EuroMix

European Test and Risk Assessment Strategies for Mixtures

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Deliverable 6.2

The EuroMix model toolbox MCRA 9

WP 6 – **Model integration into a web-based model and data toolbox**

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Description of EuroMix Deliverable 6.2

An important aim of the EuroMix project is to develop and implement a web-based platform (the EuroMix toolbox) including data and models accessible to all key-actors in risk assessment and risk management. The platform includes or links to relevant models to provide estimates of hazard, exposure and risk. The software platform builds on the Monte Carlo Risk Assessment (MCRA) system, versions of which were developed in the EU ACROPOLIS project as MCRA 8.0 (van Klaveren et al. 2015, van der Voet et al. 2015), and for the European Food Safety Authority as MCRA 8.1 (van der Voet et al. 2016a) and MCRA 8.3 (van Klaveren et al., in prep. a,b).

A demonstration prototype of the EuroMix toolbox (van der Voet et al. 2016b, EuroMix Deliverable 6.1) was developed as MCRA 8.2 (for a complete overview of features we refer to the MCRA 8.2 Reference Manual at https://mcra.rivm.nl). MCRA 8.2 has already been used for several publications in the context of EuroMix (Crépet et al. 2018, Karrer et al. subm., Kennedy et al. 2019).

This document describes the final EuroMix toolbox, MCRA 9.0, which will later be available at the same url, and is currently temporarily available at https://mcra-test.rivm.nl/EuroMix/WebApp. Documentation for MCRA 9.0 will be included in the online help system. MCRA 9.0 will be fully described in an upcoming publication (van der Voet et al., Deliverable 6.4).

The EuroMix toolbox contains a data share where data in relation to the case studies of the EuroMix project are organised.

This short document is not intended as a full description of the possibilities of the toolbox. An overview of the modules in the toolbox is given.

Modules of the EuroMix Toolbox

The data and models of the toolbox are organized in modules. Each module represents a certain type of data, which can be computed from data provided by other (sub)modules, or the data may be 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 the toolbox (Figure 1) 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 risk 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., adding default concentrations in water, which are often missing in the monitoring, 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. When running an action in the toolbox, 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.

MCRA 9 is a collection of data and models. The system consists of modules that are arranged in eight categories:

- Primary entity modules
- Consumption modules
- Occurrence modules
- Exposure modules
- Hazard modules
- In-silico modules
- Kinetic modules
- Risk modules

Table 1 specifies all relations between the modules in MCRA. A schematic overview is shown in Figure 1.

