changed

- Remove oral absorption factor for dietary (#2466)

### 13.4.3 Fixed

- Aliases of unit definitions not always include the Id name (#2375)

## 13.5 Version 10.2.21 (2026-06-01)

### 13.5.1 Added

- Implement case control comparison for occupational HBM analysis (#2455)

## 13.6 Version 10.2.20 (2026-05-13)

### 13.6.1 Added

- Add field ShiftType to table HumanMonitoringTimepoints (#2355)
- Implement shorter than lifetime exposure (#2449)
- Update HBM analysis form with settings for HBM occuaptional exposure assessment

### 13.6.2 Changed

- Show the compare outputs of a loop action in a separate tab window (#2282)
- Move 'sub-tasks' to separate tab page (#2445)
- Replaced text Commissioned by with In partnership with EFSA, for PDF report download

### 13.6.3 Fixed

- Compare output wrongly navigates to the default main page (#2448)

## 13.7 Version 10.2.19 (2026-04-24)

### 13.7.1 Added

- Update SRA 2026 to include sensitivity analysis option for U04 and update documentation
- Add EFSA logo to reports of standard regulatory actions (#2393)
- Update uncertainty analysis option descriptions for SRAs 2026 (#2446)

### 13.7.2 Fixed

- Remove exposure routes selection in the new action wizard of hbm analysis (2443)
- Updated 3rd party NuGet package(s) containing a (low level) security warning
- New task is scheduled (and fails) when simulation service exits using EnableServiceShutdown (reports 'Idle' during exit)
- Output panel is empty when opening output (timing issue in embedded (short) output component)

## 13.8 Version 10.2.18 (2026-04-14)

### 13.8.1 Added

- Add setting: calculate co-exposure (#2438)
- Add initial SRAs for prospective and retrospective 2026 (#2421)

### 13.8.2 Fixed

- MCRA Scheduler should reconnect to Kubernetes jobs after restart (#2440)
- Exposure routes cannot be specified for a Risks action when set to external target and human biomonitoring concentrations (#2431)

## 13.9 Version 10.2.17 (2026-03-23)

### 13.9.1 Added

- Add support for oral route in occupational exposures module (#2386)
- Add new output stratification settings to output details form (#2388)
- Implement default body exposure fraction in AirExposures module (#2423)
- EBD, create implement options to force PAF values >= 0 (#2427)

### 13.9.2 Fixed

- Update surrogate matrix selection options to only list matrices that are preset in the selected PBK model(s) (#2429)

## 13.10 Version 10.2.16 (2026-02-27)

### 13.10.1 Fixed

- JobSize value is not copied when cloning an action
- MCRA Scheduler: implement correct job size estimates and handling of jobs in a Kubernetes (OpenShift) cluster

## 13.11 Version 10.2.15 (2026-02-24)

### 13.11.1 Added

- Implement AirBodyExposureFractions in module AirExposureDeterminants (#2399)
- Update frontend settings form for PBK model simulation settings to include new option to allow fallback systemic (#2422)

## 13.12 Version 10.2.14 (2026-02-18)

### 13.12.1 Added

- Implement AirConcentrationDistributions module (#2343)
- Add JobSize (job size estimate) option (Small/Medium/Large) to Projects and Tasklogs tables (#2402)
- Assign max number of parallel tasks to user groups, replacing 'Priority' (#2404)

### 13.12.2 Changed

- Rename Action SoilConcentrationDistributions to SoilConcentrations (#2410)

### 13.12.3 Fixed

- Uncertainty: resampleKineticConversionsFactors not visible

## 13.13 Version 10.2.13 (2026-01-27)

### 13.13.1 Added

- Add documentation for occupational exposure (#2389)
- Add configuration and functionality for running MCRA in a Kubernetes (OpenShift) cluster (#2401)

## 13.14 Version 10.2.12 (2026-01-16)

### 13.14.1 Added

- Add new modules occupational exposures (#2299)
- Update internal exposures settings form to allow individuals from individuals module to be selected as reference set (#2385)

