Guidance on Uncertainty Analysis in Exposure Assessment

Recommendation of the BfR Commissions on Exposure Estimation and Standardisation (2008–2017) and Evidence-based Methods in Risk Assessment (since 2018) of the German Federal Institute for Risk Assessment

2nd edition[1], 12 September 2022

DOI: https://doi.org/10.17590/20220912-073707

[1] 1st Edition in German, https://www.bfr.bund.de/cm/350/leitfaden-zur-unsicherheitsanalyse-in-der-expositionsschaetzung.pdf

BfR authors:

Gerhard Heinemeyer (Managing Director of the BfR Commission for Exposure Estimation and Standardisation, 2008–2017)
Christine Müller-Graf (Executive Director of the BfR Commission for Evidence-based Methods in Risk Assessment)

Further authors:
Sub-Committee on Statistics/Uncertainty Analysis of the BfR Commission on Exposure Estimation and Standardisation (until 2017):
Olaf Mosbach-Schulz, Lothar Kreienbrock, Michael Schümann,
with the cooperation of BfR staff:
Gerhard Heinemeyer, Matthias Filter, Matthias Greiner, Matthias Herzler, Oliver Lindtner, Stephanie Kurzenhäuser, Bettina Roeder

Sub-Committee for Uncertainty Analysis at BfR
of the BfR Commission for Evidence-Based Methods in Risk Assessment (since 2018):
Natalie von Götz, Florian Fischer, Olaf Mosbach-Schulz, Yvonne Zens, Hubert Deluyker
with the support of BfR staff:
Christian Jung, Thomas Schendel, Matthias Greiner, Matthias Herzler, Stephanie Beyvers

Members of the BfR Commissions for Exposure Estimation and Standardisation (Expo, 2008–2017) and Evidence-based Methods in Risk Assessment (EBM, since 2018) of the German Federal Institute for Risk Assessment (BfR) 5

Executive summary 7

Preface to the 1st edition 9

Preface to the 2nd edition 10

1 Introduction 11

1.1 Aim of the guidance document 11
1.2 What is the purpose of an uncertainty analysis? 11
1.3 Basic principles of uncertainty analysis 12
1.4 Terminology and basic concepts 13
1.4.1 Exposure assessment within the framework of risk assessments 13
1.4.2 Variability vs. uncertainty 14
1.4.3 Introduction to tiered methods of exposure assessment and uncertainty analysis 15
1.4.4 Deterministic and probabilistic approaches 17
1.4.5 Quantitative and qualitative methods in uncertainty analysis 18
1.4.6 Expert Knowledge Elicitation 18
1.4.7 Sensitivity analysis as part of uncertainty analysis 19
1.4.8 Noxious agents 20
1.5 References to other guidance documents on uncertainty analysis 20

2 Content and structure of an uncertainty analysis 21

2.1 Aim and task of the exposure assessment 24
2.2 Exposure scenario 24
2.2.1 List of questions of the qualitative uncertainty analysis in relation to the exposure scenario 26
2.3 Exposure model 27
2.3.1 List of questions of the qualitative uncertainty analysis in relation to model selection 28
2.4 Parameters of the exposure model 29
2.4.1 Checklist of the qualitative uncertainty analysis in relation to model parameters 31
2.5 Exposure calculation method 32
2.5.1 Checklist of the qualitative uncertainty analysis in relation to the exposure calculation methods 33
2.6 Evaluation of the uncertainties and presentation of the results of the uncertainty analysis 34
2.6.1 Ranking 34
2.6.2 Semiquantitative scale 34
2.6.3 Quantitative estimation of uncertainty 35
2.6.4 Standardised representations of quantitative uncertainty analysis 36
2.6.5 Quantification of the overall uncertainty 36
2.7 Communication of uncertainties 37

3 Recommendations for the application of the guidance 38

3.1 Use in BfR risk assessments 38
3.2 Modules for special applications 38

4 References and selection of technical texts 39

4.1 References 39
5 Index 40
6 List of tables 41

Members of the BfR Commissions for Exposure Estimation and Standardisation (Expo, 2008–2017) and Evidence-based Methods in Risk Assessment (EBM, since 2018) of the German Federal Institute for Risk Assessment (BfR)

Walter Aulmann, Düsseldorf (Expo)

Christiaan Delmaar, Bilthoven (NL) (Expo)

Thomas Eikmann, Gießen (Expo)

Helmut Heseker, Paderborn (Expo, EBM)

Lothar Kreienbrock, Hanover (Expo)

Carolin Krems, Karlsruhe (Expo)

Olaf Mosbach-Schulz, Parma (I) (Expo, EBM)

Monika Neuhäuser-Berthold, Gießen (Expo, EBM)

Klaus Schneider, Freiburg (Expo)

Katrin Schröder, Hanover (Expo)

Michael Schümann, Hamburg (Chairman Expo)

Bernd Strassemeyer, Berlin (Expo)

Hubert W .Vesper, Atlanta (USA) (Expo)

Matthias Wormuth, Zurich (CH) (Expo)

Gerd Antes, Freiburg (EBM)

Florian Fischer, Ravensburg (EBM)

Sven Knüppel, Potsdam-Rehbrücke (EBM)

Christian Kohl, Quedlinburg (EBM)

Kerstin Schmidt, Rostock-Warnemünde (EBM)

Lukas Schwingshackl, Freiburg (EBM)

Henning Thole, Berlin/Gera (EBM)

Natalie von Götz, Bern (CH) (EBM)

Yvonne Zens, Cologne (EBM)

Gerhard Heinemeyer, BfR, Berlin (Managing Director Expo)

Christine Müller-Graf (Managing Director EBM)

Prepared by the Committees for Statistics/Uncertainty Analysis and for Uncertainty Analysis at BfR of the BfR Commissions for Exposure Estimation and Standardisation and for Evidence-based Methods in Risk Assessment of the German Federal Institute for Risk Assessment:

Michael Schümann (Ministry of Health and Consumer Protection, Hamburg)

Olaf Mosbach-Schulz (Rapporteur, European Food Safety Authority, Parma, I)

Lothar Kreienbrock (University of Veterinary Medicine, Hanover)

Hubert Deluyker (Antwerp, BE)

Florian Fischer (Ravensburg-Weingarten University of Applied Sciences, Ravensburg)

Natalie von Götz (Rapporteur, Federal Office of Public Health, Bern, CH)

Yvonne Zens (Institute for Quality and Efficiency in Health Care, Cologne)

Gerhard Heinemeyer (BfR, Berlin)

and other staff members of the German Federal Institute for Risk Assessment:

Matthias Filter, Matthias Greiner, Matthias Herzler, Oliver Lindtner, Stephanie Kurzenhäuser, Bettina Roeder, Christian Jung, Thomas Schendel, Stephanie Beyvers (BfR, Berlin)

Executive summary

This guidance document delineates the procedure recommended by the BfR Committee for Exposure Assessment and Exposure Standardisation and the BfR Committee on Evidence-based Methods in Risk Assessment for recording, describing and evaluating uncertainties in connection with public health related scientific statements. 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 the risk assessment process as a whole.
In principle, this guidance follows the previously published guidance documents of EFSA (EFSA Scientific Committee et al., 2018; IPCS & IOMC, 2008). The development of standardised procedures for uncertainty analysis, especially in the area of hazard characterisation, is currently subject to intensive discussion and considerable collaborative efforts at the international level, so that an update of this guidance may be necessary in the future.

The primary purpose of uncertainty analysis is to increase transparency regarding all elements of risk assessment and exposure estimation. In particular, uncertainty analysis should enable consumers, decision-makers and stakeholders to better understand risk assessments and to make their own decisions on a well-founded basis. Therefore, the uncertainty analysis should include the subject and question of the assessment, as well as the definition of the required protection goal. Deficits in knowledge about scenarios, models and parameters must also be described in an appropriate manner. This ensures that risk assessments contribute to informed decision-making under conditions of uncertainty.

The uncertainty analysis follows the sequence of the five steps of exposure assessment:

1. Interpretation of the assessment question
2. Definition of the scenario
3. Model development
4. Selection of the (model) parameters
5. Exposure estimation

As for the exposure assessment itself, in order to be efficient, it is appropriate to apply a tiered approach for the uncertainty analysis. For example, for qualitatively described exposure parameters (lower tier of exposure estimation), a qualitative description of the uncertainties is adequate (lower tier of uncertainty analysis). Furthermore, the uncertainty analysis informs the exposure estimation in determining the necessary tier (i. e. if relevant uncertainties are too large in a lower tier, a higher tier of exposure estimation may be necessary).

For the uncertainty analysis, the following tiered approach is recommended (from "simple" [1st tier] to "complex" [3rd tier]):

1. Tier: Application of uncertainty factors (if feasible)
2. Tier: Qualitative analysis of uncertainties (focus of this guide)
3. Tier: Quantitative analysis of uncertainties

This tiered approach should accompany, as far as possible, the full process of exposure assessment, which considers the mathematical model and parameters in addition to the scenario, but also includes the uncertainty of the question, the calculation and the model documentation.

Qualitative uncertainty analysis aims at a systematic procedure for the verbal description of uncertainties. The present guideline offers assistance in the form of predefined checklists, which enable an analysis of the following independent uncertainty dimensions mentioned in (IPCS & IOMC, 2008)

i **Degree of uncertainty:** Describes the possible deviation of the exposure estimate from the actual exposure
ii **Confidence in the knowledge base:** Covers the completeness of all available information that is relevant to estimate exposure
iii **Subjectivity of the choices made:** Outlines 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)

Uncertainty analyses should also assess the relevance of the uncertainties described in relation to the exposure estimate (i. e. the outcome variable). Methods of sensitivity analysis can be applied for this purpose. "Simple" sensitivity analyses consist, for example, of changing parts of a model or parameters individually and examining the influence on the target variable. Sensitivity analyses are also used in the context of model development to identify important influencing factors for which the modelling should be detailed. Identifying and naming the most appropriate model variables to prevent or mitigate exposure is also an essential product of a sensitivity analysis.

