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Identification and handling of uncertainties in dietary exposure assessment



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Abstract

Identification and handling of uncertainties in dietary exposure assessment

The RIVM and the RIKILT-Institute of Food Safety estimate the intake of chemical substances via food at the population level. The method presently used for dietary exposure assessments should be adapted to allow more insight into the extent of the uncertainties in such exposure estimates. The quantification of uncertainties is in line with international scientific endeavors that are currently being carried out in the field of uncertainty analysis of exposure assessment. In addition to the quantification of uncertainties, it is important to consider the expected impact of the (remaining) non-quantified uncertainties on the dietary exposure estimate. These are the conclusions drawn by the RIVM and Wageningen University and Research Centre (WUR) based on a study carried out by these institutes by order of the Dutch Food and Consumer Product Safety Authority (VWA). This report contains a proposal for adapting the current software program (Monte Carlo Risk Assessment) as well as two examples that illustrate the use of the Guideline of the European Food Safety Authority for describing non-quantified uncertainties.

An analysis of the uncertainties in an exposure assessment is necessary to enable a proper interpretation of the assessment results. Uncertainty analysis can also highlight those factors that are the major sources of uncertainty in the dietary exposure assessment. By decreasing (the impact of) the most important sources of uncertainties (e.g. by collecting additional data), (future) exposure assessments can be improved.

The software program currently used by the RIVM and the RIKILT is able to perform a limited quantitative uncertainty analysis. This program could be expanded in a relatively simple manner by including the quantification of a number of other sources of uncertainty.

Key words: uncertainty analysis, dietary exposure, dietary intake, exposure assessment, MCRA

Rapport in het kort

Identificeren van en omgaan met onzekerheden in de beoordeling van blootstelling aan stoffen via voeding

Het RIVM en het RIKILT-Instituut voor Voedselveiligheid schatten hoeveel chemische stoffen mensen via voeding binnenkrijgen. De huidige methode zou meer inzicht moeten kunnen geven in de mate waarin deze blootstellingsschattingen onzekerheden bevatten. Het kwantificeren van onzekerheden sluit aan bij de internationale wetenschappelijke activiteiten die momenteel op het gebied van onzekerheidsanalyse van blootstellingsschattingen gaande zijn. Naast het kwantificeren van meer onzekerheden moet de invloed van de (overgebleven) niet-gekwantificeerde onzekerheden op de blootstellingsschatting worden beschouwd.

Deze conclusies blijken uit onderzoek van het RIVM en Wageningen Universiteit en Researchcentrum (WUR), dat in opdracht van de Voedsel en Waren Autoriteit (VWA) is uitgevoerd. In dit rapport wordt een voorstel gedaan om de huidige software (Monte Carlo Risk Assessment) aan te passen. Tevens wordt aan de hand van twee recente praktijkvoorbeelden geschetst hoe de richtlijn van de Europese Voedselveiligheidsautoriteit (EFSA) toegepast kan worden voor het beschrijven van niet-gekwantificeerde onzekerheden.

Een onzekerheidsanalyse is nodig om de resultaten van blootstellingsschattingen van stoffen beter op hun waarde te kunnen schatten. Bovendien kan een onzekerheidsanalyse aanwijzen welke bronnen van onzekerheid een belangrijke bijdrage leveren aan de totale onzekerheid van de blootstellingsschatting. Door vervolgens gericht de belangrijkste onzekerheden te verminderen (door bijvoorbeeld additionele gegevens te verzamelen) kunnen (toekomstige) schattingen worden verbeterd.

Momenteel kan de software van het RIVM en het RIKILT een beperkte kwantitatieve onzekerheidsanalyse van een blootstellingsschatting uitvoeren. De methode zou relatief eenvoudig kunnen worden uitgebreid met het kwantificeren van een aantal andere bronnen van onzekerheid.

Trefwoorden: onzekerheidsanalyse, blootstellingsschatting, innameberekening, blootstelling, MCRA

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Summary

In the Netherlands, dietary exposure assessments of chemical substances are performed for the Food and Consumer Product Safety Authority at the RIKILT Institute of Food Safety and at the National Institute for Public Health and the Environment. These two institutes use the program Monte Carlo Risk Assessment (MCRA) to derive the dietary intake of substances (De Boer and Van der Voet, 2007). In the MCRA program exposure is estimated in a probabilistic way.

There are a large number of sources of uncertainty in exposure assessment (e.g. chemical analysis of food products, biased sampling, food consumption surveys, modelling usual intake) and the uncertainties can be large. An analysis of these uncertainties is required to enable a proper interpretation of the outcome of an exposure assessment. Hence, a thorough uncertainty analysis can aid policy makers in taking decisions with respect to dietary exposure to substances.

Exposure assessors should strive to assess the relative importance of all sources of uncertainty and at least quantify the most important sources. The current release of the MCRA program incorporates options to quantitatively estimate some types of uncertainty. These are the sampling uncertainties of consumption data and concentration data and specified uncertainty concerning processing factors. In addition, at present some forms of model uncertainty can be investigated by running alternative models or model variants and comparing the outputs. However, the use of the latter is limited as the true model outcome is not known.

It is recommended to extend the uncertainty analysis in the MCRA program. This can be done by taking more sources of uncertainty in dietary exposure assessment into account. Examples for which this can be carried out are the number and size of meal portions, the uncertainty in analytical measurements, the composition of the sample (unit variability) and ingredient percentages in recipes. In addition, subjective expert opinions and probabilistic elicitation techniques may be appropriate to quantify the up-till-now non-quantified uncertainties.

Whereas a fully quantitative uncertainty analysis is the most informative analysis, this cannot be reached due to the high costs. Therefore, qualitative analysis of some of the uncertainties will remain and therefore it is important to consider them. They should be listed, along with the estimated magnitude and direction, preferably according to the tabular format as is proposed by the European Food Safety Authority. Two examples are given in this report. More experience with procedures for qualitative uncertainty assessment is needed.

The quantification of uncertainties is in line with international scientific endeavors (by e.g. EFSA and WHO) that are currently being carried out in the field of uncertainty analysis of exposure assessment.

1 Introduction

There are a large number of sources of uncertainty in exposure assessment of chemical substances (e.g. chemical analysis of food products, food consumption surveys, modelling usual intake) and the uncertainties can be large. The World Health Organization states that uncertainty analysis should be an integral part of exposure assessment (WHO, 2008). A thorough uncertainty analysis allows a proper interpretation of the exposure assessment results and therefore it can aid policy makers in taking decisions on dietary exposure to substances. As uncertainty analysis is not a purpose in itself, but serves as a tool, the level of detail in the uncertainty analysis should be in line with the needs of the exposure assessment (driven by the risk assessment, i.e. what question is addressed?) and the availability of data necessary to execute the uncertainty analysis.

Uncertainty analysis in exposure and risk assessment has received increasing attention in the last decade. Since 2001, NUSAP, a framework in which quantitative and qualitative uncertainty analysis for environmental risk assessment is described, has been developed (www.nusap.net). NUSAP is a notational system which enables the different sorts of uncertainty in quantitative information to be displayed in a standardized way. In this way uncertainties in the information, whether it is a process feature or a numerical detail, become clear.

In 2006, the scientific committee of the European Food Safety Authority (EFSA) prepared a guidance document related to uncertainties in dietary exposure assessments (EFSA, 2006). An example of how this can be applied was provided in an EFSA opinion on acute dietary exposure assessment of pesticide residues in fruit and vegetables (EFSA, 2007). Additionally, in 2008, a guidance document was presented by a working group of the International Program on Chemical Safety (WHO, 2008).

The framework proposed by EFSA and WHO consists of a progression from lower, simpler uncertainty analyses to higher, more complex tiers of uncertainty analyses. Tier 0 consists of a point estimate that is derived with conservative assumptions (and default values). With Tier 1 the point estimate is more refined and an indicative range for the associated uncertainty is given. Tier 2 introduces multiple point estimates based on different combinations of assumptions; the uncertainty in the point estimates can still not be quantified. The last tier encompasses a probabilistic dietary exposure assessment (or semi-probabilistic as the ADI is deterministic). If ADIs are made probabilistic (as for example is done in Integrated Probabilistic Risk Assessment, Van der Voet and Slob 2007; Bokkers et al., 2009) Tier 4 is possible.

In the Netherlands, dietary exposure assessments of substances are performed for the Food and Consumer Product Safety Authority at the RIKILT Institute of Food Safety and the National Institute for Public Health and the Environment (RIVM, Centre of Substances and Integrated Risk Assessment). Subsequent risk assessments of those substances are performed at the RIVM. The RIVM and the RIKILT use the program Monte Carlo Risk Assessment (MCRA) to derive the dietary intake of substances (De Boer and Van der Voet, 2007). In the MCRA program exposure is estimated in a probabilistic way. The current release of the MCRA program incorporates possibilities to estimate some sources of uncertainty, but there are more sources of uncertainty in dietary exposure assessment that may be taken into account. As the confidence intervals reported by MCRA only encompass a limited number of sources of uncertainty, they can give an incomplete impression of (un)certainly.

The EFSA and WHO guidances on uncertainty analysis in dietary exposure give the first methodical guidance to uncertainty analysis in dietary exposure assessment. The present document elaborates on these two reports and specifically addresses the uncertainty analysis of the dietary exposure assessment performed with MCRA. The goal of the present report is to make an inventory of sources of uncertainty

of a population's exposure to a certain contaminant through food intake. Furthermore it is demonstrated how these sources are presently quantified in the computation of dietary exposure with MCRA.

Subsequently, the implementation of additional methods for the quantification of uncertainty in the MCRA program is proposed.

As the present report addresses exposure assessment using MCRA, this document does not address the uncertainty analysis of deterministic exposure (Tier 0, 1 and 2) assessments. In addition this report does not consider the uncertainty in the hazard characterization nor in the assessment of risks associated with the intake of a particular compound.

In chapter 2 of the present report background information is given about the method of dietary exposure assessment and the sources of uncertainty therein. Two important types of uncertainty, namely model uncertainty and model input uncertainty are described in chapter 3 and 4, respectively. Chapter 5 addresses the current methods of uncertainty analyses in dietary exposure assessment. In the final chapters proposals (chapter 6) and conclusions (chapter 7) on the optimal handling of uncertainties in dietary exposure assessment, in particular with the MCRA-program, are described.

2 Uncertainty in dietary exposure assessment

This chapter gives an introduction into dietary exposure assessment as it is performed with MCRA and the sources of uncertainty therein.

