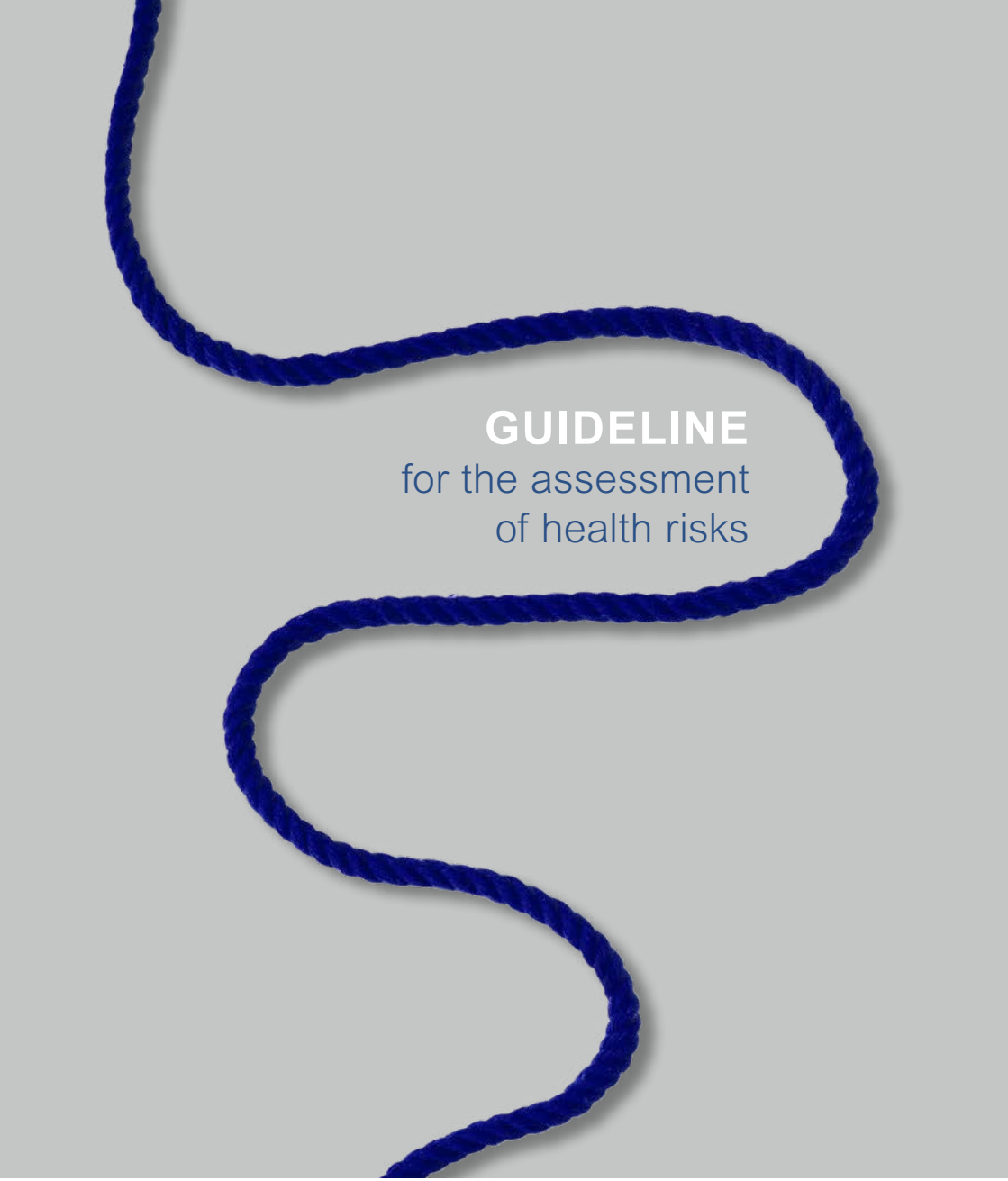


GUIDELINE
for the assessment of health risks

BfR
German Federal Institute for Risk Assessment

Legal notice
Guideline for the assessment of health risks (revised edition)

Publisher:	German Federal Institute for Risk Assessment (BfR)
Editor:	Guideline Working Group
Photos:	BfR: Cover – Arkom Krachodnok/Shutterstock: p. 8
Layout/Realisation:	Kern GmbH, Bexbach
Last updated:	September 2023

This text version is a translation of the original German text, which is the only legally binding version.

ISSN 1614-5089 (Online)

Contents

Basic principles

Aim of this guideline

The German Federal Institute for Risk Assessment (BfR) has the legal mandate to estimate and assess the risks to human health presented by food and animal feed, substances, microorganisms, products and procedures. The BfR also provides information about potential, identified and assessed risks, and recommends measures necessary for risk mitigation or avoidance. In certain circumstances, it is also necessary to assess the benefits of substances, products and procedures. The assessment process is documented and explained in full. By providing a comprehensive and comprehensible presentation of the scientific basis of its assessments, the BfR makes an important contribution to risk communication. Among other things, risk communication means the exchange of information and scientific opinion concerning risks between all target groups, which include consumers, government, research, public institutions, industry bodies, non-governmental organisations and the media.

As a result of this independent scientific assessment, research and clear-cut communication of health risks, the BfR actively contributes to the safety of food and feed, products and chemicals.

The present 'Guideline for the assessment of health risks' serves to implement the theoretical principles mentioned in practice, and therefore assure the quality of risk assessments and other health statements published by the BfR (which are referred to in this guideline as 'opinions').

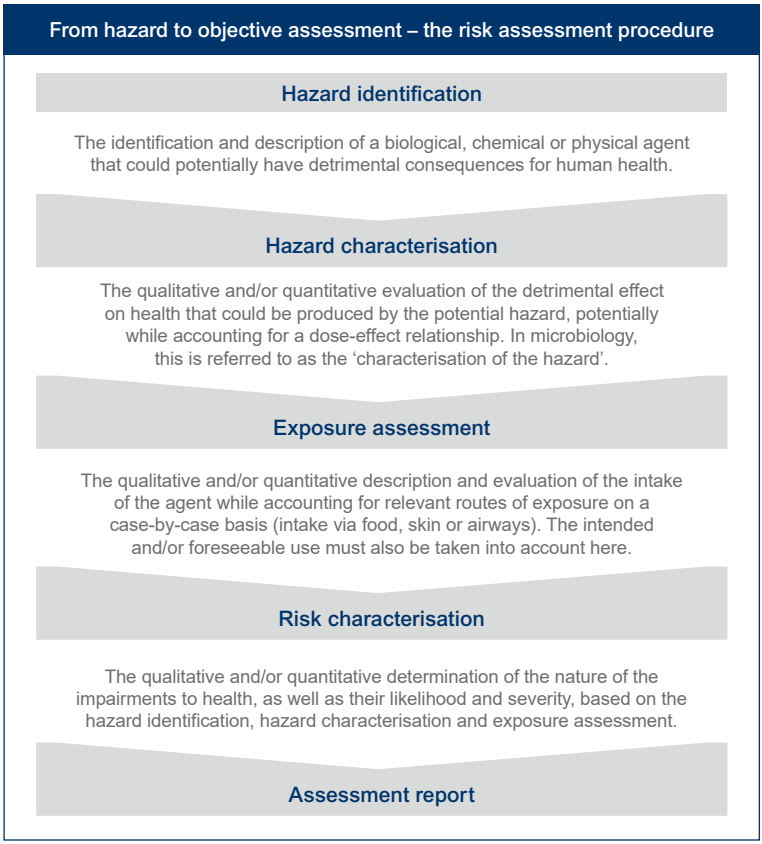
Although this guideline is a specification for the preparation and presentation of the BfR's working results, it can be applied flexibly. Modifications are possible: especially in light of relevant legal requirements or if other forms of presentation are more suitable for the subject matter in question. Opinions issued by the BfR in the course of legal proceedings are not covered by this guideline if their preparation is described in other, external guidelines.

Uncertainties and variabilities, page 15

In the assessment of risks to health, the uncertainties that could arise at any level while preparing an opinion should be accounted for appropriately and communicated transparently.

Basic principles of health risk assessments performed by the BfR

A *risk assessment* is a scientifically substantiated procedure involving the four stages of hazard identification, hazard characterisation, exposure assessment and risk characterisation.



Risks must be given a qualitative and – where possible – quantitative description. This description should be based on the structure as presented below. In addition, quantitative risk assessments are based on calculations or mathematical models in which the risks are described by means of mathematical methods. The model's numeric results must be described verbally and incorporated into the answers provided to the question under consideration.

Transparency is required at all levels of the risk assessment. The following aspects must be described in a clear, straightforward and comprehensible manner, and with an appropriate depiction of the uncertainties:

- Aim and scope of the opinion
- Sources for and type/robustness of the underlying data (including any variability these data contain and differences of opinion)
- Methods and models used
- Other assumptions made and constraints
- Results and conclusions

Weight of evidence, page 34

In order to present the evidence leading to an assessment result as transparently as possible, the risk assessment should be prepared according to the basic principles of a *weight of evidence* (WOE) approach.

Statements made by the BfR are based on current scientific findings, oriented on internationally recognised principles and justified in accordance with clearly comprehensible reasoning. Existing knowledge is given due consideration and clearly presented. Where possible, references are made to earlier statements issued by the BfR. Relevant differences of scientific opinion must be presented. If there are any differences between the statements issued by various national or international authorities, these differences must be presented in detail.