The items of the checklists included in this guidance document can be used for simple qualitative sensitivity analysis. The insights gained by the answers can help to discriminate between certain and uncertain statements and results, which is helpful for risk communication. This permits a substantiation of the "certainties", i. e. the certain ranges of the expected exposure in contrast to the possible ranges.

Preface to the 1st edition

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)

Preface to the 2nd edition

The first edition of the Guidance Document on Uncertainty Analysis in Exposure Assessment provided a solid basis for the German Federal Institute for Risk Assessment (BfR) to integrate the important aspect of uncertainty analysis into risk assessment. In line with the concept of the first edition, the guideline was tested during the preparation of various opinions and reports at the BfR. Furthermore, the guideline was compared with the corresponding, new guideline of the European Food Safety Authority (EFSA) on the basis of case studies. This work has shown that the guidance is practical and useful. At the same time, possibilities for improvement were identified.

This second edition of the guidance takes into account the results of the test phase. The most important change concerns the checklists that in the 1st edition introduced the different dimensions of uncertainty analysis (extent of uncertainty, subjectivity of the decisions made and confidence in the knowledge base). These checklists have now been replaced by a description of the dimensions in the text section in order to streamline the process and sharpen the separation of content from the actual checklists for the identification of uncertainties.

In the course of this endeavour, also the evaluation of the uncertainty analysis and its documentation were adapted. To facilitate applicability, the extent of uncertainty is now explicitly assessed for each type of uncertainty. Also, the subjectivity of the decisions made and the confidence in the knowledge base can now be described more comprehensively. In addition, a new assessment option for the extent of uncertainty has been introduced.

In general, more space was given to the quantitative assessment of uncertainties: The comparison of the advantages and disadvantages of a quantitative or qualitative uncertainty assessment was supplemented and a recommendation added that at least the total uncertainty should be quantified within the scope of the available resources.

The update of the Guidance has been elaborated by members of the sub-committee "Uncertainty Analysis" of the BfR Committees for Exposure Assessment and Exposure Standardisation and Evidence-based Methods in Risk Assessment. The aim of the update was to further improve practicability of the original guidance. The group of authors hopes that the revisions will allow staff to use the guidance even more effectively.

Natalie von Götz and Maged Younes
(Chairs of the Panel Evidence-based Methods in Risk Assessment)

1 Introduction

This guidance is intended to support exposure assessment in the context of risk assessment. The commissions that have developed this guidance document are scientific advisory bodies of the German Federal Institute for Risk Assessment. The guidance document can therefore be understood as a supplement to other guidance documents already prepared by BfR and used as a basis for its assessments. Furthermore, it can also be considered an introduction to uncertainty analysis and a possible tool for other parts of the risk assessment.

1.1 Aim of the guidance document

The German Federal Institute for Risk Assessment (BfR)[2] produced a *guideline for health assessments* to improve the comprehensibility and clarity of scientific statements, to contribute to a harmonised terminology in risk assessment and thus to ensure the best possible scientific advice in the remit of the BfR. The present *guidance document on uncertainty analysis in exposure assessment* is intended to guide uncertainty assessments that will further complement and specify risk assessments. The aim here is to achieve a uniform procedure for recording, describing and evaluating uncertainties in connection with scientific health risk assessments.

The present version of this guidance document focuses on the area of exposure assessment. However, uncertainty analysis is also relevant for hazard and risk characterisation. In a subsequent step, it should therefore be examined to what extent the principles presented here for the area of exposure assessment can be helpful for the other parts of the risk assessment. Some information in this respect is already available from the WHO-IPCS *Guidance document on evaluating and expressing uncertainty in hazard characterization* (World Health Organization & International Programme on Chemical, 2018).

With the help of this guidance document, the possibilities and limitations of a harmonised methodology for uncertainty analysis should be demonstrated. Other overarching goals of this guidance document are to provide guidance on communicating uncertainties in a transparent manner that is appropriate for the target audience.

Without an adequate description and analysis of uncertainties, a scientific health risk assessment is incomplete. The analysis and communication of uncertainties should help to enable consumers, stakeholders and decision-makers to understand the risk assessment and make their own informed decisions.

1.2 What is the purpose of an uncertainty analysis?

The uncertainty analysis serves to create transparency on all aspects of the risk assessment. It also includes the consideration of the terms of reference of the exposure assessment and the definition of the protection goal. Therefore, it is an integral part of the exposure and hazard characterisation.

In many cases, knowledge about scenarios, models and parameters is inaccurate, incomplete, flawed or the data used are not representative or of insufficient quality for the purpose of the assessment. Nevertheless, the available knowledge must be used in the best possible way to prepare informed decisions under uncertainty. To ensure that the results of the exposure assessment can be interpreted adequately, the uncertainties must be described appropriately. The uncertainty analysis describes the limits of the available knowledge and the resulting inaccuracies of the exposure assessment.

[2] https://www.bfr.bund.de/cm/350/leitfaden-fuer-gesundheitliche-bewertungen-bf.pdf

The verbal description of uncertainties is also an integral part of the communication of the risk assessment. The communication addresses which target groups could be affected by the uncertainties, how serious the effects of uncertainties can be and which options for action exist.

1.3 Basic principles of uncertainty analysis

The steps of uncertainty analysis follow the sequence of exposure assessment: terms of reference, the risk question, definition of the scenario, development of the model, choice of (model) parameters and exposure estimation[3]. Each step must be considered separately.

Furthermore, both exposure assessment and uncertainty analysis follow tiered concepts, which, however, must be clearly separated from each other (for the tiered concept, see Chapter 1.4.3).

The following guiding principles, based on WHO-IPCS (IPCS & IOMC, 2008) form the external framework that should be aimed for in any uncertainty analysis. The "additional effort" depends on the task and the respective data situation. The benefits gained from such an analysis will more than compensate for this additional effort.

1. Uncertainty analysis is an integral part of exposure and risk assessment.
2. The uncertainty analysis shall follow a tiered approach and be adapted in the necessary level of detail for the requirements (e. g. protection goals and groups) of the exposure assessment.
3. The sources of uncertainty and variation should be systematically identified and evaluated in exposure and risk assessment.
4. Dependencies between model inputs are 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. An uncertainty analysis includes the description of the possible effects of various sources of uncertainty (e. g. scenario, model and parameters) on the outcome. Thereby, it also serves to identify sources of uncertainty (e. g. by sensitivity analysis) as more or less relevant. This may also help to identify measures that are best suited to prevent or reduce the risks.
7. The uncertainty analysis shall be documented comprehensively, systematically and transparently, taking into account qualitative or quantitative aspects of methods, scenarios, models, parameters, data, results, sensitivity analysis and interpretations.
8. The uncertainty analysis should be transparent in order to allow internal or external peer review.
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. The communication of the results of the uncertainty analysis must be adapted to the requirements of the various stakeholders. It should be understandable, transparent and comprehensible.

[3] In this document in most places "exposure assessment" has been used to describe the overall process for assessing (including interpretation of the assessment question, definition of the scenario etc.) whereas "exposure estimation" describes the subprocess of determining a (quantitative or qualitative) exposure estimate. Sometimes, a clear distinction is not possible.

1.4 Terminology and basic concepts

1.4.1 Exposure assessment within the framework of risk assessments

Exposure describes the contact of individuals (e. g. humans, animals) with harmful agents. In this guide, these can be chemical substances, their degradation or reaction products, mixtures, biological agents as well as metabolic products of microorganisms. Exposure assessment is one of the four integral components of risk assessment. An exposure assessment aims to determine the level of exposure, usually using mathematical methods. For this purpose, a large amount of information has to be combined, e. g. physical or chemical properties, data on the origin and distribution of the harmful agent, information on the behaviour of the exposed individuals (e. g. contact time or consumption behaviour etc.) as well as personal characteristics (e. g. height, weight, age etc.). In the process of risk characterisation, the results of the exposure assessment are related to the hazard, so that the risk is a description of the probability of the occurrence of a negative health effect.

The BfR Guideline on Exposure Assessment should be followed when preparing an exposure assessment. Furthermore, the guideline provides guidelines for scenario and model building, for the selection of parameters and for the methodological approach.

1.4.2 Variability vs. uncertainty

Probabilistic exposure estimation allows the definition of model parameters in terms of a probability distribution rather than a single value, e. g. by using a method referred to as Monte Carlo simulation[4]. This applies to two fundamentally different situations that describe either variability or uncertainty of a parameter. Variability is expressed, when a distribution rather than a single value is chosen to represent the true quantity (e. g. a normal distribution of individual body weights). Uncertainty is expressed, when a distribution rather than a single value adequately describes the available knowledge about the true parameter (e. g. a normal distribution defined by the point estimate and standard error of an estimated mean food intake). However, it is important to note that this distinction equally applies to so-called deterministic modelling which involves the calculation of single values as outcome estimate (see section on tiered methods below). In this case variability and uncertainty can be expressed using different single values for the outcome estimate for instance for various age groups (variability) or model alternatives (uncertainty).