### 13.14.2 Fixed

- Target level selection disabled at internal exposures for biological matrix comparisons (#2351)
- Visibility of uncertainty options in internal exposures action (#2361)

## 13.15 Version 10.2.11 (2025-12-17)

### 13.15.1 Added

- Menu item and wizard for EFSA Standard Regulatory Actions (#2315)
- Documentation: update SRA documentation links (#2377)

## 13.16 Version 10.2.10 (2025-12-12)

### 13.16.1 Added

- Add uncertainty settings to Populations module (#2340)
- Add documentation for dust concentrations and dust concentration distributions (#2342)

### 13.16.2 Changed

- Save simulation log in database instead of as a file on the simulation server (#2373)

## 13.17 Version 10.2.9 (2025-12-01)

### 13.17.1 Added

- Implementation of cumulative HBM exposures in EnvironmentalBurdenOfDisease module (#2336)
- Implement U08 worst case sensitivity analysis for EFSA prospective SRA 2025 (#2347)
- New ExposureResponseFunctions table, add lower uncertainty bound (#2240)
- Add new table for individual sets, individuals as data (#2341)

### 13.17.2 Changed

- Update SRA prospective CRA 2025 data template download to not pre-fill with data when no food/substance was selected (#2328)
- Update SRA 2025 short report figure caption for retrospective and prospective (#2333)
- Update wording sensitivity analyses in prospective SRA 2025 (#2350)

### 13.17.3 Fixed

- Looping on adult-only for DAC/DAH in prospective and retrospective SRAs 2025 (#2349)

## 13.18 Version 10.2.8 (2025-11-14)

### 13.18.1 Changed

- Use population name for the loop task name in EFSA 2025 SRA loop calculations (#2281)
- Update SRA for prospective dietary CRA 2025: make options consumers only and scenario selection advanced (#2329)

### 13.18.2 Fixed

- Prospective 2025 SRA: should open with no sensitivity analysis by default instead of U09 (#2321)

## 13.19 Version 10.2.7 (2025-11-02)

### 13.19.1 Added

- Add option for defining within bin exposure (#2127)
- EU prospective dietary CRA (2025) with sensitivity analysis options U02, U08, U09 and U10 (#2254)

### 13.19.2 Changed

- Rate limiting for authentication API endpoints including MFA code login attempts (#2110)

### 13.19.3 Fixed

- Do not store jwt session token in localstorage (#2096)
- Do not disclose mfa enrolment qr code to any user (#2097)

## 13.20 Version 10.2.6 (2025-10-10)

### 13.20.1 Added

- SRAs 2025: include safety chart in short report (#2280)

### 13.20.2 Changed

- Update internal exposures settings form to make 'allow-use-surrogate-matrix' option not-advanced
- Update SRA 2025 retrospective to include looping (#2278)

### 13.20.3 Fixed

- Do not expose personally identifiable information (pii) in jwt token (#2109)

## 13.21 Version 10.2.5 (2025-10-03)

### 13.21.1 Added

- Update frontend to allow use of surrogate matrix (for target) for PBK models in internal exposures settings (#2287)

### 13.21.2 Changed

- Update internal exposures biological matrix selection to always include blood, plasma, serum and urine

### 13.21.3 Fixed

- User which is not in any user group can't start a job, exception 'Sequence contains no elements'

## 13.22 Version 10.2.4 (2025-09-26)

### 13.22.1 Added

- Implementation of uncertainty of counterfactualvalue in exposure responsefunctions (#2240)
- Add new tables for HBM Single Values module (percentiles) (#2242)
- Add new Enum for 'EBD per 100,000 (#2258)
- Implement advanced option in SRA Prospective 2025 to loop over populations (#2165)
- Create initial version of SRA EU pro- and retrospective dietary CRA 2025 (#2250)
- Add ConsumerProducts to internal exposure wizard (#2270)

### 13.22.2 Fixed

- Specification bin boundaries gives a bug when 0 and 100 are included (#2258)

