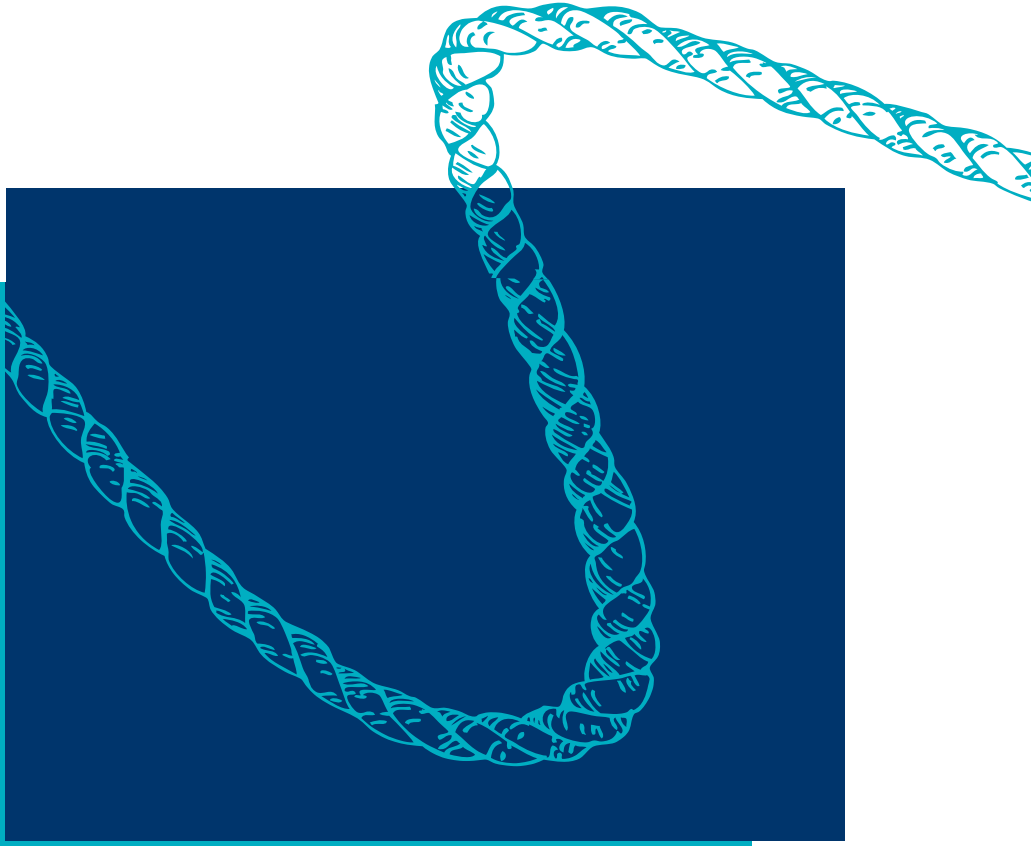
BfR
German Federal Institute for Risk Assessment

Guideline
for the assessment of health risks



Contents

Basic principles

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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 understandable presentation of the scientific basis of its assessments, the BfR makes an important contribution to risk communication. One aspect of risk communication, among other things, is the exchange of information and scientific opinion concerning risks between all target groups, which include consumers, government, research and 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 to 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.

More information:
Uncertainties and variabilities, page 22

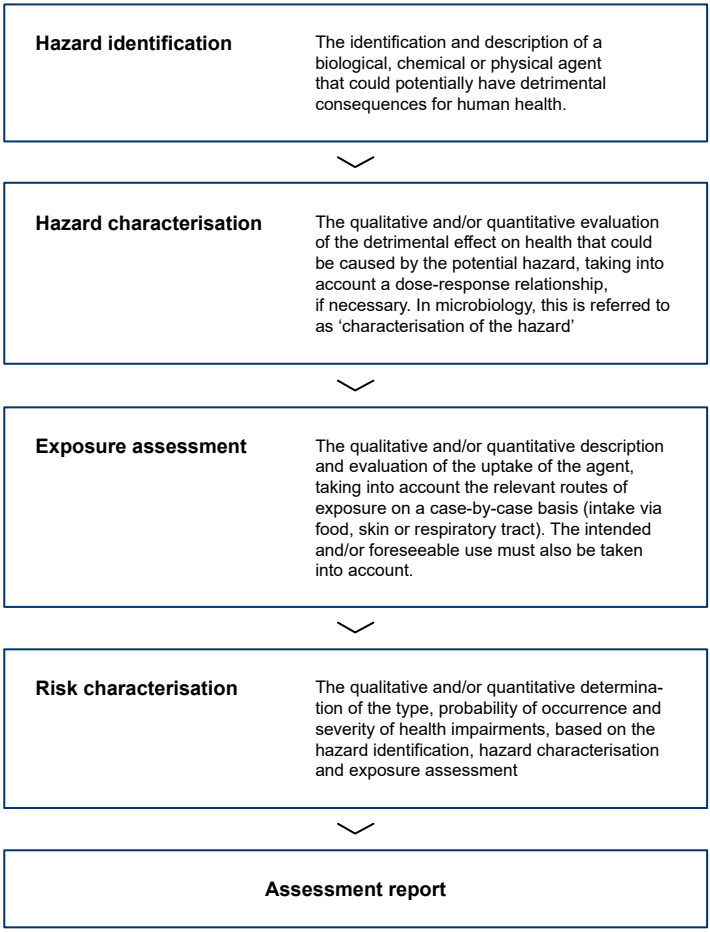
In the assessment of risks to health, the uncertainties that could arise at any level while preparing an opinion should be accounted for appropriately and communicated transparently. Uncertainties may also arise from the type of question posed. In general, therefore, it is necessary to clearly define and differentiate the subject of the assessment (e.g. which hazards, sources and routes/sites of exposure should – and should not – be considered in the opinion).

