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Guidance on Uncertainty Analysis in Scientific Assessments

EFSA Scientific Committee,

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Abstract

Uncertainty analysis is the process of identifying limitations in scientific knowledge and evaluating their implications for scientific conclusions. It is therefore relevant in all EFSA's scientific assessments and also necessary, to ensure that the assessment conclusions provide reliable information for decision-making. The form and extent of uncertainty analysis, and how the conclusions should be reported, vary widely depending on the nature and context of each assessment and the degree of uncertainty that is present. This document provides concise guidance on how to identify which options for uncertainty analysis are appropriate in each assessment, and how to apply them. It is accompanied by a separate, supporting opinion that explains the key concepts and principles behind this Guidance, and describes the methods in more detail.

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1. Introduction and scope

1.1. Background and Terms of Reference

The European Food Safety Authority requested the Scientific Committee to develop guidance on how to characterise, document and explain uncertainties in risk assessment, applicable to all relevant working areas of EFSA. For full background and Terms of Reference see the accompanying Scientific Opinion (EFSA, 2017).

1.2. Scope, objectives and degree of obligation

This document comprises the Guidance required by the Terms of Reference. More detail on principles and methods used in the Guidance is provided in an accompanying Scientific Opinion (SO) (EFSA Scientific Committee, 2018), together with justification for the approaches taken. These two documents should be used as EFSA's primary guidance on addressing *uncertainty*. EFSA's earlier guidance on uncertainty in exposure assessment (EFSA, 2007a) continues to be relevant but, where there are differences (e.g. regarding characterisation of *overall uncertainty*, for the assessment as a whole), the present Guidance and the accompanying Scientific Opinion (EFSA Scientific Committee et al., 2018) take priority. Some case studies were developed during a trial period (EFSA, 2017), and more will become available as the Guidance is implemented. Communicating uncertainty is discussed in Section 16 of the accompanying Scientific Opinion [SO16] and guidance on this will be provided in another companion document (EFSA, 2018 in prep.).

In this document, uncertainty is used as a general term referring to all types of limitations in available knowledge that affect the range and *probability* of possible answers to an assessment question (EFSA Scientific Committee, 2018). The Scientific Committee is of the view that all EFSA *scientific assessments* must include consideration of uncertainties. Therefore, the application of this Guidance is unconditional for EFSA. Assessments must say what sources of uncertainty have been identified and characterise their overall impact on the assessment conclusion. This must be reported clearly and unambiguously, in a form compatible with the requirements of *decision-makers* and any legislation applicable to the assessment in hand [SO1.4].

The Guidance contains a wide range of options to make it applicable to all relevant working areas of EFSA, and adaptable to differing constraints on time and resources. Users are free to select any options that suit the needs of their assessment, provided they satisfy the unconditional requirements stated above. Similarly, EFSA's Panels and Units are encouraged to identify the options relevant to their work and incorporate them into their own guidance documents or procedures.

1.3. How to use this document

This document is intentionally concise. Links to more detailed information in the accompanying Scientific Opinion (EFSA Scientific Committee, 2018) are provided in the format [SO $n.n$], where $n.n$ is a section number. Terms that are defined in the Glossary of this Guidance are shown in italics where they first appear in the text.

Section 2 of this Guidance distinguishes four main types of assessment, for which different *uncertainty analysis* approaches are appropriate. Note that where the term 'assessment' is used in this document, this refers to scientific assessment as a whole, while 'analysis' refers to uncertainty analysis in particular.

It is recommended that users start by consulting Section 2 to identify which type of assessment they are doing, then proceed to the section specific to that type (Sections 3, 4, 5 or 6). Those sections contain flow charts summarising key methods and choices relevant for each type of assessment. Each flow chart is accompanied by numbered notes which provide practical guidance. Some of the footnotes refer to later sections (Sections 7–17) for more detailed guidance, especially on topics that apply to multiple flow charts.

In some of the sections without flow charts, the text is presented as numbered points, for ease of reference by *assessors* when discussing how to apply this Guidance. In sections where this seems unnecessary, the paragraphs are not numbered.

This Guidance aims to provide sufficient information to carry out the simpler options within each type of assessment, and refers the reader to relevant sections in the Scientific Opinion (EFSA Scientific Committee, 2018) for other options. This Guidance also identifies situations where specialist expertise may be required. Section 13 of the accompanying Scientific Opinion (EFSA Scientific Committee, 2018)

contains an overview of all the methods reviewed by the Scientific Committee, indicating what elements of uncertainty analysis they can contribute to and assessing their relative strengths and weaknesses; detailed information and examples for each method are provided in the Annexes of the Opinion.

1.4. Roles

Uncertainty analysis is an integral part of scientific assessment. In this Guidance, those producing a scientific assessment are referred to as 'assessors' and those who will use the finished assessment are referred to as 'decision-makers' (the latter includes but is not limited to *risk managers*). Assessors are responsible for analysis of uncertainty; decision-makers are responsible for resolving the impact of uncertainty on decision-making [SO3]. Most EFSA assessments are prepared by Working Groups for review and adoption by Panels, and the same is expected for uncertainty analysis. Good engagement between assessors and decision-makers, and between Working Group and Panel, are essential to ensure that the assessment and uncertainty analyses are fit for purpose.

1.5. Main elements of uncertainty analysis

Uncertainty analysis is the process of identifying and *characterising uncertainty* about *questions of interest* and/or *quantities of interest* in a scientific assessment. A question or quantity of interest may be the subject of the assessment as a whole, i.e. that which is required by the Terms of Reference for the assessment, or it may be the subject of a subsidiary part of the assessment which contributes to addressing the Terms of Reference (e.g. exposure and hazard assessment are subsidiary parts of risk assessment). Questions of interest may be binary (e.g. *yes/no questions*) or have more than two possible answers, while quantities of interest may be *variable* or *non-variable* [SO5.1].

The main elements of an uncertainty analysis are summarised in Box 1. Most of the elements are always required; others (as identified in the list) depend on the needs of the assessment. Furthermore, the approach to each element varies, and sometimes the order in which they are conducted, depending on the nature or type of each assessment. Therefore, this guidance starts by identifying the main types of assessment, and then uses a series of flow charts to describe the sequence of elements that is recommended for each type.

Box 1: Main elements of uncertainty analysis

Identifying uncertainties affecting the assessment (Section 7). This is necessary in every assessment, and should be done in a structured way to minimise the chance of overlooking relevant uncertainties. In assessments that follow standardised procedures, it is only necessary to identify *non-standard uncertainties* (examples of these are given in Section 7.1).

Prioritising uncertainties within the assessment (Section 8) plays an important role in the planning the uncertainty analysis, enabling the assessor to focus detailed analysis on the most important uncertainties and address others collectively when evaluating overall uncertainty. Often prioritisation will be done by expert judgement during the planning process, but in more complex assessments it may be done explicitly using *influence analysis* or *sensitivity analysis*.

Dividing the uncertainty analysis into parts (Section 9). In some assessments, it may be sufficient to characterise overall uncertainty for the whole assessment directly, by *expert judgement*. In other cases, it may be preferable to evaluate uncertainty for some or all parts of the assessment separately and then *combine* them, either by calculation or expert judgement.

Ensuring the questions or quantities of interest are well-defined (Section 10). Each question or quantity of interest must be well-defined such that the true answer or value could be determined, at least in principle. This is necessary to make the question or quantity a proper subject for scientific assessment, and to make it possible to express uncertainty about the true answer or value clearly and unambiguously. Some assessments follow *standardised procedures*, within which the questions and/or quantities of interest should be predefined. In other assessments, the assessors will need to identify and define the questions and/or quantities of interest case by case.