2.1 Model for dietary exposure assessment

Conceptual model

The aim of dietary exposure assessment as it is performed at the Centre for Substances and Integrated Risk Assessment (SIR) at the RIVM and the RIKILT – Institute of Food Safety is to obtain the variability in intakes of the population. The first step of the assessment is to obtain data on food consumption by the relevant population and on concentration data of the compound of interest in the consumed foods (Figure 1). Next, it is necessary to link the concentration data with the consumed food products, as the information on the food products which is available in both data sets does not always correspond with each other (e.g. French fries are consumed, but only concentration data of potatoes are available). For this linking process, information on recipes is used. In addition, the processing (peeling, washing, cooking etc.) of food products is taken into account in this step. The final step consists of the multiplication of the consumption and concentration data, and summation over the consumed products on one day of one individual (= a person day), to obtain the dietary intake of this person day. This procedure is repeated for many person days.

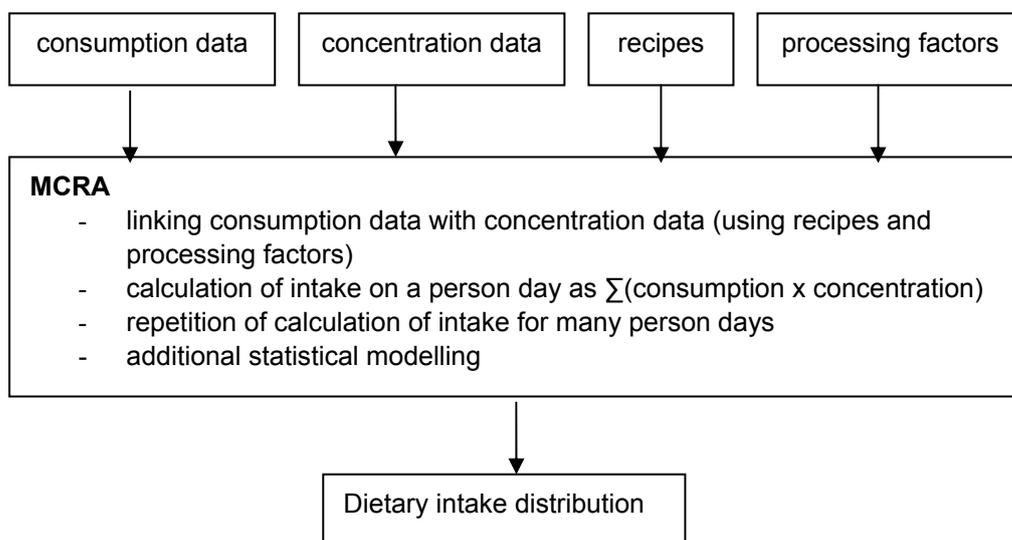


Figure 1. Conceptual model of dietary exposure assessment. Three steps can be distinguished: acquiring consumption data and concentration data, the linking of concentration and consumption data and subsequently the estimation of dietary intake with MCRA, including additional statistical modelling.

In the final step of the assessment, additional statistical modelling is used for different purposes (see below). The steps mentioned above, including the statistical modelling, together form the conceptual model of the dietary intake assessment. This conceptual model is implemented in the computer program Monte Carlo Risk Assessment (MCRA, De Boer and Van der Voet, 2007; De Boer et al., submitted). For this program the food consumption data and concentration data are the two main input datasets. Two other databases, a recipe database and a database with processing factors are used to link the two main input datasets¹.

Statistical models for acute and chronic dietary exposure assessment

For assessing acute exposure MCRA derives the intake of the compound on a large number of days randomly chosen from the set of person-days in the food consumption survey. The program accomplishes this by linking the individual's consumed products to sampled concentrations for this product. So, for each person day (one day of the survey for an individual) the total intake of a compound per kg body weight of this individual is derived by multiplying the consumed amount with the concentration of the product. By performing many iterations (drawing many person days), a dietary intake distribution (many person days for many individuals) is obtained.

For substances that are present in concentrations that exert chronic toxic effects, the distribution of long-term (usual) intakes (per kg body weight) can also be derived with MCRA. Long-term (usual) intake is defined as the average intake of an individual over an unspecified longer time period. Instead of drawing concentrations from a concentration distribution as is done in the acute exposure assessment, the average concentration in the consumed food is used to derive the intake. This is done because the average concentration is considered the best representation of the concentration 'encountered' by an individual in the long-term.

A very simple method is considering the distribution of observed individual mean intakes (OIM method). However, for chronic exposure assessment a translation is often judged necessary from the short-term survey to the long-term. In the Dutch national food consumption survey, the available consumption data consist of two independent 24-h dietary recalls (or records) per individual. As a consequence, the estimated mean consumption over the available days per individual may suffer from a large sampling error and the corresponding distribution of means over individuals obtained with the OIM-method may be too wide in comparison to the distribution of true usual intakes. For that reason, statistical modelling is used to estimate the long-term (usual) intake using the intake on the (two) survey days. Statistical models that are available for this are for example the Iowa State University model for Foods (ISUF) (Nusser et al., 1996; Dodd et al., 2006) and the Betabinomial-normal (BBN) model (Slob 2006; De Boer et al., submitted). These models take the intake frequency into account, i.e. they model that for some compounds the intake does not take place every day, but only on a fraction of days. The OIM, ISUF and BBN models are implemented in MCRA.

The present chapter addresses the sources of uncertainty in dietary exposure assessment. In the following chapters the uncertainty emerging in the model as a whole (model uncertainty, chapter 3) and in the parameters and datasets used in the different steps (model input uncertainty, chapter 4) will be discussed.

¹ Other inputs can be the percentage of a crop that was treated with a compound and the unit variability factor (see also section 4.2.2)

2.2 Uncertainty and variability in dietary exposure assessment

2.2.1 Uncertainty and variability

Data needed to perform a (dietary) exposure assessment usually do not have precise, single values; they contain uncertainty and variability. Variability is an intrinsic property of a parameter and is inherent to the system being modelled, whereas uncertainty represents ignorance or partial lack of knowledge and is thus dependent on the current state of knowledge. As the quality and quantity of the data improves, the uncertainty about their true value decreases (see section 2.2.2), whereas the variability will not decrease or increase with better or more data. There are several options to handle variability and uncertainty in dietary exposure. These are:

1. Only variability is quantified. The estimated exposure is a best estimate of variation in exposure; the resulting distribution can be used to estimate the exposure for different percentiles of the population but provides no confidence intervals.
2. Variability and uncertainty are quantified but not kept separated. The estimated exposure distribution can be used to set uncertainty limits on the exposure for a randomly chosen individual, but it gives no correct estimate of the population distribution itself, and therefore does not allow proper estimates of percentiles.
3. Variability and uncertainty are quantified separately. The output represents the exposure estimates for different percentiles of the population (variability), together with confidence intervals (uncertainty).

The use of option 1 is discouraged as it gives no impression of (un)certainty. Option 2 is also discouraged when reporting on risks for the population is the issue. Therefore, for high tier assessments as carried out in MCRA, option 3 is preferred.

2.2.2 Sources of uncertainty in dietary exposure assessment

Sources of uncertainty in exposure assessment can be roughly classified in three categories as indicated by the WHO harmonization project on uncertainty in exposure assessment (WHO, 2008). These three broad categories of uncertainty are scenario uncertainty, model uncertainty and parameter uncertainty.

- Scenario uncertainty: uncertainty in specifying a scenario that represents the use (e.g. consumption) of the product.
- Model uncertainty: uncertainty in the capability of the conceptual and statistical models to represent the scenario; gaps in scientific knowledge can hamper an adequate capture of the correct causal relations or correlations between inputs of the model (e.g. the relation between consumption frequency and consumption amount).
- Parameter uncertainty: uncertainty in the (input) data (e.g. concentration, consumption and processing data)

Classification of uncertainty using these three broad categories is not as strict as it may seem; in practice the uncertainty may arise from overlapping categories. For example, a calibrated model parameter fitted against a data set suffers from uncertainty in measurement (parameter uncertainty) as well as incompleteness of the model (model uncertainty).

The categorization used in the present report is a further specification of (and partially an amendment on) the classification proposed in WHO (2008): we prefer the term ‘purpose uncertainties’ to ‘scenario uncertainties’ because scenarios may also concern different input data. In addition, we prefer ‘model input uncertainty’ to ‘parameter uncertainty’ because in probabilistic modelling of dietary exposure

there are both data sets (concentration data, consumption data) and parameters (e.g. fraction of ingredient in a food) as model inputs, and for an uncertainty analysis these inputs should be treated similarly. On the other hand, we feel that bias and precision of model inputs should often be treated in different ways, so we have separate categories ‘model input bias uncertainty’ and ‘model input precision uncertainty’.

On this we base a main classification of uncertainties for probabilistic dietary exposure assessment:

1. Uncertainties regarding the purpose of the exposure assessment

Probabilistic dietary exposure assessment is performed using a statistical model to derive one or more specific outputs (e.g. a percentile of the exposure distribution or the probability to exceed a limit value). For an uncertainty analysis to be performed it is essential that these output variable(s) are clearly defined. For example: Is the assessment to be made for a population of persons or for person days? Is the interest in p95, or p99 or any other percentage? Is the interest in the cumulative effect of a group of compounds, or of a specific compound? Should metabolites be included? Is it internal or external exposure? For which population do we want an answer (time, space, age classes), e.g. Dutch children 1-6 years in 2008 or Dutch children 1-6 years 1997/98? Should exposure be modelled as a function of covariates (e.g. age) or overall?

Uncertainties regarding the purpose of the exposure assessment are not further discussed in this document as such uncertainties should be eliminated in collaboration between risk assessors and risk managers before the exposure assessment is started.

2. Model uncertainties

Different models may be chosen (at different levels of the intake assessment). Conceptual models may be different either in structure (e.g. estimation of dietary intake by multiplication of consumption and concentration vs. chemical analysis of 24 h duplicate diets², different statistical models for the derivation of usual intakes) and/or in level of detail (which foods are coded for consumption and concentration data? Is processing included?).

To clarify how model uncertainties are different from model input uncertainties (category 3 below) we can envisage an ideal data situation, where all (conceptual) model inputs would be exactly known, say because enormously large error-free databases on each relevant aspect (consumption, concentration, linking, processing, etcetera) were available. There would then still be remaining uncertainties due to the choice of a specific statistical model (e.g. results of ISUF and BBN models could be different due to different assumptions in both models). Thus the category ‘model uncertainty’ contains all remaining uncertainties when optimal data would be available.

Model uncertainties can be partly assessed in sensitivity analyses³ using alternative models; in the software there could be alternative options to investigate this. For example, in MCRA one can choose either the ISUF or the BBN model. Note that the comparison of two unvalidated models could be misleading: Even if the models agree, they may be subject to the same biases, or they may give the same results for different reasons. However, comparing two models is the best option when there are no validation data. It may be helpful in identifying errors in the structure of the model, the computer code

² 24 h duplicate diet: A duplicate sample of all food which has been eaten by an individual during a 24 h period is collected and pooled into one composite sample in which compounds are measured.