General principles for the description of risks

Opinions issued by the BfR should be formulated so that they can be utilised by all target groups without any further need for explanation. A neutral language register should therefore be adopted. The wording of the opinion should be chosen with clarity in mind and consistency with other opinions issued by the BfR; unnecessary repetition is to be avoided. The line of argument taken should be logical and coherent.

Statements made by the BfR are based on current scientific findings. The BfR opinion should be expressed in such a way as to highlight and underline this fact.

Opinions do not reflect a personal point of view (avoid the use of 'I', 'we' or the 'report authors') but the views of the BfR as a whole. Wherever possible, the assessment terms utilised in the opinion should be in line with internationally recognised terminology. All terms must be used appropriately, clearly and consistently. To avoid creating linguistic complexity – and the potential for related misunderstandings – synonyms are to be avoided, especially when characterising health risks. Abbreviations and technical jargon must be written out in full when used for the first time and explained in layperson's terms if necessary.

If risk-related information is being communicated, the reference and reference values must always be described clearly and should remain unchanged within a section as far as possible (see example in the box on the right). A 'reference value' describes the quantity of a substance or the number of events for individuals to which a number or risk data relates, for example.

Example: reference/reference value

- Carcinogenic in an animal experiment
- Carcinogenic in humans
- Not more than 100 g per day
- In 3 in 10 animals

The same units of measure must be used throughout in order to ensure compatibility with the figures given (e.g. mg/kg body weight).

Regarding the frequency of adverse events, the likelihood and the severity of impairments to health, etc., quantitative details are also to be used alongside qualitative formulations wherever possible. As a result, a descriptive detail (that an adverse event happens 'often', for example) should also be accompanied by a numeric detail (that 'the events occurred in x in y cases' or that 'no events have been reported to date', for example). Numeric details expressed as frequencies (10 in 1,000 cases) are easier to understand than percentages, especially if the percentages in question are small and include decimal places.

Use consistent terminology to characterise risks; these terms are defined in greater detail in the 'Risk characterisation' chapter.

Risk characterisation, page 11

Certain terms have legal definitions or have been introduced as legal terms in relation to the fields of the economy, the judiciary or civics. Using these terms in the same way in BfR opinions helps to ensure consistency between risk assessments while also making them more comprehensible to target groups.

Statements and conclusions made in opinions issued by the BfR must be made while accounting for the Institute's tasks and duties defined by law. In terms of food and feed safety, for example, a clear distinction between risk assessment and risk management must be maintained. This must be respected in particular when recommending specific risk management measures, so as not to constrain the decision-making scope on the part of the competent authorities. Categorising a specific food as 'unsafe' in the sense of article 14 of Regulation (EC) No 178/2002, for example, constitutes a legal assessment of the case in question, which does not lie within the remit of the BfR.

Opinion content and structure

Scientific assessments published by the BfR essentially utilise the following overall structure:

Cover page
1 Subject of the assessment
2 Results
3 Rationale
3.1 Risk assessment
3.1.1 Hazard identification
3.1.2 Hazard characterisation
3.1.3 Exposure assessment
3.1.4 Risk characterisation
3.2 Risk management options, recommended measures
3.3 Other aspects
4 References

Template: 'Assessment of health risks', drive G

The 'Assessment of Health Risks' layout template must be used for this purpose. The BfR does prepare opinions in a wide range of discrete specialist fields; however, some of these may require a different approach and document structure. The document structure can therefore be modified to suit the specific question in hand by specifying or amending new or existing outline elements. In individual cases, the design can be tailored to suit the subject of the opinion.

The opinions are normally sent out as an enclosure to a specific communication. This communication may also specify additional background details or information about the result, or about sharing with third parties or confidentiality.

Title

Each document is given a short, meaningful title, which can be derived from the reason for its creation, for example. A heading containing keywords should be used to enable quick document classification, and contain substance/product and matrix details, for example. For questions being investigated in relation to microbiology, the name of the agent (e. g. the bacterium or virus) or microbial group to be assessed from the corresponding matrix should be clear from the title.

1 Subject of the assessment

The motivation and background for answering the question should be specified if necessary for clarification. Repeating the question while referencing previous correspondence and the methodological status makes such an introduction easier. The question should be formulated so that the procedure for this question's assessment can be derived as a logical consequence. Typically, it will be necessary to define and constrain the subject of the assessment (e. g. which hazards, input sources and routes/sites of exposure have been – and have not been – considered in the opinion). The assumptions made during the assessment (e. g. the population group to be protected, the safety objective and safety level) or constraints (e. g. risks or other factors not considered, restriction to certain food groups) should be explained in greater detail at this juncture, and should also be part of the discussion of uncertainty in the section 'Risk characterisation > uncertainties and variabilities'.

Uncertainties and variabilities, page 15

Particularly for products, a more in-depth characterisation, e. g. by providing details of the name (product name, approval number, etc.), ingredients, presentation, indications, designation of the microorganism, the food or food group, and origin, can also prove to be helpful. If necessary or pertinent, the relevant legislation consulted to assess the risk must also be specified.

2 Results

The scientific findings are summarised clearly and comprehensively here, and conclusions are drawn. The facts should be presented as clearly and briefly as possible. The statements and wording chosen should be consistent with the risk characterisation.

If recommendations or conclusions are taken from other parts of the opinion, then these should be quoted word-for-word where possible.

Example: results

As a result of the quantitative exposure assessment performed, the BfR considers it very unlikely that the TDI for X will be exceeded even if Y is consumed in large quantities (95th percentile of consumption data). The likelihood of an impairment to health is very low.

3 Rationale

This section is used to present the arguments that lead to the assessment findings. Uncertainties and differences in scientific opinion must be discussed at a suitable juncture and in an appropriate context, and summarised under 'Risk characterisation'.

3.1 Risk assessment

Uncertainties and variabilities, page 15

Drawing its findings from the current state of scientific knowledge, this section is used to explain the extent to which exposure to the potential hazard to be assessed could lead to a risk to health, as well as the estimated severity of this risk. The applicable uncertainties must also be discussed. Variabilities are to be accounted for in data analysis.

3.1.1 Hazard identification

This section is used to describe the potential hazard (agent), such as a product, a substance (mixture of substances), a microorganism or a toxin. The following aspects can also be addressed here, if they are relevant for the opinion:

- The identification and the chemical, physical or microbiological characterisation of the agent; for microbiological agents, e. g. the characterisation of the microorganism, including its pathogenicity, virulence factors, tenacity, etc.
- A description of occurrence, production and usage
- Any general knowledge about instances of the agent interacting with food and the influence of food technology on the agent
- Any general knowledge about the qualitative (and quantitative) propagation of the agent, such as in the environment, in livestock inventories and/or in the food/feed chain

3.1.2 Hazard characterisation

The hazard potential of the hazard under investigation is to be described by taking into account the route of exposure or the intended use of the agent, together with the various population groups involved (e. g. age, immune status). As a general rule, the soundness and reliability of available data should also be described. The description provided includes details of the following parameters, for example:

- Dose-effect relationship
- Toxicokinetics/pharmacokinetics: release, intake, distribution, metabolisation, shedding
- Toxic effects: such as acute toxicity, toxicity after repeated intake, genotoxicity, carcinogenicity, reproductive and developmental toxicity, immune toxicity and neurotoxicity
- Key figures in relation to toxicology (e. g. NOAEL), infectiology (e. g. MID) and epidemiology (e. g. odds ratio); health-related guidance values, as appropriate (e. g. ADI)
- Type, duration and severity of impairments to health (incubation period, clinical symptoms, acute or chronic progression)
- Late effects and complications
- Reversibility
- Frequency of occurrence of impairments to health, illnesses and complications (in Germany) as well as the results from outbreak investigations

3.1.3 Exposure assessment

An exposure assessment determines the extent of external intake or internal occurrence of an agent in the human body, typically by the application of mathematical/statistical methods. This is achieved by linking together numerous items of data, such as physical or chemical properties, data on agent genesis and propagation, details about the behaviour of exposed individuals (e.g. contact time, consumption patterns, etc.) as well as personal particulars (e.g. height, weight, age, etc.). The exposure assessment includes the evaluation and classification of various aspects and information sources concerning exposure, including accounting for uncertainties. This section can include an independent exposure assessment or may consider both quantitative and qualitative evaluations of the degree of magnitude of exposure, such as those based on literature sources, for example. The overall assessment of exposure considers various input pathways, such as via the consumption of food and the use of products. The results of the exposure assessment are contrasted with the hazard estimate as part of the risk characterisation process in such a way that the risk is thereby derived as a description of the likelihood of a health effect.