Characterising uncertainty for parts of the uncertainty analysis (Sections 11 and 12). This is needed for assessments where assessors choose to divide the uncertainty analysis into parts, but may only be done for some of the parts, with the other parts being considered when characterising overall uncertainty (see Section 16).

Combining uncertainty from different parts of the uncertainty analysis (Sections 13–15). This is needed for assessments where the assessors quantify uncertainty separately for two or more parts of the uncertainty analysis.

Characterising overall uncertainty (Section 16). Expressing quantitatively the overall impact of as many as possible of the identified uncertainties, and describing qualitatively any that remain unquantified. This is necessary in all assessments except those *standardised assessments* where no non-standard uncertainties are identified.

Prioritising uncertainties for future investigation (Section 8). This is implicit or explicit in any assessment where recommendations are made for future data collection or research, and may be informed by influence or sensitivity analysis.

Reporting uncertainty analysis (Section 17). Required for all assessments, but extremely brief in standardised assessments where no non-standard uncertainties are identified.

1.6. Levels of refinement in uncertainty analysis

Most of the elements of uncertainty analysis listed in Box 1 can be conducted at different levels of refinement and effort, analogous to the ‘tiered approaches’ used in some areas of risk assessment. Major choices include whether to assess all uncertainties collectively or divide the uncertainty analysis into parts; whether to quantify uncertainties fully using probabilities and distributions, or partially using probability bounds; and whether to combine uncertainties by expert judgement or calculation. The flow charts in later sections guide assessors through these and other choices, helping them choose the approaches that are best suited to each assessment.

The uncertainty of an assessment is driven primarily by the quantity and quality of available evidence (including data and expert judgement) and how it is used in the assessment. Less refined options for uncertainty analysis are quicker, less complex, and characterise uncertainty more approximately. This may be sufficient for decision-making in many cases.

More refined options characterise uncertainty more transparently and rigorously, and may result in more precise characterisation of overall uncertainty, although this will always be subject to any limitations in the underlying evidence and assessment methods. However, more refined options are more complex and require more time and specialist expertise. In complex assessments, an iterative approach may be efficient, starting with simpler options and then using the results to target more refined options on the most important uncertainties, whereas in other assessments there may be less scope for iteration. The sequence of flow charts in Sections 3 and 4 is designed to help with these choices.

1.7. Expertise required

It is recommended that at least one expert in each Panel and Working Group should have received training in the use of this Guidance, and that all assessors should have basic training in *probability judgements*.

Some of the approaches described in later sections require specialist expertise in statistics or expert knowledge elicitation. This may be provided by including relevant experts in the Working Group, or as internal support from EFSA.

2. Types of scientific assessment

- 1) The recommended approach to uncertainty analysis depends on the nature of the scientific assessment in hand [S07.1]. Identify which of the following types your assessment most corresponds to and then proceed to the corresponding section for guidance specific to that type.
 - a) **Standardised assessments.** A standardised assessment follows a pre-established standardised procedure that covers every step of the assessment. Standardised procedures are often used in scientific assessments for regulated products, e.g. for premarket authorisation. They are accepted by assessors and decision-makers as providing an appropriate basis for decision-making, and are often set out in guidance documents or legislation. They generally require data from studies conducted according to

- specified guidelines and specify how those data will be used in the assessment. They may include criteria for evaluating data, and elements for use in the assessment such as *assessment factors*, default values, *conservative* assumptions, standard databases and defined calculations. Proceed to Section 3.
- b) **Case-specific assessments.** These are needed wherever there is no pre-established standardised procedure, and the assessors have to develop an assessment plan that is specific to the case in hand. Standardised elements (e.g. default values) may be used for some parts of the assessment, but other parts require case-specific approaches. Proceed to Section 4.
 - c) **Development or revision of guidance documents,** especially (but not only) those that describe existing standardised procedures or establish new ones. Proceed to Section 6.
 - d) **Urgent assessments.** Assessments that, for any reason, must be completed within an unusually short period of time or with unusually limited resources, and therefore require streamlined approaches to both assessment and uncertainty analysis. Proceed to Section 5.
- 2) In some areas of EFSA's work, the result of a standardised assessment may indicate the need for a '**refined**' or '**higher tier**' assessment in which one or more standardised elements are replaced by case-specific approaches. In principle, the assessment becomes case-specific at this point, although it may be possible to treat it as a standardised assessment with some non-standard uncertainties (see Section 3).
 - 3) Assessors often distinguish between **quantitative and qualitative assessments.** This sometimes refers to the form in which the conclusion of the assessment is expressed: either as an estimate of a quantity of interest (quantitative), or as a verbal response to a *question of interest* (qualitative). In other cases, an assessment may be described as qualitative because the methods used to reach the conclusion do not involve calculations; e.g. when the conclusions are based on a combination of literature review and narrative reasoning. In all cases, however, the conclusion of a scientific assessment must be expressed in a well-defined manner, in order to be a proper scientific statement and useful to decision-makers [SO5.1]. Any well-defined qualitative conclusion can be considered as an answer to a yes/no question; this is important for uncertainty analysis, because uncertainty about a yes/no question can be expressed quantitatively, using probability [SO5.10]. In general, therefore, the fact that an assessment uses qualitative methods or a conclusion is expressed in qualitative terms does not imply that the uncertainty analysis must be qualitative: on the contrary, it is recommended that assessors should always try to express uncertainty quantitatively, using probability [SO4.2 and 5.10]. However, qualitative methods of expressing uncertainty also have important uses in uncertainty analysis (see Section 11).

3. Uncertainty analysis for standardised assessments

When performing uncertainty analysis for a standardised assessment it is important to distinguish standard and non-standard uncertainties (see Section 7.1 for explanation and examples of these). The first step is to identify whether any non-standard uncertainties are present. If not, no further action is required other than reporting that this is the case (Section 3.1). When non-standard uncertainties are present, an evaluation of their impact on the result of the standard procedure may be sufficient for decision-making, as described in Sections 3.2–3.4, depending on how much scope was left for non-standard uncertainties when calibrating the standardised procedure (if this has been done) [SO7.1.3]. In other cases, where the non-standard uncertainties are substantial, the standardised procedure may no longer be applicable and the assessors will need to carry out a case-specific assessment and uncertainty analysis, as described in Section 4.

Assessors should start with Section 3.1 and follow the instructions that are relevant for the assessment in hand. Refer to the accompanying Scientific Opinion when needed for more information on specific methods (overview tables in SO13, summaries in SO10–12 and details in the Annexes of the Scientific Opinion).

3.1. Checking for non-standard uncertainties (Figure 1)

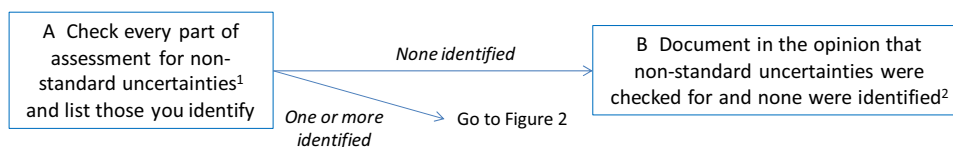


Figure 1: Check for uncertainties in standardised assessments. Numbered superscripts refer to text notes following the figure. Letters (A, B, C, etc.) are to facilitate reference to specific steps in the figure

Text notes for Figure 1:

¹ See Section 7.1. Note that some standardised procedures for assessment of regulated products specify procedures and criteria for deciding when to request additional data from an applicant, or specify standard assessment factors or default values to address data limitations. Data limitations that are addressed in these ways may be regarded as standard uncertainties, because the standard procedure is considered to include adequate provision for them. If a data limitation is addressed in case-specific ways, e.g. by using an assessment factor chosen by expert judgement, then it must be treated as a non-standard uncertainty.

