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Demonstration prototype of the EuroMix model toolbox

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

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1 Introduction

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, the latest versions of which were developed in the EU ACROPOLIS project as MCRA 8.0 (van der Voet et al. 2015), and for the European Food Safety Authority as MCRA 8.1 (van der Voet et al. 2016).

Chapter 2 of this document describes in short the new features in a demonstration prototype of the EuroMix toolbox, 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). In addition, in Chapter 3 some features intended for the final EuroMix toolbox are discussed.

2 New features of the prototype EuroMix toolbox (MCRA 8.2)

2.1 Mixture Selection

In the EuroMix project the development of a mixture selection module based on exposure was prioritised, because the choice of chemicals for the experiments depended on this (Task 6.1). A mixture selection module was therefore developed, based on a method called sparse nonnegative matrix underapproximation (SNMU) (de Boer et al. 2016, Milestone 9 or 6.1). The mixture selection module was then applied to French and Dutch data in Task 5.3, leading to a list of suggested chemicals for each adverse outcome pathway in the project (Crépet et al. 2016, Milestone 8). Practical guidance was developed for other EuroMix partners (EuroMix 2016). The mixture selection module was already made available in advance as part of MCRA 8.1, but is officially delivered in MCRA 8.2.

The new functionality can be chosen by checking 'Apply mixture selection' in the tab Mixtures in the MCRA Model interface (see Figure 1).

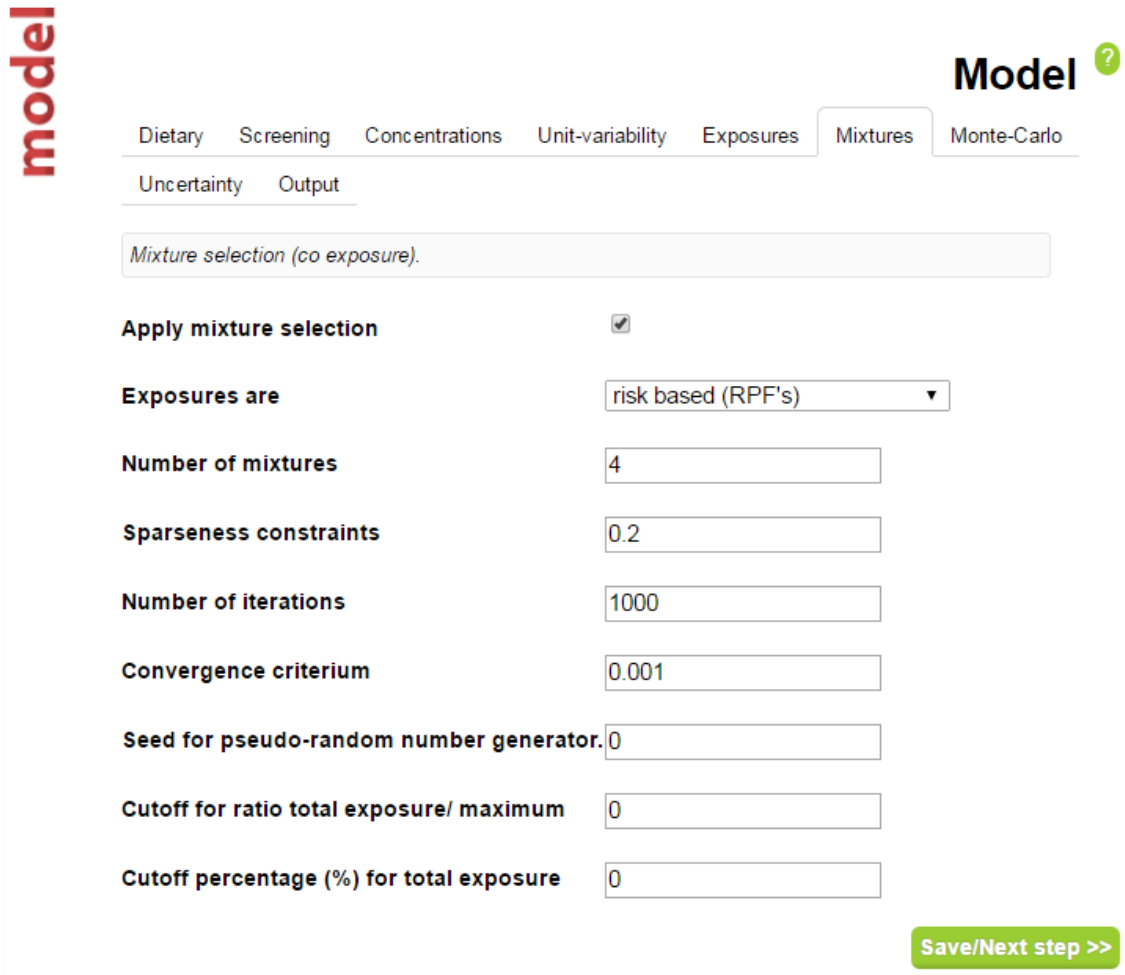

Figure 1. Screenshot of the mixture selection interface in MCRA 8.2.

The usual choice for 'Exposures are' will be 'risk based (RPFs)', which means that the exposures for all compounds will be recalculated to exposures in terms of the reference compound before the NMU algorithm is applied. The alternative option, 'standardized' is only provided for calculations similar to those in a previous publication (Béchaux et al. 2013).

The SNMU method identifies clusters of compounds with often come together in the exposure matrix. In reality there is often a very large number of possible compound-combinations (mixtures), but we are only interested in the most important combinations. The option 'Number of mixtures' specifies this.

