The MCRA toolbox of models and data to support chemical mixture risk assessment

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Abstract

A model and data toolbox is presented to assess risks from combined exposure to multiple chemicals using probabilistic methods. The Monte Carlo Risk Assessment (MCRA) toolbox, also known as the EuroMix toolbox, has more than 40 modules addressing all areas of risk assessment, and includes a data repository with data collected in the EuroMix project. This paper gives an introduction to the toolbox and illustrates its use with examples from the EuroMix project. The toolbox can be used for hazard identification, hazard characterisation, exposure assessment and risk characterisation. Examples for hazard identification are selection of substances relevant for a specific adverse outcome based on adverse outcome pathways and QSAR models. Examples for hazard characterisation are calculation of benchmark doses and relative potency factors with uncertainty from dose response data, and use of kinetic models to perform *in vitro* to *in vivo* extrapolation. Examples for exposure assessment are assessing cumulative exposure at external or internal level, where the latter option is needed when dietary and non-dietary routes have to be aggregated. Finally, risk characterisation is illustrated by calculation and display of the margin of exposure for single substances and for the cumulation, including uncertainties derived from exposure and hazard characterisation estimates.

Keywords:

risk assessment; exposure; hazard; mixtures; probabilistic model; software

1 Introduction

Human activities have drastically increased the number of chemical substances to which we are exposed and which might have a negative impact on our health. Chemical risk assessment has focused traditionally on potential risks of single substances. However, multiple substances can have the same health effect, so their combined effects on the same phenomenological endpoint should be assessed (Drakvik et al., 2020). Consequently, the need was perceived to develop risk assessment methods for combined exposure to multiple substances, i.e. mixtures of substances. The current legislative requirements for risk assessment of mixtures were recently reviewed (Rotter et al., 2018).

The tasks for mixture risk assessment are not trivial. First, decisions are needed regarding which chemical substances should be evaluated together in an assessment group (AG) when considering a specific adverse outcome (AO). For those substances, data or assumptions on both exposure and hazard are needed. A specific human population group has to be defined as the object of protection. Exposure might need to be aggregated over several sources, such as dietary exposure, dermal or inhalation exposure, sometimes for specific population groups, e.g. those working in a risky profession like pesticide spraying. Hazard data can be obtained from *in vivo*, *in vitro* and *in silico* approaches. The latter two categories require biological modelling, e.g. using adverse outcome pathways (AOPs), to assess the relevance of responses for the defined *in vivo* AO. The most common assumption for cumulating effects is the dose addition (DA) model, but its validity might need to be checked (EFSA, 2013a, 2019; OECD, 2018). Under the DA model the relative potencies of substances are expressed as relative potency factors (RPFs). It should be noted that RPFs are typically different at the external or internal biological level. Kinetic modelling can be used to bridge the gap between external and internal doses by constructing *in vitro* to *in vivo* extrapolation (IVIVE) models. Inevitably, limitations in data availability lead to the necessity to make model assumptions and to uncertainty (EFSA, 2018). Many parts of the data will be uncertain, but this has often been ignored in practical work, notably for AG membership and RPF estimates.

One of the major aims of the EuroMix project was to integrate hazard, exposure, toxicokinetic and toxicodynamic modelling approaches for mixtures of chemicals together with example data sets into a web-based model and data toolbox openly accessible for stakeholders. The system is able to assess quantifiable uncertainties and their influence on the results of cumulative and aggregated risk assessment. For this, it uses a 2D Monte Carlo approach based on quantifiable variability and uncertainty in the inputs, where an inner loop estimates variability distributions for specific outputs, characterising the variability between individuals or individual-days. Then an outer loop estimates uncertainty distributions for specific outputs, e.g. 95% confidence limits for a percentile of a variability distribution.

In the EuroMix project, the toolbox has been developed as version 9 of the Monte Carlo Risk Assessment (MCRA) platform (see van der Voet et al., 2015 for a description of the previous version MCRA 8). The toolbox also integrates the method innovations recently developed for EFSA in their approach to cumulative exposure assessment and implemented as well in MCRA version 8.3 (van Klaveren et al., 2019ab). MCRA is a web-based platform (https://mcra.rivm.nl) which employs a high-performance computation cluster to run simulations. For a full description of the toolbox we refer to the online reference documentation (MCRA, 2019). The toolbox can be used in conjunction with the EuroMix handbook (Zilliacus et al., 2019a). In this paper the aim is to provide an overview of the available methods and illustrate the use of the toolbox with several examples for hazard identification, hazard characterisation, exposure assessment and risk characterisation. These examples are not full case studies, but are only intended to illustrate existing and new functionalities that are available in the toolbox.

In section 2.1 of this paper we describe the toolbox of models and data that has resulted from the EuroMix project. The data collected in the EuroMix project are summarised in section 2.2. In sections 2.3-2.6 short descriptions are given of the methods implemented in the toolbox for the four areas of risk assessment, i.e. hazard identification, hazard characterisation, exposure assessment and risk characterisation, respectively, and the data for some simple examples are described. Sections 3.1-3.4

then show the results for the examples. The results and the intended use of the toolbox are discussed in section 4.

2 Methods

2.1 Description of the MCRA toolbox

The toolbox for mixture risk assessment has been built according to the modular design shown in Figure 1. The modules are listed in Appendix A. Modules are of three basic types: 1. Scoping modules regarding primary entities on which the risk assessment is built; 2. Data modules, specifying groups of data sources needed or optional for the assessment; and 3. Calculator modules, which calculate results of a certain type. Note, that calculator modules can in principle also act as data modules if the results are already available from previous work.

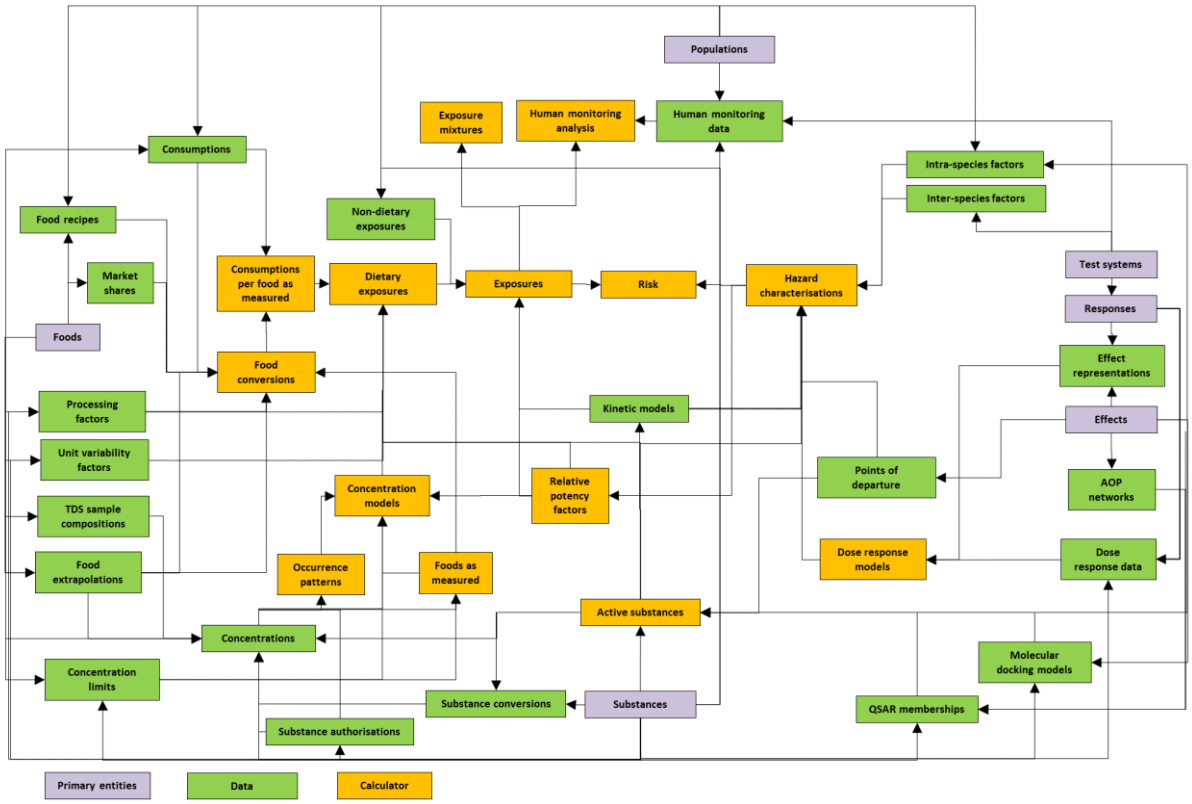

Figure 1. Modular design of the MCRA toolbox. Not all links are shown in this graph. See Appendix A for a complete list.

The primary entities in the toolbox relate to the agents of risk (Substances), the sources of dietary exposure (Foods), the objects of protection (Populations), the potential hazards (Effects), and how these are measured (Responses in Test systems). The data and calculation modules on the left side of Figure 1 are related to exposure assessment, those on the right side to hazard identification and hazard characterisation. The module for risk assessment is in the middle of the diagram, integrating exposures and hazard characterisations.

The exposures module can aggregate non-dietary exposures (which then need to be provided as data) and dietary exposures. Dietary exposures are calculated from consumptions and concentrations, possibly incorporating many detailed aspects. Food consumptions may need to be redefined by conversion of food codes from the codes used in consumption surveys to the codes used in concentration monitoring data. Occurrence data (concentrations and substance authorisations) may need to be converted due to differences between active substances and measured substances (in the pesticide field known as complex residue definitions), and such data may be condensed in concentration models (e.g. a lognormal distribution with a spike of non-detects). Total diet study (TDS) concentration data require a conversion to appropriate food codes. Exposures may also be adjusted for food processing effects and for the greater concentration variability in units of consumption compared to the composite samples used in the monitoring program. In addition, modelled exposures may be inspected for co-occurrence of substance combinations as exposure mixtures, and they may be compared to human monitoring data.

Hazard identification is concerned with identifying the active substances related to a given health effect. AOP networks may be used to identify relevant effects connected to the adverse outcome of interest in the assessment. Identification of active substances as belonging to the relevant AG may be just specified as data, or it may be derived from available toxicity data or from *in silico* models (QSAR and/or molecular docking). Effect representations data will link observed responses to effects of interest and may specify benchmark responses, which are toxicologically relevant levels for those

responses, to be used in the modelling of dose-response data to obtain benchmark doses (BMDs). BMDs as well as other points of departure (POD) specified as data can then be used for hazard characterisation, either directly or after applying assessment factors for POD type, species differences and/or within-species variability. Kinetic models (or simple absorption factors) may be use to extrapolate between external and internal doses. We use the term hazard characterisation (HC) as a generic term which can be any form of POD or health-based guidance value, depending on the purpose of the analysis. For the assessment of mixtures, RPFs are calculated as the ratio of HC for an index substance to HC for a specific substance.

The toolbox distinguishes between two types of runs: the nominal run and the uncertainty analysis loop. The nominal run represents a single calculation in which the aim is to compute the most likely, if possible unbiased estimates for the model at hand. E.g., when computing dietary exposure distributions, the nominal run computes one exposure distribution, using, as much as possible, fixed values for all uncertain inputs, and summarises the exposure distribution by point estimates of statistics such as the mean exposure or specific percentiles of variability. In the uncertainty analysis, on the other hand, the calculation run is repeated a number of times, each time with a different uncertainty scenario obtained using bootstrapping, parametric resampling, and/or re-calculation of uncertain values, yielding uncertainty distributions and confidence intervals for specific outputs. Making the distinction between the nominal run and the uncertainty loops has the practical advantage that it allows the user to setup and evaluate complex simulations first using only the nominal runs to quickly obtain a picture of the results and identify possible errors in the data or in the model settings before running the more time-consuming uncertainty analysis loop.

User work is organized in workspaces. A workspace is a collection of work items that are logically grouped together. A workspace has a name, description and, optionally, a number of tags. Users are the owners of their own workspace folders. An action is started with the module of the corresponding action type (e.g. dietary exposures), but also links to other modules that are needed for its completion (e.g. consumptions per food as measured, consumptions, foods, etc.). An action can be available in two forms: 1) a data selection action and 2) a calculation action. A data selection action comprises the

selection of already available data of that action type, optionally the specification of selections on that data, and in some cases some pre-processing of data. A calculation action is an action in which the data of that action is calculated based on relevant input and specific calculator settings. Within a workspace, multiple actions can be created. When running an action, a task is spawned that produces output. Output is available in the form of reports or in the form of data that can be used as input in other actions. Actions have multiple outputs when settings are changed. Output reports are presented as screen reports or print reports and structured according to the modules of the modular design.