² See Section 17 regarding reporting.

3.2. Assessing non-standard uncertainties collectively

This is the simplest option for assessing non-standard uncertainties, when assessors are able to evaluate them collectively (Figure 2).

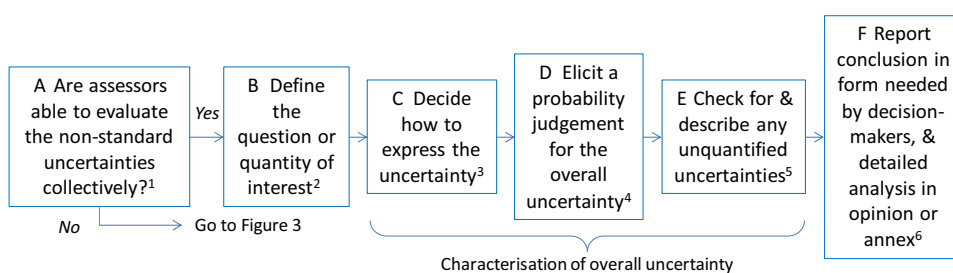


Figure 2: Assessing non-standard uncertainties collectively in standardised assessment

Text notes for Figure 2:

¹ More feasible when there are few uncertainties, less feasible when there are many or they require different expertise.

² For example, what the result of the standard procedure would be if all the non-standard uncertainties were *resolved*.

³ Using the *approximate probability scale* (see Section 12.3) is the simplest option and can be used for expressing uncertainty about the answer to a question of interest (including any conclusion that can be framed as the answer to a yes/no question, see point 3 in Section 2), or uncertainty about whether a quantity of interest exceeds a particular value of interest (e.g. whether exposure exceeds an acceptable level). If the decision-maker is interested in the probabilities of multiple values of a quantity of interest, use a probability distribution to express uncertainty (Section 12.1).

⁴ Assess this by considering how much resolving each uncertainty alone might change the result of the standardised procedure (e.g. if a poorly-done study had been conducted well), and then consider how the effects of the different uncertainties combine. Make the judgements using an elicitation method suitable to the needs of the assessment, See Section 12.6.

⁵ See Section 16.2

⁶ See Section 17.

3.3. Assessing non-standard uncertainties for separate parts of the uncertainty analysis using probability bounds (Figure 3)

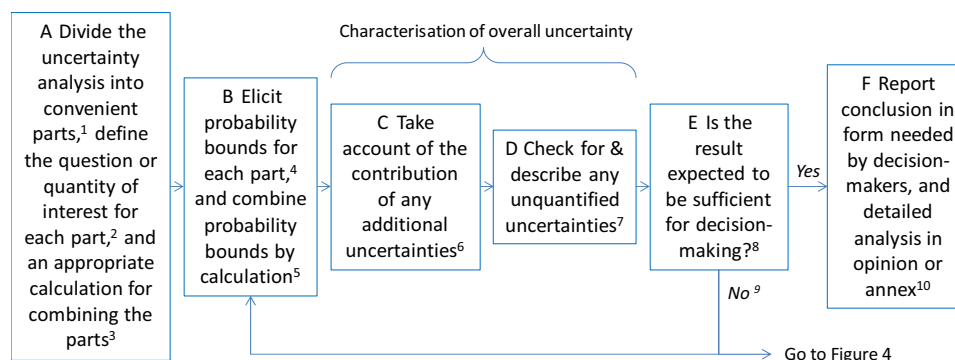


Figure 3: Assessing non-standard uncertainties for separate parts of the uncertainty analysis using probability bounds

Text notes for Figure 3:

¹ See Section 9. The choice of which parts of the uncertainty analysis to evaluate separately may be guided by initial prioritisation of the uncertainties, See Section 8.

² See Section 10.

³ See Section 9.

⁴ See Sections 12.2 and 12.6. For each part of the uncertainty analysis that will be evaluated separately, consider how different the result of that part of the standardised procedure might be if all the non-standard uncertainties affecting it were resolved. Express your judgement of this using a *probability bound*, e.g. an *approximate probability* for a quantity of interest in part of the assessment being more adverse than some specified value (see Section 12.2). Initially, choose the specified value so as to facilitate your probability judgement: other specified values can be considered in later iterations if needed. If any of the non-standard uncertainties affect parts of the assessment involving yes/no questions, this can also be expressed using approximate probabilities.

⁵ See Section 14.1.

⁶ If the preceding steps have expressed all the identified uncertainties using probability bounds then this step can be skipped. If not, go to Section 16.1 and characterise the overall uncertainty including the *additional uncertainties* by following Figure 15 and either Figure 16 or 17, then return to the present point in Figure 3.

⁷ See Section 16.2.

⁸ The result will be sufficient if the probability of a positive answer to the overall question of interest is sufficiently high or low depending on the context for decision-making (e.g. a sufficiently low probability of adverse effects). Determining this may require consultation with decision-makers, unless assessors have an understanding of what level of certainty decision-makers consider appropriate for this type of assessment [SO3.4]. Whether the result is sufficient will also depend on how much scope was left for non-standard uncertainties when calibrating the standardised procedure [SO7.1.3].

⁹ Two options are available when the conclusion of step E in Figure 3 is negative. The simpler option is to return to step B and, for some or all parts of the assessment, elicit new probability bounds which involve different ranges of values and associated approximate probabilities. This may be helpful if the initial choice of ranges for parts leads to a range or approximate probability for the output of the calculation which is not useful for decision-making, in which case it would be reasonable to consider alternative choices [see SO11.4.5 for guidance on this]. The second option is to proceed to Figure 4. This requires fully specified probabilities, distributions and dependencies, and more complex calculations, but usually decreases uncertainty about the answer to the question of interest.

¹⁰ See Section 17. If it will be useful for decision-makers to know which sources of uncertainty are most important, use an appropriate method to assess this (Section 8).

3.4. Assessing non-standard uncertainties for separate parts of the uncertainty analysis using probabilities or distributions (Figure 4)

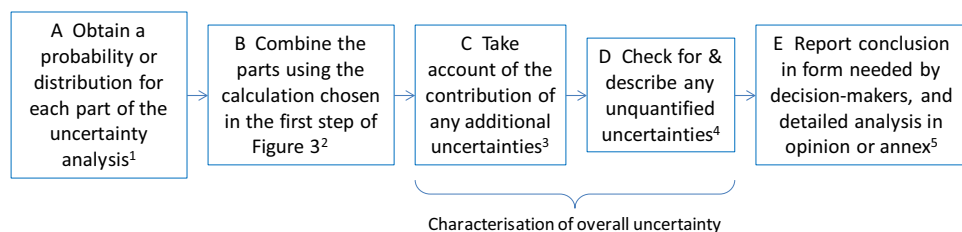


Figure 4: Assessing non-standard uncertainties for separate parts of the uncertainty analysis using probabilities or distributions

Text notes for Figure 4:

¹ See Sections 12.1, 12.5 and 12.6. For each part of the assessment that will be evaluated separately in the uncertainty analysis, consider how different the result of the standardised procedure might be if all the non-standard uncertainties affecting it were resolved. Express your judgement of this using probabilities for parts relating to questions or interest, and probability distributions for parts relating to quantities of interest.