This section should describe the degree of exposure to a substance/microbe for the relevant population groups. This can be based on the following, for example:

- Details of the exposed population groups, as well as any varying exposure scenarios, taking into account factors such as age, body weight, sex or particular nutritional formats
- Information about consumption data and other details about frequency of exposure
- Information about specific consumption habits
- Information about the contribution of specific sources of exposure – such as specific food groups – to overall exposure
- Information about the propagation and the qualitative and quantitative occurrence of an agent, as well as residues in and on the food to be assessed, in the corresponding food chain and in the products to be assessed. One example: the type of product from which the agent is released over time in various exposure scenarios (following intended and foreseeable use of the product).
- Information about the distribution of the corresponding food matrix or product (target group, trade structures)
- Details about product usage
- Purposes of use (e.g. intended preparation, foreseeable (mis-)use) of the food that could be potentially contaminated, and the resulting changes in concentration and intake quantities for the agent to be assessed

3.1.4 Risk characterisation

This section summarises and evaluates the available data and information about the potential hazard, the hazard characterisation and the exposure. It may be advisable here to characterise the risks by using a variety of scenarios.

Pages 12 to 15

In doing so, the following aspects should be summarised and accounted for:

a) Affected population or population group
b) Route and probability of exposure
c) Likelihood of impairments to health following a specific type of exposure
d) Frequency of impairments to health
e) Type, duration, reversibility and severity of impairments to health
f) Evidence of a causal relationship
g) Uncertainties and variabilities
h) Need for further research
i) Controllability of the risk

a) Affected population or population group

This subsection considers individuals at certain stages of their lives, in certain age groups, with specific characteristics (e.g. sex, body weight), and with specific nutritional habits, states of health or levels of exposure.

b) Route and probability of exposure

The intake pathway (e.g. oral, airborne/by inhalation, dermal) must be stated. Various routes of exposure and their likelihoods should also be considered separately, as appropriate.

c) Likelihood of impairments to health at certain levels of exposure

For the qualitative description of the likelihood, the following terms should be used and their explanations should be provided. Where possible, qualitative descriptions should be supplemented with quantitative details in order to make a correct interpretation easier.

For some substances, their properties or data as currently available and known mean that no intake quantity can be derived that does not give rise to concerns about harmful effects to health. This applies in particular to substances with carcinogenic effects for which no threshold limit value can be assumed (such as DNA-reactive genotoxic carcinogens). For these substances, no likelihood of impairments to health can be specified. Following an exposure to substances of this kind, the likelihood of impairments to health must always assumed to be medium at the very least. To prioritise the urgency of risk management measures, the 'margin of exposure' (MOE) approach can be applied. National risk management agencies consider an MOE of 10,000 or more, where this has been derived on the basis of a BMDL10 from an animal experiment carcinogenicity study, to give little cause for concern in terms of public health, and therefore consider this to be a criterion for assigning a low priority to related risk management measures. From a toxicological perspective, however, the conclusion that a total intake quantity with an MOE of 10,000 or higher is considered as 'less harmful' in terms of potential cancer risks is not the same as 'harmless'.

Likelihood of impairments to health	Explanation of the likelihood of health effects with the specified exposure
very high	The likelihood of impairments to health is specified as 'very high' if, in individual cases, further evidence is available in addition to the aspects described under 'high' that would attest to the occurrence of impairments to health. This is true in the following cases: ▶ A broad-based, robust data set is available that describes the regular occurrence of impairments to health in humans for the range of exposure levels under consideration. ▶ The facts show that it can be assumed that impairments to health will occur in humans in almost all cases following exposure to a biological agent.
high	The likelihood of impairments to health is specified as 'high' if impairments to health are to be expected. This is true in the following cases: ▶ In the range of exposure levels to be evaluated in humans, effects occurred (such as in epidemiological studies or well-documented case reports, for example), or robust findings are available from animal experiments or recognised alternative methods that can be transferred to humans. ▶ The facts show that it can be assumed that impairments to health will often occur in humans following exposure to a biological agent.
medium	The likelihood of impairments to health is specified as 'medium' in cases where there are specific indications that impairments to health will occur, but the prerequisites for assignment to a different category have not been fulfilled. This is true in the following cases: ▶ The level of exposure to be evaluated leads to an exceedance of a health-based guidance value (HBGV). This is the case if an ARfD is exceeded, for example, or if an ADI/TDI is repeatedly exceeded.[1] ▶ The facts show that it can be assumed that impairments to health will sometimes occur in humans following exposure to a biological agent.
low	The likelihood of impairments to health is specified as 'low' if impairments to health are not to be expected. This is true in the following cases: ▶ The extent and/or duration of the exposure under consideration does not lead to the health-based guidance value being exceeded. ▶ If the TTC model is applicable, the exposure under consideration is lower than the TTC value to be used. ▶ The facts show that it can be assumed that impairments to health will very rarely occur in humans following exposure to a biological agent.
very low	The likelihood of impairments to health is specified as 'very low' if, in individual cases, further evidence is available in addition to the aspects described under 'low' that would attest to the non-occurrence of impairments to health. This is true in the following cases: ▶ A broad-based, robust data set is available in humans, from which it can be concluded with a high degree of certainty that impairments to health are not to be expected. ▶ The facts show that it can be assumed that impairments to health will not occur in humans following exposure to a biological agent, since such impairments have not been observed to date. Their occurrence is conceivable in humans, however, in a theoretical – and exceptional – case.

[1] *The likelihood of impairments to health also depends on the amount by which the HGBV is exceeded as well as the steepness of the dose-effect curve. Depending on the available data, the likelihood of impairments to health should therefore be considered instead as 'high' or 'very high'.*

d) Frequency of impairments to health

If possible, the expected frequency of adverse events in the population or a population group is to be quantitatively specified. For many target groups, numeric details expressed as frequencies (e. g. in 10 in 1,000 cases) are easier to understand than percentages, especially if the percentages in question are small and include decimal places. If quantitative terms are used (e. g. 'frequently', 'rarely' or 'occasionally'), these must be explained.

e) Type, duration, reversibility and severity of impairments to health

In assessing impairments to health, a distinction must be made between acute and chronic exposure and clinical progression.

Example: terms for acute impairments

- Severe (life-threatening symptoms that generally require medical intervention or treatment in a hospital setting)
- Moderate (pronounced or prolonged symptoms that normally require medical treatment)
- Minor (mild, transient and self-resolving (i. e. ceasing without external intervention) symptoms)
- No impairment
- Unknownt

The severity of an acute impairment to health can be indicated using a number of different terms, for example (see box). These degrees of severity have been adapted from the WHO Poisoning Severity Score[2]. Consideration is also given as to whether the impairment is temporary or permanent.

Example: terms for chronic impairments

- Severe (e. g. life-threatening illnesses, organ failure, paralyses; mutagenic, reprotoxic and carcinogenic effects)
- Moderate (e. g. chronic joint complaints following infectious diseases, chronic inflammation)
- No impairment
- Unknown

The severity of a chronic impairment to health can be specified using a number of different terms, for example (see box). Unlike acute impairments to health, the chronic nature of such an impairment to health cannot usually be specified as 'minor'.

If pertinent rules exist for describing relevant impairments to health, then these should be taken into account. In relation to biocides, for example, or for chemicals covered by REACH, the potential hazard represented by a substance in terms of the occurrence of local health effects is described on the basis of its CLP classification[3].

---

[2] *Source: Hans E. Persson, Gunilla K. Sjöberg, John A. Haines, Jenny Pronczuk de Garbino (1998) Poisoning severity score. Grading of acute poisoning. Journal of Toxicology – Clinical Toxicology, 36 (3), 205-213 (short version of original publication: www.who.int/ipcs/poisons/pss.pdf; accessed 21 August 2018)*

[3] *Guidance on the BPR: Volume III, parts B + C, version 4.0, December 2017; chapter 4.2.3.5, table 24, p. 246 f.*

f) Evidence of a causal relationship

The evidence of a causal relationship between the potential hazard and the impairment to health is characterised as follows:

- A generally recognised fact (i. e. the causal relationship is proven and generally accepted by science)
- A suspicion, justified by robust data (i. e. data make the causal relationship plausible)
- A concern or a suspicion that is supported only by less robust data (i. e. indications for a causal relationship are comparatively vague)
- No indications of a causal relationship

It should be remembered that statistical significance is not equivalent to biological relevance. A statistically 'significant' effect may be biologically irrelevant – and vice versa.

g) Uncertainties and variabilities

The systematic uncertainty analysis completed in assessments of health risks essentially serves three purposes:

- An uncertainty analysis creates transparency throughout the risk assessment process – by describing assumptions and constraints, for example, as well as their handling.
- The uncertainty analysis serves to document the aspects mentioned in section 1.
- The uncertainty analysis indicates options for action with which the identified uncertainties could be reduced in the future.

The uncertainty analysis is divided into the following four steps:

1. Identification of uncertainties and variabilities
2. Assessment of the individual uncertainties
3. Assessment of the overall influence of the uncertainties on the final result
4. Description of options to reduce the uncertainties

h) Need for further research

A statement is made as to whether (and why) a more detailed assessment or further research could be seen as necessary, and what data or investigations would be necessary in this case.

i) Controllability of the risk

A statement is made as to whether (and how) consumers can minimise the risk, such as by following advice given in product literature that recommends consuming a quantity of the food that does not give rise to concerns about harmful effects to health.

3.2 Risk management options, recommended measures

In this section, details can be given concerning how the opinion may be used to derive recommendations or options for action on the part of government agencies, food business operators or consumers, which could also be included in risk management measures.