2.2 Data – Example data organised in the EuroMix project

The toolbox contains a repository for relevant data. Data can be uploaded by individual users or by representatives of a larger user group. Data can be shared with other users or user groups. The data administrator for each data set can decide on use, read, or read/write permission for users. The data collected during the EuroMix project (Data/EuroMix repository) are shared with project participants and other stakeholders and are summarised in Table 1. These data collected in the EuroMix project were the basis for the examples shown below.

Table 1. Data in the toolbox, as collected in the EuroMix project. For specific data regarding modules that were not in the focus of the EuroMix project and therefore not included in this table, references are van Klaveren et al. (2019ab) for Unit variability factors, Substance authorisations, Substance conversions, Concentration limits and Food extrapolations, Kolbaum et al. (2019) for TDS sample compositions, van der Voet et al. (2009) for Intra-species factors and Inter-species factors.

Module	Description data sets
Foods	2289 foods-as-eaten and foods-as-measured coded in FoodEx1 (EFSA, 2011) 32 processing types
Substances	1629 substances, classified in categories PPPs, Biocides, Alkaloids, EnvironmentalPollutants, FoodAdditives, Mycotoxins (Kyriakopoulou et al., 2017)
Effects AOP networks	48 effects in 7 AOP networks related to liver steatosis, reproductive toxicity and craniofacial malformations
Populations	15 population groups from 10 countries (different age groups) (Crépet et al., 2019a)

Module	Description data sets
Test systems Responses Effect representations	14 test systems, 477 responses, 162 effect representations (Luckert et al., 2019; Schreiber et al., 2019ab)
Consumptions	11 files with food consumption data in 10 countries (Crépet et al., 2019a)
Food recipes	5555 records specifying food ingredients in the FoodEx1 system or conversions (Boon et al., 2015)
Concentrations	Food monitoring data 2010-2014, SSD formatted data (Crépet et al., 2019a)
Processing factors	667 processing factors for pesticides and environmental pollutants (derived from Verarbeitungsfaktoren_3-0.xls, downloaded 01-09-2015 from https://www.bfr.bund.de/de/a-z_index/verarbeitungsfaktoren-8400.html)
Non-dietary exposures	Simulated non-dietary exposures from Browse and Bream2 (Kennedy et al., 2019)
Human monitoring data	Norwegian biomonitoring study (Husøy et al., 2019)
QSAR membership models	26 QSAR models applied to all substances in the EuroMix chemical inventory (Rorije et al., 2019)
Molecular docking models	20 Molecular docking models applied to all substances in the inventory (Rorije et al., 2019)
Kinetic models	EuroMix Generic PBTK model parametrised for 9 substances based on httk and for all substances in the inventory based on QSAR (Tebby et al., 2019)
Points of departure	144 NOAEL or LOAEL values related to Steatosis-liver (Crépet et al., 2019a)
Dose response data	28 files describing experiments with single substances or mixtures , on 15 responses (or groups) in 9 test systems in 6 laboratories (Luckert et al., 2019, Schreiber et al., 2019ab)

2.3 Hazard identification: AOP-based assessment groups, probabilistic memberships from *in silico* data or expert elicitation

2.3.1 Implemented methods for hazard identification

In the context of mixture risk assessment, hazard identification includes the task of identifying and grouping substances that may lead to a specified adverse outcome (AO) considered in a risk

assessment. The set of such substances together form the AG for the AO. The toolbox offers various methods to establish AGs. In this work we will focus on some of these methods The *Active substances* module of the toolbox includes several possibilities for defining AGs. First, the substances belonging to an assessment group related to a given AO can be directly specified. Secondly, only the substances for which POD data are available can be selected. Thirdly, substances can be selected based on predictions for the given AO from QSAR or molecular docking models (Cotterill et al., 2016; Rorije et al., 2019). Under the first and third options, missing PODs can be imputed (Kennedy et al., subm.).

In probabilistic modelling, substances can also be identified with a membership probability for the assessment group. Membership probability can be derived from expert knowledge elicitation, as in recent EFSA reports (EFSA et al., 2019ab), and entered as data in the toolbox. Probabilities can also be based on the fraction of positive QSAR or molecular docking models, either as a simple ratio estimate or using a Bayesian calculation that includes the sensitivity and specificity of the QSAR models when available (Kennedy et al, subm.).

2.3.2 Example

The EuroMix inventory list of 573 pesticides (Kyriakopoulou et al., 2017) was analysed for possible hazard with respect to the adverse outcome steatosis. From data available at EFSA, steatosis-specific PODs were available for a minority of pesticides. Additional indications for steatotic activity were derived from *in silico* models such as QSAR model predictions and molecular docking binding energies (Cotterill et al., 2016; Rorije et al., 2019). An AOP network for steatosis (Vinken, 2015; Mellor et al., 2016) was assessed (Luckert et al., 2018) and has been graphically outlined (Figure 2). This network was uploaded to the toolbox in the form of relational tables specifying all effects and effect relations. Based on this data, several options for non-probabilistic (crisp) or probabilistic AG membership assessments that are available in the toolbox will be illustrated.

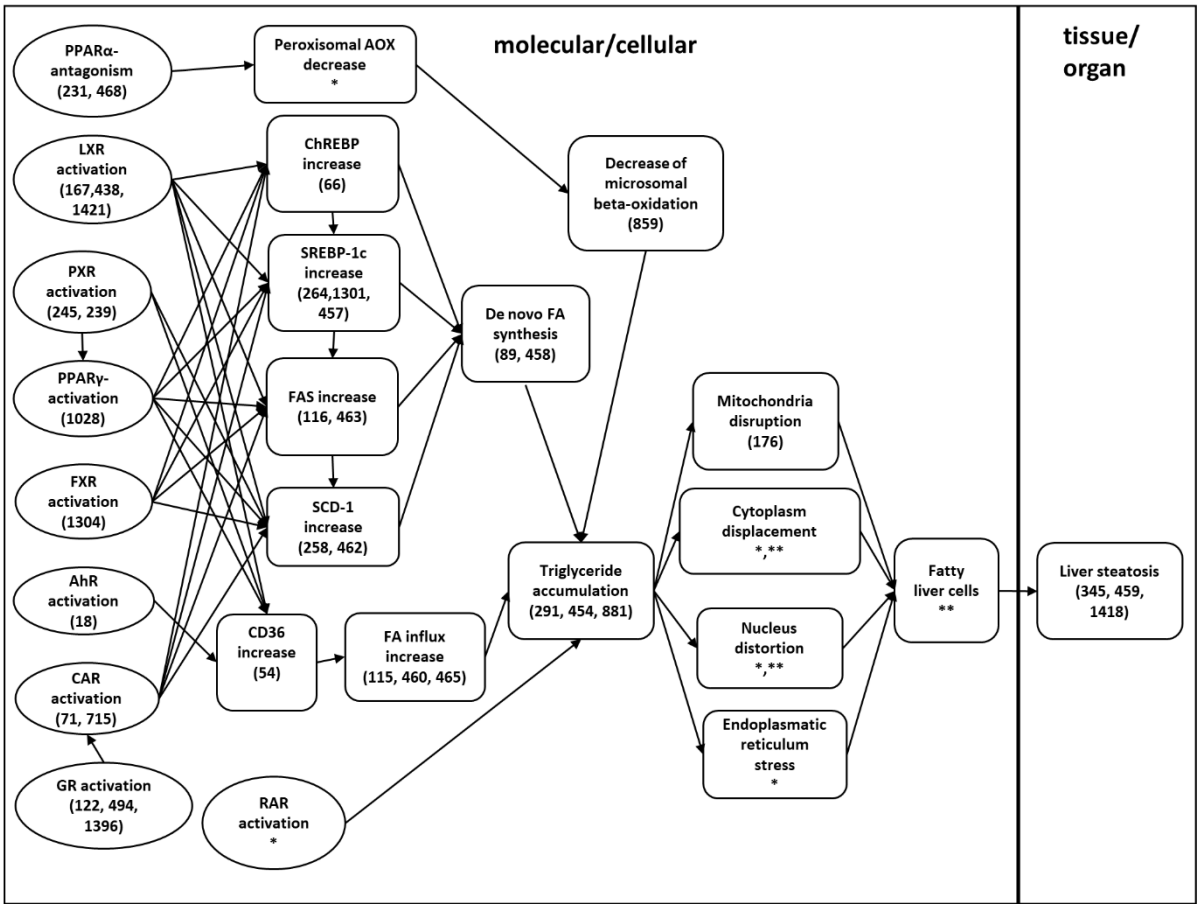

Figure 2. Adverse Outcome Pathway (AOP) network for the adverse outcome (AO) liver steatosis. The ovals are molecular initiating events (MIEs) and the boxes are other key events (KEs). The arrows depict key event relationships (KERs). The numbers in the ovals/boxes refer to KE numbers in the AOP wiki (https://aopwiki.org). * refers to KEs not included in the AOP wiki but described in Mellor et al. (2016). ** refers to KEs not included in the AOP wiki but described in Vinken (2015).

2.4 Hazard characterisation: dose response modelling, calculation of RPFs, use of kinetic models for IVIVE

2.4.1 Implemented methods for hazard characterisation

For hazard characterisation in the context of mixture risk assessment the RPF calculations are based on POD values for the substances. The POD value can be a BMD from benchmark dose modelling or a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL). Health-based guidance values, such as Acceptable daily Intake (ADI) or Acute Reference Dose

(ARfD) can also be used instead of POD, i.e. the POD divided by the assessment factors, which should be taken into consideration for comparison to exposure. Because of the many variations possible, the value used for the RPF calculation is generically called HC in this paper and in the toolbox.

Well-known softwares for benchmark dose (BMD) modelling of dose response data are BMDS (http://www.epa.gov/bmds) and PROAST (http://www.rivm.nl/en/proast) (EFSA, 2017). In module *Dose response models* of the toolbox, dose response data organised in the data repository can be fitted using the various dose response models (Slob, 2002; Slob and Setzer, 2014; EFSA, 2017), either using an internalised version of the PROAST software or using the web-based PROAST version (https://proastweb.rivm.nl). In the toolbox connections can be specified between effects, e.g. the adverse outcome or related biological effects, and responses, which are the measured quantities, *in vivo* or *in vitro*, that are available for BMD modelling. For example, it was proposed to consider the AdipoRed response after 72 hours in a HepaRG test system as one of the most appropriate and cost-effective responses in relation to the AO steatosis (Lichtenstein et al., 2019). Part of these *Effect representations* is the specification of an appropriate benchmark response (BMR), i.e. the response level considered suitable for the BMD modelling, often as a limit value for adversity (EFSA, 2017).

Whereas dose response models focus on BMD calculation related to specific responses, further or alternative steps may be needed to obtain an appropriate HC. In the *Hazard characterisations* module, many possibilities are provided to define HCs either as deterministic threshold values, such as NOAEL, ADI or ARfD, or as distributions generated from probabilistic models. HCs can be calculated for acute or chronic risk types, and for different target levels of the human body (external via some route of exposure or internal for a specific defined organ or compartment). It may be needed to align the available information to the desired target level by including assessment factors for inter-species differences, intra-species variation, different expression types (e.g. BMD or NOAEL or LOAEL) and the difference between external and internal exposure. The latter conversion is especially relevant when *in vitro* dose response data are to be used for a HC that should be compared with external, e.g. dietary, exposure data. In general this type of modelling is known as *in vitro* to *in vivo*

extrapolation (IVIVE). In this approach, we need human physiologically based toxicokinetic (PBTK) models. Within EuroMix, the Cosmos model was integrated in the toolbox as a general PBTK applicable model (Bois et al., 2019, Tebby et al., 2019).