³ In a sensitivity analysis the susceptibility of a model is determined by detecting changes in the output when the value of an input parameter is changed (or when an alternative model is being used). A sensitivity analysis is not equal to an uncertainty analysis: the latter consists of an estimation of the total uncertainty of the model output, based on an evaluation of the input uncertainties. However, partitioning the total uncertainty into contributions from several inputs is commonly called sensitivity analysis.

or the model inputs (See Cullen and Frey, 1999). Chapter 3 will describe model uncertainty in dietary intake assessment in more detail.

3. Uncertainties in model inputs

These can be divided in the bias and lack of precision of model inputs.

3a. Bias

Model inputs may be biased (i.e. they have a tendency towards being either too high or too low) (see Figure 2) and therefore not represent the true state of nature. Of course, if such biases are known quantitatively, then a correction procedure can be included in the model, and only the uncertainty of this correction would remain (as a contribution to category 3b, see below). But generally objective quantitative information about the size of the bias is not known. (An exception may be for analytical measurements, for which the use of internal standards and quality control may quantify the bias). When bias cannot objectively be quantified, it should be assessed by expert judgment.

3b. Lack of precision

Model inputs may have a limited precision (Figure 2). Datasets may be small, and parameter values may be obtained from limited information. Note that the set of parameters may include correction factors introduced in the model to avoid biases. For example, a factor for ‘percentage non-treated’ may be used to avoid that all non-detect pesticide concentrations are replaced by small values such as the limit of detection (or half the value of the limit of detection as often is performed). Lack-of-precision uncertainties are in principle open to data-based quantification in software, but expert judgment may also be needed. For example, several studies on the same processing factor may give different results, and the variation between the results may be used as a quantification of the uncertainty. In other cases, only one estimate for a processing factor may be available necessitating the use of an expert opinion on its uncertainty.

Our classification separates the uncertainties which can in principle be quantified in the software, at least partially (category 2 by having multiple options, category 3b in the estimation itself), from uncertainties that should be addressed before performing the exposure assessment (categories 1 and 3a). Note that quantitative corrections for the analytical measurements need to be performed before the MCRA-program is run.

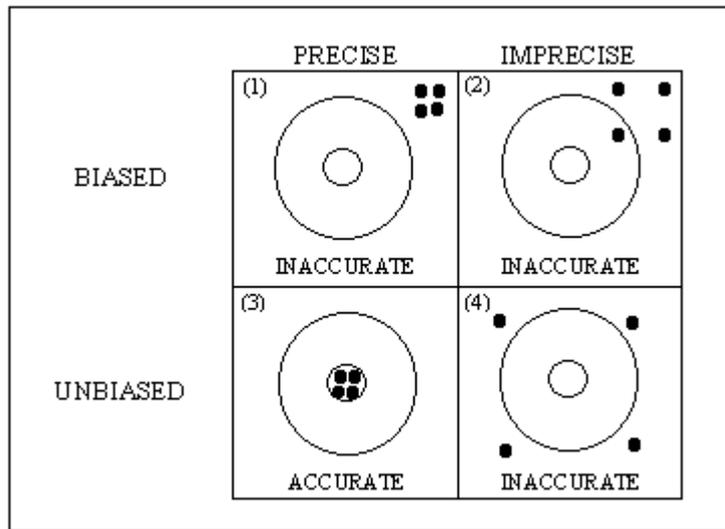


Figure 2. An example of bias and precision. Four gun shots at a target can be inaccurate due to e.g. a biased gun and/or an imprecise shooter.

The uncertainties in model inputs will be addressed in chapter 4.

3 Model uncertainty

Here we give a list of model uncertainties as mentioned in WHO (2008), and provide some specific points of attention for dietary exposure assessment as we perform it by the four steps mentioned above and using the MCRA program.

3.1 Conceptual model boundaries

Results of dietary intake assessments using MCRA are uncertain if MCRA is applied for situations other than dietary acute or chronic exposure assessment. Cumulative exposure assessment can be done by prior application of ‘relative potency factors’ (RPFs), such as toxic equivalency factors (TEFs) for dioxins, to the concentrations of individual compounds followed by an MCRA analysis of the weighted sum. Nevertheless, this is only possible if the compounds have the same mechanism of action and parallel dose-response curves. The determination of the RPFs is based on experimental data and therefore contains uncertainty. Because with the current version of MCRA the weighing has to be done outside the program, these uncertainties cannot be accounted for. In addition, working with the weighed sum in probabilistic calculations amounts to drawing from only one distribution of concentrations (for the index compound), and therefore drawing for example a high value from this distribution amounts to drawing a similarly high value for all individual chemicals. Clearly, this absolute correlation among chemicals in a sample is unrealistic and leads to uncertainty about the estimated exposure distribution.

3.2 Statistical model dependencies

In dietary exposure assessment in which consumption is multiplied with concentrations, independence of consumption of foods and concentration in those foods is assumed, which is considered a reasonable assumption in general. However, there may be exceptions, such as avoidance of allergenic compounds by allergic consumers, or avoidance of food which shows the signs of decay connected with the presence of certain compounds.

In chronic risk assessment, there is an uncertainty in the estimation of intakes by MCRA because possible dependencies between intake frequency and intake amount are not accounted for. In acute risk assessment, concentrations of a compound in multiple foods are assumed to be independent, which is uncertain to be true under all circumstances. Processing factors are modelled as fixed values or by distributions. In the case of distributions no dependencies are included in the model.

3.3 Conceptual and statistical model assumptions

In the conceptual model it is assumed that the intake can be estimated by multiplication of consumed amount of a food and the concentration measured in this (or sometimes a similar) food, using recipes and processing factors to estimate the concentrations in food products that are not analyzed themselves. In acute risk assessment not many additional model assumptions are made: the exposure assessment relies on a direct Monte Carlo resampling of individuals with their associated body weight and consumption pattern, and measured concentrations for each of the consumed foods. Uncertainty may arise from specific parts of the model. First, when concentration data are made in composite samples, a model is needed to estimate concentrations in single units. Uncertainty arises because there are various options for this model and of course none of these may capture the true situation.

In chronic exposure assessment more assumptions have to be made, which may not represent reality well. First of all, for the estimation of the long-term (usual) intake, the assumption is that a transformation to a scale can be made where the intake can be represented as an additive model. This means that the intake is represented by the sum of a general mean intake and two deviation terms: the individual deviation and the person-day deviation. The former addresses that the mean intake of an individual's intake over a large number of days deviates from the overall mean intake in the population, whereas the latter represents that the intake on any day for an individual deviates from that individual's mean intake.

For chronic exposure assessments the BBN and ISUF models are implemented in MCRA. The BBN model assumes that the usual intake amounts are normally distributed after a logarithmic or power data transformation (i.e. $y = \log(x)$ or $y = x^\lambda$, respectively). The choice of transformation is a source of uncertainty in itself. Normality may not be achieved, so the assumption of normality may not be always correct. The ISUF model is designed to generate normality at a transformed scale by the use of an additional spline⁴ transformation (so here an assumption is not made). Nevertheless, the assumption in ISUF is that the additive model mentioned above is still correct on this highly artificial spline-transformed scale⁵. Preliminary results of studies with real and simulated data seem to suggest that the assumption may not always hold (De Boer et al., submitted; Slob et al., submitted), leading to a large uncertainty.

The dependency of the chronic exposure on covariates (e.g. age, sex) is modelled. There are several possibilities to model the dependency on continuous covariables such as age, for example polynomial⁶, exponential or spline functions. There is uncertainty concerning the choice of the appropriate function for modelling the dependency on covariables, but it is generally considered low.

In the final step of the dietary exposure assessment the short-term intake is derived by the multiplication of the concentrations and the consumption amounts of the consumed foods on one day. MCRA performs this by drawing an individual from the survey, combining his or her consumption

⁴ spline: a spline is a special function defined piecewise by polynomials

⁵ this is necessary because the statistical analysis on this normal scale used for deriving the usual intake distribution relies on this additive model

⁶ a polynomial is an expression constructed from variables and constants, using the operations of addition, subtraction, multiplication, and constant non-negative whole number exponents. For example, $x^2 - 4x + 7$ is a polynomial, but $x^2 - 4/x + 7x^{3/2}$ is not, because its second term involves division by the variable x and also because its third term contains an exponent that is not a whole number

with a drawn concentration from the concentration dataset (NB in a chronic assessment: average concentration) and sums the intakes via the different approaches on one day.

3.4 Conceptual model detail

Many aspects of the real world are not represented in the model, although in principle this could be done if sufficient data are available. Most importantly, in MCRA the level of detail used in the coding of food products can be increased indefinitely, but in practice it is not useful to extend this list to a level of detail where no data are available. For example, MCRA can distinguish brands of food with their corresponding market shares, and in a future release a model for brand loyalty will be included, to give a more accurate intake estimate. Nevertheless, this is only useful when concentrations of substances are different in different brands and when information on market shares and brand loyalty is available.

3.5 Conceptual model extrapolation

Uncertainty arises when a model is used outside the intended domain of application. For example, MCRA is intended for the estimation of external exposure (intake rather than uptake), and cannot predict internal exposure or blood concentration-time curves.

3.6 Conceptual and statistical model implementation

Although new versions of MCRA are validated against the previous version (see for an example Appendix 1), implementation of models in software always runs the risk of programming errors that only become apparent for certain scenarios and input combinations. Apart from programming errors some of the algorithms⁷ need a certain data quality and quantity. The algorithms may give erroneous results when a model is fitted to too few or scattered data. For example, for the estimation of the usual intake the variation between days is needed. It is questionable if data on just 10 individuals having a positive intake on 2 days is sufficient to derive the variation. Such uncertainties may be examined by comparing results of MCRA to results of alternative programs or by performing simulation studies (see section 5.1.1).

3.7 Using other conceptual models

In the previous sections we considered a specific conceptual model and the uncertainty connected with that model. Alternatively, another conceptual model can be applied to assess the uncertainty of the conceptual model as implemented in MCRA. For example it is possible to assess dietary exposure in a different way than by combining regular consumption data with concentration data by performing a

⁷ an algorithm is a sequence of instructions, often used for estimation and data processing

duplicate diet study. In a duplicate diet study 'real' exposures of a number of participants are measured, whereas in dietary exposure assessment as described in chapter 2 the exposure of a number of individuals is estimated by combining concentration data with consumption data.

4 Model input uncertainty

In this chapter we consider the uncertainties related to inputs of the conceptual model. The model inputs are subdivided in consumption data (section 4.1), concentration data (section 4.2) and the linking of consumption with concentration data, including processing factors (section 4.3).