For distinguishing uncertainty and variability (Morgan & Henrion, 1992)) propose the so-called "clarity" test. The basis of their considerations is the "measurable variable", which is assumed to be constant (for a specific person in a specific situation) under hypothetical, ideal conditions. Deviations in the magnitude of this quantity, which arise due to imprecise methodology, constitute the uncertainty of the measurement. Deviations resulting from differences in the "measurable quantity" at different times, in different places or among different persons etc., constitute the variability of the parameter in the population under consideration.

The following definitions are recommended to describe variability and uncertainty in exposure estimation:

Variability reflects the fact that a variable is observed under different conditions. This generally refers to existing differences between individuals[5], and/or variation in time and space. Variability describes a property of the population. Variability in the population should be described but cannot be reduced. However, the variability in the data used for an assessment can be reduced by applying selection criteria (e. g. excluding individuals with specific traits). Stratification is another approach to reduce variability within the generated strata of the data. Changes over time occur on individual level (repeated observations, individual growth, changed behaviour or traits) as well as population level (population trends). The latter are often considered along with spatial factors. 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 as well.

Uncertainty reflects the fact that the knowledge required for any step of the estimation process (problem formulation, scenario, model, parameters, calculations) is limited. Parameter uncertainty may be due to measurement errors at the individual level of observation and all sources of bias when selecting and aggregating observations into summary statistics for a given target population. 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 sub-groups (e. g. age groups, specific intake and behavioural habits, regional population groups) ensures that the diversity of exposure conditions in the population is taken into account. Separate description of variability and uncertainty also supports the development and selection of useful

[4] In probabilistic (or stochastic) modelling simulated values are random numbers drawn as realizations from the defined probability density functions.
[5] "Individuals" in this sense may be living or and non-living individual elements from the respective source population.

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).

1.4.3 Introduction to tiered methods of exposure assessment and uncertainty analysis

Tiered approaches are standard practice in the field of exposure assessment. The workload can thus be limited to the extent necessary for a given question.

As a starting point for an iterative exposure assessment, extreme settings for the influencing factors (e. g. upper percentiles of the distributions) can be chosen in order not to underestimate exposure and health risk. An exposure assessment therefore starts with a rough, generic scenario and is gradually refined by additional stratifications in order to be able to more accurately represent reality with all its differences (e. g. with regard to food composition, quantity and origin of consumed food, forms of application of household products etc.). An accompanying uncertainty analysis is required to justify when modelling is sufficient and the process of refining the exposure model can be considered to be completed. The stepwise refinement may concern the scenario, the model and/or the parameters.

1. **Iteration: Initial exposure estimation**
   Exposure estimation based on a generic exposure scenario with default values (see following definition) as parameters (Initial exposure estimation)
2. **Iteration: Deterministic exposure estimation** (see Chapter 1.4.4)
   Exposure estimation based on a specific and refined exposure scenario and corresponding model with, if necessary, several stratifications, e. g. by gender, age and consumer groups, and deterministic estimation of the exposure estimate using defined values of descriptive statistics (point estimates, e. g. mean, 95^{th} percentile).
3. **Iteration: Distribution-based exposure estimation** (see Chapter 1.4.4)
   Exposure estimation based on a specific and refined exposure scenario and corresponding model with fine stratifications and distribution-based estimation of the target quantity using probabilistic methods, including the description of the distribution of the target quantity.

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

The following definitions are recommended to distinguish the different uses of so-called default values:

Default values are quantitative values that are inserted into a model as a substitute for missing parameters when there is no empirical basis for a direct estimate. These can include surrogate values (theoretical derivations from auxiliary variables, e. g. body surface area calculated from body weight and height), extrapolations (e. g. the transfer of results from other populations) or expert judgements. In addition to parameter uncertainty, the uncertainty analysis also includes model uncertainty in the case of transfer, extrapolation or expert judgement.

Reference values, or better reference ranges (standard default), are quantitative characteristics (e. g. mean, median or 95th percentile) of a varying parameter in a well-defined population or scenario that are used to simplify the calculation in the model. When inserted into the model equations, fixed values are obtained, which – as point estimates – are intended to cover[6] the central tendency (mean, median) or a substantial part of the variance (95th percentile) of the respective exposure factor.

Reference values can also be used as a benchmark to assess the outcome of modelling, e. g. reference values from other exposure studies or also from human biomonitoring. Collections of reference values for different populations can be found, for example, in exposure factor manuals (such as U.S. EPA (U.S. EPA, 2008, 2011)). Quantitative uncertainty considerations in the use of reference values refer, for example, to the statistical parameter uncertainty resulting from the limitation of the underlying sample size. Qualitative considerations discuss, among other things, the transferability of the parameters of a reference population to the target population of the analysis.

Exposure estimation at a low iteration level considers uncertainties such that underestimation is avoided, which typically leads to an overestimation of the exposure and thus the risk. This so-called conservative approach can be ensured, for example, by the mathematical combination of assumptions that lead to an upper bound exposure estimate. If such an upper bound estimate does not give rise to concerns when transferred to the risk of the target population, the same can be assumed for the actual exposure in the population. If there are otherwise no serious restrictions from other sources of uncertainty, compliance with the protection goals should be achieved, if the upper bound exposure estimate has a sufficient margin of safety to the protection goals/toxicological reference values (such as TDI, ADI). The uncertainty analysis should evaluate whether the assumptions in the exposure assessment actually lead to a conservative estimate.

The higher tiers of the exposure assessment aim to reflect the actual exposure for highly exposed subgroups and the variation within the total population.

The uncertainty analysis is not an error analysis, but supports the exposure assessment in determining the necessary iteration level of the exposure model. Irrespective of this, a tiered approach is also recommended for the uncertainty analysis in order to limit the workload to the necessary extent.

[6] In this context, it should be examined whether a sufficient risk coverage is achieved through the combination of different influencing variables.

1st Tier: Application of uncertainty factors
Uncertainty analysis in which, for example, the required distance (quotient) between the exposure estimate and the hazard endpoint is increased by means of fixed uncertainty factors. Uncertainty factors[7] usually reflect necessary extrapolations in the risk assessment. This stage of uncertainty analysis can be skipped in some areas where, for example, no reference value is available.

2nd Tier: Qualitative analysis of uncertainties (see Chapter 1.4.5)
In qualitative uncertainty analysis, the sources of uncertainty are systematically identified and documented.

3rd Tier: Quantitative analysis of uncertainties (see Chapter 1.4.5)
In quantitative uncertainty analysis, the remaining uncertainty is quantified and added as an additional dimension to the exposure estimate. These are e. g. sensitivity analyses, confidence intervals for point estimators or two-dimensional simulations in distribution-based modelling.

Systematic analysis of the sources of uncertainty is possible and appropriate at all stages of the exposure assessment. Here, as a rule, a lower tier of the exposure assessment will also entail a lower tier of uncertainty analysis. In principle, however, all combinations are possible.

Uncertainty analysis must therefore accompany the complete process of exposure assessment, which considers not only the scenario, the mathematical model and the parameters, but also includes the uncertainty of the question/terms of reference, scope as well as the conceptual model, the calculation and the documentation of the model. For an exposure assessment, tiered uncertainty analyses offer numerous advantages: On the one hand, the qualitative approaches, as implemented in this guideline predominantly with the help of checklists, provide a starting point that can be carried out for any exposure assessment. On the other hand, available information is systematically structured, evaluated on the basis of fixed criteria and, in turn, existing information gaps can be identified and their significance assessed.

The iterative procedure of exposure assessment is supported by presenting and documenting priorities for model improvement based on the significance of the information gaps. These can then justify the selected level of detail of BfR opinions. The quantitative methods describe the uncertainty that remains in the estimation and the result in a standardised and transparent form.

1.4.4 Deterministic and probabilistic approaches

Deterministic estimates are calculations of health risk or exposure that use fixed numerical values for all quantitative model input. These can describe an average or an upper bound exposure scenario. The result is a single value for the exposure estimate: the (deterministic) point estimate. In the first and second tier of the exposure assessment, conditions for the influencing factors that result in an upper bound estimate (e. g. upper percentiles of the distributions) can be combined in order not to underestimate the health risk or exposure (“worst-case” scenario). Reference values are often used in the calculations to estimate a mean risk or exposure. Confidence and uncertainty intervals are used to describe the uncertainty of the reference values. However, statements about the variation and uncertainty of exposure within the population can only be obtained with a probabilistic approach, which can include both aspects in the analysis.

The aim of the probabilistic approach is to represent the entire possible value spectrum of the exposure of a population along with its likelihood in form of a probability distribution (IPCS &

[7] In some areas of application, the term “safety factors” is used as an alternative.

IOMC, 2008). For this purpose, distributions for all influencing variables are included in the calculations, which are linked e. g. by means of Monte Carlo simulations and other methods. Probabilistic estimates therefore reflect the variation of the health risk or exposure in the population. The distributions of the model parameters are estimated from empirical data. The uncertainty of the target quantity is then obtained by combining the uncertainties of the model parameters e. g. using two-dimensional Monte Carlo simulation.

1.4.5 Quantitative and qualitative methods in uncertainty analysis

Qualitative uncertainty analysis allows for the systematic and comprehensive listing of all sources of uncertainty and, in part, a discussion of the direction and strength of their influence on the target variable. For this purpose, checklists are used that consider relevant sources of uncertainty. This analysis applies to all steps of the exposure assessment.
A qualitative description of uncertainty has the disadvantage that it has to be interpreted and the interpretation of qualitative expressions is subjective. The meaning of the statement “low uncertainty”, for example, can be different for different people. Furthermore, it is unclear how individual, qualitatively assessed uncertainties can be meaningfully combined with each other.