The next four options refer to some technical parameters, for which we refer to the Milestone report de Boer et al (2016). The last two options refer to possible pre-selection criteria for the exposure matrix based on the Maximum Cumulative Ratio (MCR) plot, discussed in the next section.

An example of the output a mixture selection is given in Figure 2. In practical cases the most predominant 'mixtures' have often only one compound, so they do not represent real mixtures. By restricting the analysis to the exposure days where the exposure form all compounds was at least five times the exposure from any single compound, more focus is placed on the truly important mixture effects.

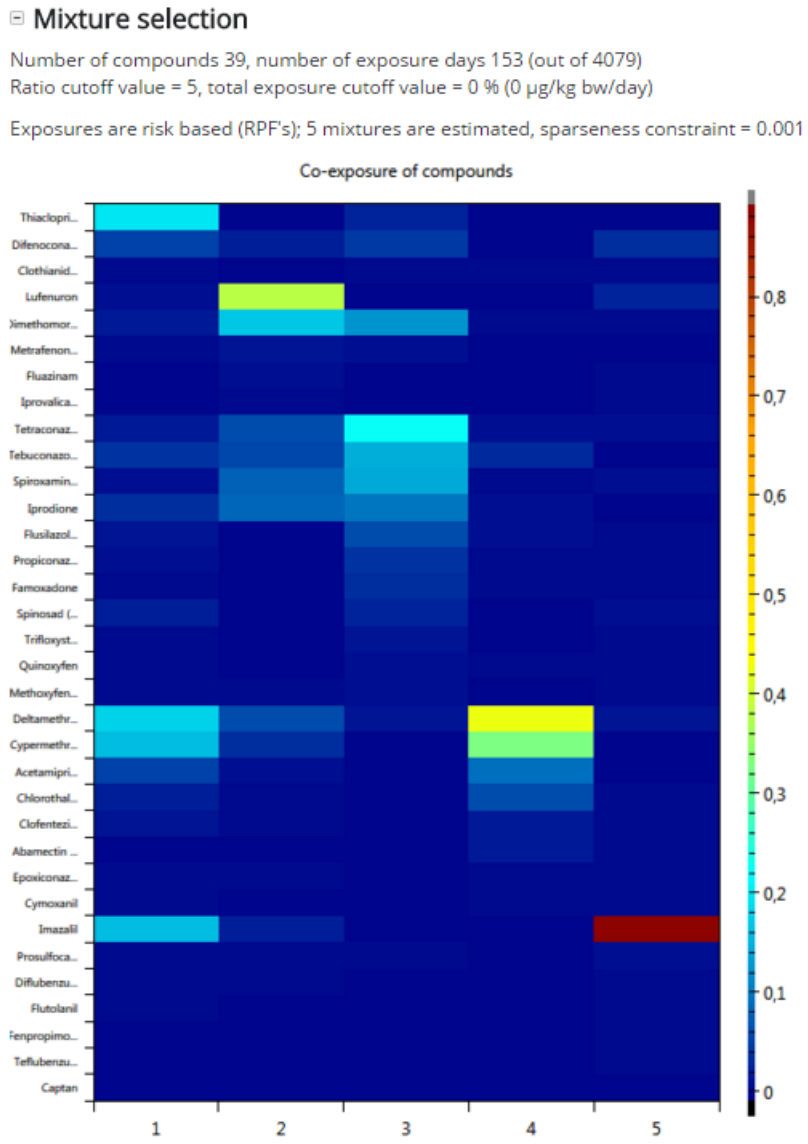

Figure 2. Example of SNMU mixture selection. Five mixtures are identified , predominant compounds in the first mixture are Thiacloprid, Deltamethrin, Cypermethrin, Imazalil. Copied from de Boer et al. (2016).

For further details on the use of the mixture selection module in MCRA see the milestone reports de Boer et al. 2016, Crépet et al. 2016, and the practical guidelines.

2.2 Co-exposure

An inventory of the degree of co-exposure can be made visible using various newly implemented instruments in MCRA 8.2:

1. qualitative approach: **co-exposure distribution**. Which part of the exposure distribution is based on co-exposure, i.e. exposure from more than one compound?
2. qualitative approach: **counting of co-exposure**. To which combinations of compounds are individuals exposed?

3. quantitative approach: **maximum cumulative ratio (MCR)**. To what degree are mixtures more important than single compounds?

Examples of these diagnostic plots and tables are shown hereafter. For detail see the milestone report de Boer et al. (2016).

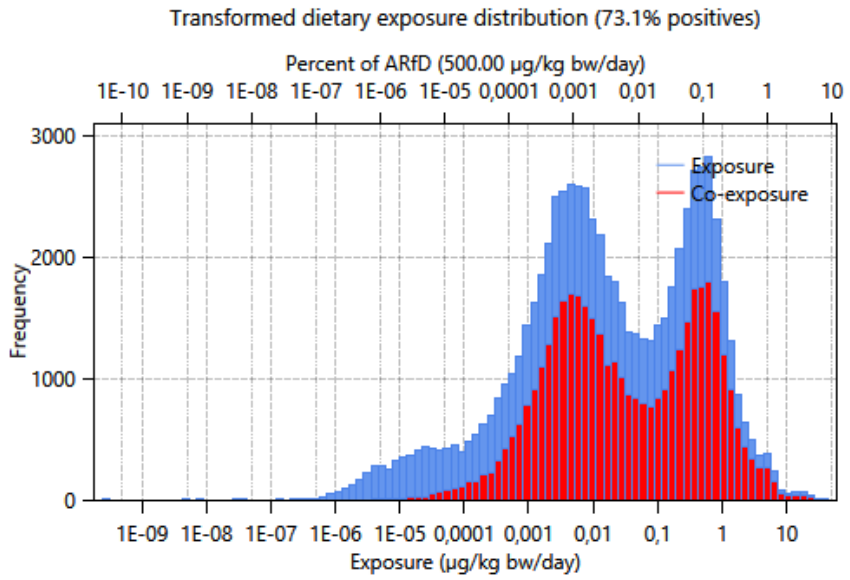

Figure 3. Example of co-exposure distribution (from >1 compound per individual-day, red) super-imposed on the total exposure distribution (blue).

