National Institute for Public Health
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RIVM Letter report 2018-0001
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Synopsis

Monte Carlo Risk Assessment (MCRA) computational model: maintenance and management 2017

This report describes the adjustments made regarding the Monte Carlo Risk Assessment (MCRA) computational model implemented by RIVM and Wageningen University & Research in 2017. MCRA is a computational model that presently gives the most realistic chemical intake via food, and that can evaluate possible health risks. The model is available for registered users via the internet (https://mcra.rivm.nl).

The current operable version of MCRA is version 8.2. In 2017, several new functionalities were added to this version to improve the exposure assessment to single chemicals or chemical mixtures via food. Within MCRA also the link was improved between the exposure estimates and calculations that indicate at which dose a harmful effect of a compound can occur (dose-response models). This link is an important part of an integrated risk assessment. These new functionalities have among others been implemented as part of the partnership between RIVM and the European Food Safety Authority (EFSA) and the EU project EuroMix.

The MCRA computational model was used in 2017 to calculate the intake of lead via the total diet and of fipronil via the consumption of egg, products containing egg as an ingredient, and vegetable products. These calculations were performed by the Front Office Food and Product Safety, commissioned by the Dutch Food and Product Safety Authority. The Front Office also used MCRA to perform an integrated risk assessment of titanium dioxide nanoparticles based on the exposure via food. Furthermore, MCRA was used to calculate the intake of various chemicals that may be present in food, such as bisphenol A, mineral oils and mixtures of pesticides.

Keywords: chemicals, intake calculations, risk assessment, probabilistic modelling, MCRA, food

Publiekssamenvatting

Monte Carlo Risk Assessment (MCRA) rekenmodel: onderhoud en management 2017

In dit rapport zijn de aanpassingen in het rekenmodel Monte Carlo Risk Assessment (MCRA) beschreven die het RIVM en Wageningen University & Research in 2017 hebben uitgevoerd. MCRA is een rekenmodel waarmee de meest realistische inname van stoffen via voedsel kan worden verkregen die op dit moment mogelijk is, en eventuele gezondheidsrisico's kunnen worden geëvalueerd. Het rekenmodel is voor geregistreerde gebruikers beschikbaar via internet.

De huidige versie van MCRA is versie 8.2. In 2017 zijn verschillende nieuwe functionaliteiten aan deze versie toegevoegd om de innameberekeningen van enkelvoudige stoffen of mengsels van stoffen via voedsel te verbeteren. Ook is binnen MCRA de koppeling verbeterd tussen de uitkomsten van innameberekeningen en berekeningen die de dosis aangeven waarbij een schadelijk effect van een stof kan optreden (dosis-respons modellen). Deze koppeling is een belangrijk onderdeel van een geïntegreerde risicobeoordeling. De nieuwe functionaliteiten zijn onder andere geïmplementeerd vanuit het partnership tussen het RIVM en de Europese voedselveiligheidsautoriteit (EFSA), en vanuit het Europese project EuroMix.

Het MCRA-rekenmodel is in 2017 gebruikt om de inname te berekenen van lood via de totale voeding, en van fipronil via de consumptie van ei, producten die ei bevatten, en plantaardige producten. Deze berekeningen zijn in opdracht van de Nederlandse Voedsel- en Warenautoriteit (NVWA) uitgevoerd door het Front Office Voedsel- en Productveiligheid van het RIVM en Wageningen UR, RIKILT. Dit Front Office beantwoordt ad-hoc-vragen van de NVWA over de veiligheid van voedsel en consumentenproducten. Het Front Office heeft MCRA ook gebruikt voor een geïntegreerde risicobeoordeling van titaniumdioxide nanodeeltjes op basis van de blootstelling via voedsel. Daarnaast is MCRA gebruikt om de inname te berekenen van verschillende stoffen die in voedsel kunnen zitten, zoals bisphenol A, minerale oliën en mengsels van bestrijdingsmiddelen.

Kernwoorden: chemische stoffen, innameberekeningen, risicobeoordeling, probabilistisch modelleren, MCRA, voedsel

Contents

1 Introduction

The Monte Carlo Risk Assessment computational model calculates the dietary exposure to chemical substances in foods, both acute and chronic, in a probabilistic manner, both in the field of nutrition and food safety. MCRA is continuously updated and adjusted based on user feedback and new (international) developments and insights regarding the performance of such assessments. The developments and major adjustments of MCRA are, predominantly financed by the European Commission as part of EU projects (e.g. SAFE FOODS[1], ACROPOLIS[2], EuroMix[3]) and the European Food Safety Authority (EFSA).