## 13.23 Version 10.2.3 (2025-09-05)

### 13.23.1 Added

- Implement use of PBK models for matrix conversion in HBM analysis (#2235)
- Implementation uncertainty of ConsumerProductConcentrations (#2237)

### 13.23.2 Changed

- Tier settings should be visible but disabled in the module panels

### 13.23.3 Fixed

- Can't delete expired registrations in MCRA admin panel (#2265)
- Tier-defined settings are editable in some front end settings panel (#2266)
- Ensure exposure routes selection combo is visible in risk from dietary action

## 13.24 Version 10.2.2 (2025-08-21)

### 13.24.1 Added

- Add download as Excel button to table toolbar additional to download as CSV button (#2246)

## 13.25 Version 10.2.1 (2025-07-25)

### 13.25.1 Added

- Implementation of bootstrap of individuals (uncertainty) in Individuals module for air, dust and soil (#2056)
- Add functionality to specify output resolution for PBK model simulations (#2117)
- Implementation ConsumerProductConcentrationDistributions module (#2223)

### 13.25.2 Changed

- Updated target .NET framework of MCRA Core to .NET 9.0
- Updated R version for MCRA to 4.5.1 (#2234)

### 13.25.3 Fixed

- User group can't be deleted when it is linked to a standard action (#2239)
- Include maleic hydrazide (RF-0267-001-PPP) in substances pick-list of SRA EFSA prospective CRA 2024 (#2245)

## 13.26 Version 10.2.0 (2025-07-07)

### 13.26.1 Added

- Implementation ConsumerProductExposures module in TargetExposures action (#2148)
- Implementation of individual subset selection in ConsumerProductUseFrequencies (#2217)
- Add Download full HTML report (zip) to output details top right menu
- Add option for lifetime PBK modelling in target exposures module

### 13.26.2 Fixed

- Create settings HTML instead of PDF in output zip files

## 13.27 Version 10.1.10 (2025-05-08)

### 13.27.1 Added

- New setting EbdApproach in ebd module (#2120)

### 13.27.2 Changed

- Update downloadable excel data template file prospective CRA 2024 (#2196)
- Update prospective scenario options in SRA prospective CRA (2024) (#2198)
- Rename sensitivity analysis option SRA prospective CRA (2024) (#2199)

### 13.27.3 Fixed

- Multiple selection dialog immediately closes when ticking an option (#2187)
- Cannot select focal concentrations and deterministic conversions data sources simultaneously in prospective SRA 2024 (#2192)

## 13.28 Version 10.1.9 (2025-04-28)

### 13.28.1 Added

- New columns for uncertainty in exposure response functions data (#2149)
- New table population characteristics (#2176)
- New column 'population size' in populations table (#2185)
- New module 'Individuals' (#2188)

### 13.28.2 Changed

- Remove standard action per data source template download button (#2190)

### 13.28.3 Fixed

- SamplePropertyValues table allows duplicate entries for SampleId and PropertyName (#2114)

## 13.29 Version 10.1.8 (2025-04-08)

### 13.29.1 Changed

- Rename exposure effect functions to exposure response functions (#2174)

### 13.29.2 Fixed

- Hide exposure routes selection in risk action wizard when conditions don't apply (#2181)

## 13.30 Version 10.1.7 (2025-03-24)

### 13.30.1 Added

- Add data template download for the user-specified data of the prospective dietary CRA (2024) (#2103)
- Add setting BoD indicator selection for EBD and allow for multiple exposure effect functions (#2122)
- Add option targetLevel in ebd module (#2123)

- Enable dietary exposures as input in ebd module (#2124)
- Add option for selecting custom bins in ebd module (#2125)
- Allow for selecting multiple indicators and eefs in ebd module (#2153)
- Update prospective SRA 2024 with option to run sensitivity analysis (#2164)
- Implementation RS Expo Air Exposures module (#2167)