² See Section 14.

³ If the preceding steps have expressed all the identified uncertainties using probabilities or probability distributions then this step can be skipped. If not, go to Section 16.1 and characterise the overall uncertainty including the additional uncertainties by following Figure 15 and either Figure 16 or 17 then return to the present point in Figure 4.

⁴ See Section 16.2.

⁵ See Section 17.

4. Uncertainty analysis for case-specific assessments

Assessors should start with Figure 5 and follow the instructions that are relevant for the assessment in hand. Refer to the accompanying Scientific Opinion when needed for more information on specific methods (overview tables in SO13, summaries in SO10–12 and details in the Annexes of the Scientific Opinion).

The first decision to be taken in Figure 5, after planning the assessment and identifying relevant uncertainties, is whether to divide the uncertainty analysis into parts (see Section 9). When this is done, the subsequent steps depend on the questions or quantities of interest for the assessment and its parts. The figure first separates assessments where no parts have quantities of interest (only questions), then distinguishes those that have only non-variable quantities of interest from those that include one or more variable quantities of interest. Note that an assessment with some quantities of interest may include some questions of interest, and an assessment with some variable quantities may include both non-variable quantities and *categorical questions*. For example, a chemical risk assessment typically includes hazard identification (yes/no question for each type of effect), some quantities that are treated as non-variable (e.g. the factor for extrapolating from animals to humans), and some quantities that are variable (e.g. exposure): following Figure 5 this would lead to Section 4.4. If an assessment does not fit any of the options identified in the Figure 5, seek specialist advice (Section 1.7) as it may require special treatment (e.g. for questions of interest which have more than two categories). The different types of questions and quantities of interest are discussed in more detail in [SO5.1].

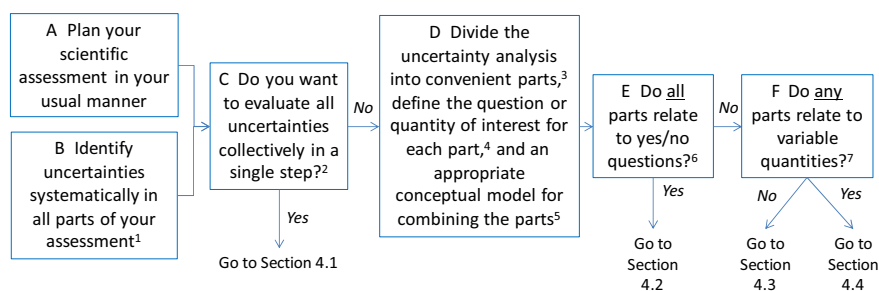


Figure 5: Deciding how to handle uncertainty in a case-specific assessment. Numbered superscripts refer to text notes following the figure. Letters (A, B, C, etc.) are to facilitate reference to specific steps in the figure

Text notes for Figure 5:

¹ Start identifying uncertainties at the planning stage, in a systematic manner (Section 7), so you can take them into account when deciding what approach to take to the scientific assessment. Add any further uncertainties which you identify as the assessment proceeds.

² If you decide to evaluate all uncertainties in a single step, go to Section 4.1. This is usually quicker and seems easier than evaluating different parts of the uncertainty analysis separately. However, it becomes increasingly difficult and approximate if the assessment is complex or if there are multiple non-negligible sources of uncertainty. In those situations, it is recommended to evaluate different parts separately (see Section 9).

³ See Section 9. The choice of which parts of the uncertainty analysis to evaluate separately may be guided by initial prioritisation of the uncertainties, see Section 8.

⁴ See Section 10.

⁵ See Section 9.

⁶ If **all** parts of the uncertainty analysis relate to yes/no questions, go to Section 4.2. If any parts relate to questions with more than two categories [SO5.1], seek specialist advice (Section 1.7).

⁷ A quantity of interest is variable if it can take more than a single *real value*, e.g. exposure values in a population, and non-variable if it takes only a single real value, e.g. a specified percentile of exposure. If all the quantities of interest are non-variable, go to Section 4.3; otherwise go to Section 4.4.

4.1. Assessing uncertainties collectively in a case-specific assessment

This is the simplest option for assessing uncertainty in case-specific assessments (Figure 6).

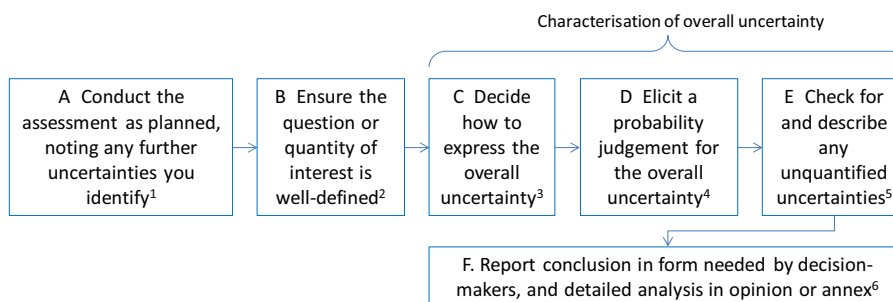


Figure 6: Assessing uncertainties collectively in case-specific assessments

Text notes for Figure 6:

¹ See Section 7. It is recommended to identify uncertainties as you plan and develop the assessment, rather than leave it to the end, to minimise the chance of missing important ones.

² See Section 10.

³ Using an approximate probability scale is the simplest option and can be used for expressing the uncertainty of the answer to a yes/no question (including whether a qualitative conclusion is correct) or the uncertainty about whether a quantity of interest (e.g. a margin of exposure) exceeds a particular value (Section 12.3). If the decision-maker is interested in the probabilities of multiple values of a quantity, use a distribution (Section 12.1).

⁴ See Section 12.6.

⁵ See Section 16.2.

⁶ See Section 17.

4.2. Evaluating uncertainties separately for parts of the uncertainty analysis that all address yes/no questions

The approach to uncertainty analysis for this type of assessment depends on whether assessors are able to, and wish to, express their uncertainty for all parts using probability and combine them with a probability calculation. Doing so requires that all parts of the uncertainty analysis, and the assessment as a whole, address yes/no questions, and that the reasoning for the assessment is expressed as a formal *logic model*, of the type described in Section 13. A logic model expresses the reasoning by which the different parts of the assessment are combined using logical operators such as 'AND', 'OR' and 'NOT', e.g. if *a* AND *b* then *c*. Then, if the uncertainty of the answer to the question of interest for each step is expressed using probability, those probabilities can be combined by calculation to derive a probability for the conclusion, which is more reliable than combining them by expert judgement. If the assessors decide to follow this approach, they should proceed to Section 4.2.2.

Alternatively, assessors may prefer to evaluate the uncertainties of the different parts separately (either qualitatively or quantitatively) and combine them by expert judgement, rather than a probability calculation. In this case, uncertainty may be evaluated qualitatively in some or all parts of the assessment, but a probability judgement should be made for the question of interest for the assessment as a whole. If the assessors decide to follow this approach, they should proceed to Section 4.2.1.

