Federal Institute for Risk Assessment (BfR)

Guidelines on Uncertainty Analysis in Exposure Assessments

Recommendation of the Committee for Exposure Assessment and Exposure Standardisation of the Federal Institute for Risk Assessment (BfR)

Imprint

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2 Foreword

Exposure assessment is part of any health risk assessment. All uncertainties in the scientific data basis, in the applied models and in the exposure parameters may have influence on the quality of such an assessment. Consumer exposure has to be assessed as accurately and comprehensively as possible. This applies to all fields of application, such as the assessment of chemicals (REACH), pesticide registration and authorisation, assessment of biocides, assessment of products and food safety, including the assessment of microbial risks. The scientists at the BfR are confronted quite often with a situation that they either do not have access to all relevant data, in which the relevant variables have not been analysed, or in which the necessary information is not adequately documented in the available literature. At the same time, they are expected to submit advisory opinions of a high quality (within a short period of time). The documentation of existing uncertainties with regard to the status of knowledge and the achievable detail with which these questions can be handled is therefore a matter of good scientific practice and transparency. It would be ignorant not to inform the management and the public about which assessments, conclusions and recommendations are underpinned by secured knowledge and which ones are based on uncertain information. The qualitative and quantitative documentation of uncertainties is part and parcel of good exposure assessment practice and complies with regulatory requirements.

Qualitative and quantitative uncertainties in expert opinions can be described and contrasted with those findings that can be stated with a higher level of certainty. This differentiation will increase the usefulness of the reported findings. The systematic use of uncertainty analysis will not only ensure the transparency and comprehensibility of opinions but will also increase their value for the purpose of risk communication.

The BfR Committee for Exposure Assessment and Exposure Standardisation supports the BfR in questions regarding to the development of standards for exposure assessment, the characterisation of appropriate exposure scenarios, the development of suitable exposure models, and the selection of model parameters (exposure distributions and exposure factors). A working group consisting of three members of the committee and competent experts of the BfR having a focus on the issue of uncertainty analysis was established. Among other things, the group had experience gained in the formulation and evaluation of corresponding guidelines for dealing with uncertainty in exposure assessments (WHO-IPCS 2008, EFSA 2006); the group has also discussed practical problems and issued recommendations that might help to promote efficiency in the process of exposure assessment.

The authors have attempted to create a guidance document that is as practicable as possible and that permits supervision of the entire process involved in the preparation of an expert opinion. This starts with the definition/analysis of the question (scope of interest) and should be a guide all the way through to documentation of the findings. One aim is to ensure that the accompanying documentation of the identified uncertainties does not create any unnecessary additional work. On the contrary: it should act as a means of avoiding unnecessary work. The committee recommends that BfR scientists will "test drive" the guidance document and subject it to critical evaluation in their daily work. Discussing it with colleagues and ourselves, might contribute to stepwise improvements. It is also recommended to document such trial applications and use it as an annex to this Guidance.

Michael Schümann
(Chairperson of the Committee for Exposure Assessment and Exposure Standardisation)

3 Guidance document on uncertainty analysis in exposure assessment

This guidance document is a recommendation of the BfR Committee for Exposure Assessment and Exposure Standardisation concerning the procedure for the documentation, description and assessment of uncertainties in connection with public health related opinions. This guidance document is chiefly based on the concept of the BfR guidance documents for risk assessment and exposure assessment. It primarily refers to the application of uncertainty analysis in the field of exposure assessment. Since exposure assessment is an essential part of risk assessment, it is recommended that the outlined principles should also be applied to risk assessment.

This draft basically follows the existing published guidance documents of EFSA (2006), WHO-IPCS (2008) and US-EPA (2008; 2011). The development of standardised procedures for uncertainty analysis, in particular with regard to the description of hazards, is currently the subject of international debate and work. In consequence this guidance document should be updated when necessary.

The aim of an uncertainty analysis is to ensure increased transparency regarding all elements of risk assessment and exposure assessment. In particular, uncertainty analysis should enable decision-makers, stakeholders (interested parties) and the public to gain a better understanding of risk assessment´s content. It should empower them to make their own fact-based decisions. The subject of assessment (scope of interest), the underlying primary questions and the selected protection goals should be described in uncertainty analysis. Knowledge deficits relating to scenarios, models and parameters and the potential impact these deficits on the conclusions of the assessment also need to be explained in an appropriate manner. This ensures that risk assessments help those involved to make suitable decisions even in the face of uncertainty.

Uncertainty analysis of an exposure assessment is based on the five steps of exposure assessment:

1. Interpretation of the formulated question
2. Formulation of the scenario
3. Development or selection of an exposure model
4. Selection of the (model) parameters
5. Calculation/Simulation of the exposure model

As is the case for the exposure assessment, a multi-tier process seems suitable for uncertainty analysis. This step-wise procedure primarily serves to restrict the assessor´s workload for the analysis to what is necessary. For example, a qualitative description of the uncertainties (lower tier) is often adequate for qualitatively described exposure parameters (lower iteration level of the exposure assessment). Uncertainty analysis contains an analysis of possible errors and weakness of results but also supports the exposure assessment in the determination of the necessary and of the achievable iteration level.

Uncertainty analysis should follow a multi-tier approach, starting with "simple" methods followed, if necessary, by more “complex" methods:

1. Level 1: application of uncertainty factors (if applicable)
2. Level 2: qualitative uncertainty analysis
3. Level 3: quantitative uncertainty analysis

This multi-tier procedure should, where possible, accompany the entire process of exposure assessment. The analysis uncovers the uncertainty in all steps from the formulation of the assessment questions up to the documentation of results. The assessor looks not only at the

scenarios but also at the corresponding mathematical exposure models, the model parameters and the calculations. In some parts, uncertainty analysis is generally confined to the qualitative level. Qualitative uncertainty analysis aims to create a systematic procedure for the verbal description of inherent uncertainties. This guidance document provides assistance in the form of pre-defined question lists with regard to the uncertainty dimensions listed in WHO-IPCS (2008):

i **Degree of uncertainty**
Describes the possible deviation of the exposure assessment from actual exposure
ii **Confidence in the knowledge base**
Comprises the completeness of all available information that can be used for exposure assessment
iii **Subjectivity of choices**
Comprises the reasons for decisions with regard to the exposure assessment (based on knowledge and opinions in the scientific community or in the group of stakeholders)

The relevance of the described uncertainties in each dimension should be evaluated in relation to the uncertainty of the target variable(s), in particular with respect to possible bias, and systematic errors and neglected variance. This can be achieved using sensitivity analysis methods. "Simple" sensitivity analysis consist of making individual changes, for example, to the parts of model or single parameters and examining the resulting effect of this change on the target variable. Sensitivity analysis should be applied in the context of model construction in order to identify influential sub-models for which in consequence modelling should be performed in greater detail. Non-influential sub-models might, in general, be kept simple. For non-influential variables using defaults might be sufficient. One key outcome of sensitivity analysis might be the identification and highlighting of those model parts, variables or assumptions that are influential for the conclusion and/or suitable for the prevention or for the mitigation of exposure.

The items of the questionnaire, outlined in this guidance document, which are related to qualitative uncertainty analysis can be used for simple qualitative sensitivity analysis. The insights gained by the answers might help to discriminate between certain and uncertain statements and results, a helpful step for the purpose of risk communication. This permits a substantiation of the "certainties", the certain ranges of the expected exposure in contrast to the possible ranges.

Communication of uncertainty is an integral part of communication of the risk assessment results. Describing inherent uncertainties within an assessment supports the transparency of the evaluation. The details of findings of an uncertainty analysis, as proposed in this guidance document, must be further summarised for communication with risk managers and the public in nontechnical language. This helps the recipients to put the findings in context. The criteria of comprehensibility, usability and transparency also apply to the communication of uncertainties. In addition, communication should also addresses the questions of who might be affected by the uncertainties (e.g. general population, consumers, producers, regulators). It should be explained, how serious the consequences of identified uncertainties might be, and which options for reduction of uncertainty or for regulatory action exist.

The requirements of this guidance document underline the fact that the quality of the risk assessment depends on good and early cooperation between the scientists involved, the technical experts, the staff responsible for communication as well as the regulators.

4 Basic principles

This guidance document is designed to support exposure assessment within the framework of risk assessment. The guidance document can therefore be seen as a supplement to other guidelines already prepared by the BfR and used as the basis of its assessments. It can, however, also be seen as an introduction to uncertainty analysis and as a possible tool for other risk assessments.

4.1 Objective of the guidance document

The Federal Institute for Risk Assessment (BfR) has prepared a *Guidance document for health risk assessments*[1] in order to improve the comprehensibility and coherence of scientific opinions, to support the use of harmonised terminology in the field of risk assessment, and therefore to ensure the provision of the best-possible advice in the various areas of activity of the BfR. This *Guidance document on uncertainty analysis* is designed as a supplement of risk assessment guideline. The aim is to ensure uniform methods for the recording, description and assessment of uncertainties in connection with health-related opinions.

The present version of this guidance document basically focuses on the area of exposure assessment. However, uncertainty analysis is generally also relevant to hazard and risk characterisation. In a subsequent step it should be reviewed to what extent the principles outlined here for exposure assessment are also valid for other parts of the risk assessment process. Work is currently ongoing at the level of WHO-IPCS on the development of a similar guidance document for uncertainty analysis in hazard assessments[2] that should supplement the earlier work of WHO-IPCS in the field of exposure assessment. It is planned that the findings of this project will be incorporated in a revised version of this guidance document.

Among other findings, two recent publications show that dealing with uncertainty in exposure and risk assessments is increasingly seen as being indispensable. Under the title "Late lessons from early warnings" on behalf of the European Environment Agency (EEA), a group of authors addressed the causes of the late recognition of (potential) hazards and the inadequate recognition of exposure and risk potential. One of their main conclusions refers to the inadequate consideration of uncertainties. At the U.S. National Academy of Sciences, the report "Environmental Decisions in the Face of Uncertainty" (IOM 2013) outlines how uncertainties incorporated in risk assessments should be taken into account when choosing courses of action. Both reports contain a number of case studies that focus on the different aspects of uncertainty analysis.

This guidance document is designed to make it easier to identify the potential and limits of a harmonised methodology for uncertainty analysis. A further goal of this guidance document is to provide a template for transparent communication of uncertainties.

A health-related opinion is incomplete that does not include an adequate description and analysis of uncertainties. The analysis and communication of uncertainties is designed to help informed decision making of the risk management, stakeholders (interested parties) and the public (consumers). After having developed BfR-guidance documents for risk assessment and exposure assessment, it is consequent to prepare a corresponding document for uncertainty analysis, too. The Committee for Exposure Assessment and Exposure Standardisation at the BfR tried to support this.

[1] http://www.bfr.bund.de/cm/350/leitfaden_fuer_gesundheitliche_bewertungen.pdf
[2] This document has been published by the WHO/IPCS in 2014:
http://www.who.int/ipcs/methods/harmonization/uncertainty_in_hazard_characterization.pdf

4.2 What is the purpose of uncertainty analysis?

Uncertainty analysis serves to create transparency regarding to all aspects of the risk assessment. It takes into consideration the subject of the assessment, the objectives of the exposure assessment and the definition of the protection target (i.e. population and effect) and goal (i.e. level of protection). Thus, it is an integral part of the exposure and hazard description.