### 13.30.2 Changed

- Move PBK model simulation settings to the modules actually running the PBK models (#2118)
- Rename uncertainty analysis options display text in all SRAs (#2159)
- Rename contribution section title in short output HTML in EFSA SRAs (#2160)
- Remove background only option in SRA prospective CRA (2024) from scenario list and make separate advanced checkbox (#2163)

### 13.30.3 Fixed

- Multiple substances should not be visible for a single substance (#2115)
- Data source selection does not appear after saving a prospective EFSA 2024 SRA (#2155)
- Retrospective SRAs 2023/24 don't work for effect NCN-Chronic (#2158)
- Cloning EFSA SRA prospective 2024 from workspace doesn't copy some settings (#2169)

## 13.31 Version 10.1.6 (2025-03-04)

### 13.31.1 Added

- New data module burden of disease infos (#2129)
- Add StandardAction ID column in admin Standard Actions table, optionally visible using a check box
- Remove set frontend limit number of simulated days for PBK model simulations to 25,000 (#2119)

### 13.31.2 Changed

- Remove deprecated functionality to hard-link additional SBML PBK models
- Change exposure route of dust and soil ingestion to oral

### 13.31.3 Fixed

- Add documentation for soil exposure module (#2113)

## 13.32 Version 10.1.5 (2025-02-10)

### 13.32.1 Added

- Update SRA EU prospective dietary CRA (2024) to use the option to apply conversion of processed derivatives (#2105)
- Implement method to run chronic PBK model simulations using single repeated exposures (#2106)
- New module Soil exposures

### 13.32.2 Changed

- Refactor 'IsCompute' functionality, move to ModuleConfiguration in project settings XML (#2101)

## 13.33 Version 10.1.4 (2025-01-31)

### 13.33.1 Added

- Update concentrations module with functionality to exclude occurrence data at the level of the processed RPC the focal commodity (#2066)
- Focal food/substance functionality for MRL replacement using a settings input field for the proposed MRL (#2085)
- Filter focal food concentrations/samples based on fieldTrialType (#2094)
- Implement default processing factor for missing processing factors (#2095)
- Add option to replace measurements of processed derivatives of the focal food, including correction for processing (#2102)

### 13.33.2 Changed

- Update SRA EU prospective dietary CRA (2024) with option to choose MRL/GAP/USE scenario (#2092)

### 13.33.3 Fixed

- Focal food-substance combination not saved in EFSA prospective CRA 2024 (#2087)

## 13.34 Version 10.1.3 (2024-12-13)

### 13.34.1 Added

- Implement first draft version of a working templates example in MCRA Web (#1894)
- Documentation on 'combining dietary and non-dietary exposures' (#2040)
- Initial implementation of uploadable PBK models via data module (#2061)
- Initial version of standard action for prospective dietary CRA 2024 (#2068)
- Initial version of standard action for retrospective dietary CRA 2024 (#2079)
- Implement uploading of SBML models (#2072)
- Add ActionType column to MCRA Tasklogs database table (#2077)

### 13.34.2 Fixed

- Can't send mail from within MCRA to other user (#1846)
- Model-then-add modeltypes and transformations are not saved (#2080)

## 13.35 Version 10.1.2 (2024-11-08)

### 13.35.1 Added

- Show last successful and failed login (#1810)
- Implement internal concentration and internal dose (systemic) (#1891)
- Download modular design based on action mappings (#2012)
- Implement expression type for kinetic conversion factors (#2019)

- Implement population alignment methods (#2040)

### 13.35.2 Changed

- Rename modules: “Human monitoring data” to “HBM occurences” and “Human monitoring analysis” to “HBM analysis” (#2001)
- Hide not-working proast link (#2015)
- Remove enum value AbsorptionFactorModel from InternalModelType, add TargetDoseLevelType.Systemic (#2026)
- Rename HBM Occurences module (previously named human monitoring data) to HBM concentrations (#2039)