Within the 'Intake calculations and modelling' (IBM) project, financed by the Netherlands Food and Consumer Product Safety Authority (NVWA), Office for Risk Assessment and Research (BuRO), MCRA is maintained and managed. In this way, the National Institute for Public Health and the Environment (RIVM) can provide contributions regarding exposure calculations in various national and international projects in a consistent way, as well as conduct national exposure calculations. These national calculations are performed by the Front Office Food and Product Safety as part of risk assessment questions of the NVWA-BuRO or in research projects, such as the IBM project, financed by the NVWA or different Dutch ministries.

Every year, a short report is provided to give an overview of the work performed regarding the maintenance and management of MCRA. This report addresses the relevant items of 2017. The 2016 report is available on the RIVM website (Boon et al., 2017b).

[1] www.safefoods.nl
[2] www.acropolis-eu.com
[3] www.euromixproject.eu

2 Tasks performed in 2017

2.1 ICT infrastructure

In 2017, the ICT infrastructure for MCRA was maintained in cooperation with Wageningen University & Research (WUR) and the Shared Service Centre.

MCRA 8.2 is available at https://mcra.rivm.nl for exposure and risk assessments. The earlier versions of MCRA are no longer available. To keep these versions available online is not feasible given the costs and financial resources. If in incidental cases, it is necessary to redo an old calculation with one of these earlier versions of MCRA, they are available offline at WUR.

2.2 Revision control and maintenance

An important aspect of model development is the management of the different versions. In 2017, MCRA 8.2 was the operational version.

2.2.1 Documentation

For a good revision control, the documentation of the different versions of MCRA is necessary. The documentation in 2017 included the documentation of MCRA versions 3 up to 8.2. This documentation is available at ‘support’ after logging on to MCRA.

2.2.2 Validation

Validation of MCRA is needed when a new version of the computational model released which contains adjustments that may affect the calculated intake estimates. This was true for MCRA 8.2. The validation consists of two parts. First, WUR performs automatic validations on the key results before the release of the new version (see section 2.2.2.1). Secondly, the new version is validated in relation to the previous version of the computational model. MCRA 8.2 was released on 15 December 2016. Due to this late release and budget constraints within the IBM project, MCRA 8.2 was not validated in relation to the previous version of MCRA before its release. This validation was performed manually at the beginning of 2017 by RIVM (see section 2.2.2.2). This second part of the validation has been further automated as described in section 2.2.2.3.

2.2.2.1 MCRA 8.2 automated tests on artificial data

A comparison of MCRA 8.2 exposure results with true exposure values is possible using artificial data in simple situations. The idea here is to deconstruct the complex model in many small modelling steps (components). For each small step, a simple calculation gives the true outcome. To combine these small steps to run a full program as done in MCRA 8.2, unit tests are constructed. A unit test is a small program that generates the appropriate data, performs the simple calculation and runs the full program to generate the same outcome as with MCRA, and finally compares the two results. Furthermore, there are integration tests, which combine a series of unit tests.

MCRA 8.2 itself has a section where test programs are specified for running automated tests (i.e. unit and integration tests). On each new release of the computational model, the automated tests can be run to check if the performance of the model is still as expected. A report of the automated test results is automatically generated. The components tested are:

- Food conversion
- Concentration modelling
- Processing
- Unit variability
- Agricultural use
- Sample-based imputation (as in the pessimistic EFSA Probabilistic Guidance method (EFSA, 2012))
- Sample-based exposure calculation
- Non-sample-based exposure calculation

When these tests show any irregularities, these will be fixed until the automated tests give the same result as the computational model. In this way, an updated overview of the validation status is available for any current version of MCRA.

2.2.2.2 Manual MCRA 8.2 validation by comparison to MCRA 8.1

The validation performed by RIVM consists of comparing the results obtained with the previous version of MCRA with the new one for a number of datasets and calculations. For this, the same input databases (so-called test databases) and selections are used to assess the acute and chronic exposure using both versions of MCRA. Also possible changes in interface, selections of input variables and output are considered. Possible differences in the output are shared with WUR resulting in an adjustment of the computational model, if relevant. This is also true for aspects of the interface that do not work properly.