The conceptual model used for the use of *in vitro* and/or *in vivo* animal study data for human hazard characterisation and risk assessment using IVIVE is shown in **Figure 3**. A typical situation is that there are many substances in a proposed AG, which could be measured all *in vitro* but not *in vivo*. The *in vitro* dose response relations are assumed to coincide with *in vivo* relations between internal dose and some early biological response. The *in vitro* data can then be used to derive internal RPFs, i.e. at the tissue or cell level. Then kinetic models (or absorption factors which are considered a lower tier of kinetic model) can be used to adjust external PODs. i.e. expressed as external exposure levels, to internal HCs, or alternatively to translate internal RPFs to external RPFs.

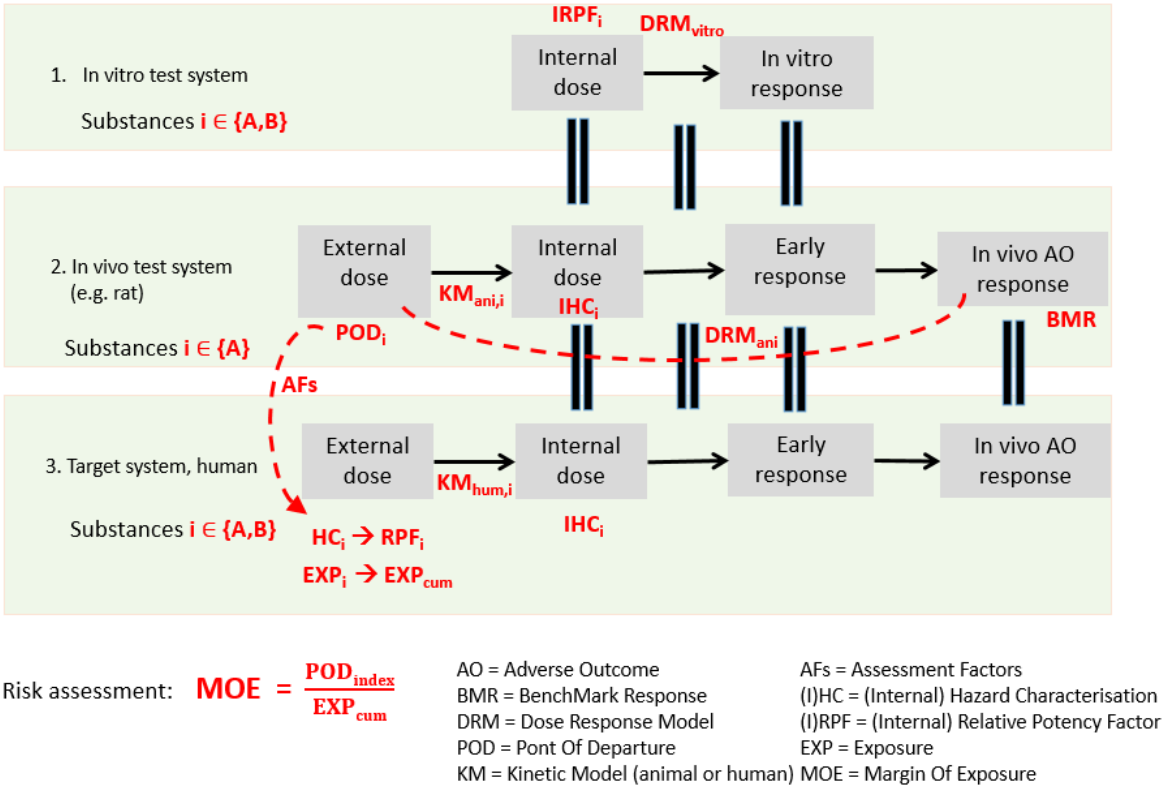

Figure 3. Overview of *in vitro* to *in vivo* extrapolation (IVIVE) model components. cum = cumulative; index = index substance; ani = animal, hum - human. Classes of substances: A: substances with *in vitro* and *in vivo* data, B: substances with only *in vitro* data.

In mixture risk assessments, RPFs are calculated by dividing the HC of a chosen index substance by the HC of each specific substance. This implies that RPFs may, and typically will be different depending on whether an external exposure or an internal exposure, e.g. at the target tissue or cell level, was used. In the module *Relative potency factors* both types can be calculated, and modelled uncertainties in the values used to derive the RPFs (e.g. from BMD modelling) are translated to uncertainties about RPFs. It may further be noted that RPFs represent the distance between parallel dose response curves, and can even be calculated when no BMR has been specified in the dose response modelling.

In the toolbox, external doses from animal studies can be adapted to external doses for humans by the use of inter-species and/or intra-species factors. Alternatively, no inter-species and intra-species factors are used, and then the final margin of exposure will have to be considered against an appropriate value representing the combined assessment factors, e.g. 100. We use the latter approach in this paper.

2.4.2 Examples

As a first example, hazard characterisations and RPFs were calculated based on the NOAELs or LOAELs available for 144 substances related to the AO steatosis, using the well-studied risk driver imazalil as an index substance. Standard inter-species and intra-species assessment factors of 10 were used for all hazard characterisations. As in Crépet et al. (2019), for 13 substances where no NOAEL was available, the LOAEL was divided by 3 to obtain an estimated NOAEL. This is a simple approach, and further refinement may be necessary in real applications. The guidance document from WHO/IPCS (2018) states that it would be much better to use dose-response data. In the current project, it was not possible to use the dose-response data for all 144 substances.

In the EuroMix project three chemicals were prioritised in relation to the AO steatosis: imazalil, thiacloprid and clothianidin based on relevance from dietary exposure and other considerations

(Crépet at al., 2019a, Lichtenstein et al., subm.). We therefore provide more detailed example calculations based on *in vitro* dose response data for these chemicals.

Dose response relations for the intracellular lipid accumulation after 72 hours were measured using the AdipoRed assay in the *in vitro* HepaRG test system for three substances in the steatosis AG (Luckert et al. 2019). Using the Proast model (https://www.rivm.nl/en/proast; Slob and Setzer, 2014), that is integrated in the MCRA toolbox, a 6-parameter parallel-curve exponential dose response model was fitted to the data. Three parameters represent the lower and upper asymptote and common slope, one parameter is the BMD for the index substance (here imazalil), and the remaining two parameters represent the RPFs for the other two substances relative to the index substance. A 10% increase in AdipoRed response was assumed to be an appropriate benchmark response (BMR) level. The appropriateness of the parallel-curve model was checked by superimposing the shifted dose response curves and the data (Kienhuis et al., 2015). The RPFs are based on *in vitro* doses in molar units. For reverse dosimetry we changed to mass units and mass-based RPFs.

Using the EuroMix Generic PBTK model that is integrated in the toolbox (Bois et al., 2019; Tebby et al., 2019) the internal liver concentration was simulated when a daily dose equal to the BMD is given. In the EuroMix project different parameterisations of the model for each substance have been investigated (Tebby et al., 2019). Here, we rely on kinetic parameters estimated by QSAR but with hepatic clearance values obtained from *in vitro* clearance measurements. The long-term exposure relevant for chronic risks was obtained by averaging over predicted liver concentrations in the period between 15 and 28 days. The ratio of this internal concentration to the external exposure per unit bodyweight was then used as the absorption factor. For all routes, the exposure is taken to be the total amount entering via that route per unit bodyweight and per day.

2.5 Exposure assessment: dietary exposure with large AG, aggregating dietary and non-dietary exposures, comparison with human monitoring

2.5.1 Implemented methods for exposure assessment

The module *Dietary exposures* of the toolbox implements the methods of the EFSA guidance on probabilistic modelling (EFSA, 2012) as well as the most recent EFSA methodology for cumulative dietary exposure assessment for acute and chronic risks of pesticides (van Klaveren et al., 2019ab; EFSA et al., 2019ab). Using the module *Food conversions* consumptions of food-as-eaten as specified in a dietary consumption survey can be recoded in terms of the foods-as-measured. In this paper concentration data according to EFSA's standard sample description (SSD1) (EFSA, 2010) were used with FoodEx1 food classification (EFSA, 2011). The toolbox however has no fixed coding systems, and could equally well use the newer SSD2 system (EFSA, 2013b) provided a table with code conversions for the foods-as-eaten is available.

The module *Dietary exposures* also implements advanced methods for long-term exposure commonly used in nutrition science, such as the logistic-normal normal (LNN) model for episodical intakes (Goedhart et al., 2012; Roodenburg et al., 2013; Boon et al., 2014; van der Voet et al., 2015).

In the module *Exposures* dietary (external) exposures can be translated to internal exposures, using simple absorption factors or integrated kinetic models. Non-dietary exposures from e.g. dermal or inhalatory routes can be aggregated with the dietary exposures (Kennedy et al., 2019; Karrer et al., 2019; Vanacker et al., in prep.). There can be multiple instances of a kinetic model (e.g. the human model for imazalil or the rat model for clothianidin). The parameters of each instance can be specified as fixed values or as variable and uncertain quantities. Distributions for variability and uncertainty are characterised by their type (log-normal, logistic-normal) and coefficient of variation.

Modelled exposures in given body compartments, e.g. blood or urine, can be compared to actually measured exposures from human (bio-)monitoring studies in the module *Human monitoring analysis*.

Dose-additivity is a common assumption in mixture risk assessment (EFSA, 2013a, 2019; OECD, 2018). With large number of substances that have the same health effect it is practically impossible to check this assumption for all combinations. It is then important to identify the main groups of substances that contribute to the cumulative exposure. The module *Exposure mixtures* implements a

multivariate method, sparse nonnegative matrix underestimation (SNMU), to find such groups (Crépet et al., 2019a).

Uncertainty about assessment group membership for substances can be addressed probabilistically as sketched in section 2.3.1. In the toolbox, such probabilities can be used in an exposure assessment to include or exclude substances in the multiple loops of an uncertainty calculation (see also EFSA, 2019ab), as described in Kennedy et al. (subm.).

2.5.2 Examples

An example is given of dietary exposure from 144 pesticides with a POD (NOAEL or LOAEL) for steatosis (Kyriakopoulou et al., 2017). Consumption data were available for a Dutch population of children (1-19 years) (van Rossum et al., 2011). These were combined with merged European food control and monitoring data 2010-2014 (Crépet et al., 2019a) using a previously established database of food conversions (Boon et al., 2015) and BfR processing factors (https://www.bfr.bund.de/de/a-z_index/verarbeitungsfaktoren-8400.html, downloaded 01-09-2015). As reported in section 3.2, the PODs were used to calculate external RPFs. For the handling of left-censored data (concentrations reported to be below a limit of reporting) the EC-EFSA method based on observed occurrence patterns was applied (van Klaveren et al., 2019ab), thus avoiding the extreme conservatism of the EFSA basic pessimistic model. Exposure percentiles for the basic observed individual means (OIM) method and the LNN method are compared, and the most important food-substance combinations (risk drivers) are identified.

In a second example, dietary exposures were combined with non-dietary exposures for the three prioritised steatotic substances imazalil, thiacloprid and clothianidin. The dietary exposures were based on consumption data of French adults (Dubuisson et al., 2010) and the same other dietary exposure data as mentioned above. The non-dietary exposures were estimates for adult residents from the Browse model (Kennedy et al., 2019). Internal RPFs for steatosis were based on *in vitro* data from AdipoRed assays (Luckert et al., 2019). For linking external to internal level exposures, the EuroMix

Generic PBTK was used, with parameterisations for the human including variability of the parameters (Tebby et al., 2019).

In a third example, the module *Human monitoring analyis* was used to combine questionnaire data on food consumption and personal care product use with monitoring data on bisphenol A (BPA) in food, and compare the resulting predicted exposures with measured urine levels. Human biomonitoring data for BPA were available from a Norwegian survey which measured bisphenols in urine and asked participants for their diet and their use of personal care products (Husøy et al., 2019). Predicted exposures were based on the recorded consumptions and personal care product use in combination with measured or modelled BPA levels (Karrer et al., 2019) using a kinetic model developed for this purpose and integrated in the toolbox (Karrer et al., 2018).