Quantitative uncertainty analysis allows the description of a range of probable values of the target variable. If, for example, empirical data are used to estimate model parameters and distributions, statistical methods can be used to specify the parameter uncertainty in the form of confidence intervals (for individual parameters) or bands (e. g. for functionally dependent parameters or a distribution function). As a result, the target variable can be represented by a probability distribution. Quantitative methods have the disadvantage that they require (sometimes significantly) more resources, time and training, since, for example, more information has to be extracted from the data or a more complex calculation has to be carried out.

If, on the other hand, summary statistics from the literature, expert estimates or default values are used for the model parameters, it can be difficult to quantify the uncertainty: Here, assumptions about the degree of uncertainty contained must usually be given in the form of value ranges (e. g. from ... to ...) or appropriate distributions. The same applies to the consideration of scenario and model uncertainty. One way of arriving at an assessment here is, for example, to draw on structured expert knowledge (see the following chapter).

1.4.6 Expert Knowledge Elicitation

In an Expert Knowledge Elicitation (EKE), a query protocol is used to try to retrieve and combine the knowledge of experts with as little subjective bias as possible. This is ensured by a protocol developed for this purpose. An important aspect here is that the experts’ assessments of the results are discussed and consensus is reached on as equal a basis as possible. With an EKE, both individual parameters (e. g. the growth rate of a microorganism under certain transport conditions) and the joint effect of several influencing variables on a result (e. g. of several uncertainties on the overall uncertainty) can be assessed.

An EKE also requires a specially trained discussion leader. This generally increases the cost of this method compared to pure expert knowledge. However, if such a facilitator is available, EKE can in principle be carried out with very few experts. Depending on the experts available and the preparation material and time, one speaks of formal EKE (the protocol was followed in all requirements) or informal EKE (at some steps, especially in the recruitment of experts, deviation from the protocol occurred).

The result of an EKE includes, on the one hand, a probability distribution of the possible results of the assessment/parameter/exposure estimate and, on the other hand, careful documentation of the main points of discussion among the experts in order to transparently communicate the considerations that led to the result.
A detailed description of the methodology, requirements and further possibilities of EKE can be found in the EFSA guidance developed for this purpose (EFSA, 2014).

1.4.7 Sensitivity analysis as part of uncertainty analysis

The term sensitivity analyses refers to procedures that measure and compare the influence of variation and possible uncertainties from model input on the target variable (Frey & Patil, 2002; Saltelli, Tarantola, Campolongo, & Ratto, 2002).

Sensitivity analyses have two tasks. They support model development and provide information on the influence of the scenarios, models and parameters on the result.

Assessing the strength of influence of individual factors requires a quantitative description of the variation and uncertainties of individual model parameters. Fixed deviations (e. g. 20 ± %), changes by one unit (e. g. number of product applications per day), empirical ranges (e. g. mean ± standard deviation), uncertainty distributions or mathematical analytical methods of model analysis can be applied here. These methods usually apply a calculation procedure in which only one parameter of the model is changed at a time compared to a standard case (e. g. a mean value for all other parameters). In distribution-based (probabilistic) sensitivity analyses, the strength of influence of the factors contained can be quantified simultaneously for several variables with the help of statistical methods.

At the stage of model development, sensitivity analysis allows the identification of less relevant drivers for which modelling can be kept rather coarse, or the identification of important drivers for which modelling should be precise. In an exposure assessment, the sensitivity analysis identifies those factors with high sensitivity that either offer the greatest opportunity for management action (e. g. large population variation) or define a need for further research. The sensitivity analysis can justify the need for research on significant drivers or rough estimates of less influential drivers.

It should be noted, however, that the results of a sensitivity analysis are always limited to the examined scenarios, models and distribution models for parameters.

Sensitivity analyses can therefore also help to clarify what influence the variability and uncertainty of the input variables have on exposure estimate. In this context, it can be examined, among other things, which combinations of exposure conditions lead to the highest exposures, which ranking of the influence on the exposure estimate is determined for the input variables considered and which of the variables – that are accessible for prevention – are to be classified as effectively reducing exposure. The influence of uncertainties of the scenarios, models and parameters on the exposure estimate can thus be evaluated.

The findings obtained from sensitivity analyses thus support the distinction of statements which are certain and others which are uncertain in risk communication. Particularly in the case of an incomplete data situation or an exposure assessment conducted at very short notice, they serve, even in a rough form, as a helpful instrument for

- the modelling,
- alternative calculations,
- the interpretation,
- the evaluation of the strength of influence
- and the communication of the results of the assessment.

A classification of the possible effect of incomplete scenarios and models (in particular the omission of intake routes or exposure sources) as well as of possible biases of the results due to the selected data (e. g. selection of quantitative values for parameters of the model equations) is possible through comparison of alternative calculations as part of the sensitivity analysis. On the other hand, sensitivity analysis also allows an indication of the certainty of the present estimate.
The identification of the most appropriate model variables to prevent or mitigate exposure is an essential product of an exposure assessment. It has a high priority in risk communication. The possibility of controlling an exposure by risk management is also an essential aspect for the subsequent communication of uncertainties.

1.4.8 Noxious agents

The term “noxious agent” is used in this guideline as a generic term for all agents that can have a harmful or pathogenic effect on an organism or on a body organ. Therefore, the term “noxious agent” is used in this guidance for chemical substances, their degradation or reaction products or mixtures (of natural or synthetic origin) as well as for biological agents. The latter are e. g. bacteria, viruses, fungi, prions etc. or the metabolic products of plants, animals and microorganisms.

1.5 References to other guidance documents on uncertainty analysis

This guideline was developed and adapted specifically regarding the needs, procedures and applications at the German Federal Institute for Risk Assessment (BfR). However, it was based on various international guidelines on uncertainty analysis in health risk assessments and is thus of general validity.

In December 2006, the Scientific Committee of the European Food Safety Authority (EFSA) adopted and published guidance on uncertainty analysis in estimates of exposure to contaminants from food (EFSA, 2007). Building on this guidance, EFSA published a more generally applicable guidance on uncertainty in scientific assessments in 2018 (EFSA Scientific Committee et al., 2018). That guidance puts a strong emphasis on quantitative description of uncertainties and in particular quantification of the overall uncertainty. It provides a detailed description of many methods for the qualitative and quantitative description of uncertainties.

The harmonisation project of the WHO International Programme on Chemical Safety (WHO-IPCS) issued guidance on characterising and communicating uncertainties in exposure estimation in 2008 (IPCS & IOMC, 2008). A hierarchical procedure is described in four stages: screening, qualitative, quantitative and population-based uncertainty analysis. The qualitative assessment is also presented in tabular form with an assessment of the strength of uncertainty, appraisal of the knowledge base and assessment of subjectivity. An analogous guideline for characterising and communicating uncertainties in hazard identification has been published in 2018 (IPCS-WHO, 2018).

Building on this work, in May 2008 the European Chemicals Safety Agency (ECHA) issued the implementation of uncertainty analysis in the REACH process in Chapter R.19 of the Guidance on Information Requirements and Chemical Evaluation (ECHA, 2012).

In the new editions of its Exposure Factor Handbook, the (U.S. EPA, 2008, 2011)(U.S. EPA, 2008, 2011)(U.S. EPA, 2008, 2011)US Environment Protection Agency (U.S. EPA, 2008, 2011) also addresses the consideration of uncertainties in exposure assessment. Here, the

assessment of the data quality for the reference values (represented as percentiles of the distribution) and the discussion of the validity of the reference values used for the respective target population are in the focus of the uncertainty consideration.

In Chapter 2 qualitative stages of uncertainty analysis are described and discussed (more detailed explanations are given in the following sections).

2 Content and structure of an uncertainty analysis

This guidance document primarily describes a qualitative methodology for the systematic identification and assessment of uncertainties. For a more detailed description of the methodology of quantitative uncertainty assessment, please refer to EFSA's guidance on uncertainty analysis (EFSA Scientific Committee et al., 2018).

The starting point of any uncertainty analysis (whether qualitative or quantitative) is the identification of uncertainties, which is also presented here below. A subsequent qualitative assessment of these identified uncertainties can also be helpful in the context of a quantitative uncertainty analysis, e. g. in the prioritisation of uncertainties. Thus, the procedure described here can also be the starting point for a quantitative continuation of the uncertainty analysis. It should be noted that even in the case of a purely qualitative assessment of uncertainties, a quantitative description of the overall uncertainties (e. g. by Expert Knowledge Elicitation, see Chapter 1.4.6) is possible and should at least be considered because the interpretation of the results is easier.

The qualitative uncertainty analysis is described in detail below. The uncertainty analysis follows the exposure assessment in the following steps:

1. Interpretation of the terms of reference, definition of aim and scope (see Chapter 2.1)
2. Exposure scenario (see Chapter 2.2)
3. Exposure model (see Chapter 2.3)
4. Parameters of the exposure model (see Chapter 2.4)
5. Method of exposure assessment (see Chapter 2.5)
6. Evaluation of uncertainties and presentation of the results of the uncertainty analysis (see Chapter 2.6)
7. Interpretation and communication of uncertainties (see Chapter 2.7)

Steps 1 to 5 of the exposure assessment are subject to a qualitative uncertainty analysis. In this guidance document, the analysis is performed by systematically identifying and characterising the uncertainties using checklists. Suitable templates for these checklists can be found in a separate document. Steps 1 to 6 are related to each other. As a consequence, the processing of the preceding steps may have an impact on the following steps. After answering the questions, the evaluator should be able to summarise the main points of uncertainty in a text. This final description is the last step in the qualitative uncertainty analysis.