Appendix A lists the different analyses that were performed to compare MCRA 8.1 with MCRA 8.2, including the outcome of the percentiles of exposure. The results of the validation showed that the differences in exposure between the two versions of MCRA were negligible. No adjustments were needed based on this analysis. This was also true for the changes to the interface and output.

2.2.2.3 Automatic MCRA 8.2 validation by regression testing

The process described in the previous section has been automated. At WUR it is now possible to create and compare output for a range of data and settings using any MCRA version from 8.1.15 (May 2016). Each night the output for these test data and settings using the current development version of MCRA is automatically compared to the current production version.

2.2.3 Help desk

WUR provided support for the use of MCRA in 2017. Furthermore, adjustments were implemented in MCRA due to bugs and user wishes. Several minor bugs related to population subset selection, unit variability and non-dietary exposure were corrected. As these adjustments were not fundamental, no validation of the adjusted

computational model or the release of a new version of MCRA was required.

In addition, many user wishes concerning new charts, new summaries, improvements on current charts and output have been implemented. Continuous attention is giving to optimize current algorithms by a multithreaded implementation to increase performance. Care is also taken to maintain reproducibility with earlier versions of MCRA (see section 2.2.2).

2.3 New functionalities

MCRA 8.2 contains a risk management tool that was developed within the EU project Total Diet Study (TDS). The tool quantifies how regulation of the use of specific compounds on a specific food can affect exposure to these compounds. Using a pragmatic approach, it is assumed that effective regulation will reduce the total exposure distribution by a fixed factor, such that only a limited percentage of the exposures will exceed a given threshold. Other risk management options exist (Boon et al., 2017b), but no priority could be given to develop them in MCRA due to other obligations within the EuroMix project and as part of the EFSA-RIVM partnership (see section 2.3).

In 2017, several optimisations were implemented in MCRA 8.2:

1. The distinction between raw and compiled databases was removed, which led to a significant speed-up of processes.
2. The full output of an MCRA run was re-organised in sections. This leads to much faster access to the relevant output sections.
3. A web service functionality (Web API) was created and secured with hash message authentication code (HMAC) authentication. This allows external web applications to call upon MCRA.

Furthermore, preparations were made for a new web interface for MCRA as part of the EuroMix project in 2017. This will allow access to MCRA modules on their own, such as the modules for food code conversion, concentration modelling, non-dietary exposure assessment or dose-response modelling. In preparation for the new, modular MCRA, the following new functionalities were already added to MCRA 8.2, financed via different projects:

1. Introduction of tiered approaches for exposure assessment (EFSA optimistic and pessimistic scenarios (EFSA, 2012), two experimental Test tiers), in addition to the custom method that allows free choice of all settings (in relation with EFSA-RIVM partnership and DG Santé agreements (see section 2.3)).
2. Hazard vs. exposure graphs were added for health impact assessment (Integrated Probabilistic Risk Assessment; IPRA) (EuroMix project and Front-Office).
3. Optimization of aggregate exposure assessment, such as the possibility to specify a fraction of non-exposed individuals (EuroMix project).

4. Possibilities to upload dose-response data and to connect these to the web based version of the PROAST model[4] (EuroMix project).
5. Possibilities to link kinetic models to MCRA (EuroMix project).
6. Imputation of missing exposure and/or hazard data (EuroMix project).

The new functionalities mentioned under 4, 5 and 6 are under development and therefore not yet visible for general users of MCRA 8.2. These will be further implemented in 2018.

[4] http://www.rivm.nl/en/Documents_and_publications/Scientific/Models/PROAST

3 International developments regarding MCRA

The use of MCRA has acquired an international dimension via the EFSA-RIVM partnership agreement[5], the agreement with DG Santé[6] and the EU project EuroMix. In these projects, new functionalities are/will be incorporated and tested, resulting in new versions of the MCRA. Furthermore, in collaboration with the World Health Organisation (WHO) MCRA is used to make Total Diet Study data present in countries outside Europe available to WHO for use in international risk assessments. These international developments are addressed in more detail below.