2.6 Risk characterisation: comparing exposure and hazard characterisation distributions

2.6.1 Implemented methods for risk characterisation

Risk characterisation is fundamentally the process of comparing exposure to hazard. Both exposure levels and hazard threshold levels (called HCs in the toolbox) can be variable (between individuals or individual-days) and/or uncertain. The toolbox module *Risks* can be used to display this comparison. More directly, the ratio of HC to exposure, i.e. the margin of exposure (MOE) is calculated and displayed. For mixture exposure, this has also been termed the MOE total (MOET) or combined MOE (e.g. Rotter et al., 2018; EFSA, 2019), but in the toolbox the term MOE is used throughout, for both single-substance and cumulative cases. For example, in a traditional risk assessment human exposures are often compared to a POD derived from an animal study. The product of assessment factors, e.g. 100 resulting from a factor 10 each for inter-species and intra-species differences, may then be used as a threshold for the MOE specified by the user.

In a more advanced calculation such as in the integrated probabilistic risk assessment (IPRA) approach (van der Voet & Slob, 2007; van der Voet et al., 2009), the assessment factors (as well as their variability and uncertainty) are internalised in the probabilistic hazard characterisation and modelled probabilistically. Probabilistic hazard and exposure estimates are then compared and the MOE compares individual human exposures to individual human HCs. Note that for this case this ratio has previously been termed the individual MOE (IMOE), but in the toolbox the term MOE is used generically, whether the HC includes the assessment factors or not. For practical risk assessment, the distribution of MOE (based on probabilistic exposure or probabilistic hazard or both) can be characterised with a lower percentile of interest, e.g. P1, or with the lower confidence limit on such a lower percentile. For an example of this fully probabilistic approach see Jacobs et al. (2015).

Uncertainty about assessment group membership for substances can be addressed probabilistically as sketched in section 2.3.1. In the toolbox, such probabilities can be used in a risk assessment to include or exclude substances in the multiple loops of an uncertainty calculation (see also EFSA, 2019ab), as described in Kennedy et al. (subm.).

2.6.2 Example

A mixture risk assessment for Dutch children was performed for the group of 144 pesticides with a POD for steatosis (Kyriakopoulou et al., 2017), calculating MOE values based on Dutch consumption data (van Rossum et al., 2011) and European monitoring data (Crépet et al., 2019) and using a user-specified MOE threshold value of 100.

3 Results

3.1 Hazard identification: Assessment groups, probabilistic memberships from *in silico* data

Running the *Active substances* module for the 573 pesticides listed in the EuroMix Chemical Inventory, 144 substances (25%) were found to belong to the AG for steatosis based on available

PODs for steatosis. The remaining 429 pesticides (75%) may or may not have steatosis as a non-critical effect, but it was not recorded in the dossiers. Therefore QSAR models may be useful to consider possible AG membership. We first illustrate non-probabilistic (crisp) options for membership assignment. From a larger collection of 29 available QSAR models collected in the EuroMix data, the five QSAR models that relate to the AOP network for steatosis were automatically identified (Table 2). Note that three of these models directly relate to the adverse outcome, whereas the remaining two relate to other effects (molecular initiating events or key events) that occur upstream in the AOP network. Using the toolbox it was calculated how many substances would belong to the AG for steatosis. This was based on the optimised FERA model, on all three available steatosis models, or on all five models related to the steatosis AOP network (Table 3). Pesticides for which no QSAR results could be calculated were omitted or added to the AG. Depending on the QSAR models chosen and the treatment of the substances without a QSAR prediction, the number of pesticides with an QSAR indication of a possible effect was between 250 and 525 (see column QSAR-based in Table 3), much higher therefore than the number for which a POD was available (n=144). In a second scenario, the QSAR results were only used to reduce the set of 144 pesticides having a POD, by omitting all substances without a QSAR prediction of steatosis. Instead of 144 pesticides we then found between 83 and 135 pesticides in the AG. In a third scenario, the QSAR-derived sets were expanded with those pesticides for which a POD was available although no QSAR-signal was obtained. This resulted in between 311 and 528 pesticides in the AG.

Table 2. QSAR models related to the adverse outcome steatosis. Note that some of the 573 substances could be analysed with the QSAR models.

Model	Model description	Effect	Number of substances with QSAR results	Fraction of these substances classified in AG
1	COSMOS Nuclear Receptor model for Steatosis liver nuclear receptors used to predict hepatotoxicity - and to predict steatosis	Steatosis-liver	513	0.60

2	at least one of the 16 Liver NR Docking models from Uni Milano above binding threshold energy	Steatosis-liver	513	0.84
3	FERA developed model using the reference dataset for Steatosis - to predict steatosis	Steatosis-liver	513	0.49
4	OCHEM AhR receptor binding model used to predict hepatotoxicity - and to predict steatosis	AhR-act-liver	512	0.40
5	OCHEM PPARg receptor binding model used to predict hepatoxicity - and to predict steatosis	PPARgamma-act-liver	508	0.45

Table 3. Classification of pesticides by use of QSAR models related to the adverse outcome steatosis.

QSAR model(s) (see Table 2)	rule for aggregation	include in AG pesticides without QSAR results	Number of pesticides in steatosis AG (% of 573 pesticides)		
			QSAR-based	Restricted to POD present	Expanded with POD present
3 (FERA model)	-	no	250 (44%)	83 (15%)	311 (54%)
		yes	310 (54%)	96 (17%)	358 (62%)
1,2,3 (steatosis only)	any	no	445 (78%)	122 (21%)	467 (82%)
		yes	505 (88%)	135 (24%)	514 (90%)
	majority	no	357 (62%)	111 (19%)	390 (68%)
		yes	417 (73%)	124 (22%)	437 (76%)
1,2,3,4,5 (include AOP-linked effects)	any	no	465 (81%)	128 (22%)	481 (84%)
		yes	525 (92%)	141 (25%)	528 (92%)
	majority	no	295 (52%)	90 (16%)	349 (61%)
		yes	355 (62%)	103 (18%)	396 (69%)

Considering the large uncertainty about steatosis AG membership, an alternative approach is to estimate probabilities of membership, and use these in the uncertainty analysis. Here, ratio-based membership probabilities were derived (Figure 4). In this analysis, a default probability 0.5 was used if QSAR classification was missing. 48 substances were excluded from the AG (all QSAR classifications negative) and 68 substances were included with certainty (all QSAR classifications positive). For the remaining 457 substances a membership probability equal to the fraction of positive QSAR models was derived. A more advanced Bayesian calculation is also available, and is described elsewhere (Kennedy et al., subm.). These membership probabilities can be used in probabilistic

assessments by including each substance in iterated uncertainty runs with the calculated probability as proposed by EFSA (EFSA et al., 2019ab), which method is also available in the toolbox.

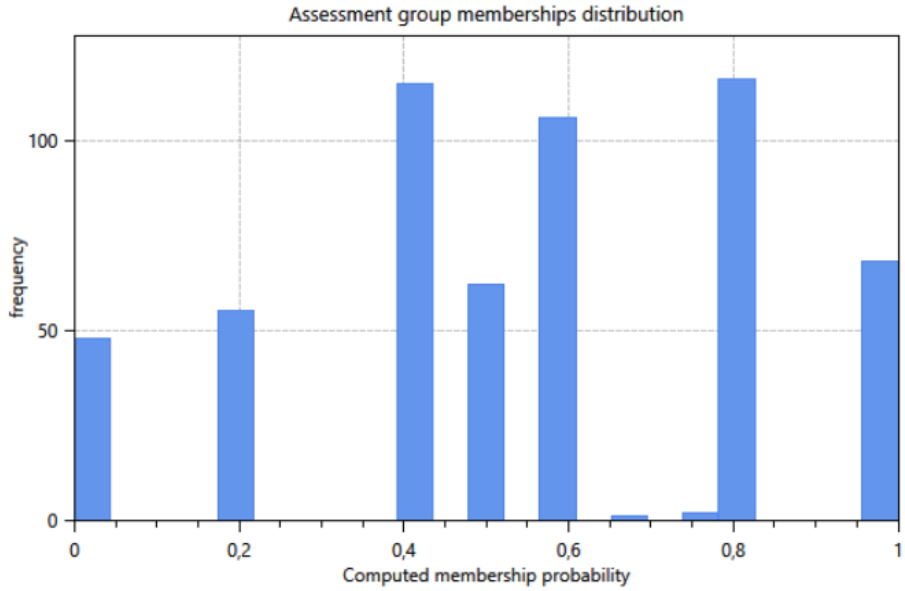

Figure 4. Probabilistic memberships for 573 pesticides for the Steatosis AG based on predictions from five QSAR models.

3.2 Hazard characterisation: Dose response modelling and relative potency factors

The preparation of the NOAEL and LOAEL data of 144 pesticides related to steatosis has been described in Crépet et al. (2019a). Hazard characterisations varied between 0.25 µg/kg bw/day (ethoprophos) and 20 mg/kg bw/day (metosulam). A complete overview is given in the supplementary material, Appendix B. Based on the hazard characterisation of 40 µg/kg bw/day for the index substance imazalil, the RPFs varied between 160 (ethoprophos) and 0.002 (metosulam). For the three substances also used in the second example, the RPFs from *in vivo* NOAELs were 1, 0.148 and 3.33 for imazalil, clothianidin and thiacloprid, respectively.

For imazalil, clothianidin and thiacloprid, dose response relations for the AdipoRed response after 72 hours were measured in the *in vitro* HepaRG test system. Using the integrated Proast model in the toolbox, a 6-parameter parallel-curve exponential dose response model was fitted to the combined data

of the three experiments, where three parameters represent the lower and upper asymptote and common slope, one parameter is the BMD for the index substance (here imazalil), and the remaining two parameters represent the RPFs for the other two substances relative to the index substance. Figure 5 and Table 4 show the results. In Figure 5b the doses for all three substances are expressed as equivalents of the index substance, $d_{eq} = RPF \cdot d$.

On visual inspection the data show no major deviations from the parallel curve model, but the variation around the fitted curve is large, which translates to wide confidence intervals for BMDs and RPFs. For example, the RPF for thiacloprid is 0.16, but is uncertain by almost a factor 3 from the 95% confidence interval (0.09, 0.26).

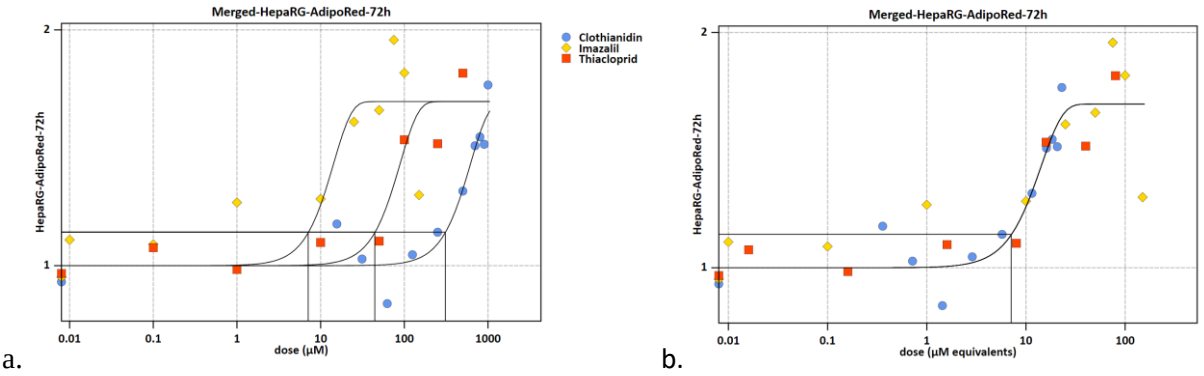

Figure 5. Dose response model AdipoRed in HepaRG test system **(a)** Parallel curves fitted for three substances. **(b)** Doses for all substances expressed in equivalents of the index substance Imazalil. BMDs for a BMR of 10% increase are shown.

Table 4. Benchmark doses (BMD, in µM) with lower (P5) and upper (P95) bounds (BMDL, BMDU), calculated from a parallel-curve exponential model to the AdipoRed dose response data, and internal and external RPFs (with bootstrap-based 90% confidence intervals).