Recommendations or proposed options for action may include the following, for example:

- Generation of data that are necessary for a risk assessment
- Restrictions on distribution or commercial usage
- Specification of thresholds/standards (e.g. maximum quantities in food, microbial concentrations in food at the point in time of consumption)
- Labelling, consumer information, recommendations and restrictions on use
- Measures to avoid or reduce the input of the pathogen or the substance, or the propagation of the pathogen, or to reduce the pathogen or the substance, or the formation of the substance in the food chain, such as are to be taken by manufacturers, retailers (e.g. as a result of introducing food technology procedures or hygiene/inspection procedures) or consumers
- Intervening in the event of misleading advertising
- Recommended consumption quantities for the population or certain population groups
- Greater provision of information to consumers (e.g. concerning recommended types of preparation or consumption, as specific as possible for the respective population group, plus rationale)
- Modifications to the affected specification for substances for which specifications are governed by legislation

If recommendations are formulated concerning actions or consumption on the part of consumers, these must be described as specifically as possible and with day-to-day relevance. If different recommendations apply for different subgroups in the population, these must be clearly differentiated from one another and appropriately described. If caution is to be advised concerning the consumption of a food or the use of a product that large parts of the population have previously considered harmless or not especially dangerous, then explicit reasons must be given to justify the withdrawal of the previous assessment and why the science has now changed concerning this food/product.

For certain actions to take or other options, the respective potential consequences may be stated for consumers (e.g. complete avoidance of the risk for the entire population in the event of careful reading of the product declaration, etc.). Any foreseeable trends for the future distribution of the affected products should be specified where possible and accounted for in the recommendations made.

If the BfR issues an opinion with recommendations or options for actions as the basis for an administrative decision in a legally governed process, the reference to such legislation should be as specific as possible. The BfR opinions and the administrative decision are collectively subject to review by the administrative courts.

In other cases, goals, strategies and options for action can be recommended. If multiple, equally suitable measures for risk mitigation could be considered, the BfR will merely indicate risk management options for the target groups.

3.3 Other aspects

Details can be given here that go beyond the risk assessment itself, as described above, or which provide additional information that has no immediate influence on the results of the risk assessment.

Comparative risk analyses for the evaluation of risks and benefits can be included, where necessary. This is necessary, for example, when assessing food and food ingredients capable of having a positive effect on health, or in the case of opinions prepared on certain dietary habits for which it is to be assessed whether the balance between the assumed health benefits and the expected risks can be said to be acceptable. As an example, the BFR recommends that, even when considering the benefits of such a diet, individuals with a weakened immune system should not consume loose-leaf lettuce, leafy vegetables and fresh herbs in a raw state. This advice is justified by the fact that these foodstuffs can be contaminated with pathogens that cannot be completely removed by simple washing.

Assessments involving similar research questions can also be referred to in this section.

4 References

If other authors are quoted in the text of the opinion, this citation must be given in the bibliography at the end of the document. Citations should quote the original text wherever possible. It can also be useful to cite reviews or assessments from expert bodies. The same citation style should be used throughout the document and should meet external requirements for citations in the sense of good research practice. Accordingly, the ‘BfR output style’ is to be used.

BfR output style: G:\PublicBfR\ Endnote-Tutorials

Additions to opinions for the BfR website

The BfR communicates opinions of general interest to the general public. These do not include the following:

- Ongoing research projects
- Undertakings that include company/trade secrets, which cannot be published for legal reasons
- Documents created as part of legal approval proceedings

For the purposes of publication, opinions are given additional features for the general public: a summary is provided in the form of the 'grey box', expressed in plain/non-technical language, and a graphical summary is provided in the form of the risk profile.

For publishing opinions on the BfR website, content is copied from the 'Assessment of health risks' template into the 'Internet opinion' Word template. This template includes details such as the formatting rules for the grey box and risk profile. In connection with the publication of the opinion, documents already published on the same topic on the BfR website – such as FAQs – should be checked to see if they need updating.

The 'grey box'

The grey box is a layperson's summary of a BfR opinion that is placed at the beginning of the opinion document. The grey box should articulate a clear-cut statement for all target groups, whatever their interest and level of expertise, and present the BfR's complex technical topics in simple, straightforward sentences. The aim is to ensure that readers can follow the BfR's argumentation and can therefore understand its conclusions. Relevant content that is not addressed in the opinion can also be discussed as part of the grey box. The overall intention is to ensure that readers can extract the maximum benefit from BfR opinions. The statements made and the wording used in the grey box, the risk profile and the opinion itself must be consistent, especially in terms of the risk characterisation and the presentation of results.

BfR risk profile

The BfR risk profile is a tool used to communicate a comprehensive and generally comprehensible graphical summary of the results of the risk assessment. The risk profile makes it easier to estimate potential risk by summarising key aspects of the risk assessment into standardised categories: the affected target groups, the route of exposure, the degree of severity and the likelihood of an impairment to health (expressed if necessary in the context of the exceedance of corresponding reference values), the quality of the available data, and options for risk mitigation on the part of manufacturers/food business operators, government agencies and consumers.

The aim of the BfR risk profile is to help consumers make informed decisions by presenting the relevant information in an easily digestible format. The BfR risk profile also uses graphical elements to present the key aspects of the risk assessment in a way that enables them to be understood at a glance.

Formatting and corporate design specifications apply for the BfR risk profile.

Glossary: typical terms used in risk assessment and risk communication

The terms listed below should be used uniformly in opinions published by the BfR. Unless a term is known to be familiar, the term should be accompanied by the definition as given here (this can be modified as appropriate in exceptional cases) the first time that this term is mentioned.

Health-based guidance value (HBGV)

ADI **Acceptable daily intake**

Related terms: tolerable daily intake (TDI), acute reference dose (ARfD)

The ADI specifies the quantity of a substance that can be consumed orally on a daily basis over an entire lifetime without a detectable risk to health. The ADI is derived for substances introduced into the food chain, including drinking water (such as food additives, plant protection products and biocides) and applied to the assessment of the health risk that is associated with chronic exposure to such substances. The ADI is typically specified in mg/kg body weight per day.

AEC **Acceptable exposure concentration**

Related terms: threshold limit value (TLV), occupational exposure limit (OEL)

The AEC specifies the maximum estimated concentration of a substance at which no unacceptable local effects are to be expected to occur in the respiratory tract, on the skin or in the gastrointestinal tract. The AEC is currently derived as a route-specific value (by inhalation, possibly oral and/or dermal) primarily for biocidal agents. The AEC is used to assess the risk for the overall population and the user, and can relate to exposure times of different lengths *(short-term, medium-term and long-term)*. Common units include mg/l, %, ppm, mg/cm², etc.).

AEL **Acceptable exposure level**

The AEL specifies the estimated maximum systemically available quantity of a substance (e. g. a biocidal agent) to which the affected groups of persons can be exposed dermally, by inhalation and/or orally (but not via food) within the respective period of time on a daily basis without any expectation of a detectable risk to health. The AEL is primarily used with biocidal agents to assess the risk for consumers and the users, and is typically derived for three separate ranges of time *(short-term, medium-term and long-term)*. The AEL is typically specified in mg/kg body weight per day.

AOEL **Acceptable operator exposure level**

The AOEL specifies the estimated maximum systemically available quantity of the substance (e. g. active substance in a plant protection product) to which exposure can occur dermally, by inhalation and/or orally (but not via food) in affected groups of individuals (e. g. users) on a daily basis over the entire season of application and lifetime without any detectable risk to health. The AOEL is typically specified in mg/kg body weight per day.

ARfD **Acute reference dose**

Related terms: acceptable daily intake (ADI), tolerable daily intake (TDI)

The ARfD specifies the estimated maximum quantity of a substance that can be consumed with food in the course of one day either during one meal or during several meals – without a detectable risk to health. The ARfD is derived for substances introduced into the food chain, including drinking water (plant protection product residues, biocides) or which otherwise arise within this chain (e. g. contaminants), and is then applied to the assessment of the health risk that is associated with acute exposure to such substances. The value is typically specified in mg/kg body weight.

DMEL **Derived minimum effect level**

If no DNEL can be derived for a substance because no threshold value exists for the corresponding toxicological effect (e. g. for genotoxic carcinogens) then, according to the ECHA's "Guidance on information requirements and chemical safety assessment, chapter R.8: 'Characterisation of dose [concentration]-response for human health'", a DMEL should be derived to assess the chemical in terms of the EU REACH Regulation. This value expresses a level of exposure that corresponds to a very low risk in the general population. The value is typically specified in mg/kg body weight per day.

DNEL **Derived no-effect level**

Defined in Annex I, Subsection 1.01 of Regulation (EC) No 1907/2006 (REACH) as the derived level of exposure to a substance 'above which humans should not be exposed'. One or more DNEL values are determined for a substance, whereby the most likely route(s) of exposure as well as the most likely duration and frequency of exposure are taken into account. The derivation of these values is based on toxicological studies (non-human or human). The value is typically specified in mg/kg body weight per day.

HBGV **Health-based guidance value**

Health-based guidance values represent a level of exposure below which no risk to health is to be expected. HBGVs are derived on the basis of toxicological data or from studies involving animal experiments. ADI, ARfD and TDI are all examples of HBGVs. From a toxicological perspective, all relevant sources of exposure should be taken into account when evaluating the degree to which a health-based guidance value is either met or in fact exceeded.