Before commencing the assessment process, a question posed by risk management authorities may need to be reformulated into a task suitable for risk assessment. If possible, risk management authorities should be contacted in order to gather more information regarding the reasoning, background and aims of the task. Should communication not be possible due to time constraints, it is the task of risk assessment authorities to determine the way in which unclear terms are interpreted. Assumptions or limitations identified in the assessment (e.g. risks or contributing factors which were not considered, restriction to certain food groups) should be specified here and communicated in the reply to the question posed.

Basic principles of health risk assessment performed by the BfR

Risk assessment is a scientifically supported procedure involving four stages; hazard identification, hazard characterisation, exposure assessment and risk characterisation.

From hazard to objective assessment – the risk assessment procedure



Risks must be described qualitatively and – where possible – quantitatively. This description should be based on the structure presented below. In addition, quantitative risk assessments are based on calculations or mathematical models in which the risks are described using mathematical methods. The model's numerical results must be described in words and incorporated into the answers provided to the question under consideration.

Transparency is necessary 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, nature and evidence of the underlying data (including any variability these data contain and different interpretations)
- Methods and models used
- Other assumptions and constraints
- Results and conclusions

More information:
Weight of evidence, page 46

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.

Opinions made by the BfR are based on current scientific findings, internationally recognised principles and are comprehensibly justified. Existing knowledge is adequately considered and presented clearly. Where possible, references are made to earlier opinions issued by the BfR. Relevant differences of scientific opinion must be presented. If there are any differences between the opinions 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 in such a way that they can be utilised by all target groups without any need for further explanation. Clear understandable language should, therefore, be used. The wording of the opinion should be clear and consistent with other opinions issued by the BfR; unnecessary repetition is to be avoided. The line of argument taken should be logical and coherent.

Opinions do not reflect a personal point of view (avoid the use of 'I', 'we' or 'the report authors') but rather 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 clearly described and should remain unchanged within a section as much as possible (see example in the box below). A 'reference value' refers, for example, to the amount of a substance or the number of events or individuals to which a number or risk data relates.

Example: reference/reference value

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

The same units of measurement must be used throughout in order to ensure comparability of the figures given (e.g. mg/kg body weight). Whenever possible, units in accordance with the International System of Units (SI) should be used.

With regard to the frequency of adverse events, quantitative information on the likelihood and the severity of health impairments etc., should, where available, be utilised in addition to the qualitative formulations. As such, a descriptive statement (e.g. that an adverse event occurs 'often') should also be accompanied by a numerical statement (e.g. 'the events occurred in x out of y cases' or 'no cases have been reported to date'). Numerical details expressed as frequencies for small numbers (e.g. '10 out of 1,000 cases' or 'one in two') are easier to understand than percentages, especially if the percentages in question are small and include decimal places. By contrast, numbers expressed as percentages are easier to understand when the numerical values in question are large (e.g. '400,000 out of 1,000,000').

More information:
Risk characterisation, page 16

Consistent terminology should be used to characterise risks; these terms are defined in greater detail in the 'Risk characterisation' chapter.

Certain terms have legal definitions or have been introduced as legal terms in relation to the fields of the economy, the judiciary or the public. The consistent use of these terms in BfR opinions helps to ensure coherence 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 legally defined tasks and duties. For 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, to ensure the decision-making scope of the competent authorities is not constrained. Classifying 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.

Opinions
Content and structure

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As a rule, scientific assessments published by the BfR utilise the following overall structure:

Title
1 Subject of the assessment
2 Results
3 Justification
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

More information:
Template ‘Stellungnahme_Bewertung’, drive V

The ‘Stellungnahme_Bewertung’ layout template should be used for this purpose. However, as the BfR prepares opinions in a wide range of discrete specialist fields; 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 adding new or amending existing subsections. In individual cases, the design can be tailored to the subject matter of the opinion.

The opinions are normally sent as an attachment to a cover letter. This communication can provide more detailed background details or information on the result, on sharing with third parties or on confidentiality.

Title

Each document is given a short and meaningful title, which, for example, can be derived from the reason for its creation. A heading containing keywords should be used to enable quick document classification and can, for example, contain substance/product and matrix details. 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

If deemed necessary for clarification, the motivation and background of the question should be specified. Repeating the question while referencing previous correspondence and the procedural status makes such an introduction easier. The question should be formulated such that the procedure for this question's assessment can be derived as a logical consequence. Typically, it is necessary to define and differentiate the subject of the assessment (e.g. which hazards, sources and routes/sites of exposure have been – and have not been – considered in the opinion). The assumptions (e.g. the population group to be protected, the safety objective, the safety level) or restrictions (e.g. risks or other factors not considered, restriction to certain food groups) made during the assessment should be explained in greater detail at this point and, where appropriate, should also be part of the discussion on uncertainties in the section 'Risk characterisation: uncertainties and variabilities'. Uncertainties should always relate to the subject of the assessment. If the assessment shows that there is little data available (e.g. regarding children), this increases the uncertainty.