In many cases, knowledge concerning exposure scenarios, models and parameters will be imprecise, incomplete or biased. Often, the available data base will be not representative for the population at stake or the data is of inadequate quality for the intended use in some other way. However, the available knowledge must be used in the best possible way in order to prepare appropriate assessments, even in the face of uncertainty. To ensure that the prepared exposure assessments can, despite this, be adequately interpreted, the associated uncertainties must be described in an appropriate manner. Uncertainty analysis outlines the limits of the current state of knowledge and describes the degree of resulting imprecision and inaccuracy.

The communication of uncertainty is an integral part of communication of the risk assessment. By looking at who and how the target population of the assessment might be affected by the uncertainties, the potential consequences of the possible effects of uncertainty might be described. Available options for preventive action and ways to reduce uncertainty might be discussed, evaluated and selected.

4.3 Basics of uncertainty analysis

The steps in uncertainty analysis follow the sequence of the exposure assessment: question definition, formulation of the scenario, creation of the model, choice of (model) parameters and calculation of the exposure assessment. Each step must be considered separately. Each of these requirements of exposure assessment and uncertainty analysis might be solved by a multi-tier concept. Section 4.4.3 describes these concepts in detail.

The following guiding principles, based on the WHO-IPCS (2008) guidance document, are used as an external framework. The associated additional workload depends on the task definition and the data situation. The benefit of such an analysis more than outweighs the amount of work.

1. Uncertainty analysis is an integral part of the exposure and risk assessment.
2. The level of detail of the uncertainty analysis should be based on a tiered approach and should be consistent with the overall scope and purpose of the exposure and risk assessment.
3. The sources of uncertainty and variability should be systematically identified and evaluated in the exposure assessment.
4. The presence or absence of moderate to strong dependencies between model inputs is to be discussed and appropriately accounted for in the analysis.
5. Data, expert judgement or both should be used to inform the specification of uncertainties for scenarios, models and model parameters. .
6. Uncertainty analysis comprises the description of the effects of all influencing components (selection of the scenario, the model and the parameters) on the exposure or risk level. It also serves to rule out any unimportant influencing aspects. Sensitivity analysis

should be an integral component of the uncertainty analysis in order to identify key sources of variability, uncertainty or both and to aid in iterative refinement of the exposure model. However, it is also suitable for the identification of the influencing variables that are best suited to prevent or mitigate the risks.

7. Uncertainty analysis should be documented in a comprehensive, systematic and transparent manner and should take account of qualitative or quantitative aspects of the methods, scenarios, models, parameters, data, findings, sensitivity analysis and interpretations of results.
8. Uncertainty analysis should be transparent in order to allow internal or external quality assurance. The uncertainty analysis should be subject to an evaluation process that may include peer review, model comparison, quality assurance or comparison with relevant data or independent observations.
9. Where appropriate to an assessment objective, exposure assessments should be iteratively refined over time to incorporate new data, information and methods to better characterize uncertainty and variability.
10. Communication of the results of exposure assessment uncertainties to the different stakeholders should reflect the different needs of the audiences. It should be comprehensible and transparent.

4.4 Terminology and basic concepts

4.4.1 Exposure assessment in the context of risk assessments

Exposure describes the contact of individuals (e.g. humans, animals) with agents. In this guidance document, these noxious agents may be chemical substances or their reaction products, mixtures or biological agents as well as metabolites of microorganisms. Exposure analysis is one of the four integral elements of risk assessment. The aim of exposure assessment is to determine the level of exposure (e.g. the amount of intake/contact per time), generally with the help of mathematical methods. To this end, it is necessary to combine numerous details of information, such as physical or chemical properties, data on the appearance and spread of the agent, details of the behaviour of the exposed individuals (e.g. contact time or intake behaviour) and personal/anthropometric information (e.g. age, gender, size, weight, etc.). The combination of information of all relevant variables relies on (mathematical) models, including existing correlation. The quality of the results is dependent on the quality of the parametric input. In the process of risk characterisation, the (numerical) results of the exposure assessment are compared with the results of the hazard assessment, (e.g. in relation to tolerable daily intake TDI, ADI). This step indicates the level of the risk for the health of the individuals, a description of the probability of the occurrence of health-related effects, in relation to the level of exposure. For microbiological risks, this characterization may involve models for growths or inactivation and concentration-response models.

The process of preparing an exposure assessment should follow the BfR guidance document on exposure assessment. The guidance document sets out rules for scenario and model creation, the choice of parameters and the appropriate methodological approaches.

4.4.2 Variability vs. uncertainty

The conceptual separation between uncertainty and variability is of particular importance. For this purpose, Morgan und Henrion (1990, p.50ff) recommend the application of the so-called Clarity Test, assuming the measurement of a "well-specified variable", which under hypothetical ideal conditions is constant for a specific person/object in a concrete situation. Deviations

in the determination of this variable resulting from imprecise methodology constitute the uncertainty of the measurement. Deviations resulting from differences in the "measurable variable" at different times, in different places or in different persons constitute the variability of the parameter in the population under observation.

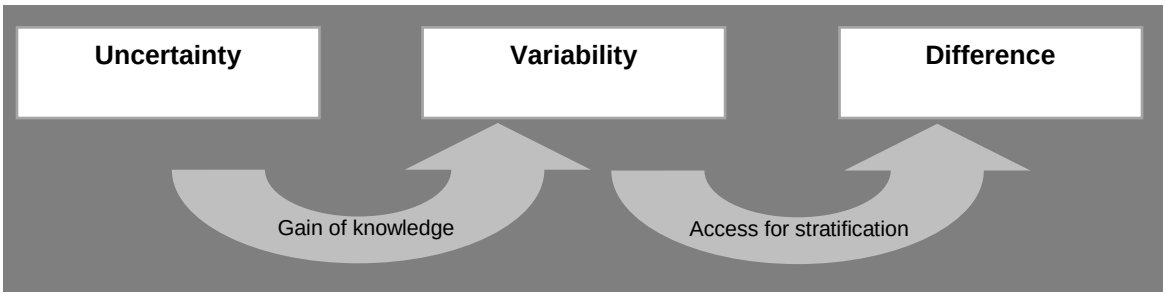
This paper used not only the terms "variability" and "uncertainty" but also the term "difference" (disparity, differentness, inequality, dissimilarity), and as a generic term "indeterminacy", as explained below.

The following definitions are recommended for the description of the indeterminacy of risk or exposure modelling:

Difference describes that part of the indeterminacy in the specification of a variable that is taken into account in separate models or model stratifications. In particular, this refers to separate models for sub-populations, such as infants, children and adults.

Variability describes that part of the indeterminacy in the specification of a variable that results from the fact that a variable is observed under different conditions. This generally refers to existing differences between individuals, and variation in time and space. Variability describes a property of the population. It has to be described and it cannot be reduced based on knowledge. A reduction of variability occurs e.g. if the selection criteria for the target population of an assessment is restricted - e.g. with observation of a sub-population. In case of changing exposure conditions of a population - e.g. due to (regional) changes in market supply over time – the variance of influential parameters might change too.

Uncertainty describes that part of the indeterminacy that occurs when specifying a fixed variable in absence of sufficient knowledge, due to imprecision of the method of measurement, or due to measuring errors. It can lead to false or distorted estimates. The lack of knowledge regarding all the factors that influence exposure or the health risks can also lead to uncertainty. Uncertainty in the area of exposure assessment comprises scenario uncertainty, model uncertainty and parameter uncertainty. The degree of uncertainty can be reduced on the basis of knowledge, at least in principle.



Full consideration of the population variability based on separate assessments for subgroups (e.g. age groups, specific intake and behavioural habits, regional population groups) ensures that the diversity of exposure conditions in the population are taken into account. Separate description of variability and uncertainty also supports the development and selection of useful and effective risk management measures (e.g. differentiated intake recommendations for different population groups) as well as the definition of further research needs (e.g. to reduce uncertainty in the case of food products that are rarely consumed).

4.4.3 Introduction to multi-tier methods of exposure assessment and uncertainty analysis

Multi-tier methods are standard practice in the field of exposure assessment. By this, the workload for exposure assessment can be limited to the scope required to assess the achievement of the protection goals.

Unfavourable conditions for the influencing factors (e.g. upper percentiles of the distributions for contact frequency, concentration or lower percentiles for body weight) can be selected as the point of departure for an iterative exposure assessment in order to ensure that exposure and the health risks are not underestimated (conservative estimation). The greater tolerance towards over-estimation of risks compared with under-estimation of a risk – although often implicit in the problem framework – is an informed choice that should be made explicit.
An exposure assessment therefore should approximate the situation with a generic scenario at first. It is refined step by step by additional stratifications, in order to reflect existing variation more accurately using more data or building models at a higher tiered level (e.g. with regard to food composition, the amount and origin of consumed food products, the ways in which household products are used etc.). An accompanying uncertainty analysis might justify the decision at which step the assessment is evaluated as sufficient. The process of refining the exposure model can be completed if no concern for high exposure is found for the population under concern or, if no additional knowledge is available for more detailed analysis. In both cases, the uncertainty should be described. Step-by-step refinements may concern the scenario, the model assumptions and/or the selection of parameters.

1. **Iteration: initial exposure assessment**
   Exposure assessment based on a generic exposure scenario using defaults assumptions (see definition below) as parameters (initial exposure assessment)
2. **Iteration: deterministic exposure assessment** (see Section 4.4.4)
   Exposure assessment(s) based on a specific exposure scenario and corresponding models possibly with multiple stratification - e.g. based on gender, age and consumer groups. The model-based calculation of the target variable within a deterministic exposure assessment is solved by using fixed values from descriptive statistics for all parameters (point estimates, e.g. mean/median value, 95^{th}/5^{th} percentiles)
3. **Iteration: distribution-based exposure assessment** (see Section 4.4.4)
   Exposure assessment based on specific and refined exposure scenarios and corresponding models with sub-group stratification using distribution-based estimates for the parameters. For the estimation of the target variable probabilistic (distribution-based) methods are used. The results of the assessment must include a statistical description of the distribution of the target exposure variable (with stratification).

Mixed and combined forms with respect to the choice of adequate iteration levels are possible.

The following definitions are recommended for differentiation of the various uses of so-called default values:

Conventions are quantitative values used for specific parameters in a model in order to standardise the model approach. This includes generic exposure scenarios, such as pesticide intake assuming a standard diet. Conventions are generally coordinated and approved by organisations of the scientific community or by a competent authority. As normative stipulations, conventions are not subject to an analysis of inherent uncertainty , but nonetheless, the appropriateness of applied default values should be evaluated in the context of analysis and within the sensitivity analysis (e.g. taking into account existing variation). The results should be evaluated and reported for these parameters, too.