4.1 Uncertainty in consumption data

In this section we discuss how consumption data may give a biased assessment of true consumption (section 4.1.1) and how the amount of consumption data may give rise to a lack of precision about knowing the true food consumption (section 4.1.2).

4.1.1 Bias in consumption data

Method of data collection

There are several methods to record the consumption: dietary recall, dietary record, household budget surveys, et cetera. In dietary exposure assessments in the Netherlands, data of the Dutch National Food Consumption Survey are often used.

The third Dutch National Food Consumption Survey (DNFCS 3) is the most recent population-wide food consumption survey. It is a dietary record study that contains the consumption data of 6250 individuals for two consecutive days (Kistemaker et al., 1998). Note that DNFCS 3 is already ten years old. The data in DNFCS 3 may provide a biased estimate of the current consumption pattern. At present, a new population-wide survey is performed, which will be finished in 2010.

In 2005 and 2006 a consumption survey on young children (2-6 y) has been performed. In this survey food consumption data was also collected using the dietary record method. In this approach caretakers of the children completed a detailed diary about all the foods and drinks consumed on two non-consecutive days by 1279 children (Ocké et al., 2008).

The methodology of dietary records is regarded as the best available method to assess individual dietary eating habits. The obtained data are suitable to assess the acute and chronic dietary exposure to compounds. However, this method may underestimate consumption levels due to high participation burden (Biró et al., 2002).

Another disadvantage of food consumption surveys is that habitual eating patterns may be influenced or changed due to the recording process. As a consequence the estimation of the exposure may be biased. For example, due to the unhealthy image of crisps and French fries the consumption of these foods may be underreported resulting in an underestimation of acrylamide intake. On the other hand, foods that are known to be healthy like fruits and vegetables may be eaten more on recording days than in practice, which may result in an overestimation of the intake of pesticides. The extent in which eating habits are changed due to the recording process and consequently the effect on the derived exposure levels is unknown.

In the DNFCS Young Children the data was checked on over- and underreporting by deriving the energy needed for basic metabolism. This showed that there was no discrepancy between energy demand and reported intake in the children's survey (Ocké et al., 2008).

There may also be alternative ways to gather consumption data. In the DNFCS the consumption is studied using dietary records or recalls. With these methods, participants evaluate their consumption on one day at a time, specifying the portions. In addition to the record or recall, participants are asked to complete food frequency questionnaires (FFQs) in which the frequency of the consumption of specific products is inquired (e.g. every day, once a week, once per month). In this method, emphasis is put on the consumption behaviour in the long run and not on the precise portion on one day. A dietary exposure assessment based on FFQs may therefore be an interesting different conceptual model for Step 1, especially when the assessment considers foods that are not frequently consumed. However, FFQs will not comprise the whole range of consumed foods, as this is unfeasible. The use of FFQs as an alternative for dietary records or recalls will therefore only be functional for cases in which a limited number of products, present in the FFQ, is relevant for the dietary intake of a substance (e.g. fish, relevant for the intake of e.g. mercury).

Another method to obtain information on food consumption is the household budget survey. This survey provides descriptions of an individual household's total consumption and expenditures in relation to characteristics of the household (e.g. size, composition, income), its accommodation and durable goods. However, the detail of a household budget survey considering food consumption is too low for a realistic dietary intake assessment.

Population

The participants of the DNFCSs are randomly chosen from (internet) panels from marketing research agencies. However, these panels are likely not representative for the Dutch population as a whole. The bias of the population of participants may be reduced by using weighing factors, giving a larger weight to individuals belonging to social-economic classes which are underrepresented in the survey. The use of weighing factors is not implemented in MCRA yet, but this is planned. It may be possible to address uncertainties about these weighting factors if such information is available.

People who do not speak Dutch are excluded from the surveys. Since this cannot be overcome by using weighing factors, the estimated consumption pattern is biased.

Survey days

To obtain an unbiased consumption data set regarding sampling moment DNFCS 3 and DNFCS-Young Children are evenly spread over the whole year and the days of the week. Holidays and anniversaries are excluded from the data. Note that this may cause bias, especially if one is interested in foods that are often consumed on these days.

4.1.2 Lack of precision in consumption data

Number of consumers in the survey

Consumption surveys only sample a small part of the relevant population. For example, in DNFCS 3 there are 6250 persons to represent a Dutch population of around 16 million. The fact that the sample has only a limited number of persons results in a sampling uncertainty of the dietary exposure. Generally, the sampling uncertainty is considered to be small in comparison to other uncertainties. In the case of long-term exposure assessment the limited number of days per person that are sampled leads to an additional imprecision in these data: With only two days per person, as in the DNFCS, the observed individual means will have a large sampling error (this is the reason to apply statistical modelling to translate the observed distribution to a better estimate of usual intake). Moreover, the consumption on two consecutive days (as in DNFCS 3) is probably not independent: on the second

survey day participants may consume left-overs from the first day. A dietary survey on two non-consecutive days, as in DNFCs-Young Children, will therefore give a better representation of reality.

Consumption frequency

Uncertainty in the food products' consumption may also reside in the percentage of consumers with a positive intake and the frequency of consumption per consumer. Basic food is consumed by a large fraction of the population frequently and the information regarding the intake frequency included in the DNFCs are relatively accurate (Figure 3). Another category of products are the special foods, which are consumed by a large fraction of the population at low frequency, such as wine. As the food consumption surveys consist of a small number of days, many of the more specific foods will not be consumed in these two days and are reported as 'zeroes'. Hence, the precision of the information on intake frequency of these special foods is less than for basic foods (Figure 3). A third food category contains the so-called niche foods, which are consumed by a very small fraction of the population. Examples are oyster, eel, couscous. The intake frequency of these foods is too low to perform a reliable intake estimation with DNFCs data (see also section 3.6 on model implementation).

Although there may be large uncertainties regarding the consumption frequencies of single foods, it should be noted that the ISUF and BBN models in MCRA use the intake across foods (total diet approach), so that uncertainties about single foods may be less relevant. It is unknown in how far the lack of information on specific foods is relevant for the percentiles of the total intake distribution. Probably this will vary from case to case. The long-term risk models estimate the percentage of 'incidental zeroes' (persondays without relevant consumption) and the ISUF model also estimates the percentage of non-consumers (persons never eating the relevant foods). However, the uncertainty about consumption frequencies is not well-known.

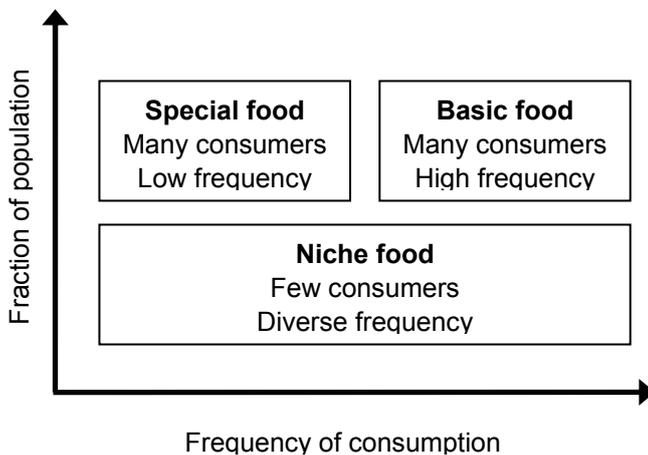


Figure 3. Three categories of food products, classified by fraction of population and frequency of consumption. (Adopted from Bakker, 2002).

Consumption amounts

There is also uncertainty on the reported amounts of consumed foods. Whereas this uncertainty is currently usually not quantified, work is ongoing to make this more explicit (e.g. in the EU-project of Food Consumption Validation (<http://www.efcoval.eu>)). For example, using the EPIC-SOFT software

interviewed consumers are guided through several choices, and several quantification methods can be used, such as choosing from a series of photos showing different amounts of a certain food or specifying a proportion of a household measure (e.g. half a bowl of yoghurt). In general, there will be uncertainty about standard portion sizes and about the number of these standard portions consumed.

4.2 Uncertainty in concentration data

The second step of a dietary exposure assessment consists of the estimation of the compound's concentration in food. The available monitoring data need to be collected or a sampling program needs to be designed to obtain a representative data set on concentrations of the compound in foods consumed by the general population.

Sources of uncertainty in the determination are the sampling uncertainty, uncertainty due to combining samples before, and the analytical error. Both can have components of bias and of lack of precision.

4.2.1 Sampling uncertainty

One of the uncertainties in the sampling of foods is: how well do the sampled foods reflect the foods consumed by the population? This depends on the variability of the concentration in the foods and the bias. When the variability of the concentration is low, a high precision can be reached with a small sample size, whereas for a large variation the sample size needs to be large to yield a precise concentration distribution. An insufficient number of samples will result in an imprecise definition of the concentration distribution (see upper right panel of Figure 4). In theory, it is possible to reduce the uncertainty associated with sampling uncertainty by taking more samples. However in practice this is very expensive.

Besides the sample size, it is important to sample the whole range of occurring concentrations.

Targeted (or biased) sampling of food products, whether on purpose or not, will result in a distribution weighted by the higher concentrations (see lower left panel of Figure 4 and Boon et al., 2008). As a result the dietary intake, both acute and chronic, will be overestimated. The bias of the sampling procedure is hard to quantify *a posteriori*. The uncertainty associated with the sampling procedure could possibly be assessed by expert judgement.

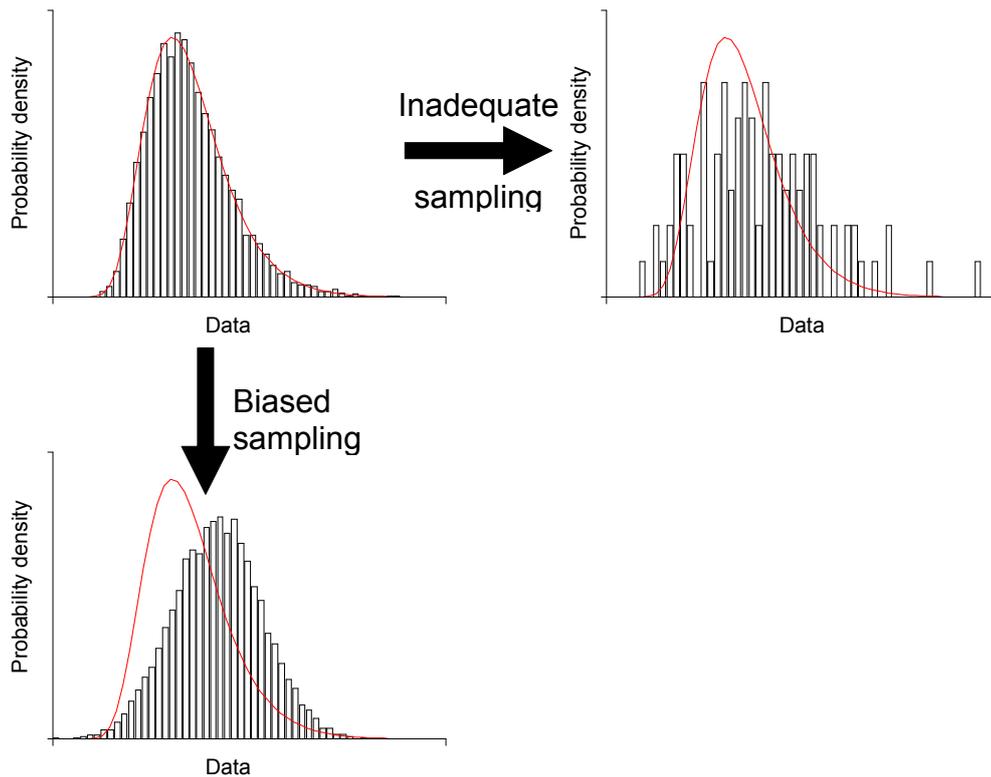


Figure 4. A graphical representation of imprecision and bias of concentration data due to a poor sampling strategy. The true, but unknown probability distribution of the concentration data are represented by a line, which is identical in each figure. The distribution of the measured concentration data is indicated by bars. The upper left panel indicates a precise and unbiased sampling of the concentration data.