More information:
Uncertainties and variabilities, page 22

Particularly for products, further characterisation can be helpful, for example, by specifying the name (product name, approval number or similar), ingredients, presentation, indications or name of the microorganism, the food or food group, and the origin. If necessary or pertinent, the relevant legislation or guidelines are specified which are used to assess the risk.

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 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 Justification

This section is used to present the arguments that led to the assessment findings. Uncertainties and differences in scientific opinion must be discussed in the appropriate context and summarised under 'Risk characterisation'.

3.1 Risk assessment

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 under assessment could lead to a health risk and the estimated severity of this risk. The applicable uncertainties must also be discussed. Variabilities must also 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 (or 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 chemical, physical or microbiological characterisation of the agent. In the case of microbiological agents, for example, the characterisation of the microorganism, including its pathogenicity, virulence factors, tenacity, etc.
- A description of occurrence, production and usage of the agent
- Where appropriate, any common knowledge regarding instances of the agent interacting with food and the influence of food technology on the agent
- Where appropriate, any common knowledge regarding instances of the agent interacting with consumer products and the influence of the manufacturing process or the conditions of use of the product on the agent
- Common knowledge about the qualitative and, where applicable, quantitative dissemination of the agent, such as in the environment, in livestock and/or in the food/feed chain

3.1.2 Hazard characterisation

The hazard potential of the hazard under investigation must be described by taking into account the exposure route or the intended use of the agent and, where appropriate, the various subpopulations involved (grouped, for example, by age, gender, immune status). As a rule, the robustness and reliability of the available data should also be described. The description provided includes, for example, details of the following parameters:

- Toxicokinetics/pharmacokinetics: liberation, absorption, distribution, metabolism, and excretion, (L)ADME
- Toxic effects: such as acute toxicity, toxicity after repeated intake, genotoxicity, carcinogenicity, reproductive and developmental toxicity, immunotoxicity, neurotoxicity, endocrine effects

- Type, duration and severity of health impairments (incubation period, clinical symptoms, acute or chronic progression)
- Dose-response relationship
- Key parameters relating to toxicology (e.g. NOAEL, BMDL), infectiology (e.g. MID) and epidemiology (e.g. odds ratio)
- Health-based guidance values, as appropriate (e.g. ADI) and, if possible, corresponding statistical parameters such as degree of confidence
- Long-term effects and complications
- Reversibility
- Frequency of occurrence of health impairments, illnesses and complications (in Germany) as well as the results of outbreak investigations. International data is often available and these findings should definitely be considered, as focusing purely on Germany is too restrictive. For example, there are extensive studies from Asia on arsenic in rice. Whether or not this is relevant to Germany might be the subject of the assessment. Preferably, German data is used; if this is not available to or supplement it, European or international data should be used, although their relevance must be critically examined.

3.1.3 Exposure assessment

The exposure assessment includes the evaluation and categorisation of various aspects and sources of information on exposure, including the consideration of uncertainties. This section may utilise both quantitative and qualitative evaluations on the level or magnitude of exposure, e.g. those based on literature sources. An exposure assessment determines the external uptake quantity or internal concentration of an agent in the human body or in relevant body compartments such as blood or different tissues, typically by the application of mathematical/statistical methods. This is achieved by connecting numerous sources of data, such as physical or chemical properties, data on the origin and spread of the agent, information on the behaviour of the exposed individuals (e.g. contact time, consumption patterns, etc.) as well as individual characteristics (e.g. height, weight, age, etc.). The overall exposure assessment considers various sources of exposure, e.g. food consumption, use of products, or inhaled air. The accuracy of the exposure assessment is based on the quality of the available data and the requirements of the risk characterisation using tiered methods.

In order to describe the degree of exposure to an agent (e.g. substance/ bacterium) for the relevant population groups, the following information might be necessary. This information should also be characterised with regards to uncertainties and variabilities.

- Information on the exposed population groups, as well as any different exposure scenarios, taking into account factors such as age, body weight, sex or special diets
- Information on consumption data and other details about exposure frequency
- Information on specific consumption habits
- Information on the contribution of individual sources of exposure – such as specific food groups – to the overall exposure
- Sales information on the relevant food matrix or product (target group, trading structures)
- Details on the use of relevant consumer products (dermal, oral, inhalative, frequency, duration, etc.)
- Information on the prevalence and qualitative and quantitative occurrence of an agent or residues in and on the foodstuffs to be assessed, in the food chain, or in the products to be assessed, e.g. from which types of products the agent is released over time in different exposure scenarios (after intended or foreseeable use)
- Intended use (e.g. preparation as intended, foreseeable but not intended use of potentially contaminated food) and the corresponding changes in concentrations (e.g. consumption of raw or undercooked products that should only be consumed when fully cooked) or intake levels of the agent being assessed

3.1.4 Risk characterisation

In this section, the available data and information on hazard identification, hazard characterisation and exposure are brought together and comprehensively evaluated. This results in the risk being a function of the likelihood and the severity of health effects (see 3.1.2) following exposure to the hazard (see 3.1.3). It may be advisable here to characterise the risks by using a variety of scenarios or referring to different population groups (adults, children, etc.).