The checklists produced in this document support the analysis of uncertainty of all elements according to the three independent dimensions mentioned in (IPCS & IOMC, 2008)). These can be summarised as follows:

i **The level of uncertainty of the exposure assessment** comprises the possible deviation of the exposure estimate from the actual exposure. On a qualitative scale, this means the assessor's estimate of how much the result of the exposure estimate can change due to a given uncertainty. Ways to formalise this description (e. g. by ranking) are described in Chapter 2.6.

ii **Confidence in the knowledge base of exposure assessment** encompasses the completeness of all available information that can be used for exposure assessment. The four aspects of this dimension are completeness, reliability, consistency and robustness of the knowledge base.

In the context of assessing the completeness of the knowledge base, questions are asked about whether the entire knowledge base has been compiled or whether this has not been done (e. g. due to time constraints), whether the knowledge base contains weak points or whether the knowledge base is sufficient to answer the necessary question at all. A possible “publication bias” must be taken into account when assessing the completeness of the knowledge base.

Reliability includes sufficient justification of the methodology in the underlying studies, whether the knowledge base is sufficiently up-to-date and – if expert opinion was used – how appropriate the use of this is.

Consistency involves assessing whether the available studies are free of contradictions or whether heterogeneity of the studies can be explained. Methodological aspects are also included, e. g. whether the procedure used corresponds to the state of the art.

Robustness assesses the extent to which the knowledge base is suitable to actually answer the specific question in the exposure assessment. For example, to what extent a study has actually investigated exactly the parameter that is necessary for the model, or whether the accuracy of the measurement is at all sufficient to parameterise the exposure estimate with sufficient precision.

iii **The subjectivity of choices made in the exposure assessment** includes the justifications for the choices made within the scientific community, but also between stakeholders of the assessment (e. g. risk managers and assessors). Examples of such decisions include (not) creating a scenario for children and adolescents, (not) using a study for a parameter, and deciding to use a particular model rather than another. The determination of a parameter with the help of an expert opinion is also ultimately a choice and must be documented as such.
Questions to be considered here are, for example, whether and which alternative decisions exist, to what extent different experts represent the same position and whether the decision was made in this way due to limited resources (e. g. research funds or time). The consideration whether a conflict of interest may have influenced the decision also falls under this dimension.

In principle, each of these dimensions affects each of the identified uncertainties. In many cases, however, it is already clear at the outset which decisions have an impact on the assessment process or the exposure estimate, or how good the knowledge base is for the variables to be used. Furthermore, many of the aspects in the individual dimensions overlap (e. g. the decision not to include a study in the assessment because of deficiencies affects both aspects of the knowledge base and the subjectivity of a selection made). It is important to document knowledge/non-knowledge as well as existing options and decisions made.

Checklists to identify existing uncertainties

As already mentioned, checklists in the form of tables are used in this guidance to identify the individual uncertainties. It is recommended to note down continuously all answers already during the working process. Possibilities to document the results in a standardised way are described in Chapter 2.6.3.
It should be noted that not all questions and criteria have the same relevance for all steps of the exposure and risk assessment. Some questions may therefore remain unanswered.

If an identified uncertainty is relevant for answering several questions, it is recommended to either mark this separately or to select one particular question after addressing the whole list and document it only there.

2.1 Aim and task of the exposure assessment

Any exposure or risk assessment should have a clear objective and question. Risk management and risk assessment are often institutionally separated.
Thus, before the assessment process begins, the question emanating from risk management often needs first to be translated into a task suitable for risk assessment.

A task is precise and unambiguous, whereas a question can often contain ambiguous and imprecise terms. For example, the question might ask "assess whether certain maximum levels in a food are safe". In this question it is unclear what exactly is meant by "safe".

In principle, there are two ways to resolve these inaccuracies: consultation with the risk manager or determining interpretations and subsequent practical implementation oneself. The first option is preferable in principle, but consultation is often not possible in terms of time or is impractical in other ways. In the second option, the risk assessment determines how unclear terms are interpreted. For example, the practical implementation for the term "children" could be to select a specific age range.
Other common determinations that may also arise from the question are:

- Are acute and/or chronic risks considered? E. g. for a chemical that shows no acute adverse effects, it may be determined that only long-term exposure scenarios are necessary.
- What are the vulnerable groups (general population, children, nursing mothers, …) to be considered and how are they exactly defined? For example, when it comes to exposure during the application of plant protection products in greenhouses, only the exposure of adult users might be relevant.
- Should model parameters be estimated more conservatively or realistically? For example, to compare different input pathways for a household chemical, it might be relevant which one has the largest contribution, because in that case a conservative estimate could bias the result.

If such decisions are made, they shall be documented as part of the uncertainty analysis/risk assessment and communicated to the risk manager as part of the response.

The verbal description of the scenario with the model parameters and target variables contained therein and the assumed interrelationships in a so-called "semantic model" can be helpful to further analyse the objectives and questions. The semantic model conceptually corresponds to a linguistic description of the exposure scenarios considered relevant. The model parameters and target variables and their assumed interactions should be described in it as concisely and clearly as possible. A description of the vulnerable population group should also be provided.

The following list of questions for qualitative uncertainty analysis serves as a guide for formulating complete objectives and questions and clarifying the aims and terms of reference between risk management and risk assessment.

2.2 Exposure scenario

The exposure scenario describes the situation and framework within which contact with a harmful agent is considered for the vulnerable group. This can be roughly described with the four steps: "generation/release", "dispersion", "decrease/degradation" and "contact" with the contaminant or noxious agent. While "generation/release" describes the characteristics and source of the noxious agent, "dispersion" follows the material flow through all media from generation to "decrease/degradation" of the concentration or the amount of substance in the contact/exposure medium. It may also have to take into account multiplication and inactivating

processes (microbial contaminants). “Contact” includes all circumstances that describe the behaviour of the exposed persons and the resulting intake of the contaminated media.

With the definition of the exposure scenario, i. e. the simplification of a concrete exposure situation, there is usually also a limitation of the framework under which an exposure of the population is possible. Exposure scenarios can be defined generically or in detail, or in aggregated form.

The uncertainty analysis of the exposure scenarios essentially has the task of checking the completeness of the intake routes and exposure sources considered and justifying the selection decisions and simplifications made.

Analogous to (IPCS & IOMC, 2008) following sources of uncertainty in the exposure scenario should be considered:

- “Formation”: Characterisation of the origin and formation of the noxious agent in the source
- “Release”: Exposure source/origin and media.
- “Dispersion”: Possible pathways of exposure
- “Reduction”: Information on the reduction of the amount of substance
- “Increase/propagation”: Information on the formation of substances or the multiplication of e. g. microbial agents.
- “Contact”: Exposed groups of people/population: characterisation of the spatial, temporal and other (e. g. socio-economic) context.
- Exposure events:
  - spatial, temporal and situational differences in the exposure scenario: lifestyles/behavioural patterns/product use/microhabitats
  - risk management measures to be considered

The following list of questions (see Tab. 1:) can be used to characterise the scenarios.

2.2.1 List of questions of the qualitative uncertainty analysis in relation to the exposure scenario

Tab. 1: Checklist of the qualitative uncertainty analysis in relation to the exposure scenario

Criterion	Questions[8]
Origin, Source Characterisation	Is the noxious agent to be assessed defined with sufficient precision? Are there degradation products that need to be included in the exposure estimation? Does the noxious agent occur predominantly in combination with other hazardous noxious agents, so that it is to be regarded as the leading substance of a group of noxious agents? Are the properties of the noxious agent sufficiently known?
Release	Are all primary sources of the noxious agent known? Is the complete material flow (e. g. quantity balance) of the noxious agent of origin, distribution and removal known? Are there multiple sources of the noxious agent that occur in a correlated manner? Are migration, release or cross-contamination possible?
Spread	Can the flows to the secondary contact media (air, drinking water, water, food, products[9]) be fully traced? Are the exposure pathways fully considered (including background exposure or inputs from other sources)? Are the exposure pathways under consideration clearly characterised? Can heterogeneous groupings be considered together by summarizing the influencing factors, the products, the life situation depicted, the environmental conditions?
Reduction	Are the mechanisms known by which the concentration/amount of the noxious agent in the contact medium is reduced and are they appropriately characterised (e. g. air exchange rate, mixing, degradation, decay)?
Contact: exposed groups of people/population	Is the target population of the exposure estimate adequately described? Are there constraints on time and place? Can the intended description and analysis of the target population be related to the group which is to be protected (or vulnerable) or are there differences between the group under protection and the definition of the target group of the exposure assessment? Are extreme groups or subgroups with special exposure behaviour to be considered adequately described?
Exposure events	Are the exposure events under consideration adequately described?
Spatial, time-based and situational differences	Are the sources consistent (e. g. clearly defined technological processes of emergence, inactivation or decontamination for microorganisms)? Are temporal 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 behaviours) and the microenvironment (e. g. pH etc.) sufficiently defined? Are the exposure conditions the same for both sexes and at different stages of life?
Risk management measures	Are the risk management measures to be considered adequately described and depicted in the scenario? Are all variables that can be influenced by known risk management measures (e. g. legal regulations) adequately considered in the scenario, provided they are intended for the analysis or the regulatory procedure used (e. g. communicated or non-communicated risk management measures)[10]?

[8] Depending on the context, not all questions are relevant for assessing the uncertainty of a scenario, model or parameter.
[9] Products are understood here as mixtures/preparations and products.
[10] Under REACH, so-called communicated risk management measures (instructions for use) should not be taken into account in the quantitative estimation of exposure.