In some assessments, some parts of the assessment may address questions that have more than two possible answers or categories rather than being yes/no questions [SO5.1]. Such assessments can still be represented as logic models by reformulating the uncertainty analysis as a series of yes/no questions, considering each of the categories in turn (for example, a chemical may cause multiple types of effect, but each effect can be considered as a yes/no question). If the assessors think it better to treat more than two categories simultaneously, then more complex logic models will be required and specialist help may be needed (Section 1.7).

4.2.1. Combining multiple yes/no questions by expert judgement (Figure 7)

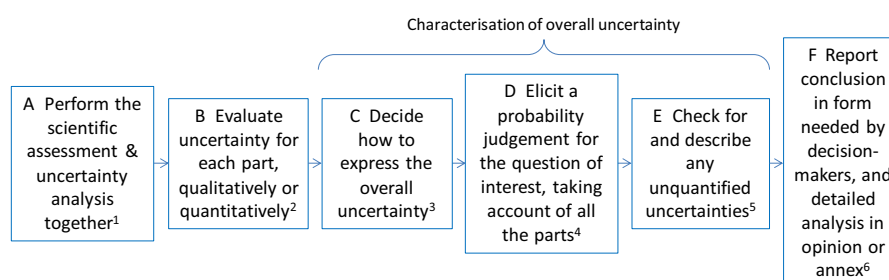


Figure 7: Combining multiple yes/no questions by expert judgement

Text notes for Figure 7:

¹ When the uncertainty analysis is divided into parts, it is recommended to perform it in parallel with, and preferably integrated with, the scientific assessment (i.e., those who are assessing each yes/no question would simultaneously evaluate its uncertainty), rather than leaving it to the end.

² When the parts will be combined by expert judgement, it may be sufficient to evaluate the uncertainty of each part qualitatively (e.g. using *ordinal scales*). See Section 11. However, using probability for some or all parts makes them less ambiguous and may help assessors when judging the overall conclusion.

³ Ensure that the question of interest for the assessment as a whole is well-defined (see Section 10) and decide how to express its uncertainty. Using an approximate probability scale is the simplest option (see Section 12.3).

⁴ This can be regarded as a *weight of evidence assessment*. Consider the parts of the assessment or lines of evidence and use them to make a probability judgement about the answer to the question of interest that takes account of your evaluation of the overall uncertainty. Expressing the reasoning of the assessment as a logic model (Section 13) increases transparency and may help assessors in judging the overall uncertainty, even if it is not used for calculations. See Section 12.6 for general guidance on probability judgements, EFSA (2017) for more detailed guidance on weight of evidence assessment.

⁵ See Section 16.2.

⁶ See Section 17.

4.2.2. Combining multiple yes/no questions by calculation (Figure 8)

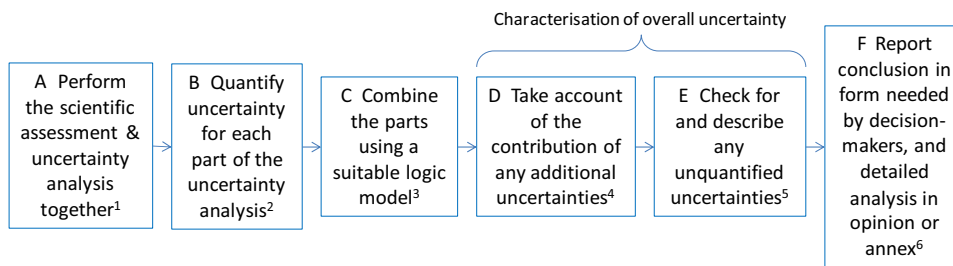


Figure 8: Combining multiple yes/no questions by calculation

Text notes for Figure 8:

¹ When the uncertainty analysis is divided into parts, it is recommended to perform it in parallel with, and preferably integrated with, the scientific assessment (i.e. those who are assessing each yes/no question would simultaneously quantify its uncertainty), rather than leaving it to the end.

² Quantify using probabilities or approximate probabilities: see Sections 12.1 and 12.2.

³ See Section 13.

⁴ There will generally be at least some additional uncertainties, e.g. uncertainties regarding the structure of the logic model and any unquantified dependencies between its parts. Go to Section 16.1 and characterise the overall uncertainty including their contribution by following Figure 15 and either Figure 16 or 17, then return to the present point in Figure 8.

⁵ See Section 16.2.

⁶ See Section 17.

4.3. Evaluating uncertainties separately for different parts of an uncertainty analysis involving non-variable quantities

This section refers to assessments where each quantitative part is a non-variable quantity taking only a single real value, e.g. the total number of infected animals entering the EU in a given year. Many non-variable quantities in scientific assessment are *parameters* that summarise variable quantities. A common example of this is the mean body weight for a specified population at a specified time. If the assessment includes some parts that address yes/no questions, their uncertainty can be quantified and included in calculation, or treated as an additional uncertainty in the characterisation of overall uncertainty (Figure 9).

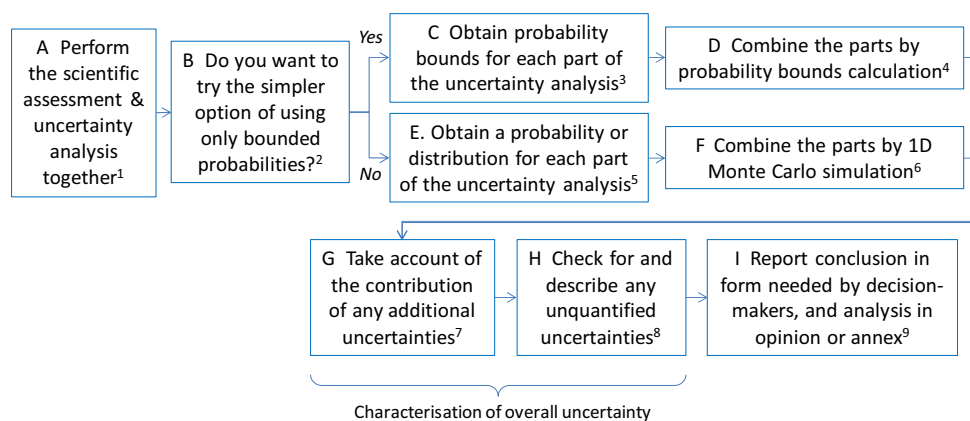


Figure 9: Evaluating uncertainties separately for different parts of an assessment involving *non-variable quantities*

Text notes for Figure 9:

¹ When the uncertainty analysis is divided into parts, it is recommended to perform it in parallel with, and preferably integrated with, the scientific assessment (i.e. those conducting each part of the assessment would simultaneously quantify its uncertainty), rather than leaving it to the end.

² *Probability bounds analysis* is simpler because it does not require full specification of distributions and of the dependencies between them, but it provides a more limited characterisation of uncertainty. It may be efficient to try it first, as it may provide sufficient information for decision-making. See Sections 12.2 and 14.1.

³ Do this for any parts addressing yes/no questions, as well as those relating to quantities of interest. See Section 12.2. Obtain probability bounds from data (Section 12.5) or by expert judgement (Section 12.6), as appropriate.

⁴ See Section 14.1 and SO.11.4.5.

⁵ Do this for any parts addressing yes/no questions, as well as those relating to quantities of interest. See Section 12.1. Obtain probabilities from data (Section 12.5) or by expert judgement (Section 12.6), as appropriate.

⁶ See Section 14.2 and SO.11.4.6.

⁷ There will generally be at least some additional uncertainties for a case-specific assessment, e.g. uncertainties affecting how the parts of the assessment combine and any dependencies between them. Go to Section 16.1 and characterise the overall uncertainty including their contribution by following Figure 15 and either Figure 16 or 17, then return to the present point in Figure 9.