Two different sampling strategies to obtain concentration data are currently used: a monitoring strategy to assess whether concentrations in food products are compliant with legal limits (for e.g. pesticides, mycotoxins) and a sample strategy which aims to derive concentration data for dietary exposure assessment. The latter strategy can be sub-divided in sampling single foods (as is performed for e.g. acrylamide, see Boon et al., in preparation) and sampling of composite food groups or units (as is done for e.g. brominated flame retardants, Bakker et al., 2008). To analyse the uncertainty of the different sampling strategies, one would need to perform more than one ‘sampling strategy’ for one compound. E.g. compare sampling of single and composite foods, or samples purchased from the supermarket with monitoring data from the Food and Consumer Product Safety Authority. However, as chemical analysis of foods is expensive, applying multiple sampling strategies to assess the concentration uncertainty is mostly not feasible.

Limited set of food products sampled

The concentration of the compound is only measured in a limited set of food products. The choice which products are incorporated in the measurements is made by experts. The experts, sometimes supported by previous studies or pilot studies, select products that are known to contain high concentrations of the contaminant and/or are a large source of possible intake. The food products that are not selected are assumed to contain no (high) contamination. This assumption introduces an uncertainty which is very difficult to quantify.

Age and timeframe of dataset

For dietary exposure assessments a recently obtained concentration dataset is preferred over an (out)dated one. This is especially true for foods which have varying concentrations of compounds in products over the years (e.g. dioxins). Furthermore, the time period in which the samples are collected may be relevant. For example, the formation of mycotoxins on food products is dependent on weather conditions and concentrations of these compounds vary from year to year. To estimate the long-term exposure, an (unbiased) average concentration is needed which reflects this long-term. Therefore, it is recommended to use samples from a range of years.

4.2.2 Uncertainty due to composition of samples

Samples of multiple food units

In most dietary intake assessments, samples are pooled, i.e. they consist of more than one food product 'unit' (more than one apple, one carton of milk etc). Using these so-called composite samples instead of individual samples introduces uncertainty because several units are taken together in one sample (and the concentration of one unit is not known). The variation in concentrations between composite samples is lower than the variation in the concentrations between the individual samples.

There is a difference in the application of composite samples between acute and chronic dietary intake assessment. This is caused by the fact that for acute intake assessment the whole distribution of concentrations is taken into account, while for chronic intake assessment the average concentration is sufficient to determine the long-term (or usual) intake distribution.

For example, an high concentration of a given pesticide on a batch of apples is diluted with low concentrations in other batches of apples. In acute risk assessment, the interest is in the total variation. So, to account for the variation among the apples a procedure is needed to 'decompose' the composite-sample concentrations to values to be expected for single units. In traditional deterministic exposure assessment a so-called (default) variability factor is used to compute a possible value for the acute dietary intake. The variability factor is defined as the 97.5th percentile divided by the mean of the concentration distribution of single unit concentrations. But since this distribution is not known for composite samples, a default value is used for the variability factor (often 3 or 7). In probabilistic assessment of acute risk (in MCRA) one of several distributions (beta, lognormal, Bernoulli) can be chosen to represent unit variability. Given variability factors, and specifications of the number of units in a composite sample and of the unit weights, are used to define parameters for these unit variability distributions (see De Boer and Van der Voet (2007) for details). All required inputs to derive the variability distribution can be uncertain, and therefore can contribute to the total uncertainty in the outputs of dietary exposure assessment.

In case of a chronic dietary intake assessment, modelling of unit variability is not used, as the average concentration is used in the estimation of the intake distribution.

Samples of multiple food products.

In chronic dietary intake assessments, to reduce costs, occasionally composite samples composed of multiple different food products are collected in order to measure the concentration of a whole group of products at once. In this case, information on the variation between the concentrations in the different products is lost.

For example, in the intake assessment of dioxins, several types of beef (meat loaf, roast beef, among others) are combined into one sample (beef), according to the proportions in which these products are consumed in the food consumption survey. The resulting concentration is an average concentration in beef (expressed per g fat). This value is then used to compute concentrations in individual beef products, using the fat concentration of these products (for example: concentration in meat loaf (per g

product) = concentration in composite beef sample (per g fat) × fat fraction of meat loaf (g fat/g product).

The assumption made here is that the (lipophilic) dioxins are all in the fat fraction of the food products. However, this assumption was never validated and therefore is a source of uncertainty.

4.2.3 Analytical uncertainty

Inter/intralaboratory variation

A second step in the determination of the food product's concentration is the chemical analysis of the substance. The analytical reproducibility variance represents the uncertainty associated with the imprecise sample preparation and analytical method in the sample's compound concentration value. The sample preparation and analysis of the samples vary among laboratories and it is uncertain if a lab (and if yes, which lab) determined the true value. The variation introduced should be specified by means of the interlaboratory measurement uncertainty. In addition to that, laboratories often report an intralaboratory uncertainty (which is in general smaller than the interlaboratory uncertainty). The inter/intralaboratory variation should be incorporated in the uncertainty analysis of dietary exposure assessment. Laboratories under accreditation schemes are obliged to have a measurement uncertainty estimate for their reported analytical results (ISO 17025). If still no information regarding the (inter/intra)laboratory variation is available a generally accepted empirical model to estimate the interlaboratory variation is the Horwitz curve (Horwitz and Albert, 2006; Thompson, 2007). The Horwitz curve depicts an empirical relationship between the relative standard deviation of reproducibility (RSD_R) and the concentration given by:

$$RSD_R = 2^{1-0.5\log_{10}(C)} = 2C^{-0.5/\log_{10}(2)} \approx 2C^{-0.15}, \quad (1)$$

where C is the concentration in mass fraction (g/g). The curve is more or less independent on analyte, matrix, method and time of publication for concentrations ranging from 10 pg/g to 0.1 g/g (Thompson 2007).

Reporting limits

At relative low levels analytical measurements become less precise. The limit of quantification (LOQ) is often defined as the level where the precision becomes less than a certain value, e.g. $RSD_R < 30\%$. The limit of detection (LOD) is the lowest concentration of a compound that can be reliably distinguished from the absence of that compound (commonly when the peak is 3 times the background noise).

In practice, laboratories frequently suppress the reporting of quantitative values below a certain limit value, which has no clear status, and instead they only report results as 'less-than' or non-detect. Such a limit is simply called the limit of reporting (LOR). Instead of just reporting the number of samples $< \text{LOR}$, for dietary exposure assessments it would be helpful if analytical laboratories would report as many quantitative results as possible, with an indication of the increased measurement uncertainty for samples $< \text{LOD}$ or $< \text{LOQ}$. This would reduce the uncertainty in the concentration data.

In dietary exposure assessments, values below LOR are often substituted by zero, $0.5 \times \text{LOR}$ and/or LOR. The two extreme scenarios (zero and LOR) give an idea of the variation between the best-case and worst-case scenarios. Another way to deal with non-detects is to model the distribution of the samples below LOR based on the concentration distribution above LOR. Several methods have been used: parametric (distribution-based) methods like the maximum likelihood estimation (MLE) and non-parametric methods like the Kaplan-Meier method (see for an evaluation of these methods Hewett and Ganser, 2007; Antweiler and Taylor, 2008). In dietary exposure assessment of e.g. pesticides it may be necessary to model the data as a mixture of true zeroes and a lognormal distribution of positive

concentrations, which is partly unobserved due to censoring of values below LOR (Van der Voet and Paulo, 2004; Paulo et al., 2005).

In 2008 the European Food Safety Authority established the Working Group on Left-Censored Data to investigate the use of different methods to handle non-detects. This Working Group will report their findings in the summer of 2009. In addition, a statistical method to handle non-detects will be implemented in MCRA by the end of 2009.

4.3 Uncertainty in linking consumption and concentration data

The concentration and consumption data need to be combined in order to calculate the dietary intake. However, the information available in both data sets does not always correspond with each other (e.g. concentrations of a substance are available in wheat, but this is consumed as bread and pasta). As a result, the measured concentrations often need to be manually linked to the consumed products, and this is a source of uncertainty (section 4.3.1). As concentrations are often measured in raw agricultural commodities a further source of uncertainty concerns the specification of processing factors which relate concentrations in food-as-consumed to concentrations in food-as-measured (section 4.3.2).

4.3.1 Different types of linking

The concentration and consumption data need to be combined in order to estimate the dietary intake. However, the information available in both data sets does not always correspond with each other. As a result, the measured concentrations often need to be manually linked to the consumed products. Several linking types can be distinguished:

1. direct link between measured and consumed product (e.g. measurement in milk, consumed product milk);
2. link between measured product and a similar consumed product (e.g. measurement in milk, consumed product chocolate milk);
3. link between measured product group (e.g. in case of composite samples) and consumed product of this group (e.g. measurement in beef, consumed product: roast beef);
4. link between measured product and ingredients of consumed product (e.g. measurements in wheat and apples, consumed product apple pie). If the concentration is available in the individual ingredients of the consumed food product, these concentrations together with the weighted fraction of the ingredients can be combined to estimate the concentration in the consumed food product (e.g. apple pie is divided in milk (5.8 %), eggs (12.1 %), wheat (14.5 %), apple (58.1 %) and sugar (10.7 %). The conversion model for primary agricultural products, CPAP (Van Dooren et al., 1995) contains weighed fractions of raw agricultural commodities (RACs) for all foods consumed in the DNFCs;

Link type 1 contains the smallest uncertainty. The uncertainty in link types 2 and 3 depends on the similarity of the consumed product with the measured product (group). Note that the level of detail of information about the food products is often higher in the food consumption survey than in the concentration data. In link type 4 the uncertainty depends on the variation of the composition of the product and the number of ingredients (uncertainty increases with the number of ingredients). The current version of MCRA has an elaborate system to link food codes (see De Boer and Van der Voet 2007 for details), but there is no quantification of uncertainty in the weight fractions. For example, using CPAP, foods as eaten are converted to a weighed fraction of a certain ingredient per food. Weighed fractions very likely vary, so there is uncertainty whether the correct fraction is used.