Substance	**BMD *in vitro* (µM)**	**RPF internal (mol based)**	**Molecular mass**	**RPF internal (mass based)**	**Absorption factor from kinetic model**	**RPF external (mass based)**
Clothianidin	309 (160-595)	0.023 (0.015-0.037)	249.68	0.027 (0.018-0.042)	0.013	0.00038

						(0.00025-0.00058)
Imazalil	7.1 (3.18-11.8)	1	297.18	1	0.91	1
Thiacloprid	44.4 (23-85.5)	0.16 (0.09-0.26)	252.73	0.19 (0.12-0.35)	0.32	0.066 (0.041-0.14)

Using the EuroMix Generic PBTK model the internal liver concentration when a daily dose equal to the BMD is given was simulated and averaged over the period between 15 and 28 days to estimate the pseudo-steady-state concentration (Figure 6). The ratio of this internal concentration to the external exposure was then used as the absorption factor to convert internal to external RPFs (Table 4, Figure 7). Note that for a given dose imazalil has the highest concentration in the liver (higher absorption factor). Consequently, the external RPFs for clothianidin and thiacloprid are much lower than the internal RPFs.

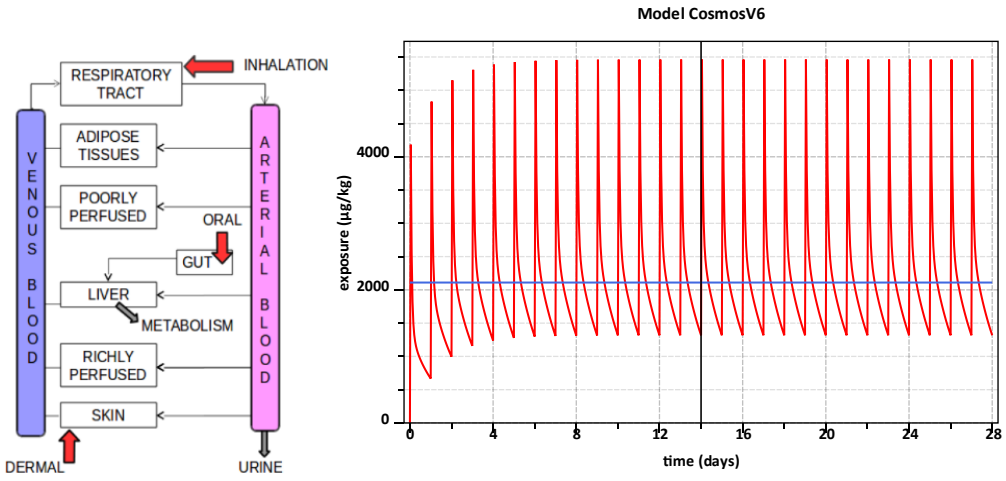

Figure 6. EuroMix Generic PBTK model and example of use to derive internal to dietary (oral) external ratio (imazalil, human model), based on one dose per day leading to an internal concentration equal to the *in vitro* BMD (zero dermal and inhalatory exposures are assumed). The horizontal line indicates the mean internal exposure in the selected interval between 14 and 28 days.

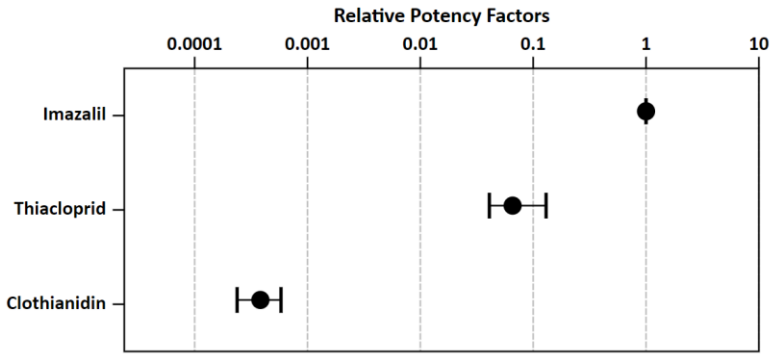

Figure 7. External, mass-based relative potency factors calculated from *in vitro* BMDs, with 90% confidence intervals based on BMD uncertainties. Index substance imazalil.

3.3 Exposure assessment: risk drivers, aggregating dietary and non-dietary exposure, comparison with human monitoring

3.3.1 Cumulative dietary exposure and risk drivers for steatosis

Following the traditional approach, the cumulative dietary exposure of Dutch children (1-19 years) to steatosis-related pesticides was calculated at the external level, using external RPFs for dose addition. In Figure 8 we show an example of cumulative exposure assessment based on NOAEL- or LOAEL-based RPFs for the 144 of 573 pesticides that were related to steatosis according to the POD data (see 3.2 and Appendix B). It can be seen that imazalil in citrus fruits are main risk drivers, where it can be noted that processing factors for the peeling and/or juicing of citrus fruits were missing and therefore suggest a possibly useful refinement of the model. For further details see Crépet et al. (2019b).

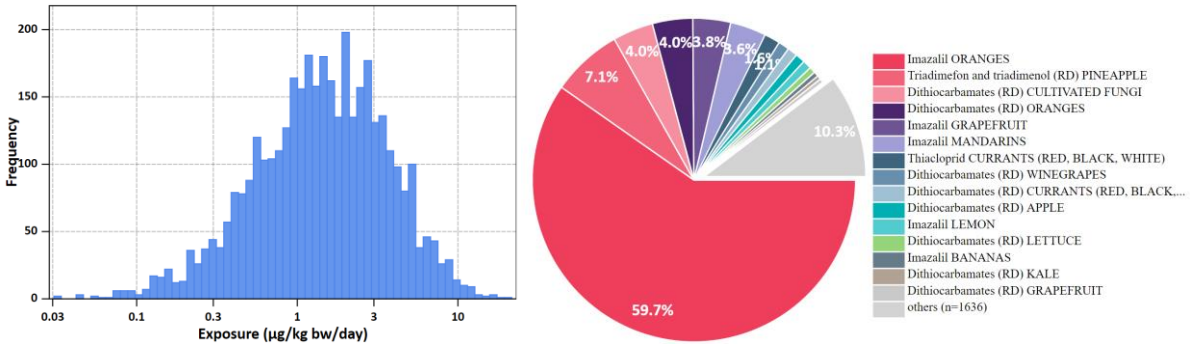

Figure 8. a) Exposure (µg/kgBW/day imazalil equivalents) Dutch population from 144 steatosis-related pesticides using NOAEL- or LOAEL-based dose addition, and OIM method. **b)** risk drivers in the upper 2.5% of the distribution.

Comparing different models for long-term exposure, the model-assisted estimates of the LNN model were found to be lower than the OIM estimates in the upper tail (Table 5), which confirms that the OIM method underestimates the median, but overestimates the upper tail percentiles (Dodd et al., 2006; Goedhart et al., 2012).

Table 5. Chronic exposure percentiles using two methods: observed individual means (OIM) and model-assisted logistic-normal normal (LNN) estimates, median and 90% confidence limits.

	Cumulative exposure (µg/kg bw/day, as imazalil)		
Percentage	**OIM**	**LNN**	**OIM/LNN**
50	1.42 (1.20-1.68)	1.74 (1.46-2.05)	0.82
90	4.51 (4.00-5.06)	4.26 (3.77-4.92)	1.06
95	5.86 (5.26-6.71)	5.37 (4.77-6.27)	1.09
99	9.32 (8.36-10.4)	7.88 (7.02-8.86)	1.18
99.9	15.1 (12.3-17.0)	10.7 (9.64-12.6)	1.42
99.99	19.0 (15.5-22.2)	12.6 (11.3-14.2)	1.51

3.3.2 Aggregated cumulative exposure using a kinetic model

With dietary and non-dietary exposures, it is essential to aggregate at the internal level. Consequently, internal RPFs are needed for dose addition. In a simple approach standard absorption factors can be used, e.g. 1 for dietary or inhalation exposure and 0.1 for dermal exposure. See Kennedy et al. (2019) for such an application. Here we illustrate the use of kinetic models in an example with just three substances. In this example the EuroMix Generic PBTK model was used to translate dietary, dermal and inhalation exposures to internal exposure in the liver. Further, for each individual the external exposures on each of the 365 days of the simulation were randomly selected from the seven daily imazalil exposures that were calculated for the seven days of this individual in the French consumption survey. In separate runs for dietary, dermal and inhalation external exposure, the mean absorption factors to the liver were estimated as (0.91, 0.96, 0.92) for imazalil, (0.35, 0.34, 0.32) for thiacloprid and (0.017, 0.019, 0.013) for clothianidin. Figure 9 shows simulated kinetic curves for the amount of imazalil in the liver for the nine individuals in the French consumption survey that had aggregated cumulative exposures closest to the 97.5^{th} percentile of the distribution. It can be seen that very variable kinetic curves were obtained, and that for some individuals the pseudo steady state is not yet reached after half a year. This is due partly to differences in dietary exposures and partly to the assumed variability of kinetic model parameters. The high variability in absorption is also evident from the plot of internal vs. external exposure (Figure 10).

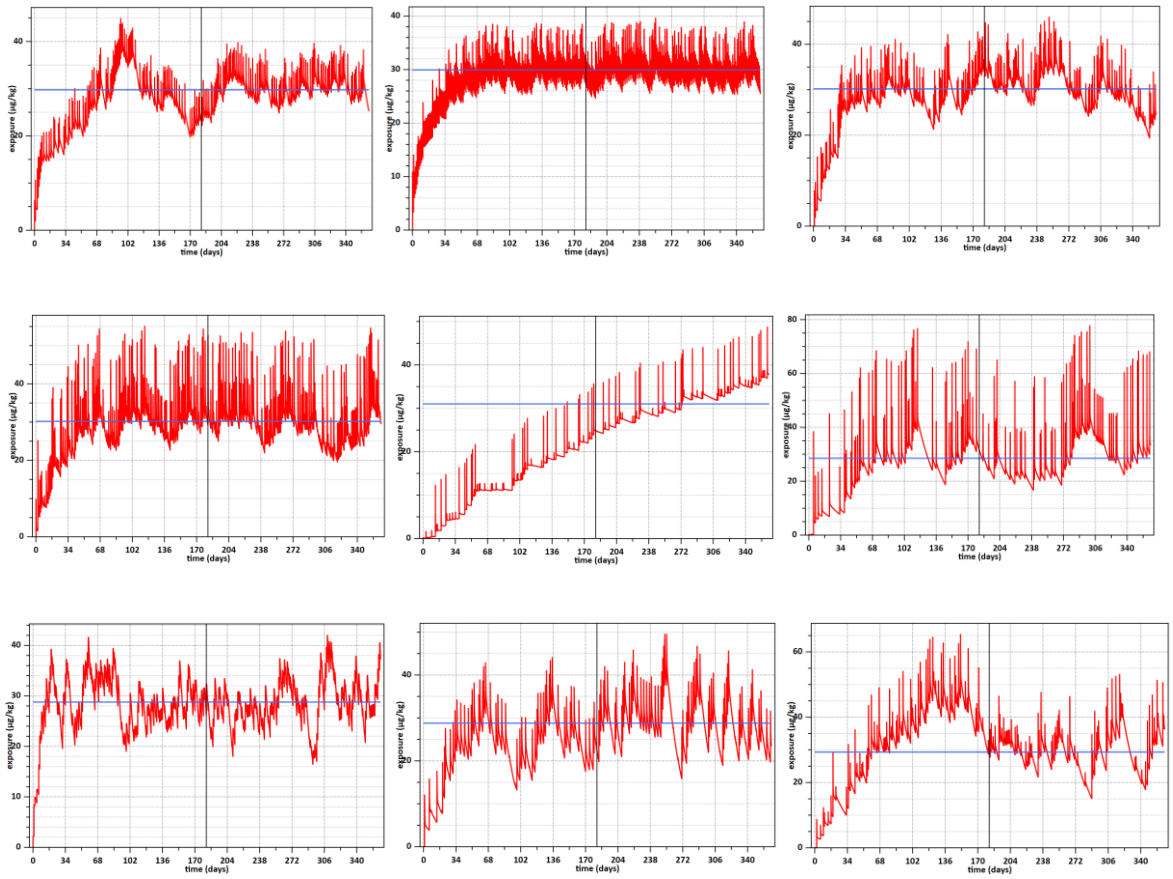

Figure 9. Simulated kinetics of imazalil for 9 individuals in the French population around the 97.5th percentile of exposure in the cumulative exposure distribution. Note the random draws from the seven survey days for the external doses.