TDI (TWI, TMI) **Tolerable daily intake**

The TDI specifies the quantity of a substance that can be consumed on a daily basis over an entire lifetime without a detectable risk to health. A TDI is derived for substances that occur as contaminants in food, for example – including drinking water – and applied to the assessment of the health risk that is associated with chronic exposure to such substances. The TDI is typically specified in mg/kg body weight per day. Depending on the toxicokinetic properties of the substance under assessment, the derivation of a guidance value related to a weekly (TWI, *tolerable weekly intake*) or monthly (TMI, *tolerable monthly intake*) period of time may be advisable.

UL **Tolerable upper intake level**

The tolerable upper intake level corresponds to the highest chronic daily total intake of a nutrient (from all food sources) for which a risk to health is not be expected.

Toxicological parameters

BMD — **Benchmark dose**
A dose calculated using mathematical dose-effect modelling that, in the investigations underlying this modelling, is associated with a certain effect size.

EFSA guidance 'Update: use of the benchmark dose approach in risk assessment' www.efsa.europa.eu/en/efsajournal/pub/1150

BMDL — **Benchmark dose lower confidence limit**
Dose associated with the lower limit of the confidence interval for the BMD

BMDU — **Benchmark dose upper confidence limit**
Dose associated with the upper limit of the confidence interval for the BMD

LD_{50} — **Lethal dose**
The median lethal dose (LD_{50}) is the statistically calculated single dose of a substance or a corresponding dose of microorganisms that is likely to lead to death within a specific period of investigation in 50% of those organisms exposed. The value is typically specified as a ratio of the mass of the test substance to the mass of the experimental animal in mg/kg body weight or as a microbial count.

LO(A)EL — **Lowest observed (adverse) effect level**
Lowest tested dose at which an adverse effect/impairment to health can be observed.

MOE — **Margin of exposure**
The ratio of a suitable reference value from the dose-effect relationship to the estimated exposure to the substance in humans. Typically, the benchmark dose lower confidence limit 10% (BMDL10) or the tumour dose 25% (TD25) is used as the reference value, i.e. the dose with which a certain increase in the tumour rate is associated for a particular substance, for example. An MOE value is not a health-based guidance value: instead, it is used to prioritise the urgency of risk management measures for substances for which no safe intake value can be derived according to the current state of scientific knowledge (this is specifically the case for genotoxic carcinogens, for example). National risk management agencies consider an MOE of 10,000 or more, where this has been derived on the basis of a BMDL10 from an animal experiment carcinogenicity study, to give little cause for concern in terms of public health, and therefore consider this to be a low priority for related risk management measures. From a toxicological perspective, however, the conclusion that a total intake quantity with an MOE of 10,000 or higher is considered as 'less harmful' in terms of potential cancer risks is not the same as 'harmless'.

EFSA glossary, 'Margin of exposure': www.efsa.europa.eu/en/topics/topic/margin-exposure

MOS **Margin of safety**

The ratio of a suitable reference value from the dose-effect relationship to the estimated exposure to the substance in humans. The reference value applied here is typically the NOAEL or the BMDL5/10. One example of the use of a MOS is to assess the risk to health that can be expected from an exposure to substances for which no health-based guidance value (ADI or TDI) can be derived. In addition, a MOS can also be applied to assess the risk to health that is associated with the exceedance of a health-based guidance value (such as the ADI or TDI).

NO(A)EL **No observed (adverse) effect level**

Highest tested dose at which no adverse effect/impairment to health can be observed.

TD_{25} **Tumour dose**

A dose derived linearly from the dose-effect relationship at which an additional tumour incidence of 25% (TD_{25}) is to be expected versus the control on the basis of the underlying investigations.

TTC **Threshold of toxicological concern**

The TTC is a tool for the prioritisation of substances as part of the risk assessment. For substances (with a known chemical structure) for which no adequate toxicological data are available, the estimated exposure for this chemical substance can be compared instead to the TTC value that has been derived for chemical substances of a similar structure (i. e. a similar structural class). If the estimated human exposure is below this TTC value, the risk to human health is low. The TTC value is based on toxicity data for substances that have similar structural properties.

EFSA glossary, 'TTC':
www.efsa.europa.eu/de/topics/topic/threshold-toxicological-concern

Microbiological parameters

CFU **Colony forming units**
Used to describe the individual, visible units of growth for microorganisms (colonies) on solid nutrient media, which originate from a single cell or multiple cells, and which serves to express the culturable number of microorganisms in a specific volume of the sample analysed.

Infectivity Capability of a pathogen to infect a host

CFR **Case fatality rate**
Specifies the ratio of deaths to number of people infected

MID **Minimal infective dose**
Minimum number of pathogens necessary in order to cause an infection.

Morbidity Specifies the frequency of illness/disease related to a specific population group.

Mortality Specifies the number of deaths related to the total number of individuals in a population or – in the case of specific mortality – as related to the number of deaths in this specific population.

MPN **Most probable number**
The MPN approach enables a statistical estimation of the number of microorganisms in a specific volume of the sample as analysed. This estimate is derived from the combination of positive and negative results from a series of separate volumes taken from the sample, which were investigated using standard tests.

PFU **Plaque forming units**
Designates the number of plaque forming units.

Virulence The term 'virulence' is used to cover a pathogen's sum total of properties that can cause illness or disease.

Parameters used in diagnosis and analysis

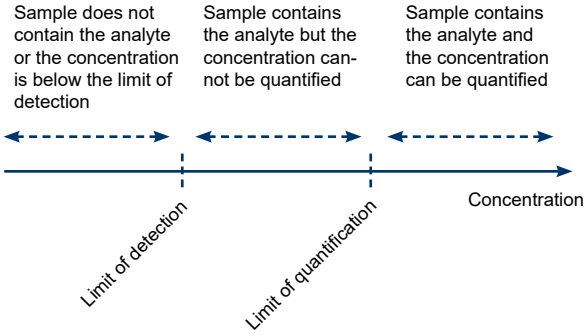
Diagnostic sensitivity Specifies the likelihood of a positive sample actually being correctly detected as such by a diagnostic test.

Diagnostic specificity Specifies the likelihood of a negative sample actually being correctly detected as such by a diagnostic test.

LOD **Limit of detection**
Synonyms: detection limit, lower limit of detection
The lowest concentration of an analyte in a sample that can be distinguished from a blank sample by using a specified measuring method.

LOQ **Limit of quantification**
Synonyms: limit of determination, quantitation limit
The lowest concentration of an analyte in a sample that can be quantified within determined limits of certainty by using a specified measuring method.

LOD/ LOQ



Result < LOD < LOQ
Sample does not contain the analyte or the concentration is below the limit of detection

LOD < Result < LOQ
Analyte is detectable but cannot be quantified within determined limits of certainty. Independently of this, a false positive may have been detected (see diagnostic sensitivity).

LOD < LOQ < Result
Analyte is detectable and can be quantified within determined limits of certainty

Epidemiological and statistical parameters

Bias	The term 'bias' is used to mean any and all systematic errors or distortion in the design, execution or analysis of a study, such that is/are capable of leading to an incorrect estimate of the effect of the exposure in question on the risk of disease/illness in question. Types of bias include selection bias, information bias and confounding.
Exposure	Contact with an agent via an oral, dermal or inhalation pathway, surveyed as a qualitative (exposure factor or risk factor) or quantitative parameter (concentration, frequency, duration, area).
Case-control study	Type of study used in epidemiology in which cases of disease are compared with suitable controls lacking this disease although both cases experienced exposure in the past.
Incidence	Number of new events occurring (such as cases of a disease) related to a specific population and a specific timeframe.
Incidence rate	Number of new cases of a disease occurring within a specific period in relation to the sum total of human time (person-years, -months, -days) of the population at risk.
Median	A value or average of two values in a data set, sample or distribution that divides it into two equal halves when the group of values is sorted by size (equivalent to the 50th percentile).
Mean	The arithmetical mean.
Mode	The value recurring most frequently within a data set.
OR	**Odds ratio** *Synonyms: cross-product ratio* Metric for the estimated effect size of a risk factor. If the confidence interval crosses 1.0, then the effect is not statistically significant.
PPW	**Positive predictive value** *Synonyms: precision* Events classified as correctly positive expressed as a proportion of the sum of total events classified as positive.
Percentile	Percentage of values in a data set or probability distribution sorted by size lying below the corresponding value (e. g. 95% of the values in the case of the 95th percentile).

Prevalence Number of individuals with the condition (such as sick persons, for example) in the defined set of individuals (population) at a particular point in time (point prevalence) or cumulatively over a specific period (period prevalence; lifetime prevalence relates to the entire lifetime).

RD **Risk difference**
Difference between the incidence of the disease in the exposed group and the incidence of the disease in the non-exposed group; if the confidence interval for the RD crosses zero, then this means that the effect from exposure is not statistically significant.

RR **Risk ratio/relative risk**
The ratio of the incidence of disease in the exposed group to the instance of the disease in the non-exposed group. The OR estimated in case-control studies is a good approximation of RR with a low prevalence of disease.

Estimate Numerical result of the calculation of a population parameter (e.g. mean weight or the 95th percentile); to be specified where possible with standard error or the confidence interval.

Estimator A calculation formula or rule for an estimate

Standard deviation Metric for the distribution of a set of values around its mean. The standard deviation of a data set is calculated as the square root of its variance.