3.1 EFSA-RIVM partnership

As follow-up of the EU project ACROPOLIS, a partnership agreement between RIVM and EFSA has been set up to develop MCRA further in relation to the needs of DG Santé, EFSA, Member States and industry regarding the performance of dietary exposure assessments to pesticides belonging to cumulative assessment groups. As part of this agreement, adjustments to MCRA have been implemented to make the computational model suitable for these type of assessments. In 2016, a report was published on the EFSA website describing the development of a scalable version of MCRA to facilitate cumulative dietary exposure assessments to pesticide residues belonging to a large cumulative assessment group (i.e. consisting of more than 100 pesticides)(van der Voet et al., 2016). In 2017, cumulative exposure calculations were performed following the EFSA guidance on the use of probabilistic methodology for dietary exposure to pesticide residues. For this, European pesticide residue data of 30 commodities were provided by EFSA. These data included monitoring data of pesticide residues belonging to two cumulative assessment groups affecting the nervous system and two having chronic effects on the thyroid. Furthermore, EFSA provided also food consumption data of ten consumer groups covering various age groups and regions within Europe. Models such as how to handle left-censored data (non-detects) based on use frequency were used and new code was written on imputing missing values. The exposure results are expected to be published in 2018 on the EFSA website.

The aim of this partnership is to have a long-term cooperation between EFSA and RIVM regarding using, testing and improving tools for the cumulative exposure assessment of pesticide residues in food and feed commodities. The first term of this agreement (two years) ended on 30 September 2017. Early 2017, EFSA and RIVM agreed on the second EFSA-RIVM partnership agreement for a period of four years.

3.2 Agreement with DG Santé

Also with DG Santé, an agreement has been reached to use MCRA to improve the understanding of cumulative dietary exposure assessments

[5] http://www.rivm.nl/en/Topics/F/Food_safety/EFSA_RIVM_Partnership
[6] http://www.tds-exposure.eu/

of pesticide residues at Member State level within the framework of Regulation (EC) No. 396/2005. For this, an electronic working group has been established aiming to discuss the risk management options for implementing cumulative pesticide risk assessment into European decision making. Furthermore, the use of probabilistic techniques for risk assessment and setting of maximum residue limits (MRLs) for pesticide residues depends on a common understanding regarding an acceptable health risk. The electronic working group also addresses the level of protection needed, so for example which percentile of the exposure distribution to choose for risk characterisation. In 2017, the MCRA user manual was delivered to DG Santé. This document aims to provide easy to use instructions for national pesticide authorisation boards.

3.3 EU-project EuroMix

In the EU-project EuroMix, test strategies and instruments are developed to identify whether chemicals share the same adverse outcome. Whereas MCRA is focused on exposure, the EuroMix calculation tools will also include routines to estimate the likelihood of CAG membership, hazard identification based on Adverse Outcome Pathways (AOP) and hazard characterisation. A functional design has been discussed within the EuroMix consortium, including descriptions of new functionality as listed below.

Typical EuroMix functionalities are:

1. To store, use and maintain experimental data for deriving hazard data for risk assessment of chemical mixtures
    - Experimental dose-response data
    - Use of experimental data from animal in vitro experiments to derive potency factors and dose- or effect addition information for risk assessment of chemical mixtures
    - Calculation of critical effect doses based on experimental data using the web based PROAST model
    - Dose- or effect addition
2. To use kinetic data for in vitro – in vivo extrapolation
    - Data structure kinetic data and/or link to external sources
    - Generic physiologically based pharmacokinetic (PBPK) model for as far relevant
    - Specific PBPK models for validation purposes
    - Internal dose calculations
3. Risk assessment of chemical mixtures
    - Integration of hazard and exposure modelling
    - Data availability and data tiers
    - Deterministic and probabilistic models
    - Dietary exposure to multiple chemicals
    - Aggregated exposure to multiple chemicals
        - Link to external models
        - Data structure
        - PBPK model to aggregated internal exposure
    - Simultaneous exposure to multiple chemicals and kinetic considerations
    - Link with biomonitoring data

4. Retain and refine cumulative assessment group (CAG) membership and uncertainty analyses
    - CAG level 2 versus CAG level 3 (Nielsen et al., 2012)
    - Link with experimental data of e.g. QSAR (Quantitative structure–activity relationship) models, molecular docking and/or receptor assays
    - Expert elicitation and probabilities of CAG membership
    - Imputation of missing values
    - Mixture Assessment Factor for unknown contribution of chemicals not being studied
    - 2D Monte Carlo simulation
5. Setting test priorities
    - When is refinement needed
    - Contribution of chemicals not studied based on (worst-case) Threshold of Toxicological Concern (TTC) values and QSAR models
    - Mixture selection based on contribution to exposure
6. Some general requirements as data sharing, downloading etc., allowing 3rd party web applications to access part of the features and/or data in the platform

By the end of 2018, the EuroMix open database and model platform will be programmed. Most likely, this will exists of one backbone and two front ends. A part of this platform remains focused on only exposure assessment, more or less similar to the currently MCRA 8.2 version, and the other front-end will host the added functionalities as described above.