Co-exposure total distribution

Co-exposure of compounds

Number of compounds	Frequency	Percentage
0	1,153	11.5
1	1,089	10.9
2	1,035	10.4
3	965	9.7
4	1,000	10.0
5	910	9.1
6	882	8.8
7	748	7.5
8	666	6.7
9	504	5.0
10	372	3.7
11	272	2.7
12	172	1.7
13	111	1.1
14	60	0.6
15	28	0.3
16	18	0.2
17	7	0.1
19	7	0.1
20	1	0.0

Most frequent mixtures of compounds occurring together are shown (a maximum number of 15 records are shown)

Number of compounds	Percentage	Compounds
0	11.53	
1	3.66	Imazalil
1	1.71	Iprodione
2	1.26	Imazalil, Iprodione
1	0.93	Acetamiprid
1	0.67	Deltamethrin (cis-deltamethrin)
2	0.59	Acetamiprid, Imazalil
1	0.58	Cypermethrin (Cypermethrin including other mixture
1	0.57	Tebuconazole
2	0.48	Imazalil, Thiacloprid
3	0.45	Acetamiprid, Imazalil, Iprodione
2	0.45	Acetamiprid, Iprodione
3	0.42	Imazalil, Iprodione, Thiacloprid
1	0.41	Dimethomorph
1	0.39	Difenoconazole

Mixtures containing the compound(s) including all other combinations with the specified combination of compound(s),

Number of compounds	Percentage	Compounds
1	54.18	Iprodione
1	53.13	Imazalil
1	49.08	Acetamiprid
1	36.95	Tebuconazole
2	35.61	Imazalil, Iprodione
2	34.85	Acetamiprid, Iprodione
1	34.34	Difenoconazole
2	31.00	Acetamiprid, Imazalil
1	30.05	Cypermethrin (Cypermethrin including other mixture
1	29.22	Spinosad (sum of Spinosyn A and Spinosyn D, expres
1	29.08	Thiacloprid
2	28.46	Iprodione, Tebuconazole
2	26.22	Acetamiprid, Difenoconazole
2	25.50	Imazalil, Tebuconazole
2	25.42	Acetamiprid, Tebuconazole

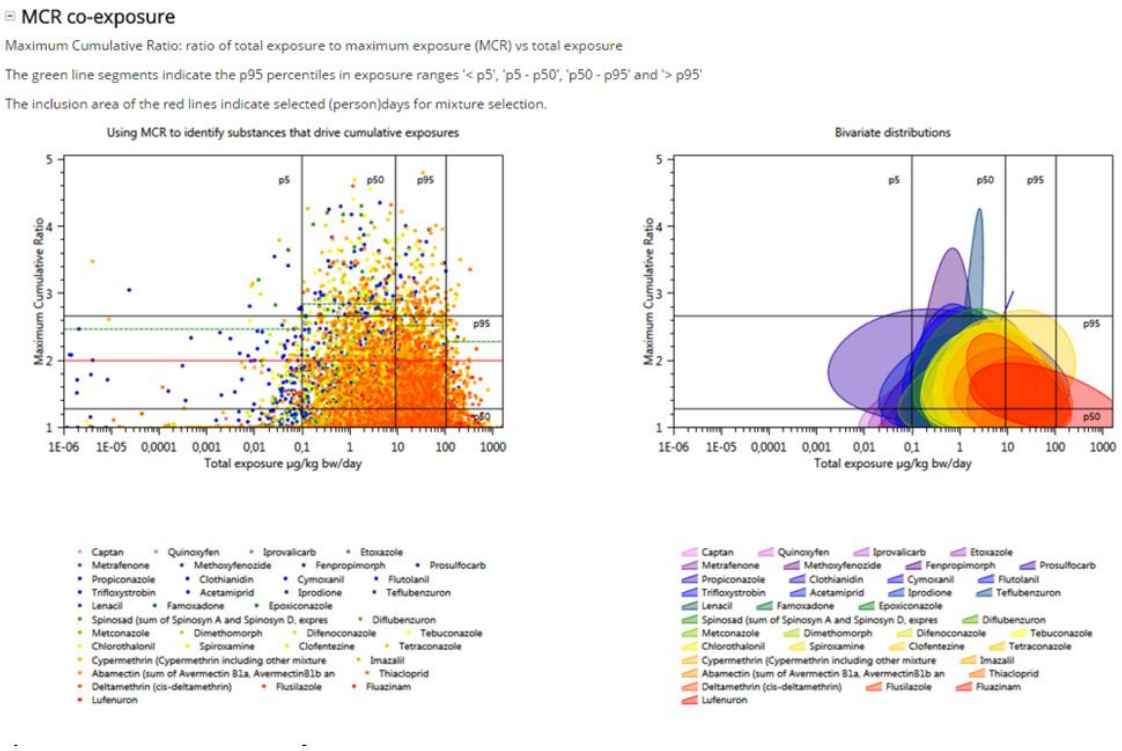

Figure 4. Example Maximum Cumulative Ratio (MCR) plots. Copied from Milestone report, de Boer et al. (2016).