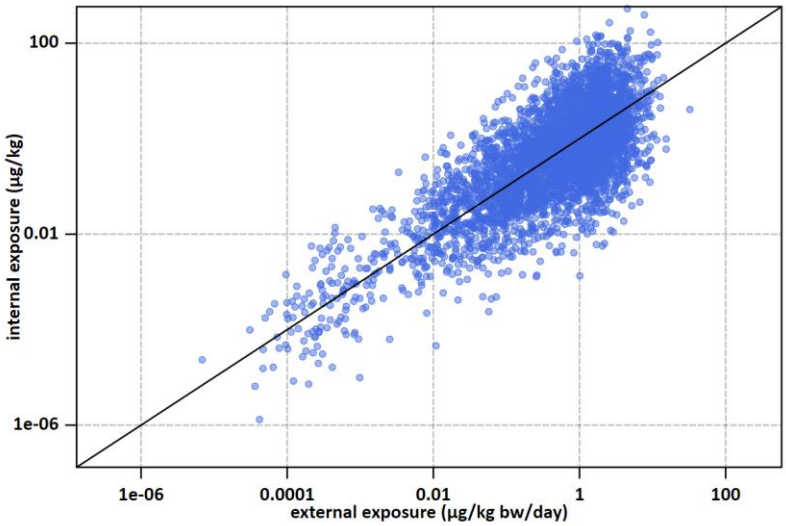

Figure 10. Internal vs. external exposure.

Using estimates that respectively 10.3%, 0.9%, 0.8% and 0.1% of the population lives near agricultural fields where wheat, potatoes, sugar beet or dessert apples are sprayed, we observe that for those people thiacloprid and imazalil via the dermal route had the largest contribution in their non-dietary exposure (Figure 11a). This is in accordance with the results based on fixed absorption factors in Kennedy et al. (2019). However, in the total exposure of the total adult population the non-dietary contributions were minor. Imazalil from dietary exposure had by far the largest contribution in this example (Figure 11b).

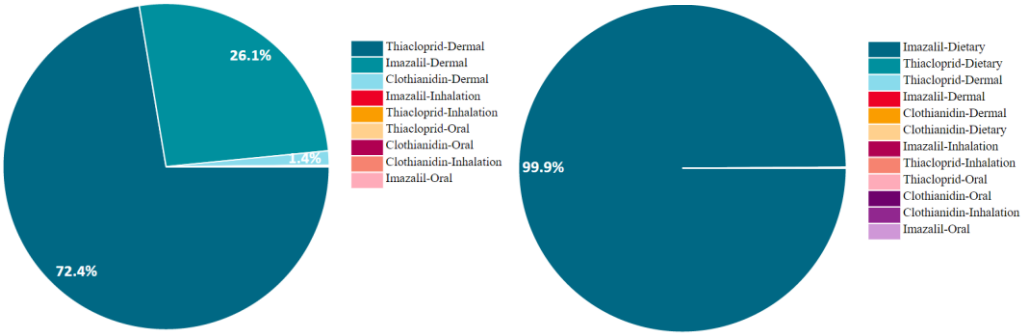

Figure 11. Contributions by route and substance to **(a)** the non-dietary cumulative exposure, **(b)** the total (dietary and non-dietary) cumulative exposure.

3.3.3 Comparison of modelled exposure with human biomonitoring data

Using the Human monitoring analysis module of the toolbox, human biomonitoring data (BPA measured in urine on a single day) from a Norwegian study (Husøy et al., 2019; Karrer et al., 2019) were compared to chronic exposure predictions based on the dietary consumptions and non-dietary uses of personal care products recorded for the survey participants (Figure 12). The results showed roughly comparable levels of BPA around 1-10 µg/kg body weight per day, but no strong correlation.

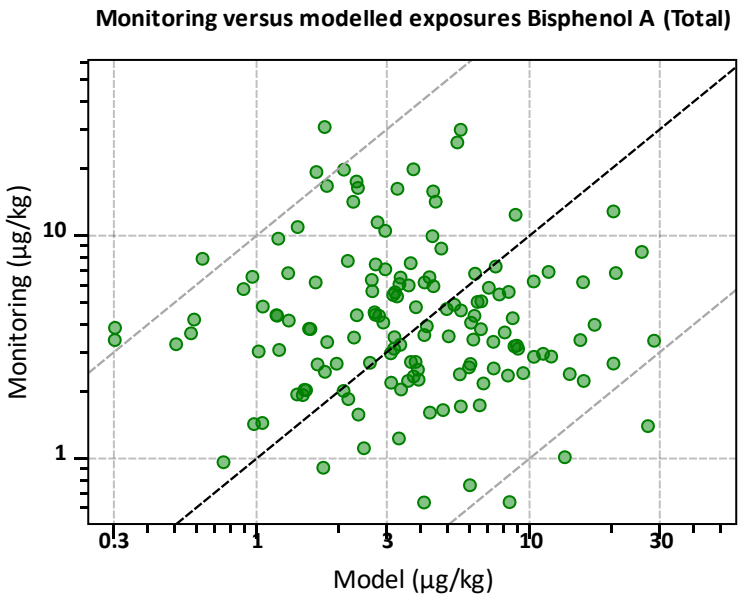

Figure 12. Bisphenol-A measured in urine vs. predicted from dietary and non-dietary exposures for 144 persons.

3.4 Risk characterisation: comparing exposure and hazard characterisation distributions

In an assessment of all 144 pesticides with a POD for steatosis, the final risk assessment is shown in two different ways. First, the HCs, which in this case were the NOAELs in or derived from the data repository, were plotted against the exposure distributions for each of the substances separately, and also cumulated (Figure 13a). The variability and uncertainty in the exposure also induce variability and uncertainty of the MOE, as represented by the diagonal line sections. Background colours have been applied to indicate possible areas of risk and safety. Note that one line (in the red area) represents equality of exposure and HC (POD), whereas the other line (in the yellow area) represents the user-specified threshold value 100 for the interpretation of MOEs.

A more direct representation of the MOEs is given in Figure 13b. In both plots it is seen that the cumulative MOE is well above 100, the 5th percentiles of the cumulative distribution is estimated as 649, with a lower 95% confidence limit of 597. Imazalil stands out as the main risk driver.

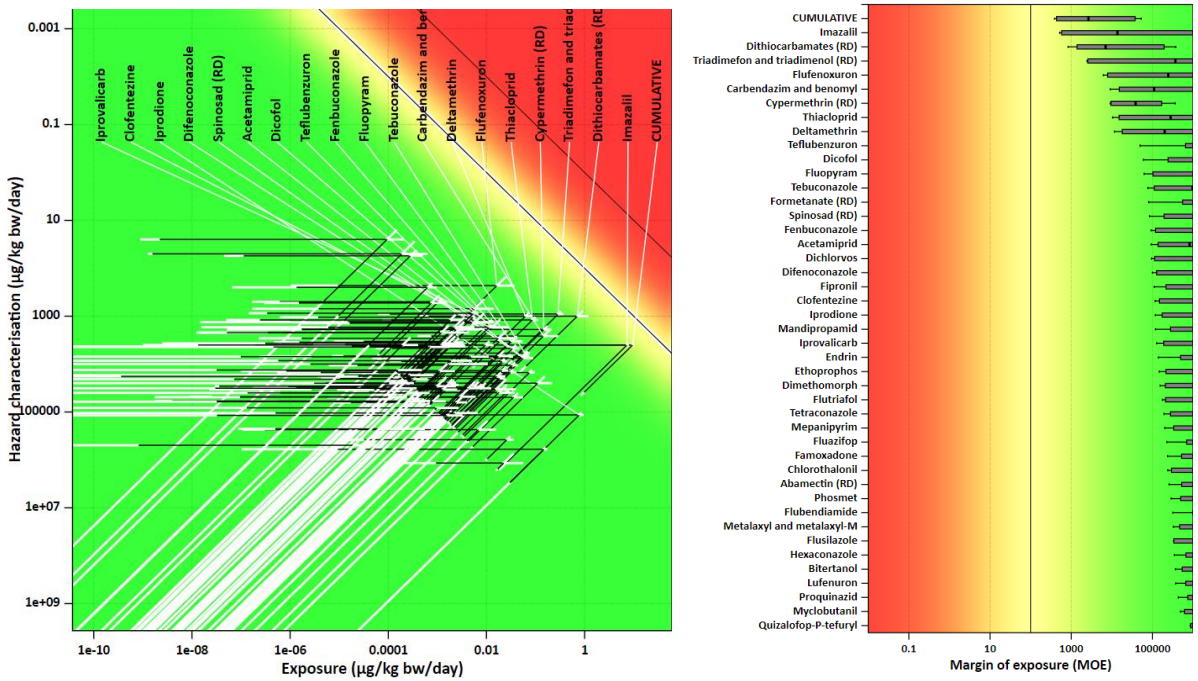

Figure 13. a. Hazard vs. exposure plot using 100 as a MOE level for risk of steatosis. Exposure ranges and induced MOE ranges are plotted for cumulative (imazalil as index substance) and for the separate substances (only 20 with lowest MOE shown). Black line segments represent the variability range between percentiles p1 and p99, with white extensions representing one-sided 95% uncertainty limits on these percentiles. **b.** Margin of exposure, cumulative and for the separate substances (restricted to substances with P1(MOE)<10^6), using 100 as a MOE threshold for risk. Bars represent MOE ranges in the population (P1-P99), with whiskers representing one-sided 95% uncertainty limits for P1 and P99.

4 Discussion

This paper has described the modular structure of the MCRA model and data toolbox developed in the EuroMix project. Simple examples have been shown how the toolbox can be used for various aspects of the risk assessment of chemical mixtures. It is stressed that this paper does not intend to present extended case studies. All examples have been given for illustration of the methodology only, and do not represent real hazard, exposure or risk assessments. For example, more study is needed regarding the large differences between the *in vivo* and *in vitro* derived RPFs for clothianidin or thiacloprid relative to imazalil. In fact, it is not the purpose of this paper to propose any specific methodology as an optimal approach for specific case studies, but rather to emphasise that a wide variety of both

simple and more complex approaches with varying degrees of conservatism can be explored and compared using an appropriate model and data toolbox.

More possibilities are available in the toolbox than could be illustrated here. For example, the toolbox also contains functionality to use molecular docking models for identifying AG membership (Cotterill et al., 2016; Kennedy et al., subm.). Missing HCs can be imputed, e.g. based on thresholds of toxicological concern (Munro et al., 1996; Kennedy et al., subm.). More refined exposure models can be applied, including the use of occurrence patterns for the imputation of left-censored data and residue definitions for measured substances which are only indirectly measuring the active substances (van Klaveren et al., 2019ab). The most relevant mixtures for which further refinement could be important can be identified (Crépet et al., 2019a). Integrated probabilistic risk assessments where the uncertainty factors are also modelled probabilistically can be run (van der Voet and Slob, 2007; van der Voet et al., 2009; Jacobs et al., 2015).

MCRA 9, developed as the EuroMix toolbox and presented in this paper, is maintained after the EuroMix project at https://mcra.rivm.nl and can be used in its current state. Users can upload their own data or can access data which are shared by other platform users or user groups. The possible links between the MCRA toolbox and the IPCHEM platform of the European Commission for supporting the assessment of chemical mixtures have been discussed (Dalla Costa et al., 2018) and the European Commission, EFSA, industry and regulators were trained in the use of MCRA (Bopp et al., 2018, Zilliacus et al. 2019b). The toolbox will also be further developed in cooperation with EFSA and other stakeholders such as national risk assessment institutes. Such development might go in two opposite directions. On the one hand, the use by less-experienced users can be optimised by offering clearly described tiers including presets of options, avoiding the need to specify all settings by hand. On the other hand, the modular design of the toolbox makes it suitable for developing interoperability with other web-based databases and models, and for adding new functionalities. A practical example would be to add the use of expert-elicited uncertainty distributions to adjust the results of risk

assessments (EFSA, 2019cd). Another extension would be to include read-across approaches for hazard assessment as have been recently proposed (Escher et al., 2019).

In conclusion, the MCRA model and data toolbox has been found useful to perform case studies of hazard identification, hazard characterisation, exposure assessment and risk characterisation, as shown in this paper and in other deliverables in the EuroMix project (Crépet et al., 2019ab; Kennedy et al., 2019; Karrer et al., 2019; Kennedy et al., subm.; Vanacker et al., in prep.). At the same time, the toolbox has been prepared to serve a wider public, and will be tested and further developed in future collaborations.