2.3 Exposure model

The exposure model is usually a mathematical translation of the scenario into a calculation for determining the level of exposure. The exposure model thus determines the type and number of model parameters as well as the structure of their interaction. Exposure can also occur through direct measurement on the body (e. g. personal sampler) or in matrices (human bio-monitoring), whereby the models can refer to possible influencing factors.

The uncertainty analysis must check whether the model sufficiently describes the scenario and whether the level of detail of the model is appropriate to the question. Criteria are plausibility, completeness, acceptance and possible evaluations of the model, the results of a sensitivity analysis or the expert discussion of model alternatives.

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

- the lack of consideration of influencing factors,
- incorrect aggregation or
- the assumption of false or oversimplified correlations in the relationship between exposure factors.

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

The (IPCS & IOMC, 2008) lists the following sources of uncertainty in the exposure model:

- Exposure estimate: definition of the target variable
- Conceptual errors and wrong assumptions in the translation of the scenario into a set of model equations
- Interrelationships/correlations: Dependencies of the variables on each other
- Model structure, e. g. stratifications
- Choice of a model equation, e. g. in the case of several alternatives
- Model extrapolation beyond the area of applicability and validity
- Model implementation and programming of the calculation algorithms

The following list of questions (see) can be used to characterise the model selection.

2.3.1 List of questions of the qualitative uncertainty analysis in relation to model selection

Tab. 2: Checklist of the qualitative uncertainty analysis in relation to model selection

Criterion	Questions[11]
Exposure estimate: Definition of the target value	Are the target variables of the modelling process described with sufficient precision (e. g. mean/cumulative/maximum dose, external/internal exposure, exposure events, etc.)? Does the exposure estimation (units of the target quantity, comparability of the calculation, reproducibility etc.) meet the requirements to be set for a (quantitative) risk characterisation[12] (e. g. toxicological reference values)? Does the calculation of exposure confirm the achievement of the protection goals (e. g. compliance with exposure limits for children) for time-based or spatial frameworks? Do alternative approaches to exposure estimation exist (e. g. human biomonitoring)?
Concept and assumptions for transferring the scenario into a model equation	Does the model equation lead to average or extreme estimates as described in the scenario? Was a deliberate overestimation of the target value aimed at through the choice of model and, if so, how large is the resulting overestimation? What are the advantages and disadvantages of using distributions for the achievable results?
Relationships/ Correlations	Are there correlations or structural relationships between the influencing variables listed in the model? For example, if there are several sources of the same noxious agent, are there any that occur in combination or correlated? How much and in which direction would a disregard of correlations and relationships affect the result?
Model structure, e. g. stratifications	Are there sufficient stratifications in the model to account for regional (e. g. climatic, spatial type, location changes, trade flows), temporal differences (e. g. seasonal, cycles, trends), different microenvironments (e. g. production, storage, packaging, preparation conditions), different lifestyles (e. g. activities, social class) etc.? Are sufficient gender and age stratifications (e. g. infants, toddlers, children, adolescents, adults, seniors etc.) taken? Are particularly exposed persons (e. g. after incorrect use of a product) taken into account in the model? Are the requirements for all model parameters of the modelling described in sufficient detail (e. g. unit, precision, stratifications, restrictions etc.)?
Choice of the model equation	Is the application of the model accepted by experts, tested or validated? Does the model include all influencing factors of the exposure scenario? Is the formula used generally scientifically accepted? Are all components and influencing factors justified and are the derivations comprehensible? Are the assumptions transparent and their influence on the target figure explained? What is the quality (e. g. goodness of fit, influencing factors considered, restrictions) of the model? Were the statistical procedures sufficiently justified? Does the level of detail of the model match that of the scenario? Does the model adequately consider the relevant processes in the pathway (e. g. transformations, growth, decomposition processes)? Does the model correctly represent all relationships between all influencing factors and exposure that are scientifically considered relevant? Are there evaluations (e. g. processing, uptake rates etc.), conversions or decision variables (e. g. intervention limits) in the model that are controversial? Have all pathways and sources of exposure been considered? Does the model equation adequately reflect the exposure process, in particular individual exposure events, temporal, spatial and pathway correlations? Is the model complexity balanced between consideration of necessary influencing factors and assumptions about relationships between influencing and target variables? What simplifying assumptions are made? Are there alternative model proposals?

[11] Depending on the context, not all questions are relevant for assessing the uncertainty of a scenario, model or parameter.
[12] Where appropriate, the uncertainties in setting reference values should be considered as part of the hazard characterisation.

Continuation Tab. 1: Checklist of the qualitative uncertainty analysis in relation to model selection

Criterion	Questions[13]
Risk management measures	Are all variables that can be influenced by risk management measures to be considered (e. g. legal regulations) taken into account in the model, provided they are appropriate for the objective?
Extrapolations of the model	Was the model taken as an analogy from another application? Does the application of the model for the scenario extrapolate to new areas? Is the model used with parameters for which it was not constructed or evaluated, e. g. changes in temporal, local aggregation?

2.4 Parameters of the exposure model

The aim of an exposure assessment is to estimate the amount of ingested noxious agents for a defined population group in order to be able to carry out a risk assessment. Among other things, a mapping should include

- the difference between individuals,
- the variability of the exposure conditions,
- inherent association between the model parameters.

Before estimating the exposure, all model parameters must therefore be quantified. If possible, this should be done with the help of representative empirical data. Point estimates should always be reported together with information on the statistical precision (standard error, variance or empirical distribution of the estimate). Precision measures serve to describe the statistical uncertainty and can also be used to describe the uncertainty quantitatively. In addition, a statement on bias should be made for each model parameter, which applies in particular to conservative assumptions. This aspect of the uncertainty of a parameter describes the correctness of an estimate in the sense of the agreement of the estimate with the true population parameter. In certain cases, this qualitative property can be described with quantitative methods (e. g. non-response bias or misclassification). In many cases, such uncertainties can and must only be described qualitatively.

In addition, model parameters are also estimated in exposure estimates on the basis of data that are not directly based on empirical analyses or that were generated for another purpose. These are, for example:

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

For the model parameters derived from such data, special uncertainty considerations are necessary, which will be discussed further below.

The uncertainty analysis must check the consistency of the quantification of the parameters from the data with the requirements of the exposure scenario. This applies in particular to the

[13] Depending on the context, not all questions are relevant for assessing the uncertainty of a scenario, model or parameter.

representativeness of the sample in which the data were collected. Basically, it has to be checked (and documented) whether model parameters are correlated and what influence is exerted on the exposure via correlated data (e. g. amount consumed per body weight stratified by age).

The highest uncertainty is usually given when using surrogate data, the lowest when using data generated for the exposure assessment itself, the accuracy of which corresponds to the spatial, temporal and epidemiological resolution required by the scenario.

When deriving parameters from empirical data, it should be described whether uncertainties can result from the following sources of error:

- Quality of data collection: study population and representativeness, sample design, size and bias
- Precision and accuracy of the measurement or survey methodology (e. g. questionnaires, protocol data, exposure or concentration measurement data, demographic data)
- Dealing with and causes of missing values (e. g. non-response, detection limit, limit of quantification)
- Statistical analysis of the data
- Consideration of correlations between parameters[14]

These aspects should be covered in the description of parameter uncertainty.

Special attention should also be paid to the uncertainty analysis regarding procedures used to fill data gaps.

When deriving parameters from sources other than empirical data, further uncertainty must often be assumed. The following aspects can be considered:

- Plausibility (the agreement of the parameter value with scientifically justified assumptions)
- Intersubjectivity (the agreement of the parameter value between different experts)
- Selection space (the width of the value range for the parameter)
- Limitations of resources (empirical data are not available due to limited resources)
- Interests/value-ladenness (the determination of a parameter value could be guided by interests undisclosed values)
- Influence (assumed or proven influence of the parameter on the result)
- Statistical methods

The following list of questions (see Tab. 3) can be used to characterise the uncertainty of each individual model parameter. It may be necessary to perform a sensitivity analysis of the model to determine the strength of influence of a model parameter on the target variable. Larger uncertainties can be accepted for model parameters if they have a smaller influence on the target variable.

[14] If several parameters are derived from one data set, correlations can be considered under the aspect of parameter uncertainty. The consideration of correlations and dependencies that have not been empirically proven should be treated under the aspect of model uncertainty.