Confounder A condition that is either constant (e.g. sex) or changeable (e.g. age) over time, which is correlated to the exposure under investigation and which can influence the probability of a manifestation of the endpoint of interest; if confounders are not controlled by the study design or the statistical analysis, they can result in a distortion of the effect estimate.

Variance A measure of spread that describes the distribution of values in a set around its mean. Variance is calculated as the sum of the mean squares normalised over the number of values for discrete random variables and as the integral over the product of the mean squares for continuous random distributions in terms of how these differ from the expected value and the probability function.

Terms for uncertainty and variability

Variability Variability results from natural fluctuations and deviations in measured values or observations. Variability cannot be reduced by refining the determination methodology.

WOE **Weight of evidence**

Weight of evidence, page 34

Reliability *Synonyms: robustness, soundness*
The reliability of study results in relation to the research question the study is investigating, based on characteristics of study design, execution and analysis, all of which could be associated with random and/or systematic errors (bias).

Relevance The suitability of study results for providing an answer to the given question.

Uncertainty Uncertainty results from a lack of knowledge about a variable that is defined in principle (parameter, model and scenario). Accordingly, uncertainty can be reduced by a more precise measurement method or a refined model. Uncertainty and variability typically occur together.

Uncertainty analysis

Risk characterisation section, page 11

Appendix

Uncertainty analysis

A distinction is made between 'uncertainty' and 'variability'. Uncertainty describes a lack of knowledge (or a lack of adequate knowledge) concerning a state (e. g. the concentration of a chemical in a sample). In principle, this lack of knowledge can be reduced – by making a suitable measurement, for example. Variability, on the other hand, describes the differences (often as a result of natural processes) between many objects of the same type. These differences cannot in principle be further reduced by measurement but can only be better described. This naturally occurring variability – as it relates to individual features in humans (such as body weight or sex), microbiological pathogens, chemical substances or processes – should be described if it could have an appreciable influence on the results of the assessment.

The uncertainty analysis is divided into the following four steps.

1. Identification of uncertainties and variabilities

The identification of existing uncertainties and variabilities in a risk assessment is the first step in an uncertainty analysis. For each step in the risk assessment, uncertainties and variabilities should be identified during the assessment procedure. A structured approach should be utilised for this identification process, so as to obtain a complete picture of the situation. One recommended option here is to use standardised lists of questions. Ideally, these lists will exist for each step in the risk assessment and it can also be useful to have specific lists of questions for subcategories (such as the exposure model). For each description of uncertainty that is made – whether qualitative or quantitative – it is important to state what is affected (such as the result, an event, a parameter).

Any variability that cannot be adequately accounted for (because of a lack of data, for example, or because of the use of default values) leads to an uncertainty, which must then be subsequently assessed as such.

2. Assessment of individual uncertainties

The identification and assessment of individual uncertainties should take place during the preparation of the opinion and can be documented in the sub-sections. This documentation of the most significant individual uncertainties as regards the overall result should be summarised in the subsection 'Risk characterisation: uncertainties and variabilities'. Optionally, this step can also be completed for other – or for all – individual uncertainties.

Uncertainties and variabilities, page 15

Each of the individual uncertainties identified should first be assessed using a simple qualitative method (e.g. a classification as to whether it should be assessed as low, moderate or strong). The criterion for this assessment is the influence of the individual uncertainty on the end result of the risk assessment.

For a qualitative assessment, the influence of the individual uncertainty on the overall result can be described verbally (e.g. small, medium or large). The effect and extent of the individual uncertainty can also be described using symbols (such as ---, --, -, +, ++, +++). In doing so, however, one should remember that verbal formulations and symbolic representations can be interpreted differently. Accordingly, verbal formulations and symbolic representations should always be accompanied by a guide to interpretation (such as that given for probability statements in 'Risk characterisation: likelihood of impairments to health').

Likelihood of impairments to health, page 12

If necessary, individual uncertainties can then be subsequently assessed using a different method, such as a quantitative method. This subsequent assessment can focus on the individual uncertainties that have the greatest influence on the end result. The method used depends on resources such as the available time or data. When utilising a quantitative method, the influence of an individual uncertainty on the end result must be calculated.

When describing a quantitative assessment, the following aspects should be taken into account:

- A numerical expression of uncertainty should be formulated as a percentage of certainty.
- Figures should be reported without expressions that qualify them (e.g. 'about', 'roughly', 'up to') and should not be replaced by verbal formulations, as these could be interpreted in different ways.
- If a numeric range is described, a central value as well as a probability (e.g. confidence) for this range should also be reported.

Figures should be supplemented with verbal descriptions to simplify their correct interpretation. This is especially important to ensure that subsequent communications are able to use consistent wording that is congruent with the numeric results of the uncertainty analysis.

Risk management options, recommended measures, page 16

If accounting for an individual uncertainty has particular importance for the assessment result (e.g. if this could result in a specific reference value being exceeded), then this should be mentioned explicitly. If an individual uncertainty has an influence on the risk management options or recommended measures, this should be taken into account by identifying these options for action in the section 'Risk management options, recommended measures'.

3. Assessment of the overall influence of the uncertainties on the final result

After assessing the individual uncertainties, their overall influence on the risk assessment's end result is then assessed. A qualitative approach can be taken, which implies a textual categorisation of the influence of all individual uncertainties on the robustness of the risk assessment's end result. However, a quantitative approach can also be adopted. The result should be presented either purely qualitatively or purely quantitatively (and in this case without aggregation). In the case of a purely quantitative approach, each individual uncertainty can be assessed quantitatively[4] and the assessments can then be combined into an overall uncertainty. Whether a qualitative or quantitative approach is chosen, the assessment of the overall influence must abide by the same principles as those used to describe the individual uncertainties.

[4] *A quantification of this kind may also consist of stating that the individual uncertainty is negligible, however, i.e. it is assessed as 0.*

In the opinion's risk characterisation section, a short and meaningful summary of the overall influence on the end result must be formulated. This must also be included in the results section and in section 3.3 on risk management options, as well as in the risk profile and the grey box. When considering the overall influence of the uncertainties on the end result, the certainty implied must not be greater or less than that permitted by the uncertainty analysis. Care must also be taken to state that the uncertainties mentioned have already been taken into account in the assessment. This underlines the fact that the end result of the risk assessment does not need to be reinterpreted once again in light of these uncertainties.

4. Description of options to reduce the most important uncertainties

For the most influential individual uncertainties, the steps necessary to reduce their influence should be determined (e. g. what would be necessary for a study). Any potential need for a more detailed assessment or further research activities should be specified, as well as the data or investigations that would be necessary in this case. If, given the existing uncertainties, a reliable risk assessment is not possible or only partially so, the options to reduce individual uncertainties must also be specified in the results section, and (potentially) in the risk profile and the grey box.

For further details of the uncertainty analysis and the communication of uncertainties, see the corresponding guidance documents in the appendix.

Guidance documents, page 40

Weight of evidence (WOE)

A WOE approach is understood to mean an internationally agreed[5] procedure for a systematic, collective evaluation and weighting of the results/data (lines of evidence) made available by various methods/approaches for the purpose of providing an answer to a research question. This approach should be adopted if multiple independent sources of evidence are available. The WOE approach is intended to present the arguments leading to a particular set of conclusions in a way that is both clear and comprehensible.

As regards the research question, this may involve a hypothesis ('Is substance X carcinogenic?') or be a problem to do with estimation ('What proportion of the population is exposed to substance X at level Y?'). The term 'evidence' can be understood to mean any relevant piece of information capable of answering the question. This may include data from scientific publications or a series of experiments that are capable of meeting the minimum requirements for reliability and relevance to be defined in each case. WOE assessments made by the BfR are oriented on the EFSA guidance document. The goal of the WOE assessment is to use the systematic collection, assessment and integration of available information in order to answer a specific scientific question on the basis of the entire (also in the sense of complete) body of knowledge available. During this process, the level of evidence – i. e. the formal and substantive quality of various potential answers – is reported explicitly.

The basic elements of a WOE assessment are the following three work steps:
1) Consolidation
2) Weighting/critical evaluationg
3) Integration of evidence

[5] *EFSA (European Food Safety Authority), 2017. Guidance on the use of the weight of evidence approach in scientific assessments, EFSA Journal 2017;15(8):4971*

WHO (World Health Organization), 2009. Food safety. Project to update the principles and methods for the assessment of chemicals in food. Principles and methods for the risk assessment of chemicals in food. EHC 240. ISBN 978 92 4 157240 8

ECHA (European Chemicals Agency), 2010. Practical guide 2: how to report weight of evidence. ECHA, Helsinki, pp. 1–26

SCHEER (Scientific Committee on Health, Environmental and Emerging Risks), European Commission, 2018. Memorandum on weight of evidence and uncertainties Revision 2018

The first step provides a precise definition of the scientific question. Key concepts are derived and criteria are specified here, which will be used as the basis for researching and selecting corresponding data sources. The overall aim here is to represent the existing body of knowledge as completely and faithfully as possible[6]. Depending on the question at hand, a wide variety of information/data can be taken into account and assigned to 'lines of evidence' as required, such as *in vivo*, *in vitro*, *in silico* or epidemiological studies. A variety of individual data sources (e.g. studies) can be present within a single line of evidence.