Default assumptions are used in exposure models as substitutes for parameters if the assessor has no or an insufficient empirical basis for a direct estimate. This may include surrogate values (theoretical derivations from auxiliary variables - e.g. the body surface calculated from body weight and height), extrapolations (e.g. the transfer of findings from other populations to the target population) or expert opinions. The analysis of uncertainty should cover not only parameter uncertainty but also model uncertainty with regard to transfer, extrapolation or expert judgement.

Reference values, more precisely reference ranges (standard defaults), describe quantitative characteristics of a varying parameter in well-defined populations (e.g. mean value, median or 5^{th}/95^{th} percentiles). In general, reference values are used to reduce the efforts for model calculations. When applied stepwise to exposure model equations, they provide fixed values as the exposure estimate. Median and mean reference values (point estimates) are designed to reflect the central tendency (mean and median of the exposure). The combination of 5^{th}/95^{th} percentiles should reflect the major part of the variance due to the exposure factor in question[3].

Applying reference values from other exposure studies can be used as a basis for the evaluation of results. Results from human biomonitoring studies are useful as a benchmark for the predicted exposure results. Collections with population reference values can, for example, be found in exposure factor manuals (such as RefXP 2007, U.S. EPA 2008, 2011). When reference values are used, quantitative uncertainty analyses focus in particular on the statistical parameter uncertainty, resulting from limitations of the underlying sample size. Qualitative analysis looks at the general applicability and transferability of the reference parameters to the target population of the assessment.

The results of the use of methods with lower tiers should cover the empirical range of exposure (e.g. using conservative approaches) and must describe all relevant risks (e.g. covering the expected range of endpoints and risks). By this, they might fulfil the requirements of the precautionary principle. The mathematical combination of unfavourable assumptions is designed to ensure that the actual exposure is not underestimated and that the potential risk range is covered. Uncertainty analysis should evaluate the question of whether or not the conditions of a conservative estimate are really fulfilled. If the deliberate model-based overestimation of exposure and risk does not give any cause for concern, then the same might be assumed for the exposure and the risk of the target population. Compliance with the stipulated protection goals should be assured if the result of the combination of unfavourable assumptions shows a sufficient margin of safety (e.g. criteria TDI, ADI). If there is no other concern resulting from uncertainty of other sources, the assessment is ready.

The higher iterations of exposure assessment aim to reflect the exposure situation for highly contaminated or exposed sub-groups as well as for consideration of the variability within the overall population.

Although uncertainty analysis is not mainly an error analysis, it helps to identify errors and knowledge gaps. The consideration of different models and parameters supports exposure assessment in the determination of the necessary iteration level. Irrespective of this, it is also advisable to use a tiered method for uncertainty analysis in order to limit the workload to what is actually necessary. If the margin of safety is small, it is recommended to carry on with the steps described below.

1. **Application of uncertainty factors**
   Evaluating estimated exposure levels in comparison to known hazard characterisations

[3] It should be checked whether the combination of different influencing variables achieves adequate risk coverage.

(NOAEL, LOAEL, BMDL) or to acceptable daily intake values should take into account intra- and inter-species variability. The application of fixed assessment factors[4] might help to determine e.g. whether the margin of exposure/safety is adequate or not. Assessment factors generally reflect uncertainty of necessary extrapolations in the risk assessment. This step in the uncertainty analysis can be omitted for some applications in which, for example, there is no reference value.

2. **Qualitative uncertainty analysis** (see Section 4.4.5)
   In qualitative uncertainty analysis, the sources of uncertainty are systematically identified and documented. This results in a qualitative evaluation of uncertainty.

3. **Quantitative uncertainty analysis** (see Section 4.4.5)
   In the quantitative uncertainty analysis, the residual uncertainty is quantified and inserted in the exposure assessment as an additional dimension. This can take the form of sensitivity analysis, confidence intervals for point estimates or two-dimensional simulations (separation of quantitative variability and uncertainty) in distribution-based modelling.

The systematic analysis of the sources of uncertainty is possible and indicated on all iteration levels of the exposure assessment. A lower level of iteration will generally also result in a lower step of the uncertainty analysis. In principle, however, all combinations of iteration levels and steps are possible. Uncertainty analysis must accompany the entire process of exposure assessment, a process that not only looks at the scenario, the mathematical model and the parameters but also addresses the uncertainty of the formulation of the scope of analysis as well as the conceptual model and the documentation of calculation results. The discussion of the scope of the assessment, the calculations and the documentation will generally remain on the qualitative level.

Multi-step uncertainty analysis have numerous advantages: First of all, the qualitative approaches implemented in this guidance document provide a list of items which can be used for any exposure assessment. Second, the evaluation of available information is systematically structured by a set of evaluation criteria. By this, existing information gaps are identified and their importance might be assessed. Third, the actual degree of detail in the exposure assessment can be justified by the identification and documentation of priorities for model improvements. The quantitative methods of uncertainty assessment describe the degree of residual uncertainty inherent in the reported estimates. The iterative approach of the assessment provides a standardised and transparent form.

4.4.4 Deterministic and probabilistic approaches

A calculation of the exposure and the resulting health risk that uses fixed numeric values for all influencing variables under consideration will result in a deterministic estimate. The parameters of the deterministic model approach jointly describe an average or a constellation of unfavourable exposure conditions. The resulting outcome of the target variable is a single value: a deterministic point estimate. In the first and second iteration of the exposure assessment, unfavourable conditions can be chosen for all influencing factors (e.g. a combination of upper resp. lower percentiles of the parameter distributions) in order to avoid underestimation of the exposure and of the health risk. Reference values are frequently used in the calculations in order to estimate an average exposure or an average risk. Confidence and uncertainty intervals serve to describe the uncertainty of the reference values. Statements about the expected variability and uncertainty of the exposure within the population are only possible, however, following a probabilistic analysis that can take account of both aspects.

[4] The terms "certainty factors", “uncertainty factors” of “safety factors” (see e.g. EC (European Commission) (2000). Communication from the commission on the precautionary principle. COM, 1) are used as an alternative.

The aim of the probabilistic approach is to depict the entire range of possible values for the exposure of a population together with a frequency distribution of exposure (WHO-IPCS 2008). To this end, the calculations incorporate distributions for all influencing variables, which can be linked using Monte Carlo simulations and other methods. Probabilistic estimates therefore reflect the variability of the health risk or of the exposure in the population. The distributions of the model parameters are estimated on the basis of empirical data. The uncertainty of the target variable is then obtained as a combination of the uncertainties of the model parameters. The uncertainty of a probabilistic estimate can be quantitatively described by confidence bands for the exposure distribution. This requires so-called two-dimensional probabilistic modelling, one dimension representing variability and one dimension reflecting numerical uncertainty (e.g. imprecision).

4.4.5 Quantitative and qualitative techniques in uncertainty analysis

Qualitative uncertainty analysis delivers a systematic and comprehensive listing of all sources of uncertainty as well as a discussion of the direction and strength of the influence of uncertainty on the target variable. We propose question lists that might be used to focus on the main sources of uncertainty. This qualitative analysis refers to all stages of the exposure assessment.

Quantitative uncertainty analysis permits the specification of a range of probable values for the target variable (together with numerical ranges for probability bounds). If, for example, empirical data is used to estimate model distributions then it is possible to specify parameter uncertainty in the form of confidence intervals (for individual parameters) or confidence bands (e.g. for functionally dependent parameters) with the help of statistical methods. This process results in the generation of a probability distribution of the resulting exposure values (and health risks).

If, on the other hand, summarised data from the literature are used, or if expert assessments or conventions are used for the model parameters, quantification of the uncertainty is difficult. In this case, it is generally necessary to specify assumptions about the degree of the contained uncertainty in the form of value ranges (e.g. from … to …) or appropriate distributions.

Using different scenarios and models might result in a description of uncertainty ranges or exposure distributions, depending on the type of exposure estimation technique.

4.4.6 Sensitivity analysis in the context of uncertainty analysis

Sensitivity analysis (SA) is an integrated part of uncertainty analysis. The aim of sensitivity analysis is two-fold. Sensitivity analysis guides the process of exposure model development and it provides information about the influence of the selection of scenario, of the exposure models and of the parameter choices on the result. Sensitivity analysis delivers information about the dependency of output to different sources of uncertainty. However, whereas the uncertainty (as described in section 3), can be assessed for each parameter separately, SA requires a holistic view on the effect of one parameter on the target outcome in the presence of all other parameters (with their associated variabilities and uncertainties) in the model. Thus, practically speaking, a SA can only be conducted with the final model available, whereas UA of all input parameters should be completed as far as possible while constructing and defining the model (parameters). Using numerical analysis SA informs the assessor about the attributed effects of input variability and uncertainty of different parameters on the results. With respect to uncertainty analysis it informs about the propagation of uncertainty from model input to model output. Methods of sensitivity analysis measure and compare the

influence of variability and potential uncertainties from scenario and model alternatives on the target variable (cf. Frey, Patil 2002, Saltelli et al. 2004).

The precondition for the assessment of the degree of influence of individual influencing factors on the result is the quantitative description of the variability and the uncertainties of individual model parameters. For the purpose of comparison all parameters might be changed by a fixed rate (e.g. ± 20 %), by changing the parameter values by one unit (e.g. number of product applications per day) or by empirical ranges (e.g. using mean ± standard deviation intervals or by applying uncertainty distributions. Mathematical methods for the comparison of results range from direct numerical comparison, evaluation of rates for change up to more complex regression techniques. First-tier methods generally use a calculation technique in which only one parameter of the model is changed at a time relative to a standard case (e.g. a mean/median value for all other parameters). In distribution-based (probabilistic) sensitivity analysis, the degree of influence of the relevant influencing factors can be simultaneously quantified for multiple variables with the help of statistical methods.

At the modelling stage, the sensitivity analysis permits the identification of less important influencing factors for which modelling can be more approximate as well as for the identification of important influencing factors for which modelling should be more precise. At the end of an exposure assessment, sensitivity analysis should identify those influence factors with a high level of sensitivity that either offer a considerable potential for management measures (wide variability in the population) or that define further need for research (due to high uncertainty). In this process, sensitivity analysis can substantiate the research need for important influencing variables or justify the application of rough estimates of less influential factors.

Sensitivity analysis therefore also helps to clarify the importance of the variability and uncertainty of the input variables for the result of the exposure. Here, the aspects that can be reviewed include the determination of the combinations of exposure conditions that lead to the highest burdens, the ranking of the considered input variables in terms of influence on the result, and the identification of the prevention-accessible influencing variables that are classified as most effective for a reduction of exposure.

The insights gained from sensitivity analysis support the distinction between certain and uncertain statements. The result of an exposure assessment should represent the state of knowledge together with the degree of inherent uncertainty, since it builds the ground for any informed risk management. A transparent communication ensures that exposure assessment and uncertainty analysis can be scrutinized by third parties for consistency with the currently available knowledge. In particular, where data are incomplete or when exposure analysis has to be delivered within a very short time, the description of uncertainty and sensitivity analysis serves - even when conducted with limited effort – as a useful instrument for explaining which parts of the assessment are certain, e.g. which range of exposure will occur with high probability and additionally, which range of exposure might exist.