⁸ See Section 16.2.

⁹ See Section 17.

4.4. Evaluating uncertainties separately for different parts of an assessment involving variable quantities

This section refers to assessments where at least some of the quantitative parts are variable quantities that take multiple values, such the body weights in a population. If some parts are non-variable quantities, they can be included accordingly. If the assessment includes some parts addressing yes/no questions, their uncertainty can be quantified and included in calculation, or treated as an additional uncertainty in the characterisation of overall uncertainty (Figure 10).

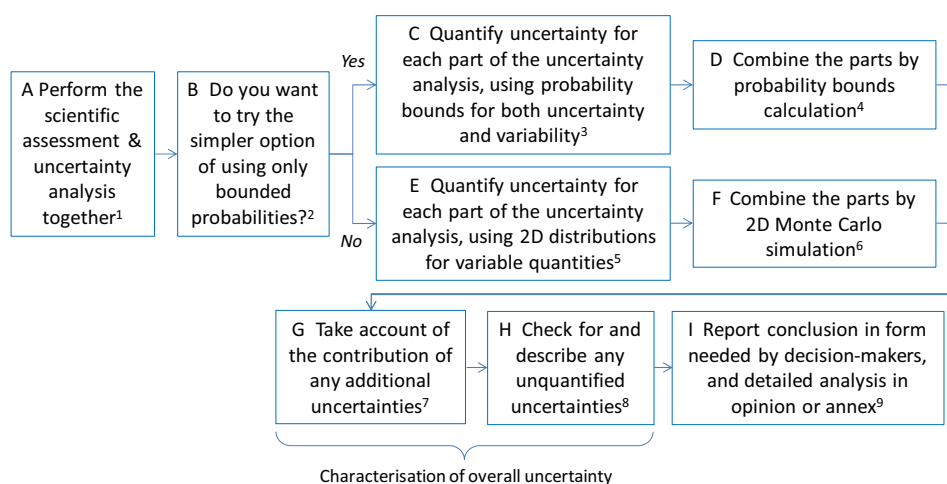


Figure 10: Evaluating uncertainties separately for different parts of an assessment involving *variable quantities*

Text notes for Figure 10:

¹ When the uncertainty analysis is divided into parts, it is recommended to perform it in parallel with, and preferably integrated with, the scientific assessment (i.e. those conducting each part of the assessment would simultaneously quantify its uncertainty), rather than leaving it to the end.

² Probability bounds analysis is simpler because it does not require full specification of distributions and of the dependencies between them, but it provides a more limited characterisation of uncertainty. It may be efficient to try it first, as it may provide sufficient information for decision-making. See Sections 12.2 and 15.1.

³ Obtain probability bounds, from data or expert judgement, for any parts addressing yes/no questions or non-variable quantities of interest, as well as variable quantities of interest. See Sections 12.2, 12.4, 12.5 and 12.6.

⁴ See Section 15.1.

⁵ Obtain suitable probability expressions, from data or expert judgement, for any parts addressing yes/no questions or non-variable quantities of interest, as well as variable quantities. See Sections 12.1, 12.4, 12.5 and 12.6. Obtaining two-dimensional distributions for uncertain variables requires specialised elicitation or statistical methods, and specialist support (Section 1.7).

⁶ See Section 15.2 and SO11.4.6. Two-dimensional Monte Carlo requires specialist support and software (Section 1.7).

⁷ There will generally be at least some additional uncertainties for a case-specific assessment, e.g. uncertainties affecting how the parts of the assessment combine and any dependencies between them. Go to Section 16.1 and characterise the overall uncertainty including their contribution by following Figure 15 and either Figure 16 or 17, then return to the present point in Figure 10.

⁸ See Section 16.2.

⁹ See Section 17.

5. Uncertainty analysis for urgent assessments

When a scientific assessment is urgent, assessors will need to choose an approach that fits within the available time and any other limitations arising from the urgency of the situation, e.g. limitations in resources and available evidence. Uncertainty analysis must still be included but this flow chart takes the quickest option, evaluating all uncertainties in a single step. This is more approximate than other options but is a reasonable basis for preliminary advice, provided the additional uncertainty implied by the streamlined assessment is reflected in the conclusions (Figure 11).

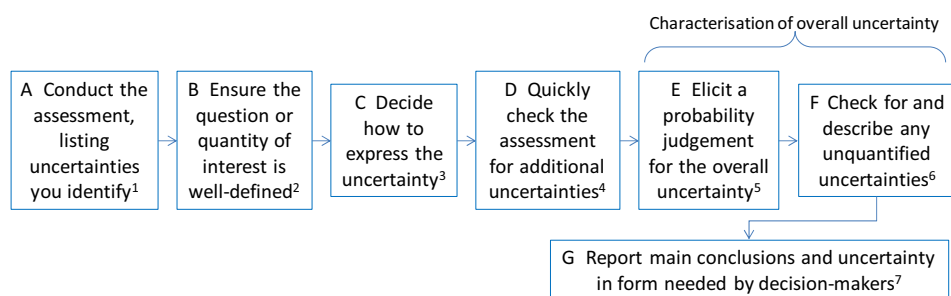


Figure 11: Uncertainty analysis for urgent assessments. Numbered superscripts refer to text notes following the figure. Letters (A, B, C, etc.) are to facilitate reference to specific steps in the figure

Text notes for Figure 11:

¹ It is recommended to make a list of uncertainties as you develop the assessment, rather than leave it to the end, to minimise the chance of missing important ones. If the assessment is a streamlined version of a standard procedure, then list only uncertainties that would be considered non-standard for that procedure (see Section 7.1).

² See Section 10. If the assessment is a streamlined version of a standard procedure, then the question or quantity of interest will already be specified in that procedure.

³ In urgent situations, time constraints are likely to make the approximate probability scale an attractive option (see Section 12.3).

⁴ Decide how much time you can allow for this and identify as many uncertainties as you can. See Section 7.

⁵ In urgent situations, time constraints are likely to make less formal methods of elicitation an attractive option (see Section 12.6).

⁶ See Section 16.2.

⁷ Seek advice from EFSA staff on the appropriate format for reporting as, in urgent situations, this may differ from normal EFSA outputs.

6. Uncertainty analysis when developing or revising standardised procedures

This section outlines how to conduct an uncertainty analysis when developing or revising a standardised procedure. This will often be necessary when creating or revising guidance documents, as they often contain standardised procedures [S07.1.3].

A standardised procedure will, when adopted, be applied repeatedly to a specified class of products or assessment problems. The purpose of uncertainty analysis in this case is to evaluate the probability that the proposed procedure will achieve the *management objectives* for that procedure to an extent which decision-makers consider appropriate for that class of products or problems. In other words, it checks whether the procedure is appropriately 'conservative', in the sense of providing appropriate cover for the standard uncertainties that normally affect assessments for this class of products or problems. This *calibration* of the procedure is what justifies its subsequent application to multiple assessments of the specified class without repeating the evaluation of standard uncertainties in every case [S07.1.3]. If uncertainty analysis is required for any other purpose during the development of a guidance document, the assessors should treat it as a normal case-specific assessment (Section 4).

Where an existing procedure is used in more than one area of EFSA's work, e.g. by more than one Panel, its calibration and, if necessary, revision should be undertaken jointly by those involved. Similarly, where a standardised procedure is part of an internationally-agreed protocol, any changes to it would need to be made in consultation with relevant international partners and the broader scientific community (Figure 12).