3.4 WHO project TDS

In 2015, WHO together with the Korean Ministry of Food and Drug Safety and the Korea Health Industry Development Institute organised the Fifth International Workshop on Total Diet Studies (TDS) in Seoul, Republic of Korea[7]. As a follow-up of this workshop, RIVM as the WHO Collaborating Centre on Chemical Food Safety[8] is facilitating the use of TDS data within dietary exposure assessments. Use of these data in dietary exposure assessments is expected to improve both national and international (Joint FAO/WHO Expert Committee on Food Additives (JECFA) and Codex Alimentarius) risk assessments and thus the understanding and acceptability of (inter)national recommendations.

Different countries outside Europe have TDS data at their disposal, including Korea, China, Australia and the USA. In this project, these countries, and others, will be trained to use their TDS data in exposure assessment with the help of MCRA. By including as many countries as possible, a common approach to harmonise exposure assessments based on TDS data may be established.

Additionally, in this project a couple of case studies will be performed to show the impact of using MCRA in combination with TDS data in relation

[7] [7] http://iris.wpro.who.int/handle/10665.1/11686
[8] http://www.rivm.nl/en/Topics/W/WHO_Collaborating_Centre_on_Chemical_Food_Safety/WHO_Collaborating_Centre_on_Chemical_Food_Safety_webpagina

to the currently used method to assess the exposure to contaminants in a deterministic way by JECFA. The results of this case study are expected at the end of 2018 or beginning of 2019.

4 Publications

In 2017, papers and reports in which MCRA was used to estimate the dietary exposure to chemical substances were published or prepared. These papers and reports include the dietary exposure to lead (Boon et al., 2017a), bisphenol A (Boon et al., In prep), mineral oils (Fragki et al., In prep) and nitrates and nitrites as food additive (Sprong et al., 2017) in the Netherlands. MCRA was also used by researchers outside RIVM to assess the cumulative dietary exposure to three groups of pesticides in Brazil (Jardima et al., 2018) and the intake of pesticide residues in Germany (Sieke et al., 2017). At the end of 2016, an exposure assessment to glyphosate via food was published in which MCRA was used to refine the exposure assessment (Stephenson & Harris, 2016). As this paper was published after the finalisation of the 2016 MCRA report (Boon et al., 2017b), it is mentioned here.

As part of the EFSA-RIVM partnership agreement, three draft external reports have been submitted to EFSA:

1. The first report describes the exposure to multiple pesticides having a potential acute effect on the nervous system. The title of the report is ‘Cumulative exposure assessment to pesticides residues regarding two acute effects on the nervous system conducted with the MCRA tool 8.2’.
2. The second report describes the exposure to multiple pesticides having a potential chronic effect on the thyroid and is titled ‘Cumulative exposure assessment to pesticides residues regarding two chronic effects on the thyroid conducted with the MCRA tool 8.2’.
3. The third report is titled ‘Development of a data model for organizing information for probabilistic cumulative dietary exposure assessments of pesticides’.

All three reports are expected to be published on the EFSA website in 2018.

Apart from this, dietary exposure assessments to chemical substances performed with MCRA are used as input in several Front Office Food and Product Safety assessments. In 2017, MCRA was used in the assessment of the intake of lead (Front Office Voedsel- en Productveiligheid, 2017b) and the acute exposure assessment of fipronil via the consumption of egg, products containing egg as an ingredient, and vegetable products (Front Office Voedsel- en Productveiligheid, 2017a). Furthermore, the IPRA model, available within MCRA 8.2, was used to perform an integrated probabilistic risk assessment of external exposure to titanium dioxide nanoparticles (Front Office Voedsel- en Productveiligheid, 2017c).

5 Conclusion

In 2017, MCRA was used both nationally and internationally for dietary exposure assessments to chemical substances, including food contaminants, pesticides and food additives. Furthermore, MCRA was used in three risk assessment questions of the NVWA through the Front Office Food and Product Safety.

MCRA 8.2 was the version for exposure and risk assessments in 2017. Several functionalities have been added, or preparations for this have been made to meet the risk assessment requirements of different stakeholders, such as EFSA, DG Santé and NVWA.