More information:
Page 16 to 23

The following aspects should be summarised and taken into account:

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

a) Affected population group

This subsection considers, for example, individuals in certain life stages, age groups, with certain characteristics (e.g. sex, body weight), specific nutritional habits, health conditions or levels of exposure.

b) Route and probability of exposure

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

c) Likelihood of health impairments following exposure

First, the opinion should summarise which data and information suggest that certain exposures can trigger health effects. If sufficient data is available, the likelihood of health impairments in the examined exposure scenarios should be described using the terms outlined below. Where possible, qualitative descriptions should be supplemented with quantitative details in order to make a correct interpretation easier.

For some substances, it is not possible to derive an uptake level that is harmless to health due to the currently available and known properties or data. This applies, in particular, to substances for which no threshold limit value can be assumed (such as DNA-reactive genotoxic carcinogens). As a rule, no likelihood of health impairments can be specified for these substances. To prioritise the urgency of risk management measures, the ‘margin of exposure’ (MOE) approach can be applied. Risk management authorities consider an MOE of 10,000 or higher, if derived from a BMDL10 from an animal carcinogenicity study, to be of low concern in terms of public health. These substances are, therefore, assigned a low priority for related risk management measures. From a toxicological point of view and considering the total uptake amount, an MOE of 10,000 or higher is to be assessed as ‘of low concern’ with regard to possible tumour diseases, but should not be equated with ‘harmless’.

Likelihood of health impairments

Likelihood of health impairments	Explanation of the likelihood of health effects for a given exposure
Very high	The likelihood of health impairments 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 health impairments. This is true in the following cases: – A broad-based, robust data set is available that describes the regular occurrence of health impairments in humans for the range of exposure levels under consideration – The facts show that it can be assumed that health impairments will occur in humans in almost all cases following exposure to a biological agent.
High	The likelihood of health impairments is specified as 'high' if health impairments are to be expected. This is true in the following cases: – In the range of exposure levels to be evaluated in humans, effects occurred (demonstrated e.g. in epidemiological studies or well-documented case reports), or robust findings are available from animal experiments or recognised alternative methods that can be transferred to humans. – It can be assumed that health impairments will often occur in humans following exposure to a biological agent.
Medium	The likelihood of health impairments is specified as 'medium' in cases where there are specific indications that health impairments will occur, but the requirements for assignment to another category are not met. 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 e.g. an ARfD is exceeded or if an ADI/TDI is repeatedly exceeded[1]. – It can be assumed that health impairments will sometimes occur in humans following exposure to a biological agent.

Likelihood of health impairments	Explanation of the likelihood of health effects for a given exposure
Low	The likelihood of health impairments is specified as 'low' if health impairments 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. – It can be assumed that health impairments will very rarely occur in humans following exposure to a biological agent.
Very low	The likelihood of health impairments 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 health impairments. 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 health impairments are not to be expected. – It can be assumed that health impairments 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 health impairments 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 health impairments should therefore be considered instead as 'high' or 'very high'.

d) Frequency of health impairments

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

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

In assessing health impairments a distinction must be made between acute and chronic exposure or the course of the disease. If they exist, clinical findings should be taken into account in the assessment. Possible reversibility should be discussed and supported with clinical findings. If the risk assessment is based on animal studies, differences in uptake, metabolism, and excretion of the agent between animals and humans should be considered and described.

The severity of an acute health impairment can be indicated using a number of different terms (see box for examples). 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 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. symptoms that resolve without external intervention)
- No impairment
- Unknown severity

[2] Source: Source: Hans E. Persson, Gunilla K. Sjöberg, John A. Haines, Jenny Pronczuk de Garbino (1998) Poisoning severity score. Grading of Acute Poisoning. 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)

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

Beispiel: 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 severity

If pertinent rules exist for describing relevant health impairments, then these should be taken into account. For example, in relation to biocides or chemicals covered by REACH, the potential hazard represented by a substance in terms of the occurrence of local health effects is described based on its CLP classification[3]. However, it should be taken into account that the CLP classification does not define all health impairments.

[3] Guidance on the BPR: Volume III Parts B+C Version 4.0 December 2017; Chapter 4.2.3.5, Table 24, p. 246f.

f) Evidence of a causal relationship

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

- Generally accepted evidence (i. e. causality is proven e.g. cy (clinical) studies and is generally accepted in science; or a mode of action (MOA) is known)
- 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:

- The uncertainty analysis creates transparency throughout the risk assessment process, for example, by describing assumptions and constraints as well as their handling.
- The uncertainty analysis serves to document the aspects mentioned in section 1.
- The uncertainty analysis indicates courses of action with which the identified uncertainties can 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

The uncertainty analysis can be integrated into the hazard or risk characterisation, for example through probabilistic methods or plausibility checks of additional uncertainty or assessment factors.

In contrast to uncertainties, variabilities if they are relevant to the assessment, should be covered in the risk assessment. Variabilities that, due to a lack of sufficient data, cannot be described but can only be assumed should be described as uncertainties or as areas requiring further research.

h) Controllability of the risk

A statement is made as to whether (and how) consumers can minimise the risk, for example, by following advice given in product literature that recommends a quantity of the food that can be safely consumed or by using different brands of the same product.