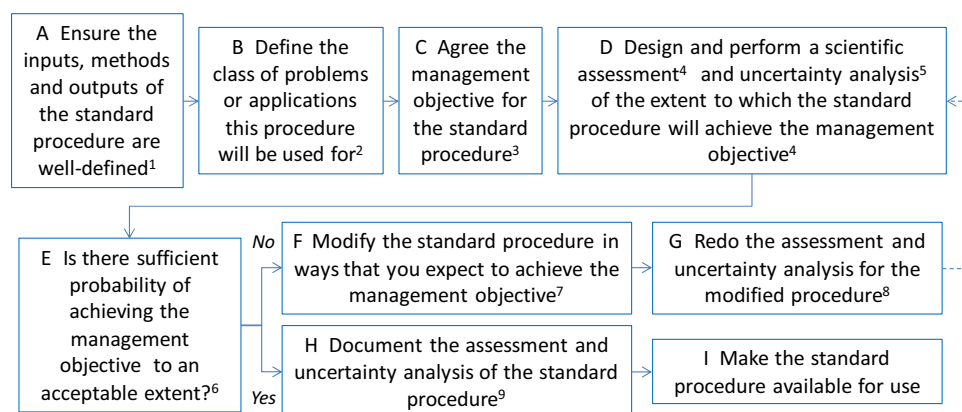


Figure 12: Uncertainty analysis to evaluate whether a procedure in a guidance document provides adequate cover for standard uncertainties. Numbered superscripts refer to text notes following the figure. Letters (A, B, C, etc.) are to facilitate reference to specific steps in the figure

Text notes for Figure 12:

¹ For example, in a guidance document.

² For example, a specified class of regulated products.

³ The management objective should specify the entity and attribute of interest and the magnitude, temporal scale and spatial scale of the effects of interest, and should be defined in dialogue with risk managers. An example of this is the criteria for *protection goals* that have been developed for environmental risks (EFSA, 2016). Analogous criteria will need to be developed to define the management objectives in other areas of EFSA's work.

⁴ Define an appropriate measure of the extent to which the management objective is met. This may include the proportions of problems or applications for which the standard procedure will result in false positives and negatives, and/or the distribution of deviations from the management objective in the class of problems or applications. Design an appropriate assessment of this measure.

⁵ Go to Section 4 and design an appropriate case-specific uncertainty analysis for the assessment of the extent to which the management objective is met. It may be appropriate to choose more rigorous options for this than for other case-specific assessments because, when finalised, the standard procedure will be applied to multiple problems or applications. Perform the scientific assessment and uncertainty analysis together, in an integrated manner (e.g. quantifying uncertainty within the *model* used for the scientific assessment). After completing the appropriate flow charts in Section 2, return to this flow chart.

⁶ Assessing the probability of achieving the management objective to any specified extent is the responsibility of assessors, but deciding what extent is acceptable and what probability is sufficient is a *risk management judgement*, and should be made by decision-makers. Take into consideration that, if the procedure is calibrated so as to achieve exactly the desired probability of achieving the defined requirements (e.g. by including an assessment factor just large enough to achieve this), this implies that any non-negligible non-standard uncertainties in a particular assessment would result in not achieving the desired probability. Although if the procedure was calibrated to be somewhat more conservative than required (e.g. by rounding up the assessment factor), this would leave more scope to accommodate non-standard uncertainties in individual assessments.

⁷ Options for this may include modifying the assessment scenario, the type or quantity of input data required, default values or assessment factors, the assessment method, or the criteria for interpreting the results (e.g. required margin of safety).

⁸ Repeat the cycle of modifications and reassessment until the estimated performance of the procedure is acceptable to decision-makers.

⁹ See Section 17. Seek advice from EFSA staff on the format, as this may differ from normal EFSA outputs. It is recommended to include in the documentation a list of the standard uncertainties that are covered by the standard procedure, as this will help assessors to identify non-standard uncertainties when using it.

7. Identifying uncertainties

7.1. Standard and non-standard uncertainties

- 1) **Standard uncertainties** are those that are considered (implicitly or explicitly) to be addressed by the provisions of a standardised procedure or standardised assessment element. For example, uncertainties due to within and between species differences in toxicity are often addressed by a *default factor* of 100 in chemical risk assessment. Similarly, measurement uncertainty in an experimental study is a standard uncertainty if the study followed (without deviations) a study guideline specified in the standard procedure. Standard uncertainties do not need to be reconsidered in each new assessment that follows the standard procedure, because they will have been assessed when the standard procedure was established (see Section 6).
- 2) All other uncertainties are **non-standard uncertainties**. These include any deviations from a standardised procedure or standardised assessment element that lead to uncertainty regarding the result of the procedure. For example, studies that deviate from the standard guidelines or are poorly reported, cases where there is doubt about the applicability of default values, the use of non-standard or 'higher tier' studies that are not part of the standard procedure, etc. Non-standard uncertainties are not covered by the allowance for uncertainty that is built into the standard procedure and must therefore be evaluated case-by-case, whenever they are present.
- 3) Both standard and non-standard uncertainties may be found in any type of assessment, but the proportions vary. In standardised assessments, there may be few or no non-standard uncertainties, while in other types of assessment there are generally more.
- 4) It is recommended that EFSA's Panels include lists of standard uncertainties within the documentation for standard procedures, as this will help assessors to distinguish standard and non-standard uncertainties. For the same reason, Panels may find it helpful to develop lists of non-standard uncertainties which they encounter frequently in their work, or use or adapt existing lists of criteria for *evidence appraisal*, which serve a similar purpose [see SO8.1].

7.2. Procedure for identifying uncertainties

- 1) Every assessment must say what sources of uncertainty have been identified [SO1.4]. For transparency, it is recommended to report them in list or tabular form.
- 2) Assessors should systematically examine every part of their assessment for uncertainties, including both the inputs to the assessment (e.g. data, estimates, other evidence) and the methods used in the assessment (e.g. statistical methods, calculations or models, reasoning, expert judgement), to minimise the risk that important uncertainties are overlooked [SO8.1]. In uncertainty analysis for standardised assessments, it is only necessary to identify non-standard uncertainties (see Section 3.1 and SO7.1.2).
- 3) Uncertainties affecting assessment inputs are identified when appraising the evidence retrieved from literature or from existing databases. Structured approaches to evaluating evidence have been established in many areas of science and are increasingly used in EFSA's work where appropriate [see Table B.45 and Table B.46 in SO Annex B.19]. When these approaches are applicable to the assessment in hand, they should be used. In other assessments, where existing approaches are not applicable, assessors may use the left column of Table 1 as a guide to what types of uncertainty to look for in their assessment inputs. In both cases, assessors should be alert for any additional types of uncertainty beyond those listed in Table 1 or the appraisal approach they are using. For example, external validity is not included in appraisal tools that focus on internal validity only (see SO10.7).
- 4) Uncertainties affecting the methods used in the assessment are generally not addressed by existing frameworks for evidence appraisal. It is therefore recommended that assessors use the right column of Table 1 (referring to [SO8.1] for details and explanation) as a guide to what types of uncertainty to look for in the methods of their assessment. Again, assessors should be alert for any additional types not listed in Table 1.