For further details on the use of these instruments see the milestone reports de Boer et al. 2016, Crépet et al. 2016, and the practical guidelines.

2.3 Data handling

In versions of MCRA up to 8.1 the raw data needed for an assessment were uploaded and then compiled in the database for further use. Data compilation thus linked all relevant entities for a certain task. This system, while straightforward, was seen as not flexible enough for the future EuroMix toolbox, in which many different tasks will be possible, each with different data requirements. Therefore the MCRA system has been restructured in version 8.2 so that tasks can be performed by directly using the raw data. The compilation of links between the entities in the datasets is then performed directly when needed. An advantage is that the sometimes lengthy compilation step can be avoided if only part of the data is replaced by new data.

2.4 Non-dietary and aggregate exposure

In EuroMix several models for non-dietary exposure are considered for linking to the EuroMix toolbox. The functionality of MCRA for aggregate exposure assessment has been reviewed and a functional design has been made for the future implementation in EuroMix of the links between BROWSE, PACEM, AOEM and possibly other non-dietary models to MCRA (Kennedy et al. 2016, Milestone 10).

In the aggregate exposure module, non-dietary exposures are linked to dietary exposures. In MCRA 8.2 this module has been revised. The following items are implemented:

- multiple non-dietary surveys are allowed
- demographic criteria (e.g. age, gender) can be set as survey properties
- cumulative assessment allowing multiple compounds
- new option for unmatched: sample non-dietary individuals from multiple non-dietary surveys with correlation or not
- improved file upload and performance

The option matching or not is made independent of the uploaded non-dietary data. This means that when the non-dietary individuals are identical to the dietary ones, these data can also be used when matching is switched off. For matching to occur, non-dietary individuals should have IDs identical to the dietary ones. All other exposures are ignored. Dietary individuals that don't have a non-dietary counterpart will receive a zero non-dietary exposure unless a non-dietary exposure is recorded with 'idIndividual = General' and the dietary individual meets the demographic criteria.

When matching is switched off, non-dietary individuals are randomly sampled and allocated to a dietary individual if they meet the demographic criteria. When multiple surveys are available, the option 'sample individuals with correlation or not' becomes relevant. When correlation is checked, non-dietary exposures of individuals with identical id's in the available non-dietary surveys are combined and allocated to a dietary individual. When correlation is unchecked, from each available survey a non-dietary exposure record is sampled, combined and allocated to a dietary individual.

2.5 Cumulative IPRA and hazard vs. exposure plots for risk assessment

Risk assessment integrates exposure assessment and hazard assessment. MCRA contains as a module the Integrated Probabilistic Risk Assessment (IPRA) model (van der Voet & Slob 2007). In MCRA 8.2 this has been generalized to cumulative assessments (as described in van der Voet et al. 2009). Further, the results of cumulative IPRA are plotted both in an Individual Margin of Exposure (IMoE) plot (Figure 5, van der Voet et al. 2009), and, in line with the ideas put forward in the RISK21 project (Figure 6, Pastoor et al. 2014, Embry et al. 2014, Moretto et al. 2016) in a hazard vs. exposure plot (Figure 7).

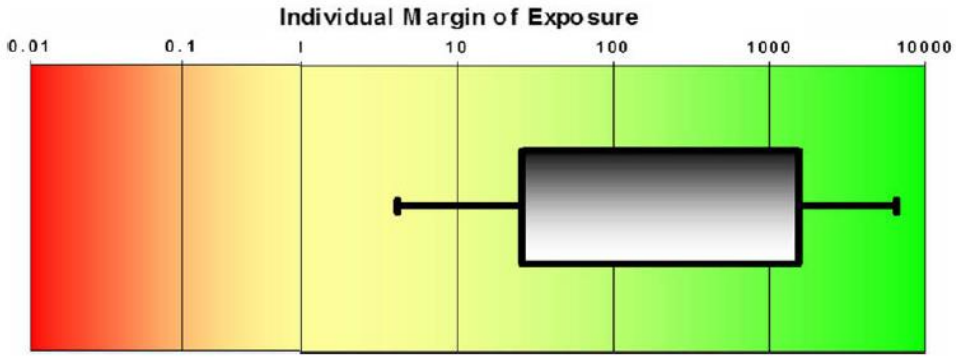

Figure 5. Individual Margin of Exposure (IMoE) plot. Copied from van der Voet et al. (2009).

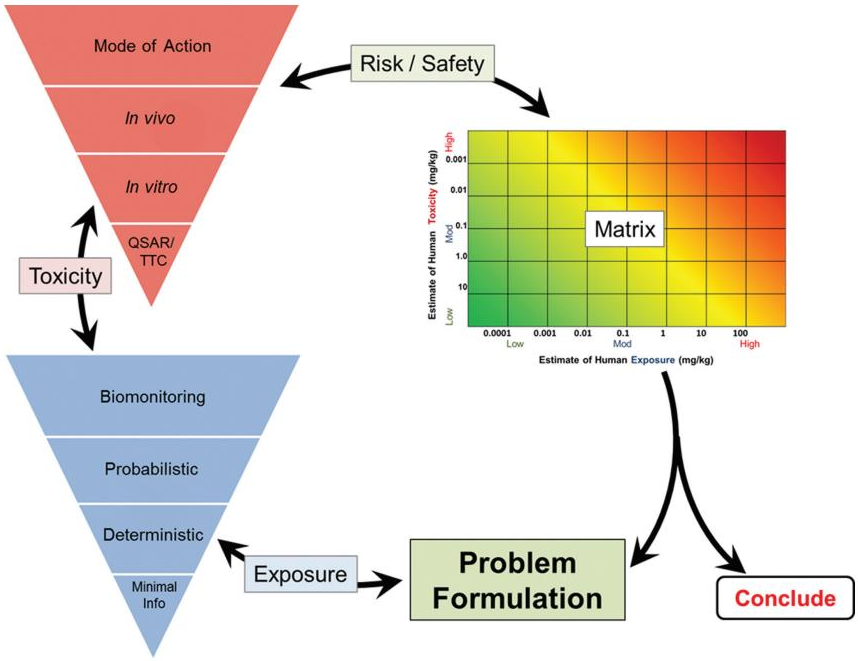

Figure 6. RISK21 road map with visualization matrix. Copied from Embry et al. (2014) .