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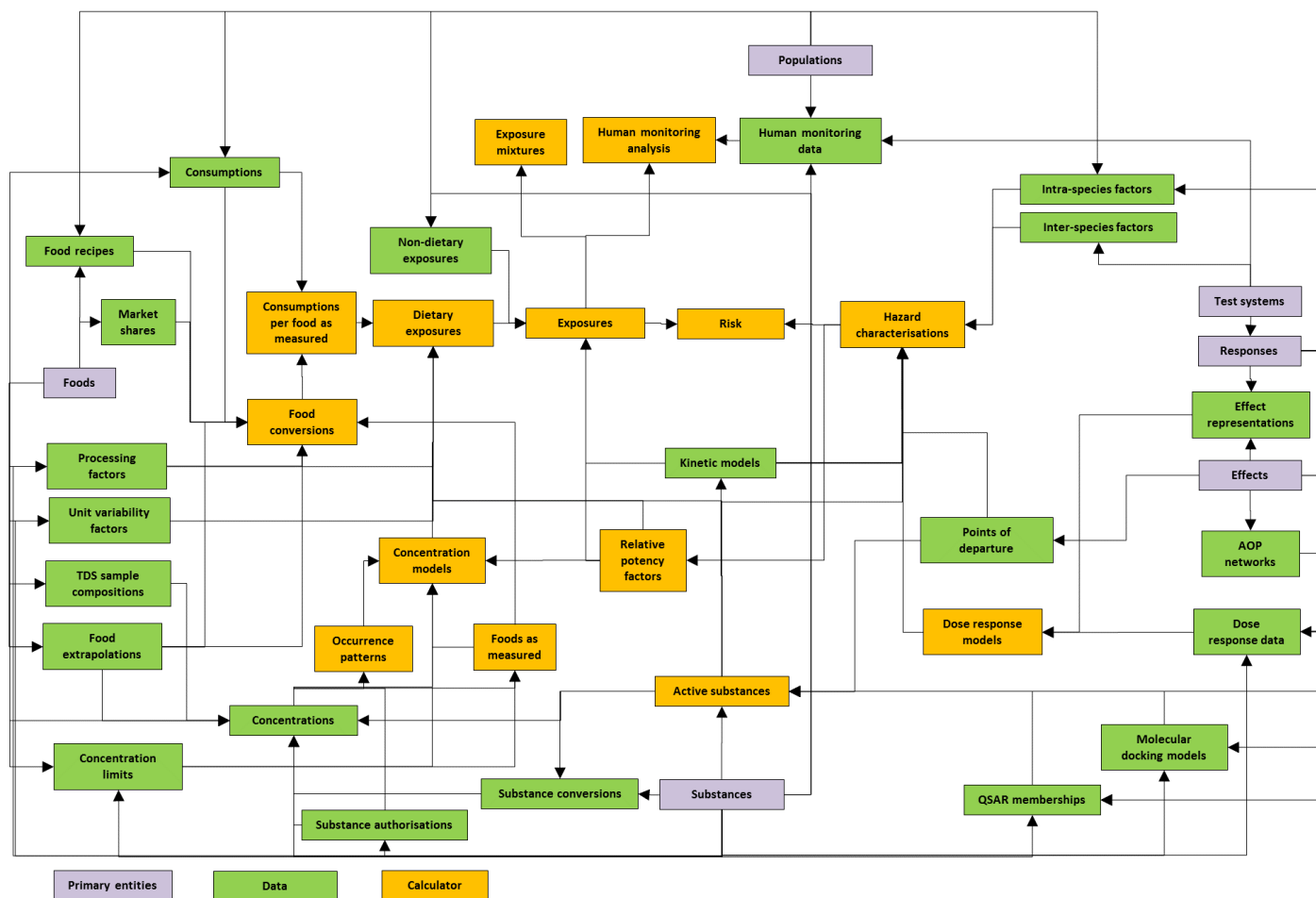
Figure 1. Schematic overview of modules in the EuroMix toolbox. Not all modules and relations are fully shown. For details consult Table 1.

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Table 1. Modules in the EuroMix toolbox MCRA 9.0.

Category	Module	Inputs [modules]	Used by [modules]	Description
Primary entity	Foods	-	Consumptions, Market shares, Food recipes, Concentrations, Processing factors, Unit variability factors, Occurrence patterns, Substance authorisations, Concentration limits, Concentration models, Foods as measured, Total diet study sample compositions, Food extrapolations, Food conversions, Consumptions per food as measured, Dietary exposures with screening, Dietary exposures, Exposures, Exposure mixtures.	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	-	Concentrations, Processing factors, Unit variability factors, Occurrence patterns, Substance authorisations, Substance translations, Concentration limits, Concentration models, Foods as	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.

Category	Module	Inputs [modules]	Used by [modules]	Description
			measured, Food conversions, Consumptions per food as measured, Dietary exposures with screening, Dietary exposures, Non-dietary exposures, Exposures, Exposure mixtures, Human monitoring data, Human monitoring analysis, QSAR membership models, Molecular docking models, Kinetic models, Active substances, Relative potency factors, Hazard characterisations, Points of departure, Dose response models, Dose response data, Inter-species conversions, Intra species factors, Risks.	
	Effects	-	Concentration models, Dietary exposures with screening, Dietary exposures, Exposures, Exposure mixtures, QSAR membership models, Molecular docking models, Active substances, Relative potency factors, Hazard characterisations, Points of departure, Effect representations, Inter-species	Effects are biological or toxicological consequences for human health, that may result from chemical exposure and are the focus of hazard or risk assessment.

Category	Module	Inputs [modules]	Used by [modules]	Description
			conversions, Intra species factors, AOP networks, Risks.	
	Populations	-	Consumptions, Consumptions per food as measured, Dietary exposures, Non-dietary exposures, Exposures, Human monitoring analysis.	Populations are groups of human individuals that are the scope of exposure or risk assessments.
	Test systems	-	Responses, Dose response models, Dose response data, Inter-species conversions.	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.
Consumption	Consumptions	Populations, Foods.	Food conversions, Consumptions per food as measured.	Consumptions data are the amounts of Foods consumed on specific days by Individuals in a food consumption Survey.