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Appendix A Input + settings for comparison of outputs MCRA 8.1/8.2

Simulation	Database (mdb)	Compound	Foods	Population	Model	Cofactor / variable	Processing	LOD[1]	Uncertainty[2]	Variability[3]	Concentrations
1A	Lead-kidsNLwater-lodisnull20131120 V80	Lead	Only foods > LOD	Children 2-6 years	Chronic/LNN/ logarithmic	Age	NR	NR	NR	NR	Monitoring 2002 - 2008
		Age	2		3	4			5	6	
8.1 pseudo-random nr 123456			Exposure in µg/kg bw per day Mean exposure: 142 P50 135 P90 202 P95 227 P99 282-		Exposure in µg/kg bw per day Mean exposure: 127 P50 121 P90 181 P95 203 P99 252	Exposure in µg/kg bw per day Mean exposure: 113 P50 107 P90 161 P95 180 P99 223			Exposure in µg/kg bw per day Mean exposure: 101 P50 96 P90 143 P95 161 P99 201	Exposure in µg/kg bw per day Mean exposure: 90 P50 85 P90 128 P95 144 P99 178	
8.2 pseudo-random nr 123456			Exposure in µg/kg bw per day Mean exposure: 142 P50 135 P90 202 P95 227 P99 282		Exposure in µg/kg bw per day Mean exposure: 127 P50 121 P90 181 P95 203 P99 252	Exposure in µg/kg bw per day Mean exposure: 113 P50 107 P90 161 P95 180 P99 223			Exposure in µg/kg bw per day Mean exposure: 101 P50 96 P90 143 P95 161 P99 201	Exposure in µg/kg bw per day Mean exposure: 90 P50 85 P90 128 P95 144 P99 178	

Simulation	Database (mdb)	Compound	Foods	Population	Model	Cofactor / variable	Processing	LOD	Uncertainty	Variability	Concentrations
1B	Lead-kidsNLwaterlodisnull20131120 V80	Lead	Only foods > LOD	Children 2-6 years	Chronic/LNN/ logarithmic	NR	NR	NR	NR	NR	Monitoring 2002 - 2008
8.1 pseudo-random nr 123456			Exposure in µg/kg bw per day Mean exposure: 118 P50 111 P90 175 P95 199								

			P99 252								
8.2 pseudo-random nr 123456			Exposure in µg/kg bw per day Mean exposure: 118 P50 111 P90 175 P95 199 P99 252								
Simulation	Database (mdb)	Compound	Foods	Population	Model	Cofactor / variable	Processing	LOD	Uncertainty	Variability	Concentrations
1C	Lead-kidsNLwaterlodisnull20131120 V80	Lead	Only foods > LOD	Children 2-6 years	Observed Individual Means	NR	NR	NR	NR	NR	Monitoring 2002 - 2008
8.1 pseudo-random nr 123456			Exposure in µg/kg bw per day Mean exposure: 118 P50 104 P90 194 P95 243 P99 372								
8.2 pseudo-random nr 123456			Exposure in µg/kg bw per day Mean exposure: 118 P50 104 P90 194 P95 243 P99 372								
Simulation	Database (mdb)	Compound	Foods	Population	Model	Cofactor / variable	Processing	LOD	Uncertainty	Variability	Concentrations
1D	Lead-kidsNLwaterlodisnull20131120 V80	Lead	All foods (incl. non-detects)	Children 2-6 years	Chronic/BBN/ logarithmic	Age[1]	NR	0.5 x LOD	NR	NR	Monitoring 2002 - 2008
		Age	2		3	4		5		6	
8.1 pseudo-random nr 123456			Exposure in µg/kg bw per day Mean exposure: 482.1 PP50 468.7 P90.00 636.1 PP95 693.6 PP99 819		Exposure in µg/kg bw per day Mean exposure: 415.4 P50 403.8 P90 549.6 P95 599.5 P99 706.8	Exposure in µg/kg bw per day Mean exposure: 369.1 P50 358.7 P90 487.6 P95 532 P99 625		Exposure in µg/kg bw per day) Mean exposure: 338.5 P50 328.8 P90 447.3 P95 487.7 P99 577.1		Exposure in µg/kg bw per day Mean exposure: 319.9 P50 311 P90 422.1 P95 461.2 P99 542.2	