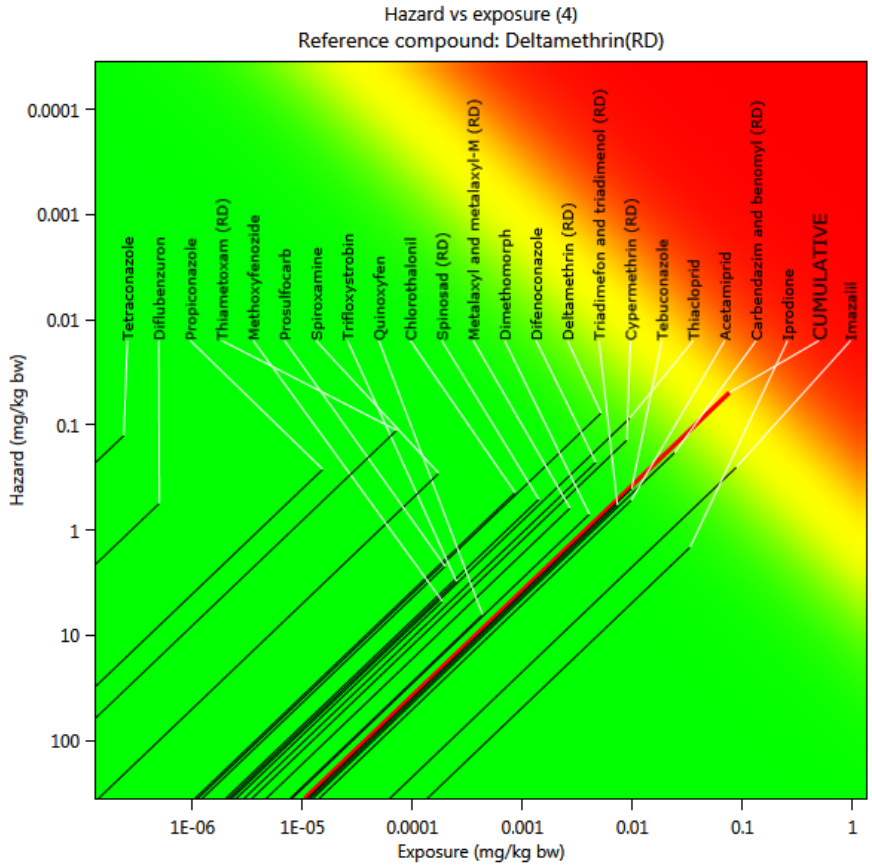

Figure 7. Example of MCRA Hazard vs. Exposure plot for multiple chemicals. Distribution of Individual Margin of Exposure (IMoE) shown as p5-p95 plotted on diagonal lines through the points (P95(IExp), CED/100)

2.6 Tiered approaches

The final EuroMix Toolbox is intended to implement a variety of tiered approaches, both with respect to data and models. In MCRA 8.2 already a few examples are incorporated.

2.6.1 Hazard doses

The higher-tier approach used in probabilistic approaches such as the IPRA module of MCRA (van der Voet & Slob 2007) is to estimate a benchmark dose (BMD) or critical effect dose (CED) from dose-response data, together with a distribution describing the uncertainty of the estimate (Slob 2002). At a lower tier, the dose-response data are not available but point estimates are used, of BMD, of CED or of other points of departure, such as the No Observed Adverse Effect Level (NOAEL) or No Observed Effect Level (NOEL). Without any appropriate data for the compound except its chemical structure a fall-back is possible to TTCxAF, which is the Threshold of Toxicological Concern (TTC) multiplied by a combined assessment factor AF, e.g. the traditional safety factor 100.

In MCRA we use as a general concept the term 'Hazard dose', which is then equated, depending on the tier chosen, to CED, NOAEL or TTCxAF. The tier can be chosen overall, or per compound.

2.6.2 Exposure

The higher-tier approach used in probabilistic assessments is to estimate for all foods the consumption distribution and the occurrence distribution, and convolute the two distributions by Monte Carlo integration. If no data are available for estimating a distribution with good precision, a lower-tier approach is to use only the geometric mean (or other point estimate). This can be applied at the consumption side or the occurrence side or both, leading to various lower-tier approaches. In the case that only point estimates are used, the exposure estimate itself is just a single value ('Point estimates' tier).

Within the limitations of a given exposure model, the precise tier is further characterised by a list of settings, e.g. nondetect imputation by 0, 0.5LOR or LOR, use of processing factors yes/no, unit variability model, etc. A certain grouping of settings can be made recognisable with a specific name. In MCRA 8.2. the following named tiers for exposure assessment are present, apart from the possibility to choose Custom settings: 'EFSA (basic) optimistic', 'EFSA (basic) pessimistic', 'Test Tier 1', 'Test Tier 2', 'Point estimates'. The EFSA Tiers follow the EFSA Guidance on probabilistic exposure modelling (EFSA 2012), the Test Tiers refer to ongoing work between RIVM, EC-SANTE and EFSA.