3.2 Risk management options, recommended measures

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

Recommendations or proposed courses of action may include the following:

- Generation of data that are necessary for a risk assessment; any potential need for a more detailed assessment or further research activities should be specified, as well as the specific data or investigations that would be necessary in this case.
- Restrictions on distribution or commercial usage
- Specification of thresholds/standards (e.g. maximum quantities in food, levels of microorganisms in food at the time of consumption)
- Labelling, consumer information, recommendations and restrictions on use
- Measures to avoid or reduce the introduction of the pathogen or the substance, or the propagation of the pathogen. Measures to reduce the pathogen, or the introduction of the substance, or the formation of the substance in the food chain by the manufacturer or retailers (e.g. as a result of introducing food technology procedures or hygiene/inspection procedures) and by consumers
- Intervening in the event of misleading advertising

- Recommended consumption quantities for the population or certain population groups
- Increased information for consumers (e.g. regarding preparation or consumption recommendations, as specifically as possible for the respective population groups, including the rationale)
- Modifications to the affected specification for substances for which specifications are governed by legislation

If recommendations concerning actions or consumption are formulated for consumers, these must be described as concretely and with as much relevance to daily life as possible. 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 hazardous, 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.

If necessary, the potential consequences for consumers of different measures or options must be stated (e.g. risk avoidance for the entire population, careful reading of the product declaration, etc). Predictable trends regarding future prevalence of the products in question should, if possible, be noted and considered in the recommendations.

If the BfR issues an opinion with recommendations or courses of action 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 courses of action can be recommended. If multiple, equally suitable measures for risk mitigation could be considered, the BfR will simply provide 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 result of the risk assessment.

Comparative risk analyses for the evaluation of risks and benefits can be included, where necessary. This is needed, for example, when assessing food and food ingredients capable of having positive health effects. This also applies to opinions prepared on certain dietary habits, where the aim is to assess whether the assumed health benefits are in an acceptable proportion to the expected risks.

Opinions regarding 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 (inter)national 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.

Opinions for the BfR website Supplements

The BfR communicates opinions of universal 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: They are preceded by a risk profile that summarises the results in a compact and tabular form. 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 and corporate design specifications. 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 opinions of the BfR should, if necessary, be published in a format that is semantically interoperable, meaning it allows various applications – such as an artificial intelligence (AI) – to extract information and interpret it correctly.

BfR risk profile

The main task of a BfR risk profile is clear communication of a scientific assessment. The BfR risk profile is provided on the first two pages of all appropriate opinions published online by the BfR.

In the risk profile, the key information from the opinion is divided into categories and formulated to be understandable. A short summary, headlined ‘in brief’, presents the central aspects and can, if necessary, be supplemented with further relevant findings.

The profile uses icons, graphic elements, and short text blocks to provide information about the following characteristics: uptake of substance, utilisation of a health-based guidance value, type and extent of a possible health risk for different target groups, quality of the available data, and options for risk reduction by the state, producers, and consumers.

For all opinions, the Press and Public Relations Unit drafts a proposal for the contents of the risk profile, the corresponding graphic representation and coordinates the proposal with the participating departments. Formatting and corporate design specifications apply for the BfR risk profile.

Glossary

Common terms used in risk assessment and risk communication

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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 given here (this can be modified, as appropriate, in exceptional cases) the first time the term is mentioned.

Health-based guidance values (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 an appreciable health risk. The ADI is derived for substances introduced into the food chain, including drinking water (e.g. 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 usually 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 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 users 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 amount of a substance (e.g. a biocidal agent) that affected groups of people can be exposed to dermally, by inhalation or orally (not via food) on a daily basis within the respective time period without any expectation of a detectable health risk. The AEL is primarily used with biocidal agents to assess the risk for consumers and users and is typically derived for three time periods (short-term, medium-term and long-term). The AEL is usually 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 or orally (not via food) in affected groups of individuals (e.g. operators) on a daily basis over the entire season of application and lifetime without any detectable health risk. The AOEL is usually 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 health risk. The ARfD is derived for substances introduced into the food chain, including drinking water (e.g. plant protection product residues, biocides) or which otherwise arise within this chain (e.g. contaminants), and is used to assess of the health risk associated with acute exposure to such substances. The value is usually 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 corresponds to a level of exposure that results in a very low risk to the general population. The value is usually specified in mg/kg body weight per day.

DNEL **Derived No Effect Level**
Defined in 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, taking into account the most likely route(s) of exposure and the most likely duration and frequency of exposure. The derivation of these values is based on toxicological studies (human or non-human). The value is usually 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 health risk is 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 extent to which a health-based guidance value is reached or 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 an appreciable health risk. A TDI is derived e.g. for substances that occur as contaminants in food, including drinking water, and applied to the assessment of the health risk that is associated with chronic exposure to such substances. The TDI is usually specified in mg/kg body weight per day. Depending on the toxicokinetic properties of the substance under assessment, it may be useful to derive an HBGV based on a weekly (TWI, Tolerable Weekly Intake) or monthly (TMI, Tolerable Monthly Intake) period.