8.2 pseudo-random nr 123456			Exposure in µg/kg bw per day Mean exposure: 482.1 P50 468.7 P90 636.1 P95 693.6 P99 819		Exposure in µg/kg bw per day Mean exposure: 415.4 P50 403.8 P90 549.6 P95 599.5 P99 706.8		Exposure in µg/kg bw per day Mean exposure: 369.1 P50 358.7 P90 487.6 P95 532 P99 625	Exposure in µg/kg bw per day Mean exposure: 338.5 P50 328.8 P90 447.3 P95 487.7 P99 577.1		Exposure in µg/kg bw per day Mean exposure: 319.9 P50 311 P90 422.1 P95 461.2 P99 542.2	
Simulation	Database (mdb)	Compound	Foods	Population	Model	Cofactor / variable	Processing	LOD	Uncertainty	Variability	Concentrations
1E	Lead-kidsNLwaterlodisnull20131120 V80	Lead	All foods (incl. non-detects)	Children 2-6 years	Chronic/LNN/ logarithmic	Age	NR	0.5 x LOD	NR	NR	Monitoring 2002 - 2008
		Age	2		3	4		5		6	
8.1 pseudo-random nr 123456			Exposure in µg/kg bw per day Mean exposure: 482 P50 469 P90 636 P95 694 P99 819		Exposure in µg/kg bw per day Mean exposure: 415 P50 404 P90 550 P95 600 P99 707		Exposure in µg/kg bw per day Mean exposure: 369 P50 359 P90 488 P95 532 P99 625	Exposure in µg/kg bw per day Mean exposure: 339 P50 329 P90 447 P95 488 P99 577		Exposure in µg/kg bw per day Mean exposure: 320 P50 311 P90 422 P95 461 P99 542	
8.2 pseudo-random nr 123456			Exposure in µg/kg bw per day Mean exposure: 482 P50 469 P90 636 P95 694 P99 819		Exposure in µg/kg bw per day Mean exposure: 415 P50 404 P90 550 P95 600 P99 707		Exposure in µg/kg bw per day Mean exposure: 369 P50 359 P90 488 P95 532 P99 625	Exposure in µg/kg bw per day Mean exposure: 339 P50 329 P90 447 P95 488 P99 577		Exposure in µg/kg bw per day Mean exposure: 320 P50 311 P90 422 P95 461 P99 542	
Simulation	Database (mdb)	Compound	Foods	Population	Model	Cofactor / variable	Processing	LOD	Uncertainty	Variability	Concentrations
2	VCPkids_opsumV80	OPs	Only foods > LOD	Children 2-6 years	Acute	NR	Distribution[4]	NR	Conc +Cons	Beta[5]	Monitoring 2006
8.1 pseudo-random nr 123456			Exposure in µg/kg bw/day Exposure level Best estimate Lower bound (P2.5) Upper bound (P97.5) Mean 0.42 0.30 0.83 P50 0.19 0.09 0.38								

			P90	1.03	0.71	1.68						
			P95	1.47	1.06	2.58						
			P99	3.10	2.41	10.0						
			P99.9	11.9	7.67	53.6						
			P99.99	33.3	20.4	148						
8.2 pseudo-random nr 123456			Exposure in µg/kg bw per day									
			Exposure level	Best estimate	Lower bound (P2.5)	Upper bound (P97.5)						
			Mean	0.43	0.28	0.85						
			P50	0.19	0.09	0.35						
			P90	1.03	0.67	1.65						
			P95	1.47	0.97	2.55						
			P99	3.11	2.14	9.01						
			P99.9	11.9	7.25	45.2						
			P99.99	33.5	21.6	143						
Simulation	Databases (.mdb)	Compound	Foods	Population	Model	Cofactor / variable	Processing	LOD	Uncertainty	Variability	Concentrations	
3	3-MPCD VCPkids 81-82 validation	3-MCPD	All foods (incl. non-detects)	Children 2-6 years	Chronic/LNN/ logarithmic	Age	NR	0	Conc + cons	NR	Survey data 2013-2014	
		Age										
8.1 Pseudo-random nr 57323		2	Exposure in ng/kg bw per day									
			Exposure level	Best estimate	Lower bound (P2.5)	Upper bound (P97.5)						
			Mean	1501	1139	1666						
			P50	1389	1059	1555						
			P90	2308	1673	2552						
			P95	2674	1919	2962						
			P99	3473	2439	3952						
		3	Exposure in ng/kg bw per day									
			Exposure level	Best estimate	Lower bound (P2.5)	Upper bound (P97.5)						
			Mean	1581	1222	1760						
			P50	1460	1144	1640						
			P90	2436	1821	2697						
			P95	2808	2092	3142						
			P99	3653	2681	4177						
		4	Exposure in ng/kg bw per day									
			Exposure level	Best estimate	Lower bound (P2.5)	Upper bound (P97.5)						
			Mean	1579	1251	1725						
			P50	1460	1158	1600						