3 Plans for the final EuroMix toolbox

3.1 General design

The final EuroMix toolbox intends to combine data and models for all aspects of chemical risk assessment. For this all data concepts are being reviewed, and a new user interface will be developed. The current ideas about the EuroMix toolbox are summarised in the schemes in Figure 8 and Figure 9.

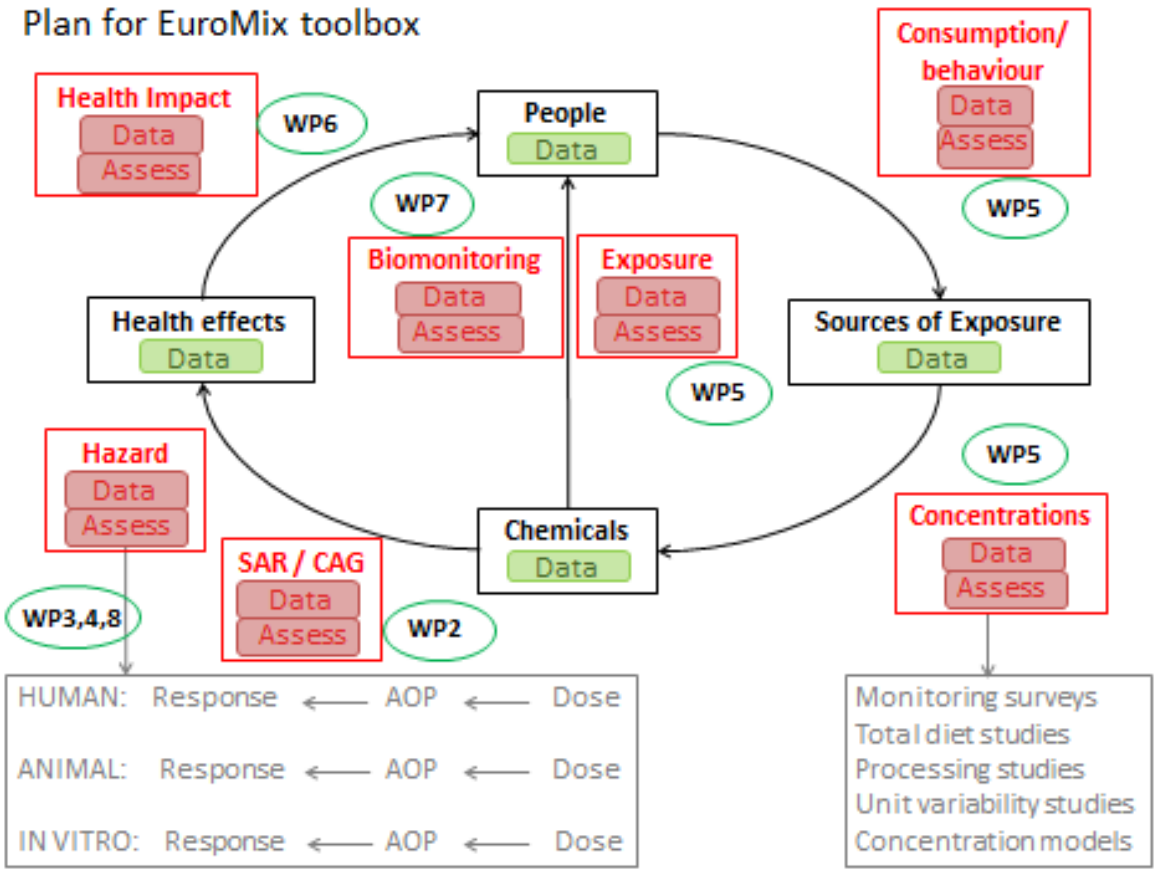

Figure 8. Basic entities (black) and functionalities (red) of the proposed EuroMix toolbox. The link with the EuroMix work packages is shown.