By this, the sensitivity analysis supports

- the development of appropriate exposure models together with an evaluation of model alternatives,
- the assessment of the strength of influence that stems from variability and uncertainty,
- the interpretation of results and
- the communication of the resulting findings

The potential effects of incomplete scenarios and models (in particular the omission of intake paths or sources of exposure) as well as potential bias of the results due to the quality of included data (e.g. selection of quantitative values for parameters of the model equations) can be evaluated in a comparative manner. At the same time, sensitivity analysis permits statements about the certainty of the estimates.

The identification of those model variables that are most suitable for prevention or reduction of exposure is a central outcome of a sensitivity analysis. Variables of the model that have strong influence on the results and which might be controlled (by the consumer, by the manufacturer or by enforcement) are candidates for this. Corresponding advice given by the assessor might be the major result of the assessment for risk management and risk communication.

4.4.7 Noxious agents

In this guidance document, the term "noxious agent" is used as a collective term for all agents that can exert a harmful or disease-promoting effect on an organism or a bodily organ. The term "noxious agent" is therefore used in this guidance document both for chemical substances, their reaction products or mixtures (of natural and synthetic origin) as well as for biological agents. The latter include such things as bacteria, viruses, fungi, prions etc. or the metabolites of plants, animals and microorganisms.

4.5 References to other guidance documents on uncertainty analysis

This guidance document was specifically designed for and adapted to the requirements, procedural routines and the fields of applications at the Federal Institute for Risk Assessment (BfR). It is based on various international guidelines on the uncertainty analysis in exposure assessment and health risk assessment.

In December 2006, the Scientific Committee of the European Food Safety Authority (EFSA) adopted and published a guidance document on uncertainty analysis in dietary exposure assessment (EFSA 2006). In this document, uncertainties are surveyed, documented and semi-quantitatively described systematically (e.g. in tabular form) in terms of their strength (three levels) and direction (overestimating/underestimating).

The harmonisation project of the International Programme on Chemical Safety (WHO-IPCS) of the WHO published a guideline on the characterisation and communication of uncertainties in exposure assessment in 2008 (WHO-IPCS 2008). The guideline outlines a hierarchical method with four steps: screening, qualitative, quantitative and population-based uncertainty analysis. Qualitative assessment is proposed in a tabular form with assessment (a) of the degree of uncertainty, (b) consideration of the knowledge base, and (c) assessment of subjectivity of choices. A similar guidance document for characterisation and communication of uncertainties in hazard assessment is currently prepared.

Building on these projects, the European Chemicals Agency (ECHA) published guidelines for the implementation of uncertainty analysis in the REACH process in section R.19 of the Guidance Document on Information Obligations and Chemical Assessment in May 2008.

In the new versions of the Exposure Factor Handbooks (EPA 2008, 2011), the US Environment Protection Agency (EPA) proposes the consideration of uncertainties in exposure assessment. The focus of uncertainty analysis is on assessment of data quality for the published reference values (e.g. percentiles of the distribution of exposure factors). Some criteria for the discussion of the applicability of the reference values usage for the target population in question are given.

Tab. 1: Iteration of uncertainty analysis in the process of exposure assessment

Process of exposure assessment			Uncertainty analysis		
1st iteration	2nd iteration	3rd iteration	1st step	2nd step	3rd step
Initial	Deterministic	Distribution-based	Uncertainty factors	Qualitative	Quantitative
Question formulation			Factors	Question list	–
Scenario			Factors	Question list	Alternative scenarios/ Sensitivity
Generic	Specific				
Model			Factors	Question list	Sensitivity/ Alternative models Stratification
Generic	Aggregated (crude stratification)	Detailed (fine stratification)			
Parameter			Factors	Question list	Sensitivity/ Interval observations/ Dependencies
Conventions	Point estimators	Variability/ Distribution			
Documentation of the calculation			Factors	Question list	Independent implementation
Depiction of results			Factors	Verbal	Standardised/ Graphic
Interpretation and communication			Factors	Standardised language	–

5 Content and structure of an uncertainty analysis

The following section describes qualitative uncertainty analysis in detail. The steps of uncertainty analysis correspond to the seven steps of the exposure assessment process.

1. Formulation of the goals and questions of the exposure assessment (see Section 0)
2. Exposure scenario (see Section 5.2)
3. Exposure model (see Section 5.3)
4. Parameters of the exposure model (see Section 5.4)
5. Method for exposure calculation (see Section 5.5)
6. Presentation of the findings of an uncertainty analysis (see Section 5.6)
7. Evaluation, interpretation and communication of uncertainties (see Section 5.7)

Steps 1 to 5 of the exposure assessment are the subject of a qualitative uncertainty analysis. In this guidance document, analysis takes the form of the systematic identification and characterisation with the help of question lists. Suitable templates might be found in a separate document (interactive version). Iteration steps 1 to 7 are dependent to each other. In consequence, processing of one step can impact the following steps (e.g. selecting a generic scenario effects the choice of the quality of parameters). Vice versa, the identification of high uncertainty due to neglect of difference and variability might result in the choice of a more sophisticated exposure model. After the items of the questionnaire have been answered, the assessor should be in a position to present the key points of uncertainty in a summarising text, following the structure of Table 1.

The question lists compiled in this document support analysis of the uncertainty based on the three independent dimensions specified in WHO-IPCS (2008):

i **The level of uncertainty of the exposure assessment**
comprises the potential deviation of the exposure assessment from the actual expected or empirical measured exposure situation

ii **Appraisal of the knowledge base of the exposure assessment**
comprises the evaluation of degree of completeness with regard to all available information that can be used for the exposure assessment

iii **Subjectivity of choices inherent in an exposure assessment**
comprises the description of reasons for all decisions made between alternatives (selection of scenarios, models, parameters), with respect to deviant rules and recommendations within the scientific community, but also between the interest groups

The question lists should be processed both for the question definition, the scenario and the model as well as for the individual parameters of an exposure assessment and for the calculation process.

Uncertainty can be caused by imperfect or unreliable methods (e.g. measurements, modelling, calculations) but also by a lack of information (ignorance). The importance of these uncertainties, however, depends on its influence on the result of the exposure assessment. It is compulsory to describe the effect of the uncertainty on the final outcome of the assessment using sensitivity analysis. All decisions to be made within the exposure assessment should be transparent to the risk management. It is therefore a good idea to take into account all three uncertainty dimensions writing an assessment report.

The *degree of uncertainty* is described on the same numerical scale as the exposure estimate, as a potential absolute or relative deviation. The other two dimensions (*confidence in the knowledge base, subjectivity of choices*) are more difficult to quantify. The two questions lists (for ii. Knowledge base and iii. Subjectivity) that are also related to the evaluation criteria

of WHO-IPCS (2008) can serve as a point of reference. In the following, lists of questions are presented along with each section of the uncertainty analysis (Tables 2-8).

Tab. 2: Question list for assessing the knowledge base

Question list on assessment of the knowledge base for scenarios, models and parameters (acc. to WHO-IPCS 2008)	
Criteria	Questions[5]
Completeness	Was the essential and relevant knowledge base compiled in a manner that is necessary to obtain an exposure assessment with the desired accuracy? Were the most important deficiencies in the knowledge base identified? Were the possible effects of these weak points on the result of the exposure assessment controlled? Were assumptions identified that can compensate the weak points of the knowledge base? Were all parameter values and results controlled using comparative calculations? Were all dependencies and interrelationships between model variables reviewed?
Reliability	Was the knowledge base checked for factual and methodological justifications? Was the knowledge base reviewed to ensure it is scientifically up-to-datedness? Was the quality standard of the knowledge base determined? Was an expert opinion assessment for suitability and appropriateness conducted?
Consistency	Was the basic scientific principles checked for consistency? Are the knowledge base and the methodology used in line with the latest scientific knowledge and the state of the art? Were scientific limits determined? Was it determined to what extent the scientific concepts and conclusions have already been reviewed in other fields of application? Was the empirical data used well-documented (internal and external validity, consistency of different sources)? How reliable (e.g. accurate, reproducible and stable over time) is the data used?
Robustness	Can the data, assumptions and information be assumed to be reliable? To which degree and in which direction do the identified data and knowledge gaps influence the result of the exposure assessment? Can existing knowledge gaps have any major impact on the result? Was the scientific knowledge base systematically reviewed and appraised in the context of the assessment problem? Has heterogeneity in published data and estimates been adequately recorded, diagnosed, documented and accounted for in the assessment procedures? What do we know about the transferability of exposure scenarios, models and data to the current application? How reliable will the results of such a transfer be? Is the degree of robustness of the scenario, the model used and the corresponding data high enough to ensure that a correct, plausible, and transparent result is obtained? Does this conform even for situations under unfavourable conditions (e.g. taking into account foreseeable misuse or possible errors in application)?

[5] Depending on context, not all questions relating to the assessment of the uncertainty of a scenario, model or parameter are relevant.

Tab. 3: Question list for assessing the subjectivity of decisions

Subjectivity of a choice of scenario, model or parameter (acc. to WHO-IPCS 2008)	
Criteria	Questions[6]
Scope of possible alternatives (decision-scope)	Were all possible alternatives for the selection scenarios, models or parameters described?
Differences between decisions of experts and stakeholders	Were concurrence and differences between the positions of different experts and/or stakeholders described?
Influence of situation-based restrictions on the decision	Was the influence of limited resources (e.g. research funds, infrastructure, working time for analysis and document preparation) on the selection decision determined?
Choice is guided by interests and values of the expert or stakeholder	Were possible effects of interests or scientific positions assessed with respect to procedural decisions? Is it to be assumed that the procedure may be guided by interests (e.g. for the application of specific methods and technologies)?
Influence of the decision on the result of the exposure assessment	Was the influence of the choice of scenarios, models and specific parameters on the result of the exposure assessment determined in a comparative manner?

5.1 Goal and question formulation of the exposure assessment

Every exposure or risk assessment should have a clear goal and should include a clear formulation of the assessment question. Risk management and risk assessment are often organised in different institutions. This means that the questions are formulated, interpreted and answered by different institutions, too. Before beginning with the assessment, uncertainty analysis of the goals and questions should reduce the ambiguity of the scope question, it should pinpoint aspects that are unclear and identify alternative interpretations. This helps to clarify the situation and supports effectivity. Where necessary, the assessor should provide reasons for decisions to be made.

The verbal description of the exposure scenarios together with a description of the model parameters, target variables and assumed interrelationships in a so-called *verbal model* facilitates the analysis of the goals and question formulations. In conceptual terms, the *verbal model* is equivalent to a linguistic description of all exposure scenarios that might be relevant. The verbal model should provide, as short and clear as possible, a description of the situations where exposure occurs, the model parameters and the target variables, together with an outline of the assumed interrelationships. It should also contain a short description of the population groups that might be affected.

The following question list for qualitative uncertainty analysis should serve as a guideline for the formulation of the objectives of the assessment. It might also be used as a content list for the clarification of the scope of analysis between risk management and risk assessment.