### 13.35.3 Fixed

- Sharing with use rights allows users with administrator role still to download the data (#1934)
- After removing a share, the sharee can still run the action (#1935)
- Terms of use window keeps appearing on repeated logins and doesn’t get saved (#2032)
- Create internal exposures action: remove option “Undefined”, remove option “External dose” issue 2059, 2060 (#2059, #2060)

## 13.36 Version 10.1.1 (2024-09-20)

### 13.36.1 Added

- Implement PbkModels interface
- Allow plug-in of additional SBML PBK models in frontend and simulation service
- Update frontend with panels and forms for new dust exposure assessment modules

### 13.36.2 Changed

- Move compartment to target exposures module
- Split kinetic models into AbsorptionFactors (KineticModels) and KineticConversionFactors module
- Remove deprecated and unused setting CodeKineticModel (#2007)

### 13.36.3 Fixed

- Imported zip of converted full action from standard action opens as standard action (#1984)
- Correct visibility update behaviour of form controls for dynamic setting groups (#2002)
- Notification of new user registration email is not sent (#2016)

## 13.37 Version 10.1.0 (2024-08-15)

### 13.37.1 Added

- Automated job to disable inactive user accounts (#1715)
- Add rate limiting for failed login attempts (#1809)

### 13.37.2 Changed

- Restructure MCRA settings XML format to group settings per module (#581)
- Migrate code base from .NET 6 to .NET 8 (#1833)
- Upgrade R to version 4.4.1 and rtools to 4.4 (#1966)
- EFSA 2023 SRAs pro- and retrospective (#1961)

### 13.37.3 Fixed

- Cannot convert to target matrix blood when blood is not present as sampling method in HBM data (#1960)

## 13.38 Version 10.0.15 (2024-06-21)

### 13.38.1 Changed

- Update EFSA 2023 Standard actions pro- and retrospective (#1961)

## 13.39 Version 10.0.14 (2024-06-18)

### 13.39.1 Fixed

- SA Risk steatosis from imazalil seems broken: can't download action+data as zipped CSV (#1948)
- Remove default CodeFocalEffect from Eu 2023 prospective standard action settings
- Update access level when access level was previously set without subfolders (#1928)

## 13.40 Version 10.0.13 (2024-05-28)

### 13.40.1 Added

- Add settings tiers for Prospective Dietary CRA (EFSA 2023) (#1924)

### 13.40.2 Fixed

- Do not show substance weighting of mixtures option in create new action dialog of dietary exposures (#1943)
- Retrospective and prospective SA 2022 defaults, remove checksums from SA definition

## 13.41 Version 10.0.12 (2024-05-21)

### 13.41.1 Added

- Add password expiration functionality (#1714)
- Kinetic conversion for specific biomarkers in hbm analysis (#1827)
- Extend registration form with fields for organisation, PARC, and purpose (#1920)
- Documentation: add more info on LOD and LOQ imputation (#1904)

### 13.41.2 Changed

- EU prospective SA 2023 should use gap scenario and default percentage should be 20
- Place standard actions in alphabetic order in window "Create new standard action" (#1914)
- Decouple MCR settings / analysis in different modules (e.g. MCR in Risks and HBM analysis) (#1931)

### 13.41.3 Fixed

- Selecting checkbox of apply biomarker conversion no longer auto selects convert to checkbox (#1923)

## 13.42 Version 10.0.11 (2024-04-12)

### 13.42.1 Added

- Filtering of hbm data on time points (#1782)
- Running two opex products for compute action single value non-dietary exposures (#1796)
- Specific gravity from creatinine urine adjustment method by Busgang et al. (#1874)
- Option in to skip privacy sensitive outputs in report (#1882)
- New expression type for specific gravity (#1896)
- Implement new option nondetects handling (#1905)

### 13.42.2 Changed

- Split Busgang urine specific gravity normalisation into age and non-age dependent methods (#1903)
- Draw from censored lognormal using nondetect and nonquantification information (#1904)
- Updates to EFSA CRA 2023 prospective and retrospective standard actions

### 13.42.3 Fixed

- Remove hbm analysis option to convert using default value 1 (#1829)