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Supplementary material to:

The MCRA toolbox of models and data to support chemical mixture risk assessment

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Appendix A. Summary of modules in the MCRA toolbox

Appendix B. Hazard characterisations and relative potency factors based on NOAELs or LOAELs of 144 pesticides

Appendix A. Summary of modules in the MCRA toolbox

Category	Module	Description
Primary entities	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) foods-as-measured: foods as coded in concentration data (e.g. wheat); 3) any other type of food (e.g. ingredients, e.g. flour).
	Substances	Substances are chemical entities. Substances can refer to: 1) active substances such as investigated in toxicology; 2) measured substances such as defined in specific analytical methods.
	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.
	Populations	Populations are groups of human individuals that are the scope of exposure or risk assessments.
	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).
	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.
Consumption	Consumptions	Consumptions data are the amounts of Foods consumed on specific days by Individuals in a food consumption Survey. For an acute exposure assessment, 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 person, so preferably two or more days per individual are needed.
	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.
	Food recipes	Food recipes data specify the composition of specific foods (typically: foods-as-eaten) in terms of other foods (intermediate foods or foods-as-measured) by specifying proportions in the form of a percentage.
Occurrence	Concentrations	Concentrations data are analytical measurements of chemical substances occurring in food samples. Optionally, concentrations data can be recalculated for active substances, extrapolated to other foods, and/or default values can be added for water.
	Processing factors	Processing factors are multiplication factors to derive the concentration in a processed food from the concentration in an unprocessed food. Processing factors can be given for identified processing types (e.g. cooking, washing, drying).
	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.
	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 can be 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.

Category	Module	Description
	Substance authorisations	Substance authorisations specify which food/substance combinations are authorised.
	Substance conversions	Substance conversions specify how measured substances are converted to active substances, which are the substances assumed to cause health effects. In the pesticide legislation such measured substances and the substance conversion rules are known as residue definitions.
	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.
	Concentration models	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. Concentration models are specified per food/substance combination.
	Foods as measured	Foods as measured are foods within the foods scope for which concentration data of substances are available (or expected).
	Focal 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 concentrations data.
	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.
	Food extrapolations	Food extrapolations data specify foods (from-foods) that can be used to impute concentration data for other foods with insufficient data (to-foods).
Exposure	Food conversions	Food conversions relate foods-as-eaten, as found in the consumption data, to foods-as-measured, which are the foods for which concentration data are available.
	Consumptions per food as measured	Consumptions per food as measured are consumptions of individuals expressed on the level of the foods for which concentration data are available (i.e., the foods-as-measured). These are calculated from consumptions of foods-as-eaten and food conversions that link the foods-as-eaten amounts to foods-as-measured amounts.
	Dietary exposures with screening	Dietary exposures with screening are just Dietary exposures, but the calculation includes a prior screening step to identify the main risk drivers (food-substance combinations). This allows computations with more substances by suppressing some details for less important food-substance combinations.
	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.
	Non-dietary 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.
	Exposures	Exposures, possibly from both dietary and non-dietary routes of exposure, to which individuals in a population are exposed per day at a chosen target level. This target level may be external exposure (dietary exposure) or internal exposure.

Category	Module	Description
	Exposure mixtures	Exposure mixtures are mixtures of substances that contribute relatively much to the overall cumulative exposure (potential risk drivers). The occurrence and concentrations of compounds in the same samples may be correlated, which is of importance for acute exposure assessments (Note that chronic assessments only use mean concentration values). Theoretically, this could be modelled and fitted to datasets. However, in practical applications (regarding pesticide residues) the number of positive values is commonly too low to allow such detailed modelling. Co-exposure of compounds is defined as the pattern of compounds occurring together on a single individual day. Co-exposure can enter the risk assessment through the use of mixtures of substances on a single food or by combining different food sources on a single day (through consumption).
	Human monitoring data	Human monitoring data quantify concentrations found in human surveys. Data are provided on the survey, the individuals in the survey, the samples taken, the analyses performed, the analytical methods used, the properties for substances analysed, and the concentrations found.
	Human monitoring analysis	Human monitoring analysis 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.
In silico	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.
	Molecular docking models	Molecular docking models specify binding energies for substances in specific molecular docking models related to a specific health effect (adverse outcome).
Kinetic	Kinetic models	Kinetic models convert exposures or hazard characterisations from one or more external routes or compartments to an internal (target) compartment. The reverse conversion from internal to external can also be made (reverse dosimetry).
Hazard	Active substances	Active substances are the substances that may lead to a specific health effect (adverse outcome). Active substances can be either specified directly as data or calculated from QSAR membership models or from Molecular docking models. Optionally, active substances can have assessment group memberships between 0 and 1.
	Relative potency factors	Relative potency factors (RPFs) describe the potency of substances with respect to a defined effect, relative to the potency of a chosen index substance. RPFs can be given as data or computed from hazard characterisations.
	Hazard characterisations	Hazard characterisations are benchmark doses for active substances and for the chosen effect at the chosen target level (external or internal) of the hazard assessment. Hazard characterisations are based on points of departure, such as BMDs from dose response models or externally specified points of departure (MDSs, NOAELs or LOAELs). The computation may involve inter-species conversion, intra-species factors and the use of kinetic models or absorption factors to convert external doses to internal doses.
	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.
	Dose response models	Dose response models specify the results of models fitted to dose response data. Dose response models 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).

Category	Module	Description
	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.
	Effect representations	Effect representations are the responses which can be used to measure specified effects and the benchmark response (BMR) that defines a hazard limit for the effect.
	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 geometic standard deviation (GSD) for a lognormal uncertainty distribution of the inter-species factor.
	Intra species factors	Intra-species factors specify how to convert a hazard characterisation from the average to a sensitive human individual. In the simplest approach, this is a fixed inter-species factor. In a higher tier, lower and upper values for the intra-species factor are used to derive a variability distribution (lognormal around 1) and an uncertainty distribution for the geometric standard deviation related to human variability in sensitivity.
	AOP networks	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).
Risk	Risks	Risks (health impacts) are quantified by comparing exposures and hazard characterisations at the chosen level (external or internal) via margins of exposure (MOE) or more generalised or integrated margins of exposure (IMOE). In addition, risks can be assessed from a plot of hazard characterisations vs. exposures.

Appendix B. Hazard characterisations and relative potency factors based on NOAELs or LOAELs of 144 pesticides

Table B1. Hazard characterisations and relatiove potency factors for pesticides for which NOAEL or LOAEL related to steatosis was available from *in vivo* study. POD: Point of departure; F1: conversion factor for POD type; F2: inter-species factor; F3: intra-species factor; HC: hazard characterisation; RPF: relative potency factor.

Substance name	Substance code	Species	POD type	Value (µg/kg/day)	F1	F2	F3	HC (µg/kg bw/day)	RPF
Ethoprophos	RF-0164-001-PPP	Dog	NOAEL	25	1	0.1	0.1	0.25	160.000
Dazomet	RF-0118-001-PPP	Dog	NOAEL	40	1	0.1	0.1	0.4	100.000
Endrin	RF-0156-001-PPP	Dog	NOAEL	50	1	0.1	0.1	0.5	80.000
Fipronil	RF-0192-001-PPP	Mouse	NOAEL	55	1	0.1	0.1	0.55	72.727
Mesotrione	RF-00003357-PAR	Rat	LOAEL	480	0.333	0.1	0.1	1.6	25.000
Flufenoxuron	RF-0204-001-PPP	Rat	NOAEL	230	1	0.1	0.1	2.3	17.391
Abamectin (RD)	RF-0011-001-PPP	Dog	NOAEL	250	1	0.1	0.1	2.5	16.000
Diclofop (RD)	RF-0128-001-PPP	Dog	NOAEL	440	1	0.1	0.1	4.4	9.091
Benfluralin	RF-0039-001-PPP	Rat	NOAEL	500	1	0.1	0.1	5	8.000
Hexaconazole	RF-0241-001-PPP	Rat	NOAEL	500	1	0.1	0.1	5	8.000
Tralkoxydim	RF-0427-001-PPP	Dog	NOAEL	500	1	0.1	0.1	5	8.000
Flusilazole	RF-0218-001-PPP	Rat	NOAEL	530	1	0.1	0.1	5.3	7.547
Teflubenzuron	RF-0407-001-PPP	Mouse	LOAEL	2100	0.333	0.1	0.1	7	5.714
Iprovalicarb	RF-0256-001-PPP	Dog	LOAEL	2600	0.333	0.1	0.1	8.67	4.615
Bifenazate	RF-00003033-PAR	Dog	NOAEL	900	1	0.1	0.1	9	4.444
Triadimefon and triadimenol (RD)	RF-0428-001-PPP	Rat	LOAEL	2700	0.333	0.1	0.1	9	4.444
Deltamethrin	RF-0120-001-PPP	Rat	NOAEL	1000	1	0.1	0.1	10	4.000
Dithiocarbamates (RD)	RF-0151-001-PPP	Mouse	LOAEL	3000	0.333	0.1	0.1	10	4.000
Emamectin benzoate	RF-0648-001-PPP	Rat	NOAEL	1000	1	0.1	0.1	10	4.000
Flutriafol	RF-0220-001-PPP	Rat	NOAEL	1050	1	0.1	0.1	10.5	3.810

Bromuconazole	RF-0053-002-PPP	Rat	NOAEL	1090	1	0.1	0.1	10.9	3.670
Amitrole (aminotriazole)	RF-0025-001-PPP	Rat	NOAEL	1200	1	0.1	0.1	12	3.333
Proquinazid	RF-0365-001-PPP	Rat	NOAEL	1200	1	0.1	0.1	12	3.333
Thiacloprid	RF-0417-001-PPP	Rat	NOAEL	1200	1	0.1	0.1	12	3.333
Fenbuconazole	RF-0176-001-PPP	Mouse	NOAEL	1300	1	0.1	0.1	13	3.077
Flufenacet	RF-0203-001-PPP	Dog	NOAEL	1300	1	0.1	0.1	13	3.077
Dichlorvos	RF-0127-001-PPP	Rat	LOAEL	4000	0.333	0.1	0.1	13.3	3.000
Tetraconazole	RF-0414-001-PPP	Mouse	NOAEL	1400	1	0.1	0.1	14	2.857
Clofentezine	RF-0098-001-PPP	Rat	NOAEL	1700	1	0.1	0.1	17	2.353
Dicofol	RF-0130-001-PPP	Rat	NOAEL	1700	1	0.1	0.1	17	2.353
Flubendiamide	RF-0199-001-PPP	Rat	NOAEL	1700	1	0.1	0.1	17	2.353
Fluazifop	RF-0698-001-PPP	Mouse	NOAEL	1860	1	0.1	0.1	18.6	2.151
Cypermethrin (RD)	RF-0112-001-PPP	Mouse	NOAEL	1900	1	0.1	0.1	19	2.105
Ipconazole	RF-0254-001-PPP	Dog	NOAEL	1900	1	0.1	0.1	19	2.105
Lufenuron	RF-0265-001-PPP	Rat	NOAEL	1900	1	0.1	0.1	19	2.105
Isoxaflutole	RF-0259-001-PPP	Rat	NOAEL	2000	1	0.1	0.1	20	2.000
Cyproconazole	RF-0113-001-PPP	Rat	NOAEL	2200	1	0.1	0.1	22	1.818
Paclobutrazol	RF-0325-001-PPP	Rat	NOAEL	2200	1	0.1	0.1	22	1.818
Carbendazim and benomyl	RF-0041-001-PPP	Dog	NOAEL	2600	1	0.1	0.1	26	1.538
Benthiavalicarb	RF-0043-001-PPP	Mouse	NOAEL	2700	1	0.1	0.1	27	1.481
Formetanate (RD)	RF-0223-001-PPP	Rat	NOAEL	2900	1	0.1	0.1	29	1.379
Fluopyram	RF-1071-001-PPP	Rat	NOAEL	3360	1	0.1	0.1	33.6	1.190
Triflumizole (RD)	RF-0440-001-PPP	Rat	NOAEL	3500	1	0.1	0.1	35	1.143
1-Naphthylacetic acid (1-NAA)	RF-0007-001-PPP	Mouse	LOAEL	10800	0.333	0.1	0.1	36	1.111
Bromopropylate	RF-0052-001-PPP	Rat	NOAEL	3700	1	0.1	0.1	37	1.081
DDT (RD)	RF-0119-001-PPP	Rat	LOAEL	12000	0.333	0.1	0.1	40	1.000
Fenarimol	RF-0174-001-PPP	Rat	NOAEL	4000	1	0.1	0.1	40	1.000
Fluazinam	RF-0198-001-PPP	Rat	NOAEL	4000	1	0.1	0.1	40	1.000
Imazalil	RF-0246-001-PPP	Rat	NOAEL	4000	1	0.1	0.1	40	1.000
Phosmet	RF-0338-001-PPP	Mouse	NOAEL	4000	1	0.1	0.1	40	1.000
Metconazole	RF-0286-001-PPP	Rat	NOAEL	4300	1	0.1	0.1	43	0.930