The second step concerns the weighting of evidence from the individual sources of information. The relevant criteria here include reliability (are the results robust or is the set of data encumbered with significant constraints?), relevance (is the information relevant for answering the question – and are the results transferable to the general conditions relevant for the question itself?) and consistency (are the results comparable, reproducible and do they point towards the same set of conclusions?). The criteria applied in each case must be presented clearly and comprehensibly. The evidence from the individual sources of information can be weighted qualitatively or quantitatively.

The third step involves integrating the insights from the individual sources of information while taking the weighting into account. Where possible, any distortion identified as affecting the body of knowledge (e.g. publication bias) should be accounted for. Integration is completed both at the level of the consolidation of insights within a line of evidence and also as part of a further step for the integration of separate lines of evidence. The spectrum of methods for these integration steps once again comprises qualitative and quantitative methods. The appropriate method in each case is selected in terms of scientific considerations, set standards (where available) and the processing time available.

---

[6] *In cases where the information concerning a significant aspect of the assessment represents a scientific controversy and the relevant scientific insights have not been systematically consolidated to date, a systematic overview (systematic review) – including a statistical analysis (meta-analysis) – should be prepared, where possible.*

Example: toxicological analysis of plant protection products (PPPs)

Consolidation

For the toxicological analysis of plant protection products, an applicant submits studies for the eye irritation endpoint that represent the existing body of knowledge for the question to be assessed, in accordance with step 1 (consolidation). These studies conform to the regulatory data requirements for plant protection products and answer the following question: is the proposed formulation to be classified as causing eye irritation or damage according to the CLP Regulation (Regulation (EU) No 1272/2008)? The studies submitted can be assigned to various lines of evidence:

- An *in vivo* study in rabbits, which was conducted using a similar formulation. This formulation is to be considered comparable without constraints, according to applicable guidance (SANCO/12638/2011).
- *In vitro* studies according to OECD TG 437 (*bovine corneal opacity and permeability test,* BCOP) and OECD TG 492 (*reconstructed human cornea-like epithelium,* RhCE), which were completed using the proposed formulation.
- A calculation of the potential for eye irritation based on the additive principle according to the CLP Regulation, by applying data on skin and eye irritation for the individual substances contained within the formulation.

Weighting/critical evaluation

In accordance with step 2 (weighting/critical evaluation), the individual studies are assessed for reliability and relevance, and the data are checked for consistency. The studies are quality-assured studies conducted and documented according to validated guidelines and good laboratory practice (GLP). The human relevance of the individual lines of evidence can be assessed with the following criteria:

- Complexity (mammalian organism > organ > cellular system > calculation of the basis of toxicodynamic data)
- Application domain: *in vitro* studies are often suitable only for predicting eye damage, or excluding eye irritation or damage. Conversely, they are not suitable for predicting eye irritation. In addition, *in vitro* tests will not typically have been validated with complex mixtures. One exception here is the RhCE test, whose validation matrix also encompasses plant protection products.
- Tested formulation (data for the proposed formulation are more relevant than data for similar formulations)

The assessment of the reliability of the studies and the calculations according to the additive principle is based on the following criteria:

- Accuracy of prediction: *in vitro* studies are compared for validation with *in vivo* studies. The accuracy of this prediction and, in particular, the probability of false-negative statements (*false negative rate* [FNR]; proportion of substances and formulations categorised as less critical in comparison to the reference method) has a role to play in the reliability of *in vitro* methods. Similar data are also available for the calculation method according to the CLP Regulation. The calculation method should supply a conservative prediction with a low FNR, however, as this method represents a minimum requirement if studies are unavailable. This is not always applicable to PPPs. While the calculation method for eye irritation is generally sufficiently conservative, the FNR for other endpoints, such as acute oral toxicity or toxicity by inhalation or sensitisation to PPP formulations, is too high (Kurth et al., 2019, A comparative assessment of the CLP calculation method and *in vivo* testing for the classification of plant protection products, https://doi.Org/10.1016/j.yrtph.2018.11.012).
- Quality of data: various criteria concerning the methodological quality and the reporting of study execution are applied here. Data for calculations made according to the additive principle are generally taken from safety data sheets and the ECHA database. Unlike the submitted *in vivo* and *in vitro* studies, these data have not necessarily been obtained by the application of good laboratory practice and have not been independently verified.

An example of the qualitative assessment of relevance and reliability is presented in table 1 (see page 38).

As a rule, *in vivo* experiments involving complex mammalian organisms are weighted more strongly than isolated organ or cellular systems (*in vitro* methods) as a result of their relevance for human toxicological analysis. For the *in vitro* methods submitted in this example, the weighting of the application domain depends on the results. If eye irritation caused by the formulation cannot be excluded on the basis of the RhCE test, for example, this test is considered unsuitable because of its application domain and will not be included in the evaluation. Lastly, the tested formulation is also relevant for the weighting. On the other hand, formulations considered comparable in accordance with the above-mentioned guidance should nonetheless be weighted less strongly than the proposed formulation. If multiple studies are submitted that do not meet the guidance criteria to the fullest extent possible, these can nonetheless be included in the assessment but with a lower weighting.

The reliability of the results can be evaluated on the basis of the quality of the studies and their predictive power. In the calculation of potential eye irritation based on the additive principle, however, the quality of the input parameters is unclear. *In vivo* studies are used as the reference methods for assessing predictive power. In regulatory terms, the FNR is also important, alongside the accuracy of the results.

Table 1: Example illustrating the qualitative assessment of relevance and reliability for the studies and calculations submitted

		in vivo	***in vitro*** **(BCOP)**	***in vitro*** **(RhCE)**	**calculation (*in silico*)**
relevance	complexity	+++ (organism)	++ (organ)	+ (cellular system)	No consideration of toxicokinetics
	application domain[7]	+++ (eye damage, eye irritation, no irritation)	++ (eye damage, no irritation)	+ (no irritation)	+++ (eye damage, eye irritation, no irritation)
	formulation	++ (similar formulation)	+++ (proposed formulation)	+++ (proposed formulation)	+++ (proposed formulation)
reliability	quality	+++ (GLP)	+++ (GLP)	+++ (GLP)	unclear
	accuracy of prediction (for plant protection products)	reference method	Kolle et al. (2015)[10] Eye damage – Accuracy: 77% – FNR[8]: 86%[9] No irritation – Accuracy: 80% – FNR: 13%	Kolle et al. (2015)[10] No irritation – Accuracy: 83% – FNR: 9%	Corvaro et al. (2017)[11] – Accuracy: 51% – FNR: 29% Kurth et al. (2019)[12] – FNR: 12%

BCOP = *bovine corneal opacity and permeability test*

RhCE = *reconstructed human cornea-like epithelium*

GLP = Good laboratory practice

+/++/+++ medium/high/very high relevance or reliability

---

[7] *The application domain here describes whether categorisation and labelling in the categories 'eye damage', 'eye irritation' or 'no irritation' is possible with the method.*

[8] *FNR = FN/(TP+FN); FNR: false negative rate, FN: number of false negative predictions, TP: number of true positive predictions*

[9] *The high FNR can be explained by the classification system used in the BCOP test. If no assignment to the category 'eye damage' or 'no irritation', further testing of the product is required. As a result, there is no final categorisation and labelling on the basis of the negative result, and a high FNR is acceptable.*

[10] *Kolle, S. N., Moreno, M. C. R., Mayer, W., van Cott, A., van Ravenzwaay, B., & Landsiedel, R. (2015). The EpiOcular™ eye irritation test is the method of choice for the in vitro eye irritation testing of agrochemical formulations: correlation analysis of EpiOcular eye irritation test and BCOP test data according to the UN GHS, US EPA and Brazil ANVISA classification schemes. Alternatives to Laboratory Animals, 43(3), 181–198.*

[11] *Corvaro, M., Gehen, S., Andrews, K., Chatfield, R., Macleod, F., & Mehta, J. (2017). A retrospective analysis of in vivo eye irritation, skin irritation and skin sensitisation studies with agrochemical formulations: setting the scene for development of alternative strategies. Regulatory Toxicology and Pharmacology, 89, 131–147.*

[12] *Kurth, D., Wend, K., Adler-Flindt, S., & Martin, S. (2019). A comparative assessment of the CLP calculation method and in-vivo testing for the classification of plant protection products. Regulatory Toxicology and Pharmacology, 101, 79–90.*

Integration of evidence

The weighted data are aggregated according to step 3 (integration).

The results of all lines of evidence are weighted and integrated by applying expert knowledge. In the present example, the overall result established concerning potential eye irritation is used as the basis for potentially recommending categorisation and labelling according to the CLP Regulation.

With knowledge of the relevant parameters influencing accuracy and the quantitative relationship of these parameters, a quantitative WOE assessment would be possible in the future. To do so, structured statistical analyses, e. g. of *in vivo*/*in vitro* data pairs, are required across a broad set of data.