2.4.1 Checklist of the qualitative uncertainty analysis in relation to model parameters

Tab. 3: Checklist of the **qualitative uncertainty analysis in relation to model parameters**

Criterion	Questions[15]
Expert opinions, default assumptions	Were default assumptions/expert opinions for the parameter used in the exposure estimates? If yes, is the derivation of the default assumption/reference value (e. g. a conservative or a plausible mean value) consistent with the objective and level of the exposure assessment? Is the value 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. unit, precision, stratifications, restrictions etc.) and does it adequately represent the target population? Is the variable with its chosen value expressions appropriate to reflect the target populations attributes under consideration? Are the characteristics of the temporal, spatial and individual variations consistent with the exposure and risk model? What is the reference interval (e. g. short-term, long-term, lifetime estimates, area under the curve, body burden indicators etc.) of the data? Was the parameter of interest measured directly or determined using conversions or assumptions from surrogate data? Is there information on the calibration and validation of the assumptions/conversion? Is information only available in a categorical form and is this categorisation sufficient for the objective of the modelling?
Reliability of the measurements	Is the survey method scientifically accepted and validated? Are the sources and methods of data collection or measurement adequately documented in the literature? What biases and measurement errors can result from sample collection and preparation (e. g. sample contamination), analysis and measurement methodology (e. g. calibration, verification, quality assurance), collection and calculation of the model parameter (e. g. validation)? Are the data e. g. self-reported from questionnaires with possible biases? What consequences, if any, does the inclusion or exclusion of values below the detection or quantification limit have on the model parameter? How were the values below the detection or quantification limit quantified? How were missing values in the data set dealt with? Have possible sources of error been adequately discussed? Are there indications of widely varying measured values in the study? Do they indicate special exposure conditions, missing factors or “statistical outliers”? Were “outliers” adequately treated? For categorical data, are the diagnostic sensitivity and specificity of the determination procedure or their positive/negative predictive value known and taken into account?
Quality of the data sources	Are the data available from studies, systematic surveys or routine data? Is the study protocol appropriate? Was the study from which the data were taken conducted with the aim of assessing risk or exposure? Are the data original or secondary? Are there indications of different origins of the data of a study (e. g. different surveys, time periods, laboratories, methods of analysis etc.)? Was heterogeneity adequately taken into account in the evaluation? Are there alternative studies on the same parameter that can confirm or question the quantification of the parameter? Is the study design sufficiently documented in the literature? Is there evidence that publication bias exists and that the available data therefore deviates from the true data?

[15] Depending on the context, not all questions are relevant for assessing the uncertainty of a scenario, model or parameter.

Continuation Tab. 3: Checklist of the qualitative uncertainty analysis in relation to model parameters

Study population	Is the study population clearly defined? Does the study cover all stratifications that are considered essential to take into account, e. g. regional, climatic, temporal differences (e. g. seasonal changes, cycles, trends), different microenvironments (e. g. production, storage, packaging, preparation conditions), different life-styles (e. g. activities, social class) etc.? Are there sufficient gender and age stratifications (e. g. infants, toddlers, children, adolescents, adults, seniors etc.)? Can selection bias be present (e. g. due to small sample size)?
Representativeness	Does the sampling ensure representative data for the study population? Can results of the sampling be extrapolated to the target population, temporal and regional scope of the exposure estimation? What assumptions and extrapolations are made? Can possible distortions arise during extrapolation?
Information on correlations/dependencies	Were relevant correlations between influencing factors collected in joint studies (e. g. consumption and body weight) and taken into account in the model (e. g. intake per kg body weight)? If there are correlations and structural dependencies, have they been described transparently and comprehensibly?
Evaluation methodology	**For deterministic estimates:** Are the statistical ratios and their calculations described in a transparent and comprehensible way? Is the sample size large enough to estimate the required statistics/parameters with sufficient precision? Was the precision assured by sample size calculations or the specification of confidence intervals? **For probabilistic estimates:** Are the statistical procedures and selection criteria for distribution fitting described in a transparent and comprehensible manner? Were considerations presented or other data used to justify the distribution assumptions? Is the sample size for the parameter under consideration large enough to fit the required distribution, especially extreme percentiles, with sufficient precision? Has the precision of the distribution fit and associated parameters been indicated by specifying confidence intervals/bands, goodness-of-fit measures (e. g. Kolmogorov-Smirnov distance)? Were relevant ratios (e. g. skewness, mean/median ratio, percentiles) of the empirical and parametrically adjusted distribution compared and discussed? What assumptions were made to fit a distribution when the sample size is small? What are the consequences of these assumptions for the exposure estimate?

2.5 Exposure calculation method

With the formulation of the exposure scenario, the specification of the exposure model and the quantifications of all parameters, the exposure assessment should be clearly described. The concrete result of the calculation may additionally depend on the program used and the selected calculation accuracy. When commercial software is used for the calculation, and the program code is neither published nor modifiable, additional simplifications and settlements could be made with the software that are unknown to the assessor. Then, the expected effects on the result of the exposure assessment should be made transparent by documenting the applied procedures and programs (including the version number) in the uncertainty analysis.

Other sources of error can arise from incorrect programming (software errors) or differences in implementation for different hardware environments (IPCS & IOMC, 2008). Such sources of

error can only be eliminated or mitigated by independent peer review or even independent implementation of the model.

For quantitative estimation of the influence of the programming, software and hardware used, the calculation must be carried out independently using different programmers, software and hardware. Due to the considerable effort involved, such an analysis will be limited to a few applications, e. g. for testing a general exposure modelling or for exposure and risk assessment with significant consequences depending on the result.

Table 4 can be used to identify uncertainties in the exposure calculation.

2.5.1 Checklist of the qualitative uncertainty analysis in relation to the exposure calculation methods

Tab. 4: Checklist of **the qualitative uncertainty analysis in relation to the exposure calculation methods**

Criterion	Questions[16]
Deviations	Are there any deviations between the exposure model and the actual implementation in the calculation procedure?
Reviewing the calculations	Are there possible sources of error in the technical realisation of the model calculation, the algorithms, the programming (e. g. incomplete documentation, reproducibility) or the input of controlling variables (e. g. random generator, number of iterations)?
Incorrect report generation	Are there possible sources of error in the report preparation?
Verification	Were the units in the calculation controlled? Has the implementation been independently assessed or repeated?

[16] Depending on the context, not all questions are relevant for assessing the uncertainty of a scenario, model or parameter.

2.6 Evaluation of the uncertainties and presentation of the results of the uncertainty analysis

The previous sections served to identify uncertainties in the exposure and risk assessment. The structured checklists support the complete and structured consideration of all uncertainties.

The documentation also includes a structured description of the identified uncertainties and an assessment of their influence on the result. Results of sensitivity studies allow quantitative estimates. In principle, the description can be quantitative (e. g. in the context of a sensitivity analysis, see Chapter 1.4.7), but purely verbal observations are also possible.

Two ways of qualitatively describing the identified uncertainties are recommended:

1) Establishment of a categorisation/ranking of the existing uncertainties (Chapter 2.6.1)
2) Individual evaluation of the identified uncertainties by means of a semiquantitative scale (Chapter 2.6.2)

In any case, the most important uncertainties should be described verbally in the form of a summary. The following aspects can help to select the “most important” uncertainties:

- What are the sources and reasons for the uncertainties?
- What is the impact (magnitude and direction) of the main uncertainties identified on the outcome of the exposure assessment? If given, can the protection goal be ensured even when remaining uncertainties are considered?
- What options can be identified to reduce the uncertainty in the exposure assessment? Are these measures suitable to enable an assessment of the protection goal?

Verbally described are also the confidence in the knowledge base and the subjectivity of the decisions made.

It is recommended to conclude with a quantification of the overall uncertainty of the assessment (Chapter 2.6.5).

2.6.1 Ranking

The identified uncertainties are ranked here using rough categories that sort them according to their influence on the final result. For this purpose, an assessment must be made for each uncertainty as to whether it has a large, medium or small influence on the outcome value. If necessary, further sorting can be done within these categories, but this is not mandatory. Each uncertainty is considered separately, a classification into the categories of the checklists is not necessary.

The result of this assessment is a list of identified uncertainties, which on the one hand documents the identified uncertainties and on the other hand can give indications which uncertainties are most relevant for the assessment.

2.6.2 Semiquantitative scale

The uncertainties are evaluated using a semiquantitative scale. For each identified uncertainty, either a sensitivity analysis or expert judgement is used to assess how large its influence is on the exposure estimate. Using a scale, this assessment can be translated into symbols or similar. This semiquantitative scale thus allows a comparison of the identified uncertainties as well

as a structured documentation. Tab. 5 shows a proposal for such a semiquantitative scale. It is based on the quantification from the EFSA guidance document (EFSA Scientific Committee et al., 2018). Depending on the direction and size of the effect, a different number of plus or minus signs is assigned, with the additional option of indicating ignorance of the size and/or direction of the effect.

2.6.3 Quantitative estimation of uncertainty

According to the Guide to Uncertainty Analysis of (IPCS & IOMC, 2008) various methods can be used for quantitative uncertainty analysis. However, they are only listed here and not commented on further.

- Determination of the lower and upper limits of the estimation result as interval estimation
- Probabilistic (distribution-based) methods
- Sensitivity analyses

The quantitative methods are essentially based on determining the possible range of an exposure estimate. For this purpose, the above-mentioned methods can be applied, which provide a description of the parameter in the form of intervals or probability distributions. In the case of distributions, the margins can be evaluated as an expression of the uncertainty.

All methods have in common that the range of variation of the modelling results is examined by varying parameters or model specifications. It is advisable to formulate and vary corresponding scenarios. These methods can also be used, for example, to investigate structural dependencies or statistical correlations. Comparative exposure and risk estimation using different models can also be considered as quantitative uncertainty analysis (cf. (IPCS & IOMC, 2008).
A more detailed description of different methods for quantitative uncertainty analysis can be found in EFSA's extended guidance (EFSA Scientific Committee et al., 2018) Chapter 9.2 and in particular Annex B).

Sensitivity analysis as an important instrument of uncertainty analysis should be recalled at this point. Its great importance has already been pointed out in chapter 1.4.7.