The following criteria are surveyed:

- Formulation of research questions
- Context of the analysis
- Protection perspective
- Protection group (e.g. consumers, by-standers and/or specific groups)
  Protection goals (e.g. prevention of adverse effects on human, animal or plant health, the environment[7])

[6] Depending on context, not all questions relating to the assessment of the uncertainty of a scenario, model or parameter are relevant.

[7] Ecological risk assessment can consider effects beyond the individual or species level and may examine a variety of assessment endpoints, an entire population, community, or ecosystem. Second, the ecological values to be protected are selected

- The aimed level of protection
- Scope and limitations of the analysis

5.1.1 Question list for qualitative uncertainty analysis in relation to the task definition

Tab. 4: Question list for qualitative uncertainty analysis in relation to the definition of the task

Criteria	Questions[8]
Question formulation	Is the question formulation sufficiently precise for the purpose of exposure assessment?
Context	Is the application context of the exposure assessment described in sufficient detail?
Protection perspective	Has it been defined at whose expense any residual uncertainty identified in the analysis is to be taken into account (consumer perspective, precautionary view, producer perspective/proof of risks)?
Population group to be protected	Is the population group to be protected defined with sufficient precision (e.g. individual persons, risk groups, special additional circumstances such as special consumption habits)?
Protection goals	Is the subject of protection (e.g. irreversible health impairment, health impacts, change in taste, general purity criteria) defined clearly and described with sufficient precision?
Protection level	Is the degree of the targeted protection levels (e.g. complete, 95% of the protection group, 95% of consumers or 95% of consumption events) defined clearly and with sufficient precision? What are specific sources and effects (on target variable) of uncertainties in the derivation of health based reference values?
Scope and limitations	Are there uncertainties due to possible exclusion of questions, scenarios or parameters (e.g. non-consideration of “background” exposure from the environment in the assessment of a specific product)? Do substitutes of the noxious agent exist that need to be taken into account?

5.2 Exposure scenario

The exposure scenario describes the framework within which contact of the affected population with a noxious agent is considered. This can be roughly described in the four steps: "Development/Release", "Spread" (fate and transport), "Reduction" and "Contact with the contaminant or the noxious agent”. While "Development/Release" describes the characteristics and the sources of the noxious agent, "Spread" describes the material flow through all media from development through to "Reduction" of the concentration or substance quantity in the contact/exposure media. Propagation and inactivation processes should be taken into account for microbial contaminants. "Contact" summarises all circumstances that describe the behaviour of the exposed persons that results in intake of the contaminated media.

Specification of the exposure scenario (i.e. simplification of a specific exposure situation) generally also entails limitation of the framework conditions under which exposure of the population is possible. Exposure scenarios can be depicted in an approximate (generic), refining the screening-level problem in a detailed or aggregated way.

The main aim of uncertainty analysis of the exposure scenarios is to check the completeness of the considered intake routes and sources, and to provide justification for the selection decisions and simplifications.

In line with WHO-IPCS (2008), the following sources of uncertainties should be considered in the exposure scenario:

from a wide range of possibilities based on both scientific and policy considerations. http://epa.gov/superfund/programs/nrd/era.htm

[8] Depending on context, not all questions relating to the assessment of the uncertainty of a scenario, model or parameter are relevant.

- "Development": characterisation of the origin and formation of the noxious agent in the source
- "Release": exposure source/origin and transport media
- "Spread": possible pathways of exposure
- "Reduction": details on the reduction (e.g. chemical fate) of the substance quantity
- "Increase, propagation": details on the development of substances or on the process of propagation (e.g. of microbial agents)
- "Contact": exposed groups of people/population: characterisation of the spatial, time-based and situational context
- Exposure events:
  - spatial, time-based and situational differences in the behaviour that are to be assumed as important influence factors in the exposure scenario, e.g. lifestyles, modes of action, application and ways in which products are used /microenvironment
  - risk management measures to be considered

The following question list can be useful to characterise the level of uncertainty for scenarios.

5.2.1 Question list for qualitative uncertainty analysis in relation to the exposure scenario

Tab. 5: Question list for qualitative uncertainty analysis in relation to the exposure scenario

Criteria	Questions[9]
Development	Is the contaminant/agent that is the subject of assessment (hazard identification) defined with sufficient accuracy? Do degradation products exist that need to be included in the exposure assessment? Does the noxious agent primarily occur in combination with other hazardous noxious agents so that it is to be viewed as the indicator substance of a group of noxious agents? Are the chemical, physical, biological and toxicological properties of the noxious agent adequately known?
Release/ sources	Are all primary sources of the noxious agent known? Is the complete material flow (e.g. quantity balance) of the noxious agent known in terms of development, spread and reduction? Are there multiple sources of the noxious agent that might occur in a correlated manner? Are processes of migration, release or cross-contamination possible?
Spread	Can be the substance flow to the secondary contact media (air, drinking water, food, products[10]) be fully traced and be described numerically? Are the exposure pathways (including the background contamination and the carryovers from other sources) fully taken into account? Are the routes of exposure that are to be taken into consideration clearly characterised? Can heterogeneous conditions of exposure be considered in summarised fashion through an aggregation of the influencing factors, by building groups of the products or food items, by generalisation of the represented life situation and by abstraction from the environmental conditions?

[9] Depending on context, not all questions relating to the assessment of the uncertainty of a scenario, model or parameter are relevant.
[10] Here, "products" is taken to mean mixtures/preparations and products.

Tab. 5 (cont.): Question list for qualitative uncertainty analysis in relation to the exposure scenario

Criteria	Questions
Reduction	Are the mechanisms by which a reduction of the concentration/amount of the noxious agent in the contact medium is possible (e.g. air exchange rate, mixing, degradation, decomposition) known and characterised?
Contact: exposed population	Is the target population of the exposure assessment adequately described? Is the exposed population considered in the assessment identical with or sufficient similar to the target population described in the scope of the assessment?? Which might be the mayor differences between the protection group and the definition of the target group of the exposure assessment? Are those groups or sub-groups with special or excessive exposure behaviour taken into account adequately and described in detail?
Exposure events	Are the exposure events to be considered adequately described? Is it possible to describe the exposure per exposure event?
Spatial, time-based and situational differences	Are the sources of exposure uniformly distributed for the exposed group (e.g. clearly defined technological processes of development, destruction or decontamination in the case of microorganisms)? Are time-based and spatial differences (e.g. concentrations, intensities, short-term or seasonal changes, cycles, trends over time, climatic, regional or local differences, differences in lifestyles or modes of behaviour) and the microenvironment (e.g. pH level …) adequately defined? Are the exposure conditions similar for the population under concern, for both genders and for all ages as well as for difference life phases (e.g. school and work days, weekends and more specific pregnancy, hospitalisation …)?
Risk management measures (RMMs)	Are the risk management measures (RMM) to be considered adequately described? Are RMMs adequately depicted for the scenarios used in the exposure assessment? Are all variables that might be influenced by known risk management measures (e.g. legal regulations, recommendations for application and usage) taken into account in the scenario description? Is noncompliant behaviour foreseen in the regulatory process (e.g. by communicated or non-communicated RMMs[11]) for application and usage part of the exposure analysis?

5.3 Exposure model

The exposure model is generally a mathematic translation of the scenario using a calculation method to determine the level of exposure. The conceptual model frames this process. The exposure model refers to the type and number of model parameters as well as the structure of their interrelationship and algorithm for executing the calculations. The target variable of an exposure model reflects the expected degree of exposure given the model and the parameters. In addition, exposure can also be measured directly (e.g. by personal sampler, duplicate diet measurement) or as the substance concentration in matrices (e.g. by human biomonitoring). Mathematical exposure models have the advantage to describe the influence of each exposure factor. Direct exposure measurements have the advantage of precision, but the analysis of influence of exposure factors demands for specific study design and sophisticated statistical methods.

Every exposure model represents only an approximation to reality, it is an instrument that serves to permit assessment of the extent to which a protection goal is achieved. In this situation, uncertainty analysis must review whether the model adequately describes the scenario and whether the degree of detail of the model is suited to the assessment questions. The criteria for the description of representational deviance between the exposure model in rela-

[11] Under REACH so-called communicated RMMs (exposure reduction by instructions for usage) should not be included in the quantitative estimation of exposure.

tion to the exposure conditions include plausibility, completeness and acceptance. The evaluations of an exposure model are supported by a sensitivity analysis which includes an appropriate discussion of model alternatives.

Typical sources of uncertainty or error in an exposure model are:

- Failures to take account of the influencing factors
- Incorrect aggregation
- Assumption of incorrect non-associations or oversimplification of the relationships between exposure factors (input variables).

Extrapolation errors can occur when transferring validated models to new areas of application.

WHO-IPCS (2008) lists the following sources of uncertainties in the exposure model:

- Exposure estimator: definition of the target variable
- Conceptual errors and wrong assumptions in the translation of the scenario into a set of model equations
- Correlations: Assuming interdependence of the input variables
- Model structure, e.g. stratifications for sub-groups with different behaviour
- Choice of an adequate model equation
- Model extrapolation beyond the area of applicability and validity
- Model implementation and programming of the calculation algorithms

The following question list can be used for the evaluation of uncertainty with respect to the choice of the model.

5.3.1 Question list for qualitative uncertainty analysis in relation to the choice of model

Tab. 6: Question list for qualitative uncertainty analysis in relation to the choice of model

Criteria	Questions[12]
Estimation of exposure : definition of the target variable	Are the variables of the exposure modelling process described with sufficient accuracy (e.g. mean/cumulative/maximum dose/concentration, unit, external/internal exposure, exposure events etc.)? Does the exposure assessment (e.g. with respect to the units of the target variable, comparability of the calculation, reproducibility etc.) meet the requirements for (quantitative) risk characterisation[13] (e.g. TDI, ARfD)? Does the calculation of exposure might confirm the achievement of the protection goals (e.g. compliance with exposure limits for children) for time-based or spatial frameworks? Are there any alternative concepts for exposure estimates (e.g. duplicate diet studies, human biomonitoring)?
Concept and assumptions for transfer of the scenario into mathematical model	Does the model equation deliver averages or extreme estimates as described in the scenario (scope of interest)? Was the aim of the choice of model the deliberate overestimation of the target value, and, if so, how great is the resulting overestimation? If yes, what are advantages and disadvantages in terms of uncertainties resulting from the use of distributions for the model parameters?
Connections/ Correlations	Are there correlations and structural dependencies between the influencing variables described? Are they accounted for in the model? In the event of multiple sources of the same noxious agent, for example, are there sources that occur in combination or correlation? To what extent and in what direction would the effect of non-consideration of correlations and interdependence affect the result?
Model structure, e.g. stratifications	Are sufficient stratifications present in the model to take account of regional (e.g. climatic, region type, change of location, trade flow), time-based differences (e.g. seasonal, cycles, trends), different microenvironments (e.g. production, storage, packaging, preparation conditions), different lifestyles (e.g. activities) etc.? Does the model contain sufficient gender and age stratifications (e.g. neonates, toddlers, children, adolescents, adults, seniors etc.)? Are particularly exposed persons (e.g. specific dietary needs or following incorrect use of a product) taken into account by the model? Are the requirements for all model parameters of modelling described with sufficient precision (e.g. unit, precision, stratifications, restrictions etc.)?
Choice of model equation	Is the application of the model accepted by experts, tested or validated? Does the model contain all the influencing factors of the exposure scenario? Is the applied formula generally scientifically accepted? Are all components and influencing factors of the model substantiated and explained? Are assumptions transparent and described in terms of their influence on the target variable? What is the quality (e.g. goodness of fit, considered influencing factors, restrictions) of model? Were the statistical methods for evaluation adequately substantiated? Does the degree of detail of the model correspond to that of the scenario? Does the model adequately consider the relevant processes in the exposure pathway (e.g. transformations, growth, degradation processes)? Does the model correctly depict the relationships between all influencing variables (e.g. age, behaviour) and exposure factors (e.g. consumption frequency, water intake per body weight) that are seen as being relevant? Are there conversions or decision variables (e.g. restricting parameter range limits) in the model that are disputable? Were all paths and exposure sources taken into account in the model formulas? Do the model equations adequately reflect the exposure process, in particular individual exposure events with regard to time- and path-specific correlations (e.g. habits of food consumption on the day of the week, season or festive days)? Is the model complexity balanced between the number of necessary influencing factors and the usage of assumptions for information gaps? Which assumptions are made? Are there alternative model proposals published?