In general, consumption data contain more detail than the concentration data. Whereas the DNFCs provides detailed information on the consumed foods (e.g. raw and cooked vegetables have different food codes, for beef there are more than 20 different food codes varying from meatballs to steak), the information about the analysed foods is often limited to a crude food category (e.g. pulses, beef). If the concentration data would be more detailed, the uncertainty in the linking process would be reduced.

The linking of consumed food products to measured ones is a 'subjective' process. This means that different experts will make different links, and therefore the exposure assessments will likely have different outcomes. To assess the uncertainty in the linking process it is recommended to use different ways of linking and see how it affects the result. Note that, as the true result is unknown, it is unclear which way of linking is the best, but at least the sensitivity to this factor is being shown.

For example, in Boon et al. (in prep.) concentration data of aflatoxin B₁ were available for a number of different nuts (e.g. walnuts, pistachio nuts, almonds, cashew nuts), whereas concentrations for peanuts were not. In the linking process consumed peanuts were linked to a concentration that was the (weighed) average of all nuts. However, the pistachio nuts had higher concentrations (about a factor of 10) than the other nuts. So, linking the peanuts to the pistachios would have resulted in a higher exposure, while linking the peanuts to e.g. almonds would have resulted in a lower exposure. It may not be known if one of the nuts can be regarded as surrogate, and if so, which one is the best 'surrogate' for peanut. However, it is recommended to study the effect on the exposure of the different ways a concentration can be assigned to peanut.

4.3.2 Processing factors

Almost all contaminants' levels are influenced by food processing. In food processing, the absolute amount of the compound is changed. For example cooking, frying, washing, and other processing can reduce the content of the contaminant in the product. In some rare cases food processing can increase the amount, e.g. when fungi or yeast are producing toxins during storage. Amounts are often measured in raw agricultural products. Hence, the influence of processing needs to be taken into account by using food processing factors, obtained from literature. The data regarding food processing factors are generally scarce and if available often highly variable; this introduces an uncertainty in the concentration data.

In MCRA processing effects can be accounted for in two ways:

1. In the simplest possibility fixed values are given to represent the change in concentration for certain combinations of food and processing.
2. In a more elaborate model it is recognised that processing effects may be variable. For example, apples may be washed differently on different occasions, and consequently the concentration of residue may be diminished more in some occasions and less in other occasions. In MCRA a statistical distribution can be specified to describe this variability (see Appendix 2).

In MCRA the uncertainty about the processing factors is modelled by introducing uncertainty distributions for either the fixed processing factor or for parameters of the variability distribution described above (see Appendix 2 and Van der Voet et al. (2009) for a more detailed discussion of these uncertainties).

5 Analysis of uncertainty in dietary exposure assessment

Uncertainty analysis of dietary exposure assessment will always reveal two categories of uncertainty: Uncertainties that are quantified and those that are not quantified but qualified. The analysis of statistical model uncertainty (quantified and qualified) will be described in section 5.1, while section 5.2 addresses quantified and qualified model input uncertainty. Examples of qualitative uncertainty analysis of two recent dietary exposure assessments are given in section 5.3

5.1 Analysis of model uncertainty

5.1.1 Quantitative analysis of model uncertainty

The long-term intake is derived using a statistical model. In MCRA, three statistical models (OIM, BBN and ISUF) are implemented. By applying multiple models the model uncertainty is addressed (See for examples Waijers et al., 2004; De Mul et al., 2005). In an appropriate statistical framework to account for the model uncertainty the outcomes of different models may be averaged if there is no science-based preference for one model (Hoeting et al., 1999), but this requires additional modelling tools and is not common practice. As mentioned earlier, one should not present similar outcomes of two unvalidated models as the true result only because they are similar.

When a statistical model has been chosen for a dietary exposure assessment, within this model different options can be chosen. The user should statistically test whether the intake is dependent on age and/or sex. Other decisions to be taken are the type of transformation of consumed amounts (logarithmic or power), whether or not a spline fit is performed on the intake amount in ISUF, and whether the covariable sex or age is fit with a spline or a polynomial in BBN. To analyze the uncertainty of the chosen model options within the selected statistical model, it is recommended to study the sensitivity of the model by varying the different options and evaluating the results.

5.1.2 Qualitative analysis of model uncertainty

Quantification of model uncertainty is not always feasible as it is not always correct to use different models for each model used in the assessment. For example, if the intake distribution is multi-modal, BBN cannot transform this to normality and therefore should be used. In those cases model uncertainty can only be described in a qualitative way, for example according to the guideline prepared by the EFSA (2006). EFSA proposed to identify and score the sources of uncertainty on an ordinal scale (low, medium and high and direction represented by - and +). In section 5.3 two examples of uncertainty assessment using this format are given. In these examples some model uncertainties are included.

5.2 Analysis of model input uncertainty

5.2.1 Quantified model input uncertainty

Quantitative model input uncertainties should be assessed as much as possible in a quantitative uncertainty analysis. The current version of MCRA (6.2) is still rudimentary regarding the possibilities to address quantified uncertainties. The only sources of uncertainty that are currently quantified are:

1. sampling (lack-of-precision) uncertainty of consumption data;
2. sampling (lack-of-precision) uncertainty of concentration data;
3. uncertainty of processing factors and the variability of processing factors.

The lack-of-precision components of the consumption data (i.e. sampling uncertainty) and of the concentration data (combined sampling and analytical uncertainties) are assessed in MCRA by the bootstrap procedure, which works well for not too small datasets. MCRA handles model input uncertainties by a two-dimensional (2D) Monte Carlo approach (see schemes in Van der Voet and Slob, 2007). In each iteration, the model inputs for which uncertainty has been quantified are varied by bootstrapping the data (see below) or by drawing parameter values from an uncertainty distribution.

For example for consumption data the bootstrap in its simplest form manifestation works as follows:

1. resample the consumption dataset D by drawing with replacement N person days from the original set of N person days. Note that some person days may be drawn more than once, whereas other person days may not be drawn. Construct a bootstrap dataset D^* containing the consumption profiles and the body weight of the resampled person days;
2. with bootstrap dataset D^* perform the exposure assessment and estimate the output statistic of interest y^* , for example a certain percentile;
3. repeat 1-2 a large number of times (e.g. 100 times for rough estimates, 10000 if a high precision is required);

The set of bootstrap results y^* approximates the sampling uncertainty distribution of y related to the consumption data. This distribution can be characterised in several ways, e.g. by the variance or by an approximate 95 % confidence interval.

A similar bootstrap analysis can be performed with the concentration dataset. Note that for a chronic exposure assessment (where only the average concentration in food products is used) it is still useful to start the analysis with individual concentration data and apply the bootstrap procedure to these before calculating this average concentration. In this way the uncertainty in the average concentration will be automatically accounted for.

The approach to assessing uncertainty in processing factors is different from the bootstrap analysis. Processing factors are specified by parameters, either only a user-defined fixed value (fixed processing factor), or a central and an upper value (representing a variability distribution of the processing factor). The approach used is to specify additional distributions to describe the uncertainty in the primary parameters, as described in Appendix 2.

5.2.2 Qualified model input uncertainty

Whereas the lack of precision of the model inputs can in principle be quantified, the bias of the model inputs is difficult to quantify and need to be evaluated as qualified uncertainties. Examples of qualitative uncertainty analyses are in the paper of De Mul et al., (2008) which concerns the long-term

intake of dioxins, and in Boon et al. (in preparation) which addresses the dietary exposure to various residues and contaminants to young children. Both examples are described below (section 5.3).

5.3 Examples of qualitative uncertainty analysis

5.3.1 Example 1: Long-term dietary intake of dioxins

De Mul et al. (2008) were among the first to analyse the uncertainty in their assessment according to the EFSA guideline. In the paper of De Mul et al. (2008), the long-term dietary intake of dioxins is estimated. The consumption data of DNFCS-3 were used; concentration data were obtained from composite samples of mixed food products, specifically drawn for dietary exposure assessment. The long-term intake was estimated using two models, ISUF method and the Statistical Exposure Model (STEM -comparable to BBN- Slob, 2006). In some cases quantified information is given. The results are summarized below.

Model uncertainty

The estimated long-term intake varies between the two used models. De Mul et al. believe the influence of model uncertainty due to choice of statistical model is small. De Mul et al. did not consider other model uncertainties.

Model input uncertainty: consumption data

The authors consider underreporting of food products which may contain dioxins. These are mainly foods containing animal fat, such as fish, meat and dairy. This uncertainty is considered of medium magnitude.

With respect to the bias of the random sampling of the consumers the authors caution to keep in mind that the dietary record method does not cover the frequent consumption of products that contain higher than average levels. For example, consumers of eggs from their own laying hens are likely to have a high intake of dioxins and dioxin-like PCBs, as the 'at-home-produced' eggs contain levels up to ten times the normal levels and as they are likely to consume more eggs than consumers without laying hens.

Model input uncertainty: concentration data

The selection of samples, the use of composite samples and the low number of composite samples introduce uncertainty in the estimation of the long-term dietary intake.

For most food groups, except milk, eggs and fish, only one composite sample was analyzed, composed of four to eleven single samples. Therefore no information is acquired concerning heterogeneity (variability of single samples). As a result of this, it is not known if the sample size is large enough to remove (most of) the uncertainty. De Mul et al. expected the limited number of samples per product group to result in a medium-sized uncertainty.

Furthermore, the composite samples introduce uncertainty because several food products are taken together in one sample. In these composite samples, the concentration of the individual food products are averaged. The uncertainty due to the composite samples is expected to be of medium magnitude, but this based on expert judgement, not on quantitative measurements.

Furthermore, almost all food products were obtained from retail sale. Hence the uncertainty from bias due to targeted sampling is believed to be small by De Mul et al.

Besides the possible bias of the pooled samples, an important source of uncertainty in the concentration data is the analysis of the samples. The uncertainty introduced in the analysis of the dioxins and dioxin-like PCBs concentrations is estimated by De Mul et al. at 10 – 25 %.