## 13.43 Version 10.0.10 (2024-03-07)

### 13.43.1 Changed

- Remove conversion factor 1 when target level external in hbm analysis (#1829)
- Update acknowledgement efsa on landing page (#1892)

### 13.43.2 Added

- Prevent password reuse (#1879)
- Tables for single value non-dietary exposures (#1860)

## 13.44 Version 10.0.9 (2024-02-27)

### 13.44.1 Added

- New module single value non-dietary exposures (#1733)
- New standard action prospective EFSA data 2019-2021 (#1856)
- Implement ‘use kinetic conversion factor subgroup’ setting (#1868)
- Add specific gravity from creatinine adjusted method Carrieri 2001 (#1874)

### 13.44.2 Changed

- HBM analysis: update biomarker conversion to allow for biomarker conversion subgroups (age/sex) (#1844)

### 13.44.3 Fixed

- Kernel calculation in R for violin plots fails when vector contains infinities (#1869)
- Human monitoring analysis settings: order of settings is incorrect (#1876)

## 13.45 Version 10.0.8 (2024-02-12)

### 13.45.1 Changed

- Update standard action retrospective CRA with EFSA 2019-2021 data (#1823)
- HBM analysis: change order of settings in input form (#1839)

## 13.46 Version 10.0.7 (2024-02-02)

### 13.46.1 Added

- First draft version of standard action retrospective SRA with EFSA 2019-2021 data (#1823)

### 13.46.2 Changed

- Add uncertainty columns to RawkineticConversionFactor table (#1845)

### 13.46.3 Fixed

- Wrong data source version is shown and used in MCRA for a datasource with multiple versions (#1848)

## 13.47 Version 10.0.6 (2024-01-26)

### 13.47.1 Fixed

- Improve loading speed frontend for large concentration datasets (#1542)
- Add 'clickjacking' protection to MCRA website by hiding content when site is loaded in an IFrame
- PDF fails to render due to large AnalyticalMethods section (#1831)
- Can't delete an MCRA user group when repositories still reference it (#1832)
- Bug in concentration models settings form in frontend: cannot set MRL fallback model (#1834)

## 13.48 Version 10.0.5 (2023-12-21)

### 13.48.1 Changed

- Additional changes for MCR analysis in risks module (#1784)

## 13.49 Version 10.0.4 (2023-12-18)

### 13.49.1 Added

- Add general information columns (publication title e.o.) to RPF table (#1772)

- Allow for hazard-characterizations to vary as function of a covariate: example age-dependent HBM-GV for PFAS (#1778)
- Implement MCR analysis in risks module (#1784)

### 13.49.2 Changed

- Rename MarginOfExposure and HazardIndex of type-definition/enum RiskMetricType (#1705)

### 13.49.3 Fixed

- Use EN-US number input field with decimal point and not decimal comma (#1781)

## 13.50 Version 10.0.3 (2023-12-01)

### 13.50.1 Added

- Terms of use and disclaimer (#1583)
- Kinetic conversion models for metabolites (#1683)
- Extend standard action mra metals for effect dnt (#1689)
- Implement BMDL (#1788)
- HBM data exclude substance - sampling method combinations (#1795)
- Show number of non-analysed samples in hbm data samples summary (#1797)

### 13.50.2 Changed

- MCRA security: make 2FA compulsory for all MCRA accounts (#1765)
- Always show top right help icon in MCRA web app

### 13.50.3 Fixed

- User groups not visible for non-admin MCRA users
- Remove strong password validation check on Lost QR code form

## 13.51 Version 10.0.2 (2023-10-26)

No changes in MCRA Web

## 13.52 Version 10.0.1 (2023-10-23)

### 13.52.1 Added

- Bootstrap hbm monitoring data (#1405)
- MCRA security: two-factor authentication (2FA) (#1582)
- Implement PARC-HBM data format reader to support codebook v2.3 (#1649)
- Basic implementation kinetic conversion factors (#1658, #1660)
- Create separate matrix selection settings for kinetic models and HBM analysis (#1684)
- Exclude substances from urine or blood normalisation - standardisation (#1659, #1703)
- Implement kinetic conversion factors (#1695)
- Add biological matrix and expression type to points of departure (POD) data table (#1724)