[12] Depending on context, not all questions relating to the assessment of the uncertainty of a scenario, model or parameter are relevant.

[13] Where applicable, the uncertainties should be considered when defining reference values within the framework of hazard characterisation.

Tab. 6 (cont.): Question list for qualitative uncertainty analysis in relation to the choice of model

Criteria	Questions[14]
Extrapolations of the model	Was the model adopted as in analogy from another application? Does the application of the model extrapolate to new areas for the scenario? Is the model used with parameters for which it initially was not designed or evaluated; (e.g. for the evaluation of time trends or for a different degree of local aggregation)?
Risk management measures	Are all variables that can be influenced by risk management measures (e.g. legal regulations) taken into account in the model? Are parameters describing such mitigation options selected in accordance with observed, expected or intended practice?

5.4 Parameters of the exposure model

The objective of an exposure assessment is to estimate the quantity of intake (and distribution) of noxious agents for defined population groups in order to perform a risk assessment. The exposure assessment should represent:

- the differences between individuals
- the variability of the exposure conditions
- inherent associations between the model parameters

All model parameters must be quantified, if possible, using representative empirical data. The parameter estimates should generally be specified together with details on statistical precision, e.g. sample size, variance, standard error. Precision benchmarks serve to describe the statistical uncertainty and can also be used for quantitative description of the uncertainty. In addition, a statement on possible bias should be made for each model parameter. This aspect of the parameter uncertainty describes the correctness of an estimator in terms of the representativeness of the estimate in relation to the true population parameter. In certain cases, this quality parameter can be described using quantitative methods (e.g. distortion due to non-response or misclassification). It might even be used to adjust the final estimate for the respective bias. In many cases, however, these uncertainties can only be described qualitatively.

In addition, exposure assessments might contain model parameters based on data that is not based on empirical studies or that was generated for different purposes:

- Surrogate data used in the absence of more suitable data (e.g. biomonitoring data as a substitute for exposure data)
- Data referring to other populations, regions, time periods, situations, survey purposes etc. that is transferred (extrapolated) to the application case (e.g. exposure data from country A is used for an assessment for country B)
- Expert opinions (e.g. estimation of the minimum, most likely value and the maximum value for a parameter that has not been empirically investigated)
- Parameter values used by default or based on a convention (e.g. proposals from regulatory or scientific committees)

A different type of uncertainty analysis is necessary for the evaluation of such model parameters. The uncertainty analysis must review these quantifications of the parameters with respect to the requirements of the exposure scenario. This is particularly the case with regard to the representativeness of the parameter values for the population described within the scope and within the scenario definition. Additionally it should be checked (and documented)

[14] Depending on context, not all questions relating to the assessment of the uncertainty of a scenario, model or parameter are relevant.

whether model parameters are correlated[15], which inter-variable influences are expected to be influential, a strong influence of age (or body weight) on the consumption (amounts eaten of food items) might e.g. require an age-stratified exposure analysis.

The highest uncertainty generally occurs using surrogate data. The lowest uncertainty is seen with the usage of data generated for the exposure assessment itself. When deriving parameters from empirical data, it should be specified whether uncertainties can result from the following error sources:

- Quality of data collection for the given purpose: study population and representativeness of the sample: sample plan, intentional (risk-based) and nonintentional deviations from systematic or random sampling, sample size and stratification, selection and non-responder bias
- Precision and correctness of the measurement methodology (e.g. questionnaires, protocol data, quality of measurement for exposure factors and concentrations in laboratory analysis, collection of personal and demographic data)
- Handling of missing values (e.g. non-response rates, precision of the questionnaire items, detection limits and limits of quantification, data access)
- Quality of the statistical analysis of the data with respect to the content of the descriptive analysis, reporting of cumulative distribution functions, data aggregation into scales and indices, classifications, stratification by age, gender and consumer behaviour)
- Consideration of correlations between parameters[16]

The description of parameter uncertainty should cover these aspects.

Uncertainty analysis should also pay particular attention to the methods that were used to fill data gaps (e.g. dealing with missing values). Other sources of uncertainty have to be assumed when deriving parameters without empirical data. The following aspects can be considered:

- Plausibility (concordance between the parameter value and scientifically based assumptions)
- Intersubjectivity (agreement on the parameter value by different experts)
- Selection space (the width of the possible range for the parameter values)
- Consequences of limited resources (parameter estimates describing empirical data are not available due to lacking resources or time for the assessment)
- Interests/Value (the selection of a parameter value could be influenced by interests)
- Influence (assumed or calculated degree of influence of the parameter choice on the result)

The following question list can serve to characterise the uncertainty of each model parameter. It will typically be necessary to perform a sensitivity analysis in order to determine the degree of influence of a model parameter on the target variable. Correspondingly greater uncertainties can be accepted for model parameters if these parameters have a small degree of influence on the target variable.

[15] Technical note: Copula methods are theoretically attractive for this purpose as they overcome limitations of Pearson's product moment correlation to describe the phenotype of correlation where it really matters (e.g. in the tails of the distribution). Ref. e.g. Joe, H. (2015): Dependence Modeling with Copulas (Monographs on Statistics and Applied Probability 134); CRC Press

[16] If multiple parameters are derived from one data set, it is possible to consider correlations with respect to parameter uncertainty. Consideration of correlations and dependencies that are assumed to have an impact on the results without having an empirical database to check the degree of association should be weighed by criteria for the evaluation of model uncertainty.

5.4.1 Question list for qualitative uncertainty analysis in relation to model parameters

Tab. 7: Question list for qualitative uncertainty analysis in relation to model parameters

Criteria	Questions[17]
Expert opinions, default assumptions	Were default assumptions/expert opinions used for the value of parameters in the exposure estimates? If so, does the derivation of the default assumption/reference value (e.g. risk-covering or average, probable value) correspond to the objective and the step of the exposure assessment? Do agencies use deviating default values for the same parameter and if so, how can this be explained? Are the values plausible in terms of the objective?
Definition and quantification of the influencing variables	Does the model parameter meet the requirements of the exposure model (e.g. units of measurement, precision, stratifications, restrictions etc.) and adequately depict the range of variability for the subjects under examination? Is the variable with its chosen value characteristics suitable for the description of the considered attributes of the target population? Do the characteristics of the time-based, spatial and inter-individual variations correspond to the exposure and risk model? What is the time interval (e.g. short-term, long-term, lifetime estimate, area under the curve, body burden indicators etc.) of the data? Is the parameter of interest measured directly or calculated using conversion or assumptions of surrogate data? Are data available for the calibration and validation of the assumptions / conversion? If only classified (interval-scaled or binned) data are available, is this classification sufficient for the purpose of the modelling? If parameters are derived from confidential data, is the level of information that can be provided sufficient to judge its adequacy?
Reliability of measurements	Is the data collection method scientifically accepted and validated? Are the sources and the methods for data collection or measurement adequately documented in the literature? Which bias and measurement errors might result from sampling and sample processing (e.g. contamination of the samples), analysis and the measuring methodology (e.g. calibration, quality assurance), determination and calculation of the model parameter (e.g. validation)? Might the data, e.g. self-provided data from questionnaires, have systematic errors (over-/underreporting, bias due to social desirability)? What are the possible consequences of the inclusion or exclusion of values below the detection or quantification limit? How were the values below the detection or determination limit quantified? How were missing values in the data set handled? Were possible sources of systematic error and bias adequately discussed? Are there indications of widely differing values in the study? Do they point to special exposure conditions, missing influencing factors or "outliers"? Were "outliers" adequately handled? In the case of categorical data, is the diagnostic sensitivity and specificity of the determination method or its positive/negative predictive value known and taken into account?

[17] Depending on context, not all questions relating to the assessment of the uncertainty of a scenario, model or parameter are relevant.

Tab. 7 (cont.): Question list for qualitative uncertainty analysis in relation to model parameters

Criteria	Questions
Quality of data sources	Are data available from studies, systematic surveys or routine data? Is the study protocol appropriate? Was the study from which the data was taken performed with the aim of risk or exposure assessment? Is the data set used original or secondary data? Are there indications of different origins of the data in a study (e.g. different surveys, timeframes, laboratories, analysis methods etc.)? Was the resulting heterogeneity taken into account in the evaluation? Are there alternative studies on the same parameter that might confirm the quantification of the parameter choice(s)? Is the study design adequately documented and in correspondence to pertinent scientific standards? Is it likely that declared or undeclared interests unduly compromise the relevance or reliability of the data?
Study population	Is the study population clearly defined? Does the study cover all stratifications that are seen as important in order to take account of (for example) regional, climatic, time-based differences (e.g. seasonal variation, cycles, trends over time), different microenvironments (e.g. production, storage, packaging, preparation conditions), different lifestyles (e.g. activities, dietary requirements) etc.? Are there sufficient gender and age stratifications (e.g. babies, small children, children, adolescents, adults, seniors etc.)? Which selection effects may occur with a small sample sizes? In which way would known biases associated with the respective study design affect the reliability of the data?
Representativeness	Does the sampling strategy and the size of the sample ensure representativeness for the study population? Can results of the sample be transferred to the target population and the scope (regional, temporal) of the exposure assessment? Which assumptions and extrapolations are made, described and justified?
Details of correlations/dependencies	Have relevant correlations between influencing factors (e.g. consumption and body weight) been described and taken into account in the model (e.g. intake/breathing rate/body surface per kg body weight)? If there are correlations and structural dependencies, were they described in a transparent and logical way?
Evaluation methodology	**With deterministic estimates:** Are the statistical descriptions reported in a transparent and logical manner? Is the sample large enough to estimate the required parameters with sufficient precision? Which level of statistical precision (standard error of estimate, SEE and confidence intervals) has the exposure estimate? **With probabilistic estimates:** Are the statistical methods and selection criteria for distributions described in a transparent and logical way? Were considerations reported or additional data sets used to justify the selection of the distribution type? Is the sample size for the parameters considered large enough to accommodate the required distribution, especially extreme percentiles, with sufficient precision? Was the precision of the distribution fit and the corresponding parameters specified by providing confidence intervals, goodness-of-fit measures (e.g. Kolmogorov-Smirnov distance)? Were relevant statistical indicators (e.g. skewness, mean/median ratio, percentiles) of the empirical and the parametrically distribution compared and discussed? Which assumptions were made to fit a distribution using small samples? What are the consequences of these assumptions for the target variable of the exposure assessment?