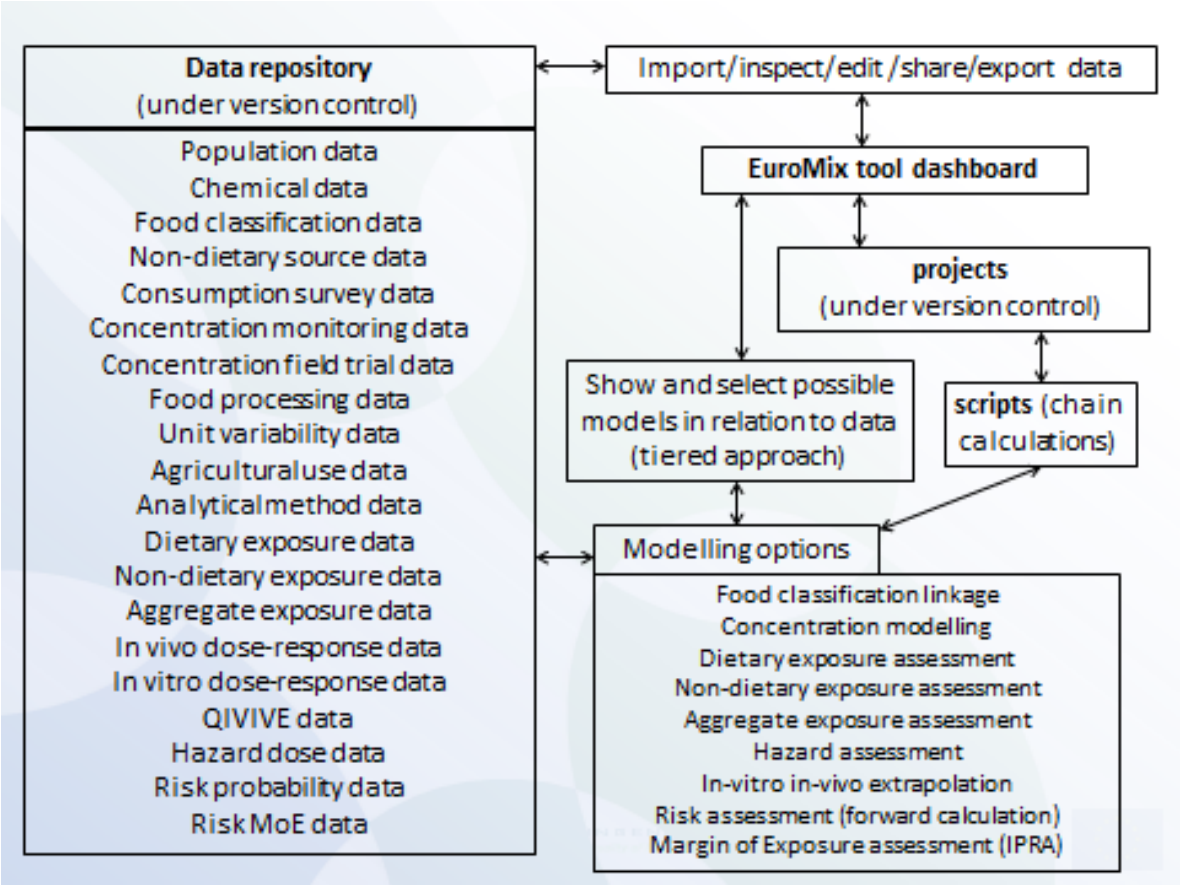

Figure 9. Proposed structure for data and modelling options in the EuroMix toolbox.

3.2 Non-dietary and aggregate exposure

The EuroMix platform will be a web-based system, implemented in the MCRA environment. Figure 10 shows the intended links to be developed. In principle there are two ways to link to external nondietary models:

1) via web-services; this applies if the nondietary model is also available in a web-based environment;

2) via uploading data files generated by the nondietary models.

Clearly, the first solution is most desirable, but depends on the availability of web-based versions of the nondietary models, and the possibility to invest in programming the web services at both sides. In the current functional design, the development of web-based functionality for the nondietary models is not foreseen within the EuroMix project, but is proposed for future implementation.

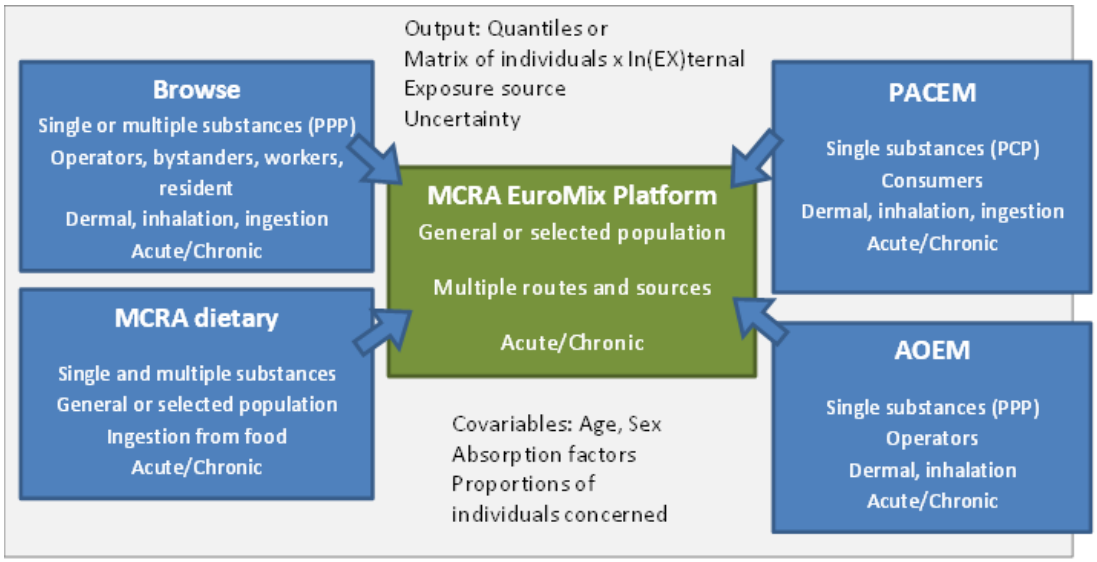

Figure 10. Scheme showing the intended linking of non-dietary models to the EuroMix platform.

3.3 Tiered approaches

A tier is defined here as a specified level of detail/complexity within risk assessment. Lower tier calculations refer to calculations with low data granularity (i.e., limited data) or low model complexity (e.g., using deterministic models instead of probabilistic models) or both.

Different forms of tiers:

1) Data-tiers: tiers defined by the required data (e.g. a large portion consumption or a database of individual-day consumptions). Note that some models (e.g. IESTI) can take or calculate the required input (in this case the large portion consumption) from multiple data tiers, but other models (e.g. the probabilistic models) only work with higher-tier data (see 3).

2) Model-tiers: tiers defined by different model complexities (e.g. the OIM or the LNN model for long-term exposure). Note that for sometimes alternative models require the same input data, but in other cases different models require different data (see 3)

3) Data- and model-tiers: this will be the more common situation because limited data granularities often limit the models that can be applied.