A second source of uncertainty introduced during the analysis of the dioxin concentrations are the non-detects. The middle bound ($0.5 \cdot \text{LOR}$) exposure estimates were 10 % higher than the lower bound ($\text{LOR}=0$) estimate.

Model input uncertainty: linking of concentration and consumption data

De Mul et al. refer to the uncertainty that is introduced by linking consumed products to analyzed products as ‘extrapolation of mixed samples to consumed foods’. All consumed products are not analyzed themselves but have to be directed through the composite samples to estimate the intake via the consumed products individually. The uncertainty introduced due to the integration of these two completely different information sources is believed to be of medium magnitude.

The effect of cooking of food on the dioxin levels has not been included in the exposure assessment due to highly variable results on the effect of cooking on dioxin levels which are reported. The effects of cooking on the dioxin concentrations are expected to be moderate.

The choice of the authors not to include highly varying processing factors is questionable. By including these factors (estimates of the remaining fraction between 0.50 and 0.86 are mentioned), and including them in the uncertainty analysis, the available information on processing could have been used, thus avoiding a known bias, and the attached contribution to the overall uncertainty could have been estimated.

Overall conclusion

De Mul et al., conclude that, overall, the exposure in highly exposed individuals may be underestimated. Furthermore, they conclude that there is a small to medium-sized uncertainty (direction unknown) mainly due to the sampling uncertainty and analytical error. It may be incorrect that for processing an increase in concentration is included in Table 1 (page 35).

Table 1. Sources, direction and magnitude of uncertainty in the exposure assessment of dioxins (adapted from De Mul et al., 2008).

Source of uncertainty	Direction and Magnitude^a
Model uncertainty: several models can be used to estimate long-term exposure	+/-
Model input uncertainty: consumption data	
Underreporting of consumption	--
Undersampling of consumers with specific consumption patterns (sport fishermen); consumers expected to consume more contaminated foods	--
Model input uncertainty: concentration data	
Composite samples: mixed food groups, not precisely one food type analysed. Extrapolation of mixed samples to consumed foods	++/--
Choice for composite food groups above monitoring samples	?
Low number of samples per product group	++/--
Bias of sampled foods for consumed foods	+/-
Analysis, measurement error 10-25%	++/--
Analysis, sensitivity of method	+/-
Assumption that vegetable products do not contain dioxins if measurement was below LOR	+/--
Model input uncertainty: linking process and processing factors	
Effect of cooking on dioxin concentrations in food	++/-

Qualitative evaluation of overall effect of identified uncertainties: Highly exposed consumers may be underrepresented, resulting in an underestimate of percentage of population above exposure limits. There might be a small to medium effect of the uncertainty in dioxin concentrations, of which the direction cannot be determined.

^aKey to direction and magnitude

+, ++, +++ = uncertainty likely to cause small, medium or large over-estimation of exposure

-, --, --- = uncertainty likely to cause small, medium or large under-estimation of exposure

5.3.2 Example 2: Dietary intake of various compounds by children

Boon and colleagues of the RIKILT and the RIVM performed a study concerning the dietary intake of young Dutch children (in the age of 2 – 6 years) of a number of compounds, i.e. acrylamide, dioxins, several mycotoxins, nitrate and organophosphorus insecticides (Boon et al., in prep.). Depending on the expected toxicity estimations of both acute and chronic exposure were made. The estimation of the acute/chronic exposure levels is accompanied with a quantitative uncertainty (bootstrap) analysis of model inputs. Furthermore, a qualitative uncertainty analysis is given in the EFSA format.

Model uncertainty

Boon et al. used two different statistical models to estimate the acute and chronic dietary exposure of contaminants, i.e. the beta-binomial-normal (BBN) and the Iowa State University Foods (ISUF) model. Which one of the models gives the most realistic result of exposure will depend on the compound addressed (see section 5.1). The choice for any of the available statistical models to represent the true exposure is subject to uncertainty. It is assumed to be small.

Model input uncertainty: consumption data

Data of the Dutch National Food Consumption Survey Young Children was used in the dietary intake assessment performed by Boon and co-workers. The sampling uncertainty is the only source of uncertainty in consumption data that was incorporated by Boon et al. (2009) in the uncertainty analysis by means of bootstrapping. The uncertainty in the estimated dietary intake is not expected to be largely affected by the uncertainty in the consumption data.

Model input uncertainty: concentration data

Boon and co-workers used monitoring concentration data to assess the exposure. As explained in chapter 4, monitoring data may not be representative of the concentrations people are exposed to. Targeted sampling was considered predominantly to be an issue for pesticides and mycotoxins. For these compounds the overestimation of the exposure was estimated to be medium-sized. Besides targeted sampling, the size of the sampling plays a role in the uncertainty of the concentration data. Since monitoring data are available in abundance the uncertainty due to sampling is considered to be small (negative and positive).

Another source of uncertainty within the concentration data set considered by Boon et al., (2009) is the uncertainty due food products that were not incorporated in the exposure assessment. The influence of the uncertainty due to non-sampled foods on the total uncertainty is expected to be small.

The chemical analysis of the compounds is estimated to raise an uncertainty of medium scale in both directions. In addition, the analytical results have a limit of reporting (LOR). The LORs of the analytical results are quite high, since the VWA takes samples to check compliance with legal limits rather than to monitor concentration data for exposure assessments. The magnitude of the uncertainty due to non-detects is estimated to be a small underestimation (when non-detects are replaced by zero) to a small overestimation (when non-detects are replaced by the LOR).

Model input uncertainty: linking process

For most compounds (except acrylamide) addressed by Boon and co-workers concentration data are available mainly at the level of raw agricultural commodities (RACs; e.g. vegetable, fruits, cereals, nuts, etc.) which can mostly not be linked directly to the foods as consumed. For this they used the food conversion model CPAP (see section 4.3). The researchers expected the uncertainty of linking consumption to concentration data on ingredient level to be of a medium magnitude.

In contrast with the linking on ingredient/RAC level, Boon et al., used directly measured concentrations of contaminants in food products. Due to a large diversity in consumed foods and a limited number of food products analyzed not all consumed food could be linked to concentration data. The consumed foods with no concentration data available were grouped in such a way that they resemble best the foods analyzed. The grouping was mainly based on similar characteristics and ingredients in combination with expert judgements. The uncertainty arising from this type of linking is expected to be of medium size.

Model input uncertainty: processing factors

Almost all compound concentrations are influenced by processing. For example cooking, frying, washing, and other food processing can diminish the content of the contaminant in the product. In the exposure assessment of Boon et al., processing factors were incorporated if available. However, the

amount of data available on food processing factors was very limited and in some cases highly variable. The uncertainty due to the limited amount or unavailable processing factors is in general expected to result in an overestimation of the exposure level (as food processing is considered to diminish the concentration) of small magnitude for compounds with some processing factors to medium magnitude for compounds with no available or highly variable processing factors.

Overall uncertainty

Based on their characterization and qualitative evaluation of different sources of uncertainty Boon et al., concluded that for most compounds the dietary exposure will be overestimated (including dioxins, organophosphorus insecticides, mycotoxins). The main reasons for the overestimation Boon et al., put forward are the use of biased monitoring data, a high limit of reporting in combination with the substitution of non-detects with $0.5 \times \text{LOR}$ (Note however that substitution with $0.5 \times \text{LOR}$ can also result in an underestimation if the true concentration is between $0.5 \times \text{LOR}$ and LOR) and lack of information on processing effects.

The exception is acrylamide. For acrylamide the dietary intake may be slightly underestimated due to incomplete coverage of food products and possible underreporting of unhealthy products that are known to contain substantial amounts of acrylamide.

Table 2. Sources, direction and magnitude of uncertainty in the exposure assessment of various compounds of young Dutch children (adapted from Boon et al., in preparation).

Source and relevant substances	Source of uncertainty	Direction and magnitude ¹
Model uncertainty		
Pesticides (cumulative)	Summation of exposure distributions per pesticide	+
Pesticides (cumulative)	Summation of residue levels per composite sample	-
Pesticides (cumulative)	Summation of cumulative intake during the day	++
Long-term	BBN for acrylamide, dioxins, DON and nitrate	-/+
Long-term	ISUF for aflatoxin B ₁ , fumonisin, OTA and patulin	+
Model input uncertainty: Food consumption data		
All	Under / overreporting	-/+
All	Sampling uncertainty (bootstrap) ²	--/+++
Model input uncertainty: Concentration data		
Pesticides and mycotoxins	Biased sampling	++
All (except pesticides and mycotoxins)	Biased sampling	-/+
All	Non-sampled RACs / foods	-
All	Analytical precision	--/+++
All	Sampling uncertainty (bootstrap) ²	--/+++
All (except pesticides)	Non-detect samples: ½LOR	-/+
Pesticides	Non-detect samples: 0 mg/kg	-
Model input uncertainty: Linking food consumption and concentration data		
All (except acrylamide)	Estimation via RACs	--/+++
Acrylamide	Estimation via food groups	--/+++
Model input uncertainty: Processing factors		
All (except acrylamide and dioxins)	Processing effects: limited data, conservative assumptions	++
Dioxins	No processing	+
Pesticides (cumulative)	Grouping of processing effects	++
Overall assessment: Based on this qualitative evaluation of different uncertainty sources we conclude that for OPs the exposure will be most likely conservative (i.e. overestimating exposure levels) due to the use of monitoring data to assess the exposure. This is also true for all mycotoxins, including also a high LOR, and the use of the ISUF model to assess the long-term exposure for aflatoxin B ₁ , fumonisin, OTA and patulin. For dioxins the exposure may be slightly conservative due to limited information available on processing effects. For acrylamide the intake may have been slightly underestimated due to incomplete coverage of foods and possible underreporting of unhealthy foods containing acrylamide (e.g. crisps and chips) or adjusted eating habits during the recording days (like crisps and French fries).		+ / +++

¹ Key to direction and magnitude

+, ++, +++ = uncertainty likely to cause small, medium or large overestimation of exposure

-, --, --- = uncertainty likely to cause small, medium or large underestimation of exposure

² In the analyses sampling uncertainty of food consumption and concentration data was quantified simultaneously via a bootstrap analysis. Although it is possible to quantify which part of the sample uncertainty was due to food consumption data and which due to concentration data, such an analysis was not reported. For more details, see section 2.6.

6 Discussion

Conceptual model uncertainty

Uncertainties in the conceptual model may be assessed by implementing and running alternative conceptual models and comparing the results. In most cases this will be done by applying alternative already implemented models on the same data. However, if the true outcome is not known and the alternative models give similar but wrong results, this may give a false idea of uncertainty. Nevertheless, in principle it is possible to compare modelling results with true exposures. The closest solution to this is a 24-hr duplicate diet study (Van der Voet et al., 2003; Boon et al., 2003; EFSA 2007). A duplicate diet study reflects real exposure. However, the number of individual intakes obtained with this method is limited by the relative low number of available duplicates. Furthermore, since only one pooled 24-hr sample is available, the information on the contribution of the various food items to the overall exposure is lost. Another disadvantage of duplicate diets is that due to a strong dilution of contaminated foods with uncontaminated ones the determination of substances in the duplicate diet may be difficult.