Cyflufenamid	RF-0107-001-PPP	Rat	NOAEL	4400	1	0.1	0.1	44	0.909
Difenoconazole	RF-0133-001-PPP	Mouse	NOAEL	4700	1	0.1	0.1	47	0.851
Florasulam	RF-0195-001-PPP	Dog	NOAEL	5000	1	0.1	0.1	50	0.800
Bromoxynil	RF-00003327-PAR	Mouse	NOAEL	5100	1	0.1	0.1	51	0.784
Benfuracarb	RF-00003374-PAR	Mouse	LOAEL	15400	0.333	0.1	0.1	51.33	0.779
Isopyrazam	RF-00000025-PAR	Rat	NOAEL	5500	1	0.1	0.1	55	0.727
Tebuconazole	RF-0403-001-PPP	Mouse	NOAEL	5900	1	0.1	0.1	59	0.678
Silthiofam	RF-0389-001-PPP	Rat	NOAEL	6400	1	0.1	0.1	64	0.625
Famoxadone	RF-0171-001-PPP	Mouse	NOAEL	6800	1	0.1	0.1	68	0.588
Acetamiprid	RF-0014-001-PPP	Rat	NOAEL	7000	1	0.1	0.1	70	0.571
Mepanipyrim	RF-0274-002-PPP	Rat	NOAEL	7000	1	0.1	0.1	70	0.571
Quizalofop-P-tefuryl	RF-0384-003-PPP	Mouse	NOAEL	7000	1	0.1	0.1	70	0.571
Spinosad (RD)	RF-0393-001-PPP	Mouse	NOAEL	7500	1	0.1	0.1	75	0.533
Bixafen	RF-1056-001-PPP	Mouse	NOAEL	8500	1	0.1	0.1	85	0.471
Metalaxyl and metalaxyl-M	RF-0281-001-PPP	Rat	NOAEL	8700	1	0.1	0.1	87	0.460
Dimethenamid-P	RF-0137-002-PPP	Dog	NOAEL	10000	1	0.1	0.1	100	0.400
Propaquizafop	RF-0356-001-PPP	Mouse	NOAEL	10000	1	0.1	0.1	100	0.400
Tolfenpyrad	RF-0943-001-PPP	Dog	NOAEL	10000	1	0.1	0.1	100	0.400
Chlorothalonil	RF-0084-001-PPP	Rat	NOAEL	10600	1	0.1	0.1	106	0.377
Isoxaben	RF-0258-001-PPP	Mouse	NOAEL	12000	1	0.1	0.1	120	0.333
Trichlorfon	RF-0435-001-PPP	Rat	NOAEL	13300	1	0.1	0.1	133	0.301
Myclobutanil	RF-0308-001-PPP	Mouse	NOAEL	13700	1	0.1	0.1	137	0.292
Pyrethrins	RF-0374-001-PPP	Mice	NOAEL	14000	1	0.1	0.1	140	0.286
Bitertanol	RF-0048-001-PPP	Rat	NOAEL	14900	1	0.1	0.1	149	0.268
Dimethomorph	RF-0140-001-PPP	Dog	NOAEL	15000	1	0.1	0.1	150	0.267
Isoproturon	RF-0257-001-PPP	Rat	NOAEL	15000	1	0.1	0.1	150	0.267
Triazoxide	RF-0433-001-PPP	Rat	NOAEL	15000	1	0.1	0.1	150	0.267
Valifenalate	RF-1057-001-PPP	Mouse	NOAEL	16800	1	0.1	0.1	168	0.238
Triticonazole	RF-0447-001-PPP	Mouse	NOAEL	17000	1	0.1	0.1	170	0.235
Metazachlor	RF-00003344-PAR	Rat	NOAEL	18000	1	0.1	0.1	180	0.222
Oxadiazon	RF-0318-001-PPP	Rat	NOAEL	18000	1	0.1	0.1	180	0.222
Pencycuron	RF-0330-001-PPP	Rat	NOAEL	18000	1	0.1	0.1	180	0.222

Bupirimate	RF-0055-001-PPP	Dog	NOAEL	20000	1	0.1	0.1	200	0.200
Diflufenican	RF-0135-001-PPP	Mouse	LOAEL	62000	0.333	0.1	0.1	206.7	0.194
Fluxapyroxad	RF-00000024-PAR	Mouse	NOAEL	21000	1	0.1	0.1	210	0.190
Pyraflufen-ethyl	RF-00003367-PAR	Mouse	NOAEL	21000	1	0.1	0.1	210	0.190
Acequinocyl	RF-0013-001-PPP	Mouse	NOAEL	21000	1	0.1	0.1	210	0.190
Fenazaquin	RF-0175-001-PPP	Hamster	NOAEL	25000	1	0.1	0.1	250	0.160
Mandipropamid	RF-0268-001-PPP	Dog	NOAEL	25000	1	0.1	0.1	250	0.160
Prothioconazole	RF-0868-001-PPP	Mouse	NOAEL	25000	1	0.1	0.1	250	0.160
Penthiopyrad	RF-00002609-PAR	Rat	NOAEL	27000	1	0.1	0.1	270	0.148
Clothianidin	RF-0101-001-PPP	Rat	NOAEL	27000	1	0.1	0.1	270	0.148
Cymoxanil	RF-0111-001-PPP	Mouse	NOAEL	29000	1	0.1	0.1	290	0.138
1-Naphthylacetamide (1-NAD)	RF-0006-001-PPP	Dog	NOAEL	30000	1	0.1	0.1	300	0.133
Etridiazole	RF-0170-001-PPP	Rat	NOAEL	30000	1	0.1	0.1	300	0.133
Metrafenone	RF-0299-001-PPP	Rat	NOAEL	30000	1	0.1	0.1	300	0.133
Prosulfocarb	RF-0366-001-PPP	Dog	NOAEL	30000	1	0.1	0.1	300	0.133
Bensulfuron	RF-0493-001-PPP	Rat	NOAEL	30000	1	0.1	0.1	300	0.133
Diflubenzuron	RF-0134-001-PPP	Mouse	NOAEL	32000	1	0.1	0.1	320	0.125
Flutolanil	RF-0219-001-PPP	Mouse	NOAEL	32000	1	0.1	0.1	320	0.125
Dodemorph	RF-0645-001-PPP	Dog	NOAEL	32000	1	0.1	0.1	320	0.125
Triasulfuron	RF-0431-001-PPP	Dog	NOAEL	33000	1	0.1	0.1	330	0.121
Fenoxycarb	RF-0182-001-PPP	Mouse	LOAEL	101000	0.333	0.1	0.1	336.67	0.119
Tepraloxydim	RF-00003039-PAR	Rat	NOAEL	34000	1	0.1	0.1	340	0.118
Epoxiconazole	RF-0157-001-PPP	Rat	NOAEL	34000	1	0.1	0.1	340	0.118
Azadirachtin	RF-0030-001-PPP	Rat	NOAEL	36000	1	0.1	0.1	360	0.111
Pethoxamid	RF-0333-001-PPP	Rat	NOAEL	36200	1	0.1	0.1	362	0.110
Pyriofenone	RF-00003031-PAR	Rat	NOAEL	36400	1	0.1	0.1	364	0.110
1-Methyl-cyclopropene	RF-0005-001-PPP	Rat	NOAEL	39000	1	0.1	0.1	390	0.103
Trifloxystrobin	RF-0439-001-PPP	Mouse	NOAEL	39000	1	0.1	0.1	390	0.103
Quinoxyfen	RF-0382-001-PPP	Dog	LOAEL	119000	0.333	0.1	0.1	396.67	0.101
Bentazone	RF-0042-001-PPP	Dog	NOAEL	40000	1	0.1	0.1	400	0.100
fenamidone	RF-0172-001-PPP	Rat	NOAEL	48000	1	0.1	0.1	480	0.083

Dicloran	RF-0129-001-PPP	Mouse	NOAEL	49000	1	0.1	0.1	490	0.082
Propiconazole	RF-0358-001-PPP	Mouse	NOAEL	49400	1	0.1	0.1	494	0.081
Carbetamide	RF-0064-001-PPP	Rat	NOAEL	50000	1	0.1	0.1	500	0.080
Fenpyrazamine	RF-00002610-PAR	Rat	NOAEL	51900	1	0.1	0.1	519	0.077
Iodosulfuron methyl sodium	RF-0252-001-PPP	Mouse	NOAEL	54000	1	0.1	0.1	540	0.074
Benalaxyl (RD)	RF-0038-001-PPP	Rat	NOAEL	59000	1	0.1	0.1	590	0.068
Etoxazole	RF-0169-001-PPP	Mouse	NOAEL	60000	1	0.1	0.1	600	0.067
Desmedipham	RF-0121-001-PPP	Mouse	NOAEL	61000	1	0.1	0.1	610	0.066
Fenpropimorph	RF-0185-001-PPP	Rat	NOAEL	63000	1	0.1	0.1	630	0.063
Chlorotoluron	RF-0092-001-PPP	Rat	NOAEL	80000	1	0.1	0.1	800	0.050
Chloridazon (aka pyrazone)	RF-0080-001-PPP	Dog	NOAEL	82000	1	0.1	0.1	820	0.049
Tolylfluanid	RF-0425-001-PPP	Rat	NOAEL	105000	1	0.1	0.1	1050	0.038
Resmethrin	RF-0385-001-PPP	Mouse	NOAEL	105500	1	0.1	0.1	1055	0.038
Iprodione	RF-0255-001-PPP	Mouse	NOAEL	115000	1	0.1	0.1	1150	0.035
Halosulfuron methyl	RF-0234-001-PPP	Rat	NOAEL	116000	1	0.1	0.1	1160	0.034
Lenacil	RF-0262-001-PPP	Rat	NOAEL	118000	1	0.1	0.1	1180	0.034
Penflufen	RF-00003362-PAR	Mouse	NOAEL	146000	1	0.1	0.1	1460	0.027
Tri-allate	RF-0430-001-PPP	Hamster	NOAEL	146000	1	0.1	0.1	1460	0.027
Amisulbrom	RF-0470-001-PPP	Rat	NOAEL	147000	1	0.1	0.1	1470	0.027
Trifluralin	RF-0442-001-PPP	Rabbit	NOAEL	225000	1	0.1	0.1	2250	0.018
Spirodiclofen	RF-0394-001-PPP	Mouse	NOAEL	234000	1	0.1	0.1	2340	0.017
Ethofumesate	RF-0163-002-PPP	Rat	NOAEL	300000	1	0.1	0.1	3000	0.013
Picloram	RF-0343-001-PPP	Mouse	LOAEL	1000000	0.333	0.1	0.1	3333	0.012
Methoxyfenozide	RF-0296-001-PPP	Rat	NOAEL	379000	1	0.1	0.1	3790	0.011
Ethoxysulfuron	RF-0166-001-PPP	Mouse	NOAEL	492000	1	0.1	0.1	4920	0.008
Rimsulfuron (aka renriduron)	RF-0386-001-PPP	Rat	NOAEL	495000	1	0.1	0.1	4950	0.008
Orthosulfamuron	RF-0315-001-PPP	Rat	NOAEL	500000	1	0.1	0.1	5000	0.008
Captan	RF-0061-001-PPP	Dog	NOAEL	600000	1	0.1	0.1	6000	0.007
Thiamethoxam	RF-0418-001-PPP	Mouse	NOAEL	1163000	1	0.1	0.1	11630	0.003