Tiers can be defined at multiple levels of an hierarchy. A risk assessment is a hierarchical structure of calculations. A risk (or health impact) assessment builds on an exposure assessment and a hazard assessment, the exposure assessment builds on a dietary and a nondietary exposure assessment, the dietary exposure assessment builds on a consumption assessment and an occurrence assessment, etc. An example are the tiers 'IESTI', 'EFSA basic optimistic' and 'EFSA basic pessimistic' which are defined at the level of a dietary exposure assessment.

Further, at any level of the hierarchy, there can be entities (potential risk drivers) that can be specified to have different tiers (tiered entities). For example, in a hazard assessment, some compounds may be assessed using a tier 'CED' (which requires appropriate dose-response data), other compound may be assessed using a tier 'TTCx100' (which only requires knowledge of the Cramer class of the compound). As another example, in dietary exposure assessment some food-compound combinations may be recognised

as risk drivers for which a higher-tier approach (e.g. probabilistic modelling) is required, whereas a lower-tier approach (e.g. deterministic modelling) may be sufficient for all other food-compound combinations.

Retain and refine: The concept refers to the idea that all potential risk drivers are retained in the modelling, but that it is not needed (and usually also not possible) to model all such entities at the same level. The 'art of modelling' is to increase the level of detail/complexity for the parts of the data/model needed to refine the assessment output to a fit-for-purpose level.

A typical risk assessment will start at a low tier for all tiered entities (potential risk drivers). However, based on data availability and ease of application, the initial assessment does not need to be the lowest tier possible.

If the initial calculations produce risk estimates that do not exclude concern, refinement of the modelling for the perceived risk drivers is useful for checking whether this concern is real.

Different scopes of tiering and tiering orders:

As described above, tiering may occur in different parts of the model and on different levels within a model. Moreover, tiering at more global levels may restrict the tiering options for sub-models. That is, tiering may be done within a sub-model (e.g., choosing different models/tiers at the level of concentration modelling), or at a higher level: e.g., choosing a global tier in which all sub-tiers are defined by the global choice.

The wording "levels of granularities" should not be understood to mean a strict hierarchy between tiers (i.e., one model is from a higher tier than another). One tier may be more detailed in one part of the model, while another is more detailed in another part of the model.

References

Béchaux C, Zetlaoui M, Tressou J, Leblanc JC, Héraud F, Crépet A (2013). Identification of pesticides mixtures and connection between combined exposure and diet. Food Chemical Toxicology 59: 191-198.

Crépet A, Sprong C, Béchaux C, de Boer W, Beukers M, Blaznik U, Svab A, Rorije E, Peijnenburg A, van der Voet H, van Klaveren J (2016). List of mixture compounds from combined dietary exposures. Milestone MS8 related to Task 5.3: Identification of relevant mixtures based on exposure consideration. http://www.euromixproject.eu/

de Boer WJ, van der Voet H, Kruisselbrink JW, van Lenthe MS, Béchaux C, Crépet A (2016). Milestone MS9 (6.1): Report on Task 6.1: Implementation mixture selection. http://www.euromixproject.eu/

EFSA (2012). Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues. EFSA Journal 2012;10(10):2839. http://dx.doi.org/10.2903/j.efsa.2012.2839.

Embry MR, Bachman AN, Bell DR, Boobis AR, Cohen SM, Dellarco M, Dewhurst IC, Doerrer NG, Hines RN, Moretto A, et al. (2014). Risk assessment in the 21st century: Roadmap and matrix. Critical Reviews in Toxicology, 44:6-16.

EuroMix WP 5 and 6. Practical guideline: Mixture selection from combined exposure with the Euromix tool (2016). http://www.euromixproject.eu/

Kennedy M, van der Voet H, de Boer W, Bokkers B, Grosskopf C, Karrer C, von Goetz N, Crépet A (2016). A functional design for aggregate exposure linking dietary and non-dietary exposure modules. Milestone 10 report. http://www.euromixproject.eu/

Moretto A, Bachman A, Boobis A, Solomon KR, Pastoor TP, Wilks MF, Embry MR. (2016). A framework for cumulative risk assessment in the 21st century. Critical Reviews in Toxicology, In Press.

Pastoor TP, Bachman AN, Bell DR, Cohen SM, Dellarco M, Dewhurst IC, Doe JE, Doerrer NG, Embry MR, Hines RN, et al. (2014). A 21st century roadmap for human health risk assessment. Critical Reviews in Toxicology, 44:1-5.

Slob W (2002). Dose-response modeling of continuous endpoints. Toxicological Sciences, 55: 298-312.

van der Voet H, de Boer WJ, Kruisselbrink JW, Goedhart PW, van der Heijden GWAM, Kennedy MC, Boon PE, van Klaveren JD (2015). The MCRA model for probabilistic single-compound and cumulative risk assessment of pesticides. Food and Chemical Toxicology, 79: 5-12. http://dx.doi.org/10.1016/j.fct.2014.10.014.

van der Voet H, de Boer WJ, Kruisselbrink JW, van Donkersgoed G, van Klaveren JD (2016). MCRA made scalable for large cumulative assessment groups. EFSA supporting publication 2016:EN-910. http://www.efsa.europa.eu/en/supporting/pub/910e.htm

van der Voet H, Slob W (2007). Integration of probabilistic exposure assessment and probabilistic hazard characterization. Risk Analysis, 27: 351-371. http://dx.doi.org/10.1111/j.1539-6924.2007.00887.x

van der Voet H, van der Heijden GWAM., Bos PMJ, Bosgra S, Boon PE, Muri SD, Brüschweiler BJ (2009). A model for probabilistic health impact assessment of exposure to food chemicals. Food and Chemical Toxicology, 47: 2926-2940. http://dx.doi.org/10.1016/j.fct.2008.12.027.