5.4.2 Quantitative estimation of parameter uncertainty

According to the guidance document on uncertainty in exposure assessment published by WHO-IPCS (2008), various methods can be used for quantitative uncertainty analysis. The reader is referred to this document for details. The methods might be categorised as

- the calculation of the lower and upper limits of the exposure in the form of an interval estimate
- the application of probabilistic (distribution-based) methods
- sensitivity analysis

The quantitative methods are mainly based on determination of the possible bandwidth of an estimation. Methods that supply a description of the parameter in the form of intervals or probability distributions can be used for this purpose.

All methods have in common that the variance (or range) of the results is analysed in dependence of the variability (or range) of inputs parameter. Uncertainty with respect to scenarios should be evaluated by varying the scenarios stepwise, e.g. including different routes and pathways in an age- or gender-related manner. The influence of structural dependencies (e.g. the age- and body-weight related breathing rates) or statistical correlations (e.g. the association of food ingredient's concentration) on the results, should be analysed in a qualitative manner (e.g. the diminishing influence of the body weight in the denominator together with an increasing influence of body-weight related intake in the nominator). If parameters are qualified as influential and show stronger association to another variable in the model, than the effect should be evaluated quantitatively. The comparative exposure and risk assessment of various model specifications can also be interpreted as a quantitative uncertainty analysis (cf. WHO-IPCS, 2008). At this point, it is important to repeat that sensitivity analysis is the key instrument of uncertainty analysis (Section 4.4.6).

5.5 Methods and software for exposure calculation

The formulation of the exposure scenario, details of the exposure model and the quantification of parameters should determine the result of an exposure assessment. This requirement does not hold necessarily in the case of complex models and sophisticated calculation methods, such as distribution-based simulations. The results of the calculation may additionally depend on the program used, on the choice of the accuracy (e.g. standard error of the estimation) and the selected calculation/simulation method. If commercial software is used for calculation purposes the algorithms and the program code is generally neither published nor changeable. The use of a software tool can result in additional simplifications whose effects on the result of the exposure assessment are to be made transparent by uncertainty analysis. For this purpose, at least the program's name (including version number) and the choice of available methods and defaults should be documented.

Other potential sources of error are incorrect programming (software error) or differences in implementation for different hardware environments (WHO-IPCS 2008). Error sources of this kind can be avoided or mitigated by independent review or even independent implementation of the model.

For the purpose of quantitative estimation of the influence of the used programming environment (e.g. software and hardware) on the results, the calculation would have to be performed independently by different programmers using different software. Due to the considerable workload, this kind of analysis will be confined to a small number of applications - e.g. testing and evaluation of a generic exposure model or, in cases of exposure and risk assessments where the results might have considerable consequences.

5.5.1 Question list for qualitative uncertainty analysis in relation to the procedure for exposure calculation

Tab. 8: Question list for qualitative uncertainty analysis in relation to the method of exposure calculation

Criteria	Questions[18]
Deviations	Are there deviations between the exposure model and the implementation of the calculation method?
Review of calculations	Are there potential sources of error in the technical realisation of the model calculation process, the applied algorithms, the programming process (e.g. incomplete documentation, reproducibility) or the input of controlling variables (e.g. selection of the random number generator, number of iterations)?
Deficient report compilation	Are there potential sources of error in the report compilation process?
Verification	Were the units in the calculation controlled (e.g. within the SI system)? Was the model implementation independently repeated or assessed for quality?

5.6 Presentation of the findings of uncertainty analysis

The above sections have served to identify and specify uncertainties in the exposure and risk assessment. The questionnaires should support the consideration of all types of uncertainties that might influence the results, the conclusions and the consequences of an exposure analysis.

It is recommended to document all identified answers in a structured manner. The following section contains a proposal for this (see Section 5.6.1). It is advisable to continuously record the degree of uncertainty, looking for different aspects (questions), during the assessment process. These notes can be verbal descriptions and might have a less standardised form. During the course of practical implementation, a uniform mode of expression for the description of uncertainties might be developed. The proposal of WHO-ICPS (2008) is to consider the known criteria individually in connection with

- Degree of uncertainty
- Confidence in the knowledge base
- Subjectivity of choices

It should be noted that the criteria do not possess the same relevance for all steps of exposure and risk assessment. Items of the questionnaire may remain unanswered, if irrelevant.

A systematic presentation in the form of a table serves the purpose of primary documentation. Every section should not only describe the identified uncertainties but also evaluate the possible effects on the end result. This creates a uniform form of documentation that enables comparisons between the cells.

An attempt can be made – with reference to other guidance documents – to categorise the uncertainties in each step of the exposure assessment. EFSA (2006) describes the result of an analysis of direction and magnitude, combined into a single measure using plus and minus signs. For the degree of uncertainty three levels: "low"/"medium"/"high" with additional specification of the potential effect of uncertainty on final outcome of assessment: "over-estimation (+)"/" unknown (–/+)"/" under-estimation (–)" is used. Some uncertainties might be evaluated as potentially causing either over- or under-estimation. Five levels are proposed for risk communication (EFSA 2012): "Not discernible – negligible"/"low"/"medium"/"high"/"unknown". For all uncertainty criteria, mentioned above, WHO-IPCS (2008) proposes a categorisation by three levels: "low"/"medium"/"high".

[18] Depending on context, not all questions relating to the assessment of the uncertainty of a scenario, model or parameter are relevant.

The following categories, symbols and colour codes are proposed for presentation purposes:

Tab. 9: Categories, symbols and colour codes for the classification of uncertainty

Degree of potential effect	Possible direction		
	Underestimation	Not known/Underestimation and overestimation possible	Overestimation
Not discernible/ Negligible	0: Uncertainty has no discernible or a negligible effect on estimation of the risk	0: Uncertainty has no discernible or a negligible effect on estimation of the risk	0: Uncertainty has no discernible or a negligible effect on estimation of the risk
Low	–: Uncertainty can result in a low underestimation of the risk	–/+: Uncertainty can result in a low deviation in the estimation of the risk in both directions	+: Uncertainty can result in a low overestimation of the risk
Moderate	– –: Uncertainty can result in a moderate underestimation of the risk	– –/++: Uncertainty can result in a moderate deviation in the estimation of the risk in both directions	++: Uncertainty can result in a moderate overestimation of the risk
High	– – –: Uncertainty can result in a high underestimation of the risk	– – –/+++: Uncertainty can result in a high deviation in the estimation of the risk in both directions	+++: Uncertainty can result in a high overestimation of the risk
Not known	? –: Uncertainty can result in a underestimation of the risk of unknown magnitude	? –/+: Uncertainty can result in a deviation in the estimation of the risk in both directions and of unknown magnitude	? +: Uncertainty can result in a overestimation of the risk of unknown magnitude

Colour highlighting of the cells in the table (see Section 5.6.1) underscores the areas of exposure and risk assessment for which the uncertainty might show strong influence on the results. The aim of these categorisation efforts is to highlight the primary sources of uncertainty. In general, not all aspects are of equal importance. A sensitivity analysis might provide quantitative information to these qualitative assessments.

Finally, the uncertainties with the greatest relevance should be summarised. Results of a sensitivity analysis might substantiate the qualitative results. This evaluation should be attached to the exposure and risk assessment report. The focus should be on the following questions:

- Which sources and reasons for inherent uncertainties have high importance?
- What are the effects (degree and direction) of the most important identified uncertainties on the result of the exposure assessment? If defined, can the level of protection be warranted in view of the reported uncertainties?
- What are the specific options for uncertainty reduction in the exposure assessment? Are these options suitable to allow a sufficient and appropriate assessment of the protection goals?

5.6.1 Standardised qualitative presentation of uncertainty analysis

Tab. 10: Standardised qualitative presentation of the findings of uncertainty analysis for primary documentation

Identified aspects and magnitude of uncertainties in the exposure assessment			
	Degree of uncertainty	Confidence in the knowledge base	Subjectivity of choices
1. Goal and question formulation of the exposure assessment			
Question formulation			
Context			
Protection perspective			
Protected population			
Goals of protection			
Protection level			
Restriction of scope			
2. Exposure scenario			
Characterisation of the noxious agent			
Exposure source and origin, exposure routes and pathways (media)			
Possible exposure paths			
Exposed groups of people/population			
Exposure events			
Assumed spatial, time-based and situational differences/lifestyles/modes of behaviour and microenvironment			
Risk management measures			
3. Exposure model			
Exposure estimator: definition of the target variable			
Concept and assumptions used for the translation of the scenario into model equations			
Dependencies/Correlations			
Model structure, e.g. stratifications			
Choice of model equation			
Model extrapolation			
Risk management measures			
4. Parameters (to be completed separately for each parameter)			
Definition, units and quantification of the influencing variables			
Reliability of measurements			
Quality of the data sources			
Study population			
Representativeness			
Correlation structure			
Evaluation methodology			
5. Documentation of the exposure calculation			
Deviations			
Review of calculations			
Deficient report compilation			
Verification			

5.6.2 Standardised presentations of quantitative uncertainty analysis

It is not intended to present the approaches for a quantitative uncertainty analysis within this document. The choice of methods depends on the level and on the approaches of uncertainty analysis that are useful (see Section 5.4.2). If a quantitative assessment is required, in general, it is necessary to get involved scientists with methodological and statistical compe-

tence. Quantitative sensitivity analyses are strongly recommended/required to describe the potential effect of uncertainties on the final outcome of the assessment.

5.7 Communication of uncertainties

In contrast to the technical report and primary documentation of the findings, that should support the decision-making process, the interpretation and the communication of results are addressed to an extended audience. This is ranging from risk managers all the way through to informed target groups and interested consumers. This means communication requires further preparation ad differentiation in order to meet the various needs.

Firstly, there are general communication needs, e.g. the need for comprehensible, transparent and practical information that apply to all kinds of risk communication. Some aspects are outlined in more detail in Section 5.7.1.

Secondly, there are additional needs with regard to the communication of uncertainties. People generally strive to achieve safety. Simple categorisations (e.g. “safe – not safe”) are sought for the decisions of risk management as well as for discourse with the public. However, often results of an uncertainty analysis are irreducible to this kind of categorisation. It is necessary to summarise the differentiated findings of uncertainty analysis (see Tables 8 and 9 in Section 5.6) in a conclusion which puts the findings in context and takes account of the most important communication needs of the risk management as well as for the consumers. These are outlined in Section 5.7.2.