- Hazard characterisations uncertain (#1742)

### 13.52.2 Changed

- Update HBM demo standard action on bisphenols to include Karrer kinetic model (#1251)
- Update frontend action details form to show progress spinner on setting/change data sources (#1672)
- Remove action tiers from module definitions to tier/template files per tier (#1673)
- Using new risk metric names for section paths in standard actions (#1679)
- Allow multiple/nested HTML tab panels in output section views

### 13.52.3 Fixed

- Wrong thousands separator in number of Monte Carlo iterations (#1645)
- Import HBM data should read in correct biological matrix (#1685)
- Convert to single target for hazard characterisations (#1696)
- Substance-specific intraspecies conversion of HC does not work (#1710)
- Delete data folder and show data source usage (#1713)

## 13.53 Version 10.0.0 (2023-06-23)

Public release of Open MCRA Core source code on GitHub.

### 13.53.1 Changed

- Update short report template for EFSA 2022 acute cranio
- Adjust text on MCRA home page for MCRA 10 (#1627)
- Adjust documentation, settings and URIs for MCRA 10 (#1627)

### 13.53.2 Fixed

- Inconsistencies in setting visibility and selected module tiers, add documentation (#1632)
- Delete action unnecessarily loads settings (#1646)
- Username is not saved when creating an external repository
- Wrong tier selection in SA EU chronic exposure assessment (2018) and Training Prospective Chronic (#1650)

## 13.54 Version 9.2.10 (2023-06-01)

### 13.54.1 Changed

- Download loop task output (html, tables, charts) creates a zip file with all sub-task outputs (#1530)

### 13.54.2 Fixed

- Version number of data source in RPF action input summary shows wrong version (#1604)
- Show correct tier setting for single value risk in SA cranio efsa 2022 (#1635)

## 13.55 Version 9.2.9 (2023-05-24)

### 13.55.1 Added

- Implement support for missing bodyweights in MCRA (#1585)
- Documentation imputation with zero and biological matrix conversion (#1603)
- Add 'compare sub tasks' to single value risk module (#1606)

### 13.55.2 Changed

- Clean up the contents of the downloadable HTML zip report: move CSV, SVG and metadata files into subfolders (#1361)
- Update EFSA 2022 SRA cranio to use the new EFSA 2022 settings tiers (#1544)
- Update create action wizard of risks module (and single value risks) to include risk metric choice (#1574)
- Update the two standard actions for training prospective CRA with option to run scenario GAP + 20% use (#1621)

### 13.55.3 Fixed

- Data folders in Workspace data tab are not scrollable (#1572)
- Human monitoring data allows to run without specifying survey (#1593)
- Correct update method of automatic forms so that also the item visibilities are also properly updated after form submission (#1628)

## 13.56 Version 9.2.8 (2023-04-25)

### 13.56.1 Added

- Update HTML report in zip download with toc-functionality to make it easier to browse through (#1409)
- Risks: Implement cumulative as sum of single-substance ratios (Exposure/Hazard) (#1528)
- Add documentation core and web (#1448)

### 13.56.2 Fixed

- Data sources view is not updated/refreshed after upload new data source version (#1512)
- User name input check for reset password is not correct (#1594)
- Setting Multiple effects gives error (#1595)

## 13.57 Version 9.2.7 (2023-04-03)

### 13.57.1 Added

- Separate substance-weighing option for MCR and mixtures analysis and add checkbox to compute or not compute MCR in HBM analysis actions (#1499)
- Show 'Created' date in admin users panel (#1523)
- Add standardisation methods for blood and urine (#1359, #1477)
- Implement initial version of SRA acute CRA of craniofacial alterations EFSA 2022 (#1464)