In comparison with the duplicate diet method, a larger number of individual exposure estimates are available with the more indirect method of combining food consumption and food concentration data. The latter method furthermore provides information on the contribution of various food items to the overall exposure.

In the Netherlands, duplicate diet studies have been performed once every decade. The duplicate diet samples of about 100 participants have been analysed for e.g. mycotoxins, pesticides and brominated flame retardants (e.g. Van Egmond, 2000; Sizoo et al., 2004).

Results of the two methods (duplicate diet and combining consumptions and concentrations) are sometimes similar and other times they are not. For example, for ochratoxin A results of the duplicate diets differed about 15-20 % from the derived intakes: for some percentiles the duplicate diets were higher, for others they were lower than the calculated intakes (Bakker and Pieters, 2003). On the other hand, for deoxynivalenol the median intake of young children was a factor 2 higher in the duplicate diets than in intake estimations with MCRA (although high percentiles were similar) (Schothorst et al., 2005). A final example is that of brominated flame retardants. For polybrominated diphenylether (PBDE) 47 the duplicate diet study agrees well with the exposure estimations, while for PBDE 99 the duplicate diets were threefold higher than the derived intakes (Te Biesebeek et al., 2009). The reason for this large difference is unclear.

Nevertheless, for most exposure assessments no data are available from duplicate diets for an external validation of the exposure assessment model, and uncertainties have to be assessed by considering differences between models and uncertainties in model inputs.

Quantified model input uncertainties

A careful assessment of uncertainties in model inputs of dietary exposure assessment will address uncertainty in two ways: Quantitative and qualitative analysis of uncertainties. Exposure assessors should strive to assess the relative importance of all sources of uncertainty and at least quantify the most important sources. In both steps, subjective expert opinions are helpful, and probabilistic elicitation techniques may be appropriate tools (see e.g. Walker et al., 2001; Hoffmann et al., 2007). When using such techniques experts are presented with a range of questions to delimit the range of values that they consider plausible for specific model inputs. For example, experts may consider it unlikely that the fraction of apple in apple pie will be < 2% or > 50%, while considering 10% or 30% to be possible values for this recipe fraction. Upon further questioning limits may be established to serve as a 95 % credible interval.

The current version of MCRA (6.2) is still rudimentary regarding the possibilities to address quantified uncertainties. The only sources of uncertainty that are currently quantified are:

1. sampling (lack-of-precision) uncertainty of consumption data;
2. sampling (lack-of-precision) uncertainty of concentration data;
3. uncertainty of processing factors and the variability of processing factors.

The lack of precision in consumption and concentration data is assessed in MCRA using the bootstrap method. Consumption and concentration data are typically provided as large datasets. The bootstrap is a useful resampling strategy to address sampling uncertainty in those cases. However, its use in small-sample situations should be investigated more thoroughly, and alternatives may need to be found for cases where the bootstrap would not be appropriate.

The uncertainty associated with processing factors is assessed using an approach to specify additional distributions to describe the uncertainty in the primary parameters. This method could also be used to address the uncertainty of other model inputs which are currently outside the quantified uncertainty analysis.

One could think of adding uncertainty modules for:

4. individual consumption estimates given as a number of standard portions (where uncertainty may exist both about the number and about the standard portion size);
5. recipe fractions and recipe uncertainty and variability;
6. composition of samples (unit variability);
7. concentration measurement uncertainty (analytical error).

Given any number of quantified sources of uncertainty, the MCRA uncertainty analysis could estimate the overall uncertainty distribution in specified outputs. For example, an approximate 95 % confidence interval for p99 can be estimated which incorporates the uncertainty due to all the quantified sources. The way to do this is exactly the same as already currently used for uncertainty sources 1-3 given above: a two-dimensional Monte Carlo approach is used where the variabilities and the uncertainties are separately simulated.

Additionally it would be possible to estimate the relative contributions from each of the quantified uncertainty sources. In this way the uncertainty analysis can point at issues that are the major sources of uncertainty and which perhaps can be improved in the future. An algorithm to do this for some specific sources of uncertainty has been described in Van der Voet and Slob (2007), and has been implemented in the IPRA (Integrated Probabilistic Risk Assessment) software. It is not yet available in the current version of MCRA.

To quantify as many uncertainties as possible, we recommend adding uncertainty modules for all four subjects mentioned above. An uncertainty module in MCRA for standard portions (number 4) is presently investigated. Adding a module for calculating the uncertainty due to recipe variability (number 5) would be labour-intensive but not difficult work. The methodology on the uncertainty in the composition of samples (number 6) is available and only needs to be implemented in the program. For adding an uncertainty module for analytical error, a specification of measurement uncertainty, e.g. based on method validation studies and quality control should be provided by the analytical laboratories as is typically required in the process of accreditation.

A method to handle non-detects with statistical modelling will be implemented in MCRA late 2009.

Qualified model input uncertainties

Any remaining qualified uncertainties should be described and discussed, preferably using the tabular format proposed by EFSA (2006). If possible some estimate should be given of the order of magnitude

of the qualified uncertainties in relation to the quantified uncertainties. Although the estimation of the magnitude of the qualified uncertainties is subjective, the listing elucidates which sources of uncertainty are considered relevant, but not quantified in the intake estimations.

From the (small) experience with the use of these tables, it is clear that sampling uncertainty and analytical error may be the most important uncertainties in dietary exposure assessment. Sampling uncertainty is already quantified in MCRA, whereas analytical error is not. It is therefore highly desirable to develop a method to quantify the latter source of uncertainty.

Final remarks

One should keep in mind that exposure assessment is only one step in risk assessment. Therefore, uncertainties in exposure should be compared to uncertainties in the toxicological evaluation of compounds. An example of such an approach to uncertainty analysis is given in the Integrated Probabilistic Risk Assessment model (Van der Voet and Slob, 2007; Bokkers et al., 2009).

7 Conclusions

An analysis of the uncertainties in an exposure assessment is necessary to enable a proper interpretation of the assessment results. In addition, uncertainty analysis can identify the major sources of uncertainty in an assessment. This offers the opportunity to focus on the most effective interventions for improving the exposure assessment by reducing important uncertainties, e.g. by collecting more data.

Exposure assessors should therefore strive to assess the relative importance of all sources of uncertainty and quantify the most important sources. In both steps, subjective expert opinions are helpful, and probabilistic elicitation techniques may be appropriate tools.

In the current version of MCRA (6.2) there are a number of possibilities for uncertainty analysis. The sampling uncertainties of consumption and concentration data can be calculated using the bootstrap method. The use of this method in small-sample situations should be investigated more thoroughly, and alternatives may need to be found for cases where the bootstrap would not be appropriate.

With respect to model input uncertainty, it is recommended to add extra modules to MCRA concerning the uncertainty in standard portions, recipe variability, the composition of food samples (unit variability), and, in particular, analytical measurement uncertainty. With the inclusion of modules to calculate the uncertainty of these model inputs, the major sources of model input uncertainty are covered within MCRA. As a consequence, a better view of the overall uncertainty is obtained.

Investigating model uncertainty by running alternative models or model variants and comparing the outputs is of limited use. Nevertheless it is the only possibility when validation data are not present. Averaging the outputs of different models is an option if there is no science-based preference for one model, but this requires additional modelling tools and is not common practice.

In practice, quantification of all uncertainties will not be possible and is also not necessary. A number of non-quantified uncertainties will remain. These need to be addressed, preferably according to the tabular format of EFSA. More experience with qualitative uncertainty assessment of dietary exposure by exposure assessors is needed to obtain a more standardized qualitative uncertainty assessment.

The quantification of uncertainties is in line with international scientific endeavors (by e.g. EFSA and WHO) that are currently being carried out in the field of uncertainty analysis of exposure assessment.

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Appendix 1 Validation of new versions of MCRA

New versions of MCRA are validated against the previous version. For example, in a validation study, the output of MCRA 6.2 was compared to the output of MCRA 6.1. This was done for three example datasets (captan, acrylamide and aspartame), for acute and chronic exposure assessment, and covering a wide range of input options (in total 135 scenarios). The validated output concerned a set of percentiles of the exposure distribution (p50, p90, p95, p99, p99.9, p99.99), model parameters and loglikelihoods. Results of release 6.1 were compared with results of release 6.2.

Point estimates of release 6.1 were compared with point estimates and the 95% uncertainty intervals (Monte Carlo variation only) of release 6.2. For acute exposure assessment and the chronic BBN-model, cases outside the intervals were flagged and further investigated. For ISUF, only point estimates were compared. Find below, the number of iterations and the number of runs * number of MC-iterations for estimating the uncertainty intervals.

	MCRA 6.1	MCRA 6.2	runs * MC-iterations
acute	1,000,000	1,000,000	100 x 100,000
chronic BBN	100,000	100,000	100 x 50,000
chronic ISUF	-	-	-

For acute risk assessments, 25 different configurations of input options were run for three example datasets. The configurations represented different choices for reducing the population to consumption days only, modelling of processing factors, treatment of nondetects, modelling of unit variability and modelling of concentration distributions.

For chronic risk assessments 20 different configurations of input options were run for three example datasets. The configurations represented different choices for data transformation, usual intake model, modelling of covariables, modelling of cofactors and model selection.

The results are reported in a validation report.

Appendix 2 Variability and uncertainty of processing factors in MCRA

IN MCRA a statistical distribution can be specified to describe the variability and uncertainty of processing factors.

For processing effects that cannot increase concentrations (e.g. washing) the distribution is a normal distribution for the logit of the processing factor. For processing effects that can also increase concentrations the distribution is a normal distribution for the logarithm of the processing factor. In both cases the user has to specify, for each relevant combination of food and processing, a nominal value pf_{nominal} and an upper limit pf_{upp} , that is equated respectively to the p50 and the p95 of the processing factor distribution. Note that the logit of a number p between 0 and 1 is given by: $\text{logit } p = \log(p/1-p)$. The logit spans the whole real axis, which makes it a reasonable scale for simple statistical modelling using e.g. linear models and normal distributions. The nominal value is a user-specified value that will be interpreted as the median value of the uncertainty distribution.

MCRA assumes normal distributions on the logistic (for e.g. washing) or log scale (for e.g. drying) to model the uncertainty in pf_{nominal} and a chi-square distribution to model the uncertainty in the variability of processing (for option 2 in section 4.3.2). The chi-square distribution; is a standard distribution used in statistics to describe uncertainty of a variance or standard deviation.

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