5.7.1 General communication principles

EFSA (2012) has published some basic principles of good risk communication. In the context of uncertainty analysis, the following aspects are of particular importance:

- **Comprehensibility:** the findings of the exposure and risk assessment including uncertainty analysis should be carefully translated from scientific language into a generally understandable language. Secured knowledge should be identified accordingly.
- **Usability:** if uncertainty (and esp. sensitivity) analysis supplies concrete advice for meaningful measures, these should also result in concrete recommendations for action that are of relevance for those affected. Concrete advice for possible exposure reductions are to be preferred to general recommendations. Alongside administrative regulations, individual preventive measures should also be outlined. The text should contain familiar units of daily life.
- **Transparency:** risk communication should state whether other risk assessments and opinions have already been published and, if so, the BfR should provide the references, the results together with a transparent assessment of the reliability of other sources.
- **Up-to-date character:** risk communication can take place in parallel to the exposure and risk assessment if partial results of the exposure and risk assessment are available. The content should contain the results from current iterations and stepwise refinements. This also requires that the identified uncertainties and the further progress of the analysis are also portrayed. This allows timely communication of findings, even if not all definitive assessments are present in validated form.

Alongside the aforementioned criteria, content-related aspects also have to be taken into account. Unlike the risk assessors, the users of risk assessments often assess risks based on additional criteria such as controllability or the extent to which the consumers or their families are affected. Risk communication must therefore attempt to address all expected

information needs. In particular, risk communication should address the questions listed below and, for this purpose, therefore needs information on these topics from the risk assessor:

- **Affected groups:** how many people are likely to be affected by the risk? Which level of exposure is expected to exist for the population? Is the level of exposure different for different population groups? Do those persons affected include sensitive groups, like children, pregnant or older people?
- **Voluntariness/Controllability:** does the exposure occur voluntarily or involuntarily? Can exposure be avoided? What is done by risk management and the competent institutions to control/reduce the exposure? What can those persons that are affected do to minimise the exposure and the risk?
- **Severity:** how direct and severe is the risk in terms of the impacts on human health? Do potential impairments is expected to occur immediately or with latency? Are possible health effects reversible?

5.7.2 Communication of the findings of uncertainty analysis

Communication of uncertainty is an integral part of communication of the risk assessment. The differentiated findings of uncertainty analysis, as proposed in this guidance document, are to be summarised for communication with risk managers and the public. This underpins the transparency of the assessment and enables the recipients to put these findings in context. Moreover, the requirements for risk communication outlined in the previous section also imply that the assessor may possibly have to address and answer questions that are beyond the scope of the assessment task.

The criteria of comprehensibility, usability and transparency also apply to the communication of uncertainties. An easy-to-understand description of uncertainties in the exposure and risk assessment is a precondition for informed decision-making by the management as well as by the affected people (and the public). The usability of the gained knowledge is directly related to the existing knowledge base. Transparency comprises the disclosure of subjective decisions, the lack of sufficient knowledge and of the existence of different scientific assessments.

The assessor should try to predict which aspects of uncertainty analysis will be of particular relevance for the risk management and for the public at large. The communication of an uncertainty assessment should in particular address who may be affected by the uncertainties, how serious the possible impacts of uncertainties might be, and what can be done to control and reduce these impacts.

This results in the following questions, which communication of the findings of uncertainty analysis should answer alongside the expert assessment as part of the risk communication process:

The findings of uncertainty analysis should give hints how to give answers for the following questions:

- Which findings can be reported as "based a sound scientific knowledge", and which ones are to be categorised as "uncertain"? How can this be presented in a way that the abstraction level of the answers corresponds to the knowledge of the population?
- Which are the uncertain elements with the greatest influence on the result of the exposure and risk assessment? Which causes and sources contribute to existing uncertainties?
- Who (which groups) and how the population might be affected by the uncertainties?

- Which assumptions were used to solve an assessment task despite inherent uncertainties? How are these assumptions justified? Which diverging opinions on these assumptions are known to the assessors? The choice of assumptions should be explained.
- Which measures can be taken to reduce or remove uncertainties? How to procure missing information? Which resources (e.g. workload, human and laboratory resources, infrastructure and budget) are necessary for this purpose? How other departments of the BfR can help to reduce the uncertainty?
- Which recommendations can be given, e.g. for improving regulation, enforcement of existing rules, contracts and laws, monitoring and preventive measures?

The requirements for risk communication show that the quality of an exposure and risk assessment depends on good and early cooperation between the scientific specialists and those responsible for management and communication.

6 Recommendations for application of the guidance document

This guideline is a recommendation of the BfR Committee for Exposure Assessment and Exposure Standardisation. It is written to assist and facilitate the necessary procedures with regard to the development of health related scientific BfR opinions. One step of the assessment procedure is the assessment of exposure. The identification, the description and the evaluation of inherent uncertainties conducting this step should be supported by the document.

The BfR Commission has identified the need for further close cooperation with BfR for developing case studies. It is also expected that the implementation of best practices of UA will be a matter of international cooperation with EFSA and other national and international agencies.

6.1 Use in BfR risk assessments

The BfR Committee for Exposure Assessment and Exposure Standardisation recommends that the BfR incorporate uncertainty analysis as an integral part of every exposure and risk assessment. The uncertainty analysis should be attached to the dossier as a separate section. This permits a uniform and harmonised description of the uncertainties in exposure assessments, within the description of hazards and within risk characterisation. As the scientific debate on uncertainty analysis is still ongoing, the guidance document should be revised accordingly if necessary.
(Decision of the Committee for Exposure Assessment and Exposure Standardisation, following adoption of the guidance document at its 10th meeting on 18 and 19 April 2013).

6.2 Modules for specific applications

The guidance document attempts to cover the risk assessment for all agents that can have a damaging or disease-promoting effect on an organism or on a bodily organ. This includes both chemical substances, their reaction products or mixtures of natural and synthetic origin as well as biological substances (e.g. bacteria, viruses, fungi, prions etc. or the metabolites of plants, animals and organisms).

For specialised areas of risk assessment supplementary modules should be developed that take into account the specific needs and requirements.

6.3 Abstract

This guideline is a recommendation of the BfR Committee for Exposure Assessment and Exposure Standardisation. It is written to assist and facilitate the necessary procedures with regard to the development of health related scientific BfR opinions. One step of the assessment procedure is the assessment of exposure. The identification, the description and the evaluation of inherent uncertainties conducting this step should be supported by the document.

The main purpose of uncertainty analysis is to increase transparency regarding all elements of a risk assessment/exposure assessment and to support appropriate decision-making taking into account inherent uncertainty.

For the purpose of uncertainty analysis, it is advisable to use a multi-tier procedure using uncertainty factors (1st step), conducting qualitative uncertainty analysis (2nd step) and iterating to quantitative uncertainty analysis (3rd step), if necessary. This multi-tier procedure should, where possible, be associated with the entire process of exposure assessment. Uncertainty analysis with exposure assessment looks not only at the scenario but also the conceptual and mathematical model and the parameters, it should cover the process starting with the formulation of assessment questions and ending with the calculation and the model documentation.

Uncertainty analysis is often confined to the qualitative tier. Qualitative uncertainty analysis aims to create a systematic procedure for the verbal description of uncertainties. This guidance document provides assistance in the form of content specific questionnaires. If necessary, a quantitative assessment of the population exposure and inherent uncertainties is conducted.

The communication of uncertainty is an integral part of the risk communication. In particular, it addresses the questions of who might be affected by the exposure and by the remaining uncertainties, how serious the effects of the uncertainties might be, and which options for action (e.g. for prevention, reduction of exposure) exist on the current state-of-knowledge.

7 References and selected specialised texts

ECHA (2008). European Chemicals Agency (ECHA). Guidance on information requirements and chemical safety assessment Chapter R.19: Uncertainty analysis. Helsinki: European Chemicals Agency, 2008.
→ http://echa.europa.eu/documents/10162/13632/information_requirements_r19_en.pdf

EFSA (2006). European Food Safety Authority (EFSA). Guidance of the Scientific Committee on a request from EFSA related to Uncertainties in Dietary Exposure Assessment. Request No EFSA-Q-2004-019. EFSA Journal 438, 1–54.
→ http://www.efsa.europa.eu/en/efsajournal/pub/438.htm

Frey HC, Patil SR (2002). Identification and review of sensitivity analysis methods. Risk Analysis 22; 553–578.
→ http://onlinelibrary.wiley.com/doi/10.1111/0272-4332.00039/abstract

U.S. EPA (2008). U.S. Environmental Protection Agency (U.S. EPA). Child-Specific Exposure Factors Handbook 2008. Washington D.C.: EPA/600/R-06/096F, 2008.
→ http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=484738

U.S. EPA (2011). U.S. Environmental Protection Agency (U.S. EPA). Exposure Factors Handbook: 2011 Edition. Washington D.C.: EPA/600/R-09/052F, 2011.
→ http://www.epa.gov/ncea/efh/pdfs/efh-complete.pdf

WHO-IPCS (2008). World Health Organization (WHO)/International Programme on Chemical Safety (IPCS). Uncertainty and Data Quality in Exposure Assessment. Part 1: Guidance Document on Characterizing and Communicating Uncertainty in Exposure Assessment. Geneva: WHO-IPCS Harmonization Project Document No. 6, 2006.
→ http://www.who.int/ipcs/publications/methods/harmonization/exposure_assessment.pdf

7.1 Cited references

EEA (2013). European Environment Agency (EEA). Late lessons from early warnings: science, precaution, innovation. EEA Report No 1/2013. Copenhagen: European Environment Agency, 2013.
→ http://www.eea.europa.eu/publications/late-lessons-2

EFSA (2012). Europäische Behörde für Lebensmittelsicherheit (EFSA). Wenn sich beim Essen etwas zusammenbraut: bewährte Rezepte für die Risikokommunikation/Leitlinien für die Risikokommunikation. Parma: Europäische Behörde für Lebensmittelsicherheit, 2012.
→ http://www.efsa.europa.eu/en/corporate/doc/riskcommguidelines_de.pdf

IOM (2013). Institute of Medicine (IOM). Environmental decisions in the face of uncertainty. Washington, DC: The National Academies Press, 2013.

Morgan MG, Henrion M (1990) Uncertainty – A Guide to Dealing with Uncertainty in Quantitative Risk and Policy Analysis. Cambridge: University Press, 1990.

Saltelli A, Tarantola S, Campolongo F, Ratto M (2004). Sensitivity analysis in practice: a guide to assessing scientific models. Chichester: Wiley, 2004.

Xprob (2007). Mekel O, Mosbach-Schulz O, Schümann M, Okken PK, Peters C, Herrmann J, Hehl O, Bubenheim M, Fehr R, Timm J. Evaluation von Standards und Modellen zur probabilistischen Expositionsabschätzung. Berlin: WaBoLu-Hefte Nr. 02–05/2007.
→ http://www.uba.de/xprob/

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