The following categories and symbols are suggested for representation:

Tab. 5: Categories and symbols for the classification of uncertainty

Strength of the distortion of the final result	Possible direction of the distortion of the final result		
	Underestimation	Not known/ under- and overestimation possible	Overestimation
Not identifiable/negligible	0: Uncertainty has an unrecognisable or negligible effect on the estimate of risk Underestimation of maximum 20 %	0: Uncertainty has an unrecognisable or negligible effect on the estimate of risk Over-/underestimation of maximum 20 %	0: Uncertainty has an unrecognisable or negligible effect on the estimate of risk Overestimation of maximum 20 %
Low	–: Uncertainty can cause a slight underestimation (up to a factor of 2) of the risk	–/+: Uncertainty can cause a small deviation (up to a factor of 2) in the estimate of the risk in both directions	+: Uncertainty can cause a small overestimation (up to a factor of 2) of the risk
Moderate	– – Uncertainty can cause a moderate underestimation (up to a factor of 5) of the risk.	– –/++: Uncertainty can cause a moderate deviation (up to a factor of 5) in the estimate of the risk in both directions	++: Uncertainty can cause a moderate overestimation (up to a factor of 5) of the risk
Strong	– – –: Uncertainty can cause a strong underestimation (more than a factor of 5) of the risk	– – –/+++: Uncertainty can cause a large deviation (more than a factor of 5) in the estimate of the risk in either direction	+++: Uncertainty can cause a strong overestimation (more than a factor of 5) of the risk
Not known	? – Uncertainty can cause an underestimation of the risk of unknown amount	? –/+: Uncertainty can cause a deviation in the estimate of the risk in both directions and in unknown amounts	? +: Uncertainty can cause an overestimation of the risk of unknown amount

2.6.4 Standardised representations of quantitative uncertainty analysis

A systematic presentation of the quantitative uncertainty analysis is not proposed here. It will depend on the methods and approaches of quantitative uncertainty analysis applied in each case. For a description of possible forms of presentation, please refer again to the EFSA guidance document (EFSA Scientific Committee, 2018).

2.6.5 Quantification of the overall uncertainty

The possibilities for quantifying the overall uncertainty depend on the method used to assess the individual uncertainties. Since this guidance primarily presents a qualitative method for evaluating uncertainties, only a brief discussion is provided here of the possibilities for making a quantitative statement about the overall uncertainty from qualitatively evaluated uncertainties.

With the help of expert knowledge, a quantified overall uncertainty can be given also for a purely qualitative uncertainty assessment. Typically, a quantitative result is already available as a result of the exposure assessment.[17]
The quickest way to quantify is an assessment by the risk assessor. The risk assessor estimates, for example, how much the uncertainties change the result upwards or downwards. This entire range, together with the central value, can be reported to account for uncertainty in the exposure assessment. Other forms of presentation (e. g. a probability distribution for an exposure estimate) are also possible.
It should be noted that such an assessment is very subjective and would probably be made differently by different assessors. Also, only a statement about the range is made, not about the probability of occurrence of each possible value within the range. This can be partially compensated by specifying a distribution function, but requires a further subjective assessment by the assessor. However, in situations with limited time, this may be the only possible way to obtain a quantitative description of the overall uncertainty.

In situations with more resources, however, Expert Knowledge Elicitation is preferable. This reduces the effect of the subjectivity of the assessment just described. To quantify the overall uncertainty, the influence of unquantified uncertainties on the result of the exposure estimate is asked. Typically, the result in this case is a probability distribution.

In general, it can be noted that both the quantification of the total uncertainty with expert knowledge and by means of Expert Knowledge Elicitation benefit from the fact that parts of the uncertainties have already been quantified. In this case, the risk assessor or the experts only have to evaluate the influence of the uncertainties that have not already been quantified and can then combine the result with the already existing results.

2.7 Communication of uncertainties

The communication of uncertainty is an integral part of the communication of the risk assessment. The differentiated results of an uncertainty analysis, as proposed in this guidance, are to be summarised for communication with risk managers and with the public. This serves both the transparency of the assessment and the classification of the results. The criteria of comprehensibility, usability and transparency also apply to the communication of uncertainties.

The communication of uncertainties is a topic that goes beyond the specific aspects relevant to uncertainty analysis in exposure assessment. This is addressed in the BfR guidance document for health assessments as well as in an EFSA guidance document (European Food Safety Authority et al., 2019).

[17] If this is not the case, the present risk assessment is often without a clear result. In these cases, it should be checked whether this could be changed by quantifying the uncertainty, and if not, it should be abandoned.

3 Recommendations for the application of the guidance

This guidance document is a recommendation of the BfR Commission on Evidence-based Methods in Risk Assessment on the procedure for recording, describing and evaluating uncertainties in connection with statements on health assessments.

3.1 Use in BfR risk assessments

The BfR Commission Evidence-based Methods in Risk Assessment recommends to the BfR that, also in the sense of the predecessor commission Exposure Assessment and Standardisation, to include uncertainty analysis as an integral part of every risk assessment. Furthermore, the "Guideline for Uncertainty Analysis in Exposure Estimation" presented here should be used in the workflow and serve as a suggestion for other areas of risk assessment at BfR. (6th meeting, 22.11.2021)

3.2 Modules for special applications

This Uncertainty Analysis Guidance document seeks to cover risk assessments for all agents that may exert a harmful or disease-causing effect on an organism or body organ. This includes chemical substances, their degradation and reaction products or mixtures (of both natural and synthetic origin) as well as biological substances. The latter are e. g. bacteria, viruses, fungi, prions etc. or the metabolic products of plants, animals and microorganisms.

For individual areas of risk assessments, supplementary modules should be developed that further map the specific processes.

4 References and selection of technical texts

4.1 References

ECHA, European Chemicals Agency. (2012). Uncertainty Analysis. In *Guidance on Information Requirements and Chemical Safety Assessment* [1.1]. Retrieved from http://echa.europa.eu/documents/10162/13632/information_requirements_r19_en.pdf

EFSA. (2007). Opinion of the Scientific Committee related to Uncertainties in Dietary Exposure Assessment. *EFSA Journal, 5*(1). doi:10.2903/j.efsa.2007.438

EFSA. (2014). Guidance on Expert Knowledge Elicitation in Food and Feed Safety Risk Assessment. *EFSA Journal, 12*(6), 3734. doi:doi:10.2903/j.efsa.2014.3734

EFSA Scientific Committee, Benford, D., Halldorsson, T., Jeger, M. J., Knutsen, H. K., More, S., . . . Hardy, A. (2018). Guidance on Uncertainty Analysis in Scientific Assessments. *EFSA Journal, 16*(1). doi:10.2903/j.efsa.2018.5123

European Food Safety Authority, Hart, A., Maxim, L., Siegrist, M., Von Goetz, N., da Cruz, C., . . . Hardy, A. (2019). Guidance on Communication of Uncertainty in Scientific Assessments. *EFSA Journal, 17*(1), e05520. doi:10.2903/j.efsa.2019.5520

Frey, C., & Patil, S. (2002). Identification and Review of Sensitivity Analysis Methods. *Risk Analysis, 22*(3), 553-578. doi:10.1111/0272-4332.00039

IPCS, International Programme on Chemical Safety, & IOMC, Inter–Organization Programme for the Sound Management of Chemicals. (2008). *Uncertainty and Data Quality in Exposure Assessment. Part 1: Guidance Document on Characterizing and Communicating Uncertainty in Exposure Assessment. Part 2: Hallmarks of Data Quality in Chemical Exposure Assessment* (ISBN 978-92-4-156376-5). Retrieved from Geneva, CH: http://www.who.int/ipcs/methods/harmonization/areas/hazard_assessment/en/

Morgan, M., & Henrion, M. (1992). *Uncertainty: A Guide to Dealing With Uncertainty in Quantitative Risk and Policy Analysis*.

Saltelli, A., Tarantola, S., Campolongo, F., & Ratto, M. (2002). *Sensitivity Analysis in Practice*.

U.S. EPA. (2008). *Child-Specific Exposure Factors Handbook 2008*. Retrieved from Washington DC, USA: http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=484738

U.S. EPA. (2011). *Exposure Factors Handbook: 2011 Edition*. Retrieved from Washington DC, USA: http://www.epa.gov/ncea/efh/pdfs/efh-complete.pdf

World Health Organization, & International Programme on Chemical, S. (2018). *Guidance document on evaluating and expressing uncertainty in hazard characterization* (2nd ed ed.). Geneva: World Health Organization.

5 Index

Extent of uncertainty	10
Presentation of the results	34, 36
Default assumptions	15, 31
Deterministic exposure estimation	17
Deterministic estimates	17
Influence strength	19, 30
Exposure model	15, 21, 29, 31
Exposure scenario	15, 17, 21, 24, 29, 31
Exposure estimation steps	21
Research needs	15, 20
Initial exposure estimate	15
Iteration/Tier	7, 12, 14, 15, 17, 35
Guiding principles	12
Model parameters	11, 12, 18, 19, 21, 29, 35
Noxious agents	20, 26, 29
Probabilistic approach	14, 16, 17, 19, 35
Qualitative uncertainty analysis	17, 18, 20, 21, 34, 36
Quantitative uncertainty analysis	17, 18, 19, 20, 21, 33, 34, 35, 36
Reference values	16, 17, 21
Risk characterisation	13
Risk management measures	15, 25
Sensitivity analysis	8, 11, 19, 20, 27, 30, 34, 35
Subjectivity of a selection made	8, 20, 22, 34, 37
Trust in the knowledge base	8, 20, 22, 34
Uncertainty factors	6, 17
Variation	12, 15, 16, 17, 18, 19, 35

6 List of tables

Tab. 1: Checklist of the qualitative uncertainty analysis in relation to the exposure scenario 26

Tab. 2: Checklist oft he qualitative uncertainty analysis in relation to model selection 28

Tab. 3: Checklist of the qualitative uncertainty analysis in relation to model parameters 31

Tab. 4: Checklist of the qualitative uncertainty analysis in relation to the exposure calculation methods 33

Tab. 5: Categories and symbols for the classification of uncertainty 36