Selected technical guidelines

Biocides

Guidance on the biocidal products regulation, volume III: human health, part A: information requirements. Version 1.2, May 2018
www.echa.europa.eu/guidance-documents/guidance-on-biocides-legislation

Guidance on the biocidal products regulation, volume III: human health – assessment & evaluation (parts B+C). Version 4.0, December 2017
www.echa.europa.eu/guidance-documents/guidance-on-biocides-legislation

Format templates for biocide assessment reports
www.echa.europa.eu/de/support/guidance-on-reach-and-clp-implementation/formats (under the heading 'BPR')

- Competent authority report
- Product assessment report of a biocidal product (family) for national authorisation applications
- Product assessment report of a biocidal product (family) for union authorisation applications

Chemicals

Guidance documents from the European Chemicals Agency (ECHA)
http://guidance.echa.europa.eu
Includes guidance on the evaluation of chemicals

Food

Codex Alimentarius Commission. Procedural manual – 17th edition, 2008
Also includes definitions of the terms used in the risk analysis of foodstuffs

Food safety risk analysis – A guide for national food safety authorities
www.fao.org/3/a-a0822e.pdf

FAO/WHO guide for application of risk analysis principles and procedures during food safety emergencies
www.fao.org/docrep/014/ba0092e/ba0092e00.pdf

Application of risk analysis to food standards issues, report of the joint FAO/WHO expert consultation, 1995
Lists definitions for the risk assessment/evaluation of biological/bacterial hazards and on uncertainty/variance

Risk management and food safety, report of a joint FAO/WHO consultation, Food and Nutrition Paper 65, 1997
Defines risk management terms as used in the field of food safety

Principles for the safety assessment of food additives and contaminants in food, WHO International Programme on Chemicals Safety ICPS, Environmental Health Criteria 70, 1,1996
Lists definitions of terms and also includes descriptions of the methodological requirements for the assessment of chemicals (contaminants, residues, etc.) in food

Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age
http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4849/pdf

Principles for evaluating health risks in children associated with exposure to chemicals
www.inchem.org/documents/ehc/ehc/ehc237.pdf

EFSA guidance documents

The European Food Safety Authority (EFSA) has presented an overview of policies, guidance documents and other working documents from EFSA and other organisations on risk assessment in its 'EFSA technical report', which is regularly updated.

Database of guidance on different toxicity end-points, risk assessment methodologies and data collection related to food, feed, animal health and welfare and plant health
www.efsa.europa.eu/en/scdocs/scdoc/1518.htm

Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: part 1, human and animal health
www.efsa.europa.eu/en/efsajournal/pub/5327
www.efsa.europa.eu/de/applications/feedadditives/regulationsandguidance

Opinion of the scientific committee on a request from EFSA related to a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic
https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2005.282

Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment
www.efsa.europa.eu/de/efsajournal/pub/2379

Clarification of some aspects related to genotoxicity assessment
www.efsa.europa.eu/de/efsajournal/pub/5113

Genotoxicity assessment of chemical mixtures
https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2019.5519

Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals
https://doi.org/10.2903/j.efsa.2019.5634

Update: use of the benchmark dose approach in risk assessment
https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2017.4658

Guidance on the use of the threshold of toxicological concern approach in food safety assessment
https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2019.5708

Collection and routine analysis of import surveillance data with a view to identification of emerging risks
www.efsa.europa.eu/en/scdocs/scdoc/1531.htm

Guidance on expert knowledge elicitation in food and feed safety risk assessment
www.efsa.europa.eu/de/efsajournal/pub/3734

Guidance on the assessment of the biological relevance of data in scientific assessments
www.efsa.europa.eu/en/efsajournal/pub/4970

Principles and process for dealing with data and evidence in scientific assessments: PROMETHEUS (Promoting methods for evidence use in scientific assessments)
https://doi.org/10.2903/j.efsa.2015.4121

Genetically modified organisms (GMO)

Principles for risk analysis and guidelines for safety assessment of foods derived from modern biotechnology, Joint FAO/WHO Food Standards Programme, 2003
Also includes definitions of the terms used in the risk analysis of GMO

Microbiology

Principles and guidelines for the conduct of MRA (CAC/GL-30 (1999). Amendments 2012, 2014
www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCXG%2B30-1999%252FCXG_030e_2014.pdf

Microbial risk assessment guideline: pathogenic organisms with focus on food and water
www.fsis.usda.gov/shared/PDF/Microbial_Risk_Assessment_Guideline_2012-001.pdf?redirecthttp=true

Plant protection products

A recent overview of guidance documents for the evaluation of plant protection products is provided by the EU Commission.
https://ec.europa.eu/food/plant/pesticides/approval_active_substances/guidance_documents_en

Testing methods and guidance documents for active ingredients and plant protection products can be found in the following communications from the EU Commission:
2013/C 95/01:
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52013XC0403(02)
2013/C 95/02:
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52013XC0403(03)

Review

Scientific advice by the scientific committee: internal and external review: proposal for a review system for EFSA's scientific activities
https://doi.org/10.2903/j.efsa.2007.526

Application of systematic review methodology to food and feed safety assessments to support decision making
www.efsa.europa.eu/en/efsajournal/pub/1637

Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No. 1107/2009
www.efsa.europa.eu/de/efsajournal/pub/2092

Animal feed

Codex Alimentarius Commission. Guidelines on the application of risk assessment for feed – CXG 80-2013

Codex Alimentarius Commission. Guidance for governments on prioritizing hazards in feed – CXG 81-2013

Codex Alimentarius guideline collection
www.fao.org/fao-who-codexalimentarius/codex-texts/guidelines/en/

Guidance documents for feed
www.efsa.europa.eu/de/applications/feedadditives/regulationsandguidance

Risk assessment of contaminants in food and feed
https://doi.org/10.2903/j.efsa.2012.s1004

Risk communication

EFSA guidance on communication of uncertainty in scientific assessments
https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2019.5520

Risk communication guidelines – a joint initiative of the European Food Safety Authority and national food safety organisations in Europe
www.efsa.europa.eu/sites/default/files/corporate_publications/files/riskcommguidelines170524.pdf

OECD guidance document on risk communication for chemical risk management, 2002
www.olis.oecd.org/olis/2002doc.nsf/LinkTo/NT00002D5A/$FILE/JT00129938.pdf
Lists definitions and recommendations for risk communication in the field of chemical safety

FAO/WHO: The application of risk communication to food standards and safety matters

Report of a joint FAO/WHO expert consultation, 1998
www.fao.org/docrep/005/x1271e/x1271e00.htm
Lists definitions and recommendations for risk communication in the field of food safety, and especially in conjunction with the Codex Alimentarius

BfR risk communication in practice
www.bfr.bund.de/cm/350/die-risikokommunikation-des-bfr-in-der-praxis.pdf

Uncertainty analysis and communication of uncertainties

Guidelines on uncertainty analysis in exposure assessments
www.bfr.bund.de/cm/350/guidelines-on-uncertainty-analysis-in-exposure-assessments.pdf

Guidance on uncertainty analysis in scientific assessments
www.efsa.europa.eu/en/efsajournal/pub/5123

Guidance on communication of uncertainty in scientific assessments
www.efsa.europa.eu/en/efsajournal/pub/5520

See also:
van der Bles, A. M., van der Linden, S., Freeman, A. L. J., Mitchell, J., Galvao, A. B., Zaval, L., & Spiegelhalter, D. (2019). Communicating uncertainty about facts, numbers and science. Royal Society Open Science, 6(5), 181870. doi: 10.1098/rsos.181870

Terminology

Lewalle, P., Risk assessment terminology: Methological considerations and provisional results. Terminol Standard Harmoniz. 11, 1–28. 1999

WHO/IPCS risk assessment terminology. Part 1: IPCS/OECD key generic terms used in chemical hazard/risk assessment. Part 2: IPCS glossary of key exposure assessment terminology. International Programme on Chemical Safety, 2004
Lists the terminology for chemicals (in food)

Scientific opinion on risk assessment terminology
https://doi.org/10.2903/j.efsa.2012.2664

Transparency

Guidance of the Scientific Committee on Transparency in the scientific aspects of risk assessments carried out by EFSA. Part 2: General principles
https://www.efsa.europa.eu/en/efsajournal/pub/1051
Lists general requirements for transparency in risk assessments carried out by EFSA, including the structure and content of an assessment or the documentation of the underlying data

Use of mathematical models

Guidance on good practice in conducting scientific assessments in animal health using modelling
www.efsa.europa.eu/en/scdocs/scdoc/1419.htm
Provides guidance on model selection and integration of the mathematical modelling in answering the question at hand, using applications in the field of animal health as an example (does specify generally applicable rules, however, http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4658/pdf)

Weight of evidence approach

Guidance on the use of the weight of evidence approach in scientific assessments
https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2017.4971

ECHA (European Chemicals Agency), 2010. Practical guide 2: how to report weight of evidence. pp 1–26

SCHEER (Scientific Committee on Health, Environmental and Emerging Risks), European Commission, 2018. Memorandum on weight of evidence and uncertainties Revision 2018

Also covered as one of several methods in:
WHO (World Health Organization), 2009. Food safety. Project to update the principles and methods for the assessment of chemicals in food. Principles and methods for the risk assessment of chemicals in food. EHC 240
https://apps.who.int/iris/bitstream/handle/10665/44065/WHO_EHC_240_eng.pdf

German Federal Institute for Risk Assessment (BfR)
Max-Dohrn-Straße 8–10
10589 Berlin
GERMANY

Phone +49 30 18412-0
Fax +49 30 18412-99099
bfr@bfr.bund.de
www.bfr.bund.de/en