Category	Module	Inputs [modules]	Used by [modules]	Description
	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 foods-as-measured) by specifying proportions in the form of a percentage.
Occurrence	Concentrations	Foods, Substances, Focal food concentrations, Total diet study sample compositions, Food extrapolations, Substance translations, Relative potency factors, Substance authorisations, Active substances, Concentration limits.	Occurrence patterns, Concentration models, Foods as measured.	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.

Category	Module	Inputs [modules]	Used by [modules]	Description
	Processing factors	Foods, Substances.	Food conversions, Dietary exposures.	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	Foods, Substances.	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.
	Occurrence patterns	Foods, Substances, Concentrations, Substance authorisations.	Concentration models.	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	Inputs [modules]	Used by [modules]	Description
	Substance authorisations	Foods, Substances.	Concentrations, Occurrence patterns.	Substance authorisations specify which food/substance combinations are authorised.
	Substance translations	Substances, Active substances.	Concentrations.	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	Foods, Substances.	Concentrations, Concentration models, Foods as measured.	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	Concentrations, Concentration limits, Foods as measured, Occurrence patterns, Relative potency factors.	Dietary exposures with screening, Dietary exposures.	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

Category	Module	Inputs [modules]	Used by [modules]	Description
				models are specified per food/substance combination.
	Foods as measured	Concentrations, Concentration limits.	Food conversions, Concentration models.	Foods as measured are foods within the foods scope for which concentration data of substances are available (or expected).
	Focal food concentrations	-	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	Foods.	Concentrations.	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.	Concentrations, Food conversions.	Food extrapolations data specify foods (from-foods) that can be used to impute concentration data for other foods with insufficient data (to-foods).

Category	Module	Inputs [modules]	Used by [modules]	Description
Exposure	Food conversions	Foods, Substances, Consumptions, Foods as measured, Processing factors, Food recipes, Food extrapolations.	Consumptions per food as measured.	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, Food conversions.	Dietary exposures with screening, Dietary exposures.	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	Consumptions per food as measured, Concentration models, Active substances, Relative potency factors.	Dietary exposures.	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.

Category	Module	Inputs [modules]	Used by [modules]	Description
	Dietary exposures	Consumptions per food as measured, Concentration models, Processing factors, Unit variability factors, Dietary exposures with screening, Active substances, Relative potency factors.	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	Populations, Substances, Active substances.	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	Dietary exposures, Non-dietary exposures, Kinetic models, Relative potency factors.	Exposure mixtures, Human monitoring analysis, Risks.	Exposures are the amounts of substances, expressed per kg bodyweight or per individual, 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	Inputs [modules]	Used by [modules]	Description
	Exposure mixtures	Exposures.	-	Exposure mixtures are mixtures of substances that contribute relatively much to the overall cumulative exposure (potential risk drivers).
	Human monitoring data	Substances.	Human monitoring analysis.	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 data, Exposures.	-	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	Substances, Effects, A OP 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

Category	Module	Inputs [modules]	Used by [modules]	Description
				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	Kinetic models	Substances, Active substances.	Exposures, Hazard characterisations.	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	AOP networks, Points of departure, Molecular docking models, QSAR membership models.	Concentrations, Substance translations, Non-dietary exposures, Kinetic models, Dietary exposures with screening, Dietary exposures, Hazard characterisations.	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.

Category	Module	Inputs [modules]	Used by [modules]	Description
	Relative potency factors	AOP networks, Hazard characterisations.	Concentrations, Concentration models, Dietary exposures with screening, Dietary exposures, Exposures.	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	AOP networks, Active substances, Dose response models, Effect representations, Points of departure, Inter-species conversions, Intra species factors, Kinetic models.	Relative potency factors, Risks.	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-reponse 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	Substances, Effects.	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.

Category	Module	Inputs [modules]	Used by [modules]	Description
	Dose response models	Dose response data, Effect representations.	Hazard characterisations.	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).
	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	AOP networks.	Hazard characterisations, Dose response models.	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	Test Systems, Substances, Effects.	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 geometic standard deviation (GSD)

Category	Module	Inputs [modules]	Used by [modules]	Description
				for a lognormal uncertainty distribution of the interspecies factor.
	Intra species factors	Substances, Effects.	Hazard characterisations.	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	Effects.	QSAR membership models, Molecular docking models, Active substances, Relative potency factors, Hazard characterisations, Effect representations.	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	Exposures, Hazard characterisations.	-	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

Category	Module	Inputs [modules]	Used by [modules]	Description
				margins of exposure (IMOE). In addition, risks can be assessed from a plot of hazard characterisations vs. exposures.