### 13.57.2 Changed

- Remove MCRA version select page, MCRA 9 is now the default
- Update exposure mixtures module with option to log-transform data before network analysis (#1531)

### 13.57.3 Fixed

- Hide option for reference substance equivalents when cumulative does not apply for the action (#1502)

## 13.58 Version 9.2.6 (2023-03-10)

### 13.58.1 Added

- Add compartments including cumulative amounts like urine (#1272)
- Allow hbm as input for risks (#1394)
- Add documentation about allocation of substances (#1473)
- Add new model substance approvals (#1461)

### 13.58.2 Changed

- Remove service worker functionality from Angular app
- Change MCRA URLs to point to static Documentation URL (#889)
- Move and update documentation section on HBM4EU/PARC HBM data format (#1427)
- Update Angular version to v15.0 (#1468)
- Unique constraint of Hazard Characterisations table is too strict (#1491)
- Keep report name tabs visible when scrolling through report comparison view

### 13.58.3 Fixed

- File upload failed: max upload file size was not configured correctly
- Fixed subset range editor
- Transaction deadlocked on lock resources in Job scheduler and simulation worker (#1487)
- Job scheduler does not assign jobs correctly (#1489)
- Null reference exception when changing data source (#1501)
- Exception when trying to view task settings in admin tasks panel
- Report comparison fails to load
- Can't compare outputs of a loop task in tabbed output view, TOC doesn't work (#1509, #1510)
- Error messages are not displayed correctly in web application
- Missing user account when e-mail verification fails (#1520)

## 13.59 Version 9.2.5 (2023-02-10)

### 13.59.1 Added

- Documentation: added section on CLI (#1450)

### 13.59.2 Changed

- Update third party packages (NuGet) for MCRA Web

### 13.59.3 Fixed

- Failed dataset upload still creates a data source record in the repository (#1483)

## 13.60 Version 9.2.4 (2023-02-03)

### 13.60.1 Added

- Add documentation of HBM4EU/PARC HBM data format (#1427)
- Add maximum percentage missing value percentage imputation hbm data (#1470)
- Add population characteristics Real Life Mixtures (#1475)

### 13.60.2 Changed

- Update HBM analysis module to include imputation of missing data method established within HBM4EU/PARC RLM (#1397)
- Update HBM data/analysis module to allow for analysis of concentrations of multiple sampling methods/matrices (#1398)
- Implement changed rules for sending automatic mail from WUR and RIVM (#1466)
- Move internalconcentrationtype to assessment settings

### 13.60.3 Fixed

- Download action + data (data as zipped csv) fails (#1451)
- Loop task output doesn't show the comparison between the looped actions (#1459)
- New user registration in MCRA returns 400 Bad Request (#1465)
- Load correct png mime type for safety chart
- Upload of Demo HBM bisphenols standard action data fails (#1472)

## 13.61 Version 9.2.3 (2023-01-16)

### 13.61.1 Added

- Implement chlorpyrifos kinetic model with metabolites (#1285)

### 13.61.2 Changed

- Removed unit test report results from admin page (#1441)
- Allow links to MCRA documentation on other servers (#1457)

### 13.61.3 Fixed

- Documentation shows no version of MCRA in colophon
- Documentation links to web API documentation and web application
- Can't view info in data browser of a shared data source (#1458)

## 13.62 Version 9.2.2 (2022-12-20)

### 13.62.1 Added

- Documentation: Add PARC Real-life mixture guidance documents (pdf) and related data to the User guide - Examples section (#1366)

### 13.62.2 Changed

- Update HBM analysis module with non-detects imputation method according to method established within HBM4EU/PARC RLM (#1396)

### 13.62.3 Fixed

- Fix reference to dietary exposures section in risks output section (#1331)
- MCRA Build date-time not displayed correctly (#1410)
- Settings in overview only show headers and no settings (#1442)
- Mixtures crashes when no concentrations for HBM data are available (#1443)
- Output collection of task with subtask fails (#1444)
- MCRA settings loading fails: allow floating point literals (NaN, Inf etc) in Json serialization

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