UL **Tolerable Upper Intake Level**
The tolerable upper intake level corresponds to the highest chronic daily total intake of a substance (from all sources) for which no health risk is 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':
https://www.efsa.europa.eu/en/efsajournal/pub/7584

BMDL **Benchmark Dose Lower Confidence Limit**
Dose associated with the lower limit of the confidence interval for the BMD. Usually, a 90 % or 95 % confidence interval is applied.

BMDU **Benchmark Dose Upper Confidence Limit**
Dose associated with the upper limit of the confidence interval for the BMD. Usually, a 90 % or 95 % confidence interval is applied.

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 expected to cause death in 50 % of the exposed organisms within a specific period of investigation. The value is usually expressed as a ratio of the mass of the test substance relative 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/health impairment is observed.

MOE **Margin of Exposure**

The ratio of a suitable reference value from the dose-response relationship relative to the estimated exposure to the substance in humans. The benchmark dose lower confidence limit 10 % ($BMDL_{10}$) or the tumour dose 25 % (TD_{25}) is usually used as the reference value, i. e. a dose of a substance that is associated e.g. with a certain increase in tumour rates. An MOE value is not a health-based guidance value: rather, it serves to prioritise the urgency of risk management measures for substances for which, based on current scientific knowledge, no safe intake value can be derived (in particular, for example, for genotoxic carcinogens). Risk management authorities consider an MOE of 10,000 or higher, if derived from a $BMDL_{10}$ from an animal carcinogenicity study, to be of low concern in terms of public health. Consequently, these substances are assigned a low priority for risk management measures. From a toxicological point of view and considering the total intake amount, an MOE of 10,000 or higher is is to be assessed as 'of low concern' with regard to possible tumour diseases, but should not be equated with 'harmless'.

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

MOS **Margin of Safety**
The ratio of a suitable reference value from the dose-response relationship relative to the estimated exposure to the substance in humans. The reference value applied here is usually the NOAEL or the BMDL5/10. One example of the use of a MOS is to assess the health risk that can be expected from an exposure to substances for which no health-based guidance value (ADI or TDI) can be derived. In addition, an MOS can be applied to assess the health risk 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/health impairment is observed.

TD_{25} **Tumor Dose**
A dose derived linearly from the dose-response 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 of the risk management 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 is compared instead to the TTC value derived for chemical substances of a similar structure (i. e. a similar structural class). The TTC concept is exclusively a prioritisation tool. 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/thresholdtoxicologicalconcern

Microbiological parameters

CFU	**Colony Forming Units** Refers to individually visible growth units of microorganisms (colonies) on solid culture media, which originates from a single cell or multiple cells, and serve to express the culturable number of microorganisms in a certain volume of the analysed sample.
Infectivity	Capability of a pathogen to infect a host.
Lethality	**Case Fatality Rate (CFR)** Refers to the ratio of deaths to number of people infected.
MID	**Minimal Infectious Dose** Minimum number of pathogens necessary to cause an infection.
Morbidity	Refers to the frequency of illness/disease in a specific population group.
Mortality	Refers to the number of deaths relative to the total number of individuals in a population or, in the case of specific mortality, relative 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 given volume of the analysed sample. This estimate is derived from the combination of positive and negative results from a number of different volumes of the sample examined using standard tests.
PFU	**Plaque Forming Units** Designates the number of plaque forming units.
Virulence	Refers to the sum of all the disease-causing properties of a pathogen.

Parameters used in diagnosis and analysis

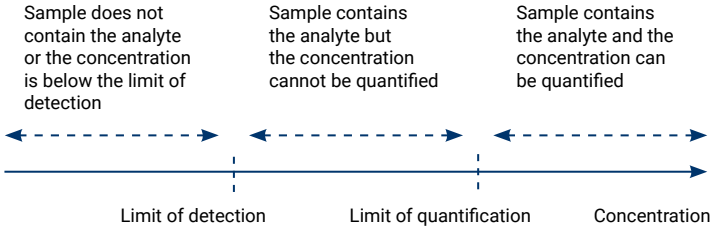
Diagnostic Sensitivity Indicates the probability that an actual positive sample will be correctly identified as such in a diagnostic test.

Diagnostic Specificity Indicates the probability that an actual negative sample will be correctly identified as such in 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 measurement method.

LOQ **Limit of Quantification**
Synonyms: limit of determination, quantitation limit.
The lowest concentration of an analyte in a sample that can be quantitatively determined with sufficient certainty using a specified measurement 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.

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

Epidemiological and statistical parameters

Bias The term ‘bias’ refers to any systematic errors or distortion in the design, execution or analysis of a study that can lead 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. Bias can work in both directions, i. e. under- or overestimation of the true effect and can vary in severity.

Case-control study Type of study used in epidemiology in which cases (e.g. cases of disease) are compared with suitable controls lacking this disease although both groups experienced exposure.

Confounder A condition that is either constant (e.g. sex) or variable (e.g. age) over time, that is correlated to the exposure under investigation and 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.

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.

Exposure Oral, inhalative or dermal uptake of an agent (e.g. a chemical substance, a pathogen or an environmental factor) and, if applicable, the amount of uptake. The exposure can refer to individuals or groups.