		P90	2426	1865	2668
		P95	2800	2106	3118
		P99	3666	2667	4206
	5	Exposure in ng/kg bw per day			
		Exposure level	Best estimate	Lower bound (P2.5)	Upper bound (P97.5)
		Mean	1491	1144	1624
		P50	1379	1069	1512
		P90	2289	1740	2519
		P95	2642	1974	2935
		P99	3454	2473	3872
	6	Exposure in ng/kg bw per day			
		Exposure level	Best estimate	Lower bound (P2.5)	Upper bound (P97.5)
		Mean	1339	1040	1499
		P50	1235	967	1414
		P90	2063	1552	2314
		P95	2386	1763	2684
		P99	3132	2257	3540
8.2 Pseudo-random nr 57323	2	Exposure in ng/kg bw per day			
		Exposure level	Best estimate	Lower bound (P2.5)	Upper bound (P97.5)
		Mean	1501	1127	1688
		P50	1389	1059	1561
		P90	2308	1661	2617
		P95	2674	1888	3021
		P99	3473	2420	3907
	3	Exposure in ng/kg bw per day			
		Exposure level	Best estimate	Lower bound (P2.5)	Upper bound (P97.5)
		Mean	1581	1200	1701
		P50	1460	1116	1566
		P90	2436	1807	2641
		P95	2808	2052	3064
		P99	3653	2589	4077
	4	Exposure in ng/kg bw per day			
		Exposure level	Best estimate	Lower bound (P2.5)	Upper bound (P97.5)
		Mean	1597	1187	1701
		P50	1460	1109	1563
		P90	2426	1783	2662
		P95	2800	2054	3094
		P99	3666	2616	4067
	5	Exposure in ng/kg bw per day			
		Exposure level	Best estimate	Lower bound (P2.5)	Upper bound (P97.5)

		Mean	1491	1064	1587
		P50	1379	1003	1465
		P90	2289	1592	2442
		P95	2642	1817	2827
		P99	3454	2332	3747
	6	Exposure in ng/kg bw per day			
		Exposure level	Best estimate	Lower bound (P2.5)	Upper bound (P97.5)
		Mean	1339	1049	1452
		P50	1235	964	1348
		P90	2063	1555	2273
		P95	2386	1775	2620
		P99	3132	2252	3564

Simulation	Databases (.mdb)	Compound	Foods	Population	Model	Cofactor / variable	Processing	LOD	Uncertainty	Variability	Concentrations
4	MeHg-Kids20150511	MeHg	Only foods > LOD	Children 2-6 years	Model then add	NR	NR	NR	Conc + cons	NR	Monitoring 2009 - 2014

8.1 Pseudo-random: 57323	Exposure in ng/kg bw per day		
	Exposure level	Best estimate	Lower bound (P2.5)	Upper bound (P97.5)
	Mean	23.4	17.7	29.1
	P50	14.4	8.44	20.6
	P90	52.1	34.3	68.2
	P95	72.7	44.8	102.4
	P99	135	73.0	210
8.2 Pseudo-random: 57323	Exposure in ng/kg bw per day		
	Exposure level	Best estimate	Lower bound (P2.5)	Upper bound (P97.5)
	Mean	23.4	17.4	29.6
	P50	14.5	7.51	20.4
	P90	52.6	33.3	71.2
	P95	73.6	42.6	107
	P99	135	69.0	218

Conc: concentration data; cons: individual food consumption data; BBN: Beta Binomial Normal; LNN: Logistic-Normal Normal; LOD: limit of detection; NR: not relevant

[1] Refers to the replacement of the samples with an analysed level at or below the limit of detection by a fraction of this limit value.

[2] Refers to the quantification of the uncertainty due to the size of the food consumption and concentration database by the bootstrap approach. Uncertainty is expressed via a 95% confidence interval around the best estimate of exposure.

[3] Refers to the inclusion of unit variability in the exposure assessment. This input variable is relevant in acute exposure assessments in which concentrations analysed in composite samples are used.

[4] Processing was included via a distribution as described in Boon et al. (2008).

[5] Unit variability was modelled according to a beta distribution as described in Boon et al. (2008).

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