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 (e.g. of a disease) occurring within a certain time period relative to the sum total of human time (person -years, -months, -days) of the population at risk.
Mean	The arithmetical mean
Median	A value that divides a data set/ sample/ distribution (sorted by size) into two equal halves (corresponding to the 50th percentile).
Mode	The value that occurs most frequently in a data set.
OR	**Odds Ratio** Synonym: cross-product ratio Statistical metric for the estimated effect size of exposure.
Percentile	Specific quantile for integer percentage values between 0 and 100 % (e.g. 50 % of the values are below the 50th percentile).
PPV	**Positive Predictive Value** Synonyms: Relevance, efficacy, precision Events classified as correctly positive expressed as a proportion of the total events classified as positive.
(p-) Quantile	Value of a data set sorted by size for which p% of the values are below the value (e.g. 95 % of the values are below the 95th quantile).
Prevalence	Number of individuals with the condition (such as sick people) 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 relative 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.
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.
Variance	A measure of spread that describes the distribution of values of a characteristic around its mean. For discrete random variables, the variance is calculated as the sum of the mean squares normalised to the number of data points. For continuous random distributions, it is calculated as the integral over the product of the squared deviations from the expected value and the probability function.

Terms for uncertainty and variability

Relevance The suitability of study results for answering the given question

Reliability Synonyms: Robustness, soundness
The dependability of study results in relation to the research question the study is investigating, based on characteristics of the study design, execution and evaluation, all of which may be subject to random and/or systematic errors (bias).

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, page 16

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 46

Appendix

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Uncertainty analysis

A distinction is made between 'uncertainty' and 'variability'. Uncertainty describes a lack of knowledge (or incomplete knowledge) concerning a state (e.g. the concentration of a chemical in a sample). In principle, this lack of knowledge can be reduced, for example, by making an appropriate measurement. 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. Naturally occurring variability in terms of individual human characteristics (e.g. body weight, sex), microbiological pathogens, chemical substances or processes should be described if it will have a considerable influence on the assessment results.

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 models). 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 (e.g. due to a lack of data or 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 be documented in the subsections. The documentation of the most significant individual uncertainties with regards to the overall result should be summarised in the subsection 'Risk characterisation: uncertainties and variabilities' or in the subsection 'Hazard characterisation'. This should be the case if no risk assessment has been performed or if the uncertainties or variabilities should be taken into account for a HBGV. Optionally, this step can also be completed for other – or all – individual uncertainties.

More information:
Uncertainties and variabilities, page 22

Each of the identified individual uncertainties should first be assessed using a simple qualitative method (e.g. a classification of whether it is assessed as mild, moderate or severe). The criterion of this assessment is the influence of the individual uncertainty on the final 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 differently interpreted. Accordingly, verbal formulations and symbolic representations should always be accompanied by an interpretation guide (such as that given for probability statements in 'Risk characterisation: likelihood of impairments to health').

More information:
Likelihood of impairments to health, page 17

If necessary, individual uncertainties can 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 final 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 final result must be calculated. The combination of several worst-case assumptions (95th percentile) of all uncertainties generally leads to an overestimation of the overall uncertainty. In this case, the use of approximate probabilistic analysis (APROBA) can lead to a realistic calculation of the uncertainty.

WHO IPCS (2018): Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd ed. World Health Organization, Geneva. ISBN: 9789241513548. https://apps.who.int/iris/handle/10665/259858

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.
- Numbers should be reported without qualifying expressions (e.g. 'about', 'roughly', 'up to') and should not be replaced by verbal formulations, as these could be interpreted in different ways.
- If a numerical 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 aid in 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.

More information:
Risk management options, recommended measures, page 23

If accounting for an individual uncertainty is of particular importance for the assessment result (e.g. if it could result in a certain reference value being exceeded), this should be explicitly stated. If an individual uncertainty has an influence on the risk management options or recommended measures, this should be taken into account when identifying courses of 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 final result is then evaluated. A qualitative approach can be taken, which involves a textual categorisation of the influence of all individual uncertainties on the robustness of the final result of the risk assessment. However, a quantitative approach can also be used. The result should be presented either purely qualitatively or purely quantitatively (and thus without combination). In a purely quantitative approach, each individual uncertainty can be assessed quantitatively[4] and these assessments can then be combined to give the overall uncertainty. Whether a qualitative or quantitative approach is chosen, the assessment of the overall impact must abide by the same principles as those used to describe the individual uncertainties.

In the opinion's risk characterisation section, a short and meaningful summary of the overall impact on the final result must be formulated. This must also be included in the results section, in section 3.3 on risk management options and in the risk profile. When considering the overall influence of the uncertainties on the final result, no more or less certainty should be implied 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 final result of the risk assessment does not need to be reinterpreted against the background of these uncertainties.

[4] However, such a quantification can also consist of assessing that the individual uncertainty is negligible, i.e., it is rated as 0.

4. Description of the options for reducing the most important individual uncertainties

For the most influential individual uncertainties, the steps necessary to reduce their impact 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, including the data or studies that would be necessary in this case. If, given the existing uncertainties, a reliable risk assessment is not (or only partially) possible, the options for reducing the individual uncertainties must also be stated in the results section, and, where appropriate, in the risk profile.

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

More information:
Guidance documents, page 54

Weight of Evidence (WOE)

A WOE approach is an internationally agreed upon procedure for the systematic, collective evaluation of and weighting of the results/data (lines of evidence) made available by various methods/approaches in order answer to research question.

This approach should be adopted if multiple independent sources of evidence are available. The WOE approach is intended to present the considerations that led to a particular set of conclusions in a transparent and comprehensible manner.

As regards the research question, this may involve a hypothesis ('Is substance X carcinogenic?') or be a problem concerning estimation ('What proportion of the population is exposed to substance X at level Y?'). The term 'evidence' is 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 meet the minimum requirements for reliability and

relevance as defined in each case. WOE assessments made by the BfR are oriented on the EFSA[5] guidance document. The aim 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 body of knowledge available. During this process, the level of evidence, i. e. the formal and substantive quality of various potential answers, is explicitly reported.

The basic elements of a WOE assessment are the following three work steps:

1) Consolidation
2) Weighting/critical evaluation
3) Integration of evidence

In the first step, the scientific question is precisely defined. Key concepts and criteria are derived from this on the basis of which appropriate data sources are selected and researched. 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. Within a single line of evidence, there may be a variety of individual data sources (e.g. studies).

[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

[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 evaluation (meta-analysis) – should be prepared, where possible.

The second step concerns the weighing 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 tend 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 different lines of evidence. The range of approaches for these integration steps once again comprises of qualitative and quantitative methods. The appropriate method in each case is selected in terms of scientific considerations, set standards (where available) and available processing time.

Example: Toxicological assessment of Plant Protection Products (PPPs)

Consolidation

For the toxicological assessment 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)?

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 test,* RhCE), performed 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 should be conducted and documented in accordance with 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 > cell system > calculation on the basis of toxicodynamic data)

Application domain: *in vitro* studies are often only suitable for predicting eye damage, or excluding eye irritation or damage. However, they are not suitable for predicting eye irritation. In addition, *in vitro* tests have generally not been validated with complex mixtures. One exception here is the RhCE test, the validation matrix of which also includes 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 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 compared to the reference method) plays a role in the reliability of *in vitro* methods. Similar data are also available for the calculation method according to the CLP Regulation. However, the calculation method should provide a conservative prediction with a low FNR, as this method represents a minimum requirement in the absence of studies. 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, 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 may not have been independently verified.

An example of the qualitative evaluation of relevance and reliability is presented on page 51.

As a rule, *in vivo* experiments involving complex mammalian organisms are weighted more strongly than isolated organ or cell systems (*in vitro* methods) due to their relevance for human toxicological assessment. 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.

Finally, the tested formulation also plays a role in the weighting of relevance. As such, formulations that can be considered comparable according to the above-mentioned guidance should be weighted less strongly than the proposed formulation. If multiple studies are submitted that do not fully meet the guidance criteria, 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, together with the accuracy of the results.

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)	+ (cell 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 test
GLP = good laboratory practice
+ / ++ / +++ medium/high/very high relevance or reliability

[7] The application domain here describes whether classification 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 of the BCOP test. If no classification into the category 'eye damage' or 'no irritation' is made, further testing of the product is required. As a result, there is no final classification 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 EpiOcularTM 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 classification and labelling according to the CLP Regulation.

With knowledge on 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.

Technical guidelines
Selection

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Biocides

Guidance on the Biocidal Products Regulation, Volume III: Human health, Part A: Information Requirements. Version 2, March 2022
https://www.echa.europa.eu/en/guidance-documents/guidance-on-biocides-legislation

Guidance on the Biocidal Products Regulation, Volume III: Human health – Assessment & Evaluation (Parts B+C). Version 6.0, August 2023
https://www.echa.europa.eu/en/guidance-documents/guidance-on-biocides-legislation

Format templates for biocide assessment reports
https://www.echa.europa.eu/en/web/guest/support/guidance-on-reach-and-clp-implementation/formats (see 'BPR')

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 – 28th Edition, 2023
Also includes definitions of the terms used in the risk analysis of foodstuffs
https://www.fao.org/fao-who-codexalimentarius/publications/procedural-manual/en/

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
http://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 nanomaterials to be applied in the food and feed chain: human and animal health
https://www.efsa.europa.eu/en/efsajournal/pub/6768

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://www.efsa.europa.eu/en/efsajournal/pub/7584

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
https://www.fao.org/4/y1579e/y1579e05.htm

Microbiological risk assessment: guidance for food FAO and WHO. 2021. Microbiological Risk Assessment Series No. 36.
https://www.who.int/publications/i/item/9789240024892

Microbial Risk Assessment Guideline: Pathogenic Organisms with Focus on Food and Water
https://www.epa.gov/risk/microbial-risk-assessment-guideline-pathogenic-microorganisms-focus-food-and-water

Plant protection products (PPP)

A recent overview of guidance documents for the evaluation of plant protection products is provided by the EU Commission.
https://food.ec.europa.eu/plants/pesticides/approval-active-substances-safeners-and-synergists_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

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 Guidelines
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
https://one.oecd.org/document/ENV/JM/MONO(2002)18/en/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

BfR 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 Harmonis. 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 EFSA 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://www.who.int/publications/i/item/9789241572408

Legal notice

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Max-Dohrn-Straße 8–10
10589 Berlin
T +49 30 18412-0
bfr@bfr.bund.de
bfr.bund.de

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

T +49 030 18412-0
bfr@bfr.bund.de
bfr.bund.de/en

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