- 5) Assessors are advised to avoid spending excessive time trying to match uncertainties to the types listed in Table 1 or other frameworks: the purpose of the lists is to facilitate identification of uncertainties, not to classify them.
- 6) Assessors should determine which of the uncertainties they identify in an assessment are standard and which are non-standard (Section 7.1), as this will affect their treatment in subsequent stages of the uncertainty analysis.

Table 1: Generic list of common types of uncertainty affecting scientific assessments (see SO8.1 for details)

Uncertainties associated with assessment inputs	Uncertainties associated with assessment methodology
1) Ambiguity	1) Ambiguity
2) Accuracy and precision of the measures	2) Excluded factors
3) Sampling uncertainty	3) Distributional assumptions
4) Missing data within studies	4) Use of fixed values
5) Missing studies	5) Relationship between parts of the assessment
6) Assumptions about inputs	6) Evidence for the structure of the assessment
7) Statistical estimates	7) Uncertainties relating to the process for dealing with evidence from the literature
8) Extrapolation uncertainty (i.e. limitations in external validity)	8) Expert judgement
9) Other uncertainties	9) Calibration or validation with independent data
	10) <i>Dependency</i> between sources of uncertainty
	11) Other uncertainties

8. Prioritising uncertainties

- 1) Prioritising sources of uncertainty may be useful at different stages of the assessment and uncertainty analysis. In the early stages, it can be used to select more important uncertainties to be analysed by more refined methods, e.g. to be evaluated individually rather than collectively, to be expressed with probabilities or distributions rather than bounds, to be elicited by more rather than less formal methods, etc. Prioritisation can also be used during the course of an assessment, to identify parts of the assessment where it might be beneficial to search for more data, use more complex models, or invite additional experts. At the end of the assessment, it may be useful to prioritise uncertainties to identify potential areas for further research.
- 2) Prioritisation, at any stage of the assessment, should be based on the contribution of individual sources of uncertainty to the uncertainty of the assessment as a whole. This is determined by a combination of the magnitude of each uncertainty and how much it affects the result of the assessment, both of which need to be taken into account [SO5.7].
- 3) The relative influence of different uncertainties can be assessed in a simple and approximate way using qualitative methods based on expert judgement. An ordinal scale can be used to express expert judgements of the magnitude and/or direction of impact of each uncertainty on the question or quantity of interest, as in 'uncertainty tables' [SO10.5 and 10.6]. Or separate ordinal scales could be used to express judgements of the magnitude of each uncertainty and its influence, as in the Numeral, Unit, Spread, Assessment and Pedigree (NUSAP) approach [SO10.4].
- 4) When the assessment involves a calculation or quantitative model, the contributions of uncertainties about the model inputs can be assessed rigorously by sensitivity analysis. These range from simple 'what if' calculations and 'minimal assessment' (EFSA, 2014a) to sophisticated sensitivity analyses [see SO12] for which specialist help might be required (Section 1.7). The influence of uncertainties relating to choices regarding the structure of the model or assessment may need to be addressed by repeating the assessment with alternative choices. Prioritisation at the early stages of an assessment must necessarily be done by expert judgement or by sensitivity analysis using a preliminary model, as the assessment model is still under development.

9. Dividing the assessment into parts

- 1) Often an assessment will comprise a number of main parts (e.g. exposure and hazard in a chemical risk assessment) and smaller, subsidiary parts (e.g. individual parameters, studies, or lines of evidence within the exposure or hazard assessment).
- 2) The uncertainty analysis may also be divided into parts. Assessors should choose at what level to conduct it:
 - a) Evaluate all uncertainties collectively, for the assessment as a whole.
 - b) Divide the uncertainty analysis into parts, which evaluate uncertainties separately in major *parts of the scientific assessment* (e.g. exposure and hazard in a risk assessment). Then, combine the parts of the uncertainty analysis and include also any other identified uncertainties that relate to other parts of the scientific assessment as a whole, so as to characterise the overall uncertainty.
 - c) Divide the uncertainty analysis into still smaller parts, corresponding to still smaller parts of the scientific assessment (e.g. every input of a calculation or model). Evaluate uncertainty collectively within each of the smaller parts, combine them into the main parts, and combine those to characterise overall uncertainty for the whole assessment.
- 3) If the uncertainty analysis will be divided into parts, assessors will need to combine them to characterise overall uncertainty. Assessors should define in advance how the parts will be combined, as this will increase transparency and rigour. It is recommended to use a *conceptual model diagram* (see glossary for explanation) to show how the parts will be combined. The parts may be combined by expert judgement (Section 12.6), or by calculation (Sections 13, 14 or 15) if assessors quantify the uncertainty for each part and can specify an appropriate quantitative or logical model to combine them. Calculation is likely to give more reliable results, but should be weighed against the additional work involved.
- 4) Assessors should judge what is best suited to the needs of each assessment. For example, it may be more efficient to evaluate uncertainty for different parts separately if they require different expertise (e.g. toxicity and exposure). Evaluating all uncertainties collectively (first option in point (2) above) is generally quicker and superficially simpler but requires integrating them all subjectively by expert judgement, which may be less reliable than evaluating different parts of the uncertainty analysis separately, if they are then combined by calculation. For this reason, it is recommended to treat separately those parts of the assessment that are affected by larger uncertainties (identified by a simple initial prioritisation, see Section 8).
- 5) When a part of the scientific assessment is treated separately in the uncertainty analysis, it is not necessary to evaluate immediately all of the uncertainties affecting it; some of them can be set to one side and considered later as part of the overall characterisation of uncertainty, if this is more convenient for the assessor. However, it is recommended that only the lesser uncertainties are deferred to the overall characterisation, since it will be more reliable to combine the larger uncertainties by calculation.
- 6) When the scientific assessment includes a quantitative or logical model, assessors may find it convenient to quantify uncertainty separately for every parameter of the model. In such cases, it will still be necessary to identify additional uncertainties that are not quantified within the model, e.g. uncertainties relating to the structure of the model (see Section 7.2) and take them into account in the characterisation of overall uncertainty (Section 16). In other cases, assessors might find it sufficient to analyse all the uncertainties affecting a model collectively (simplest option in point (2) above), or for major parts of the model without separating the individual parameters (intermediate option in point (2)).

10. Ensuring questions and quantities of interest are well-defined

- 1) In order to evaluate uncertainty, the questions and/or quantities of interest for the assessment must be well-defined. This applies both to the assessment as a whole and to different parts of the uncertainty analysis, if it is separated into parts. Any *ambiguity* in the definition of questions or quantities of interest will add extra uncertainty and make the evaluation more difficult. When a question or quantity of interest is not already well-defined

for the purpose of scientific assessment, assessors should define it well for the purpose of uncertainty analysis.

- 2) A quantity or question of interest is well-defined if, at least in principle, it could be determined in such a way that assessors would be sure to agree on the answer. A practical way to achieve this is by specifying an experiment, study or procedure that could be undertaken, at least in principle, and which would determine the true answer for the question or quantity with certainty [see [SO5.1](#) for more discussion]. For example:
 - a) a well-defined measure for a quantity of interest, and the time, population or location, and conditions (e.g. status quo or with specified management actions) for which the measure will be considered;
 - b) for a question of interest, the presence or absence of one or more clearly-defined states, conditions, mechanisms, etc., of interest for the assessment, and the time, population or location, and conditions (e.g. status quo or with specified management actions) for which this will be considered;
 - c) the result of a clearly-defined scientific study, procedure or calculation, which is established (e.g. in legislation or guidance) as being relevant for the assessment.
- 3) When drafting the definition of each question or quantity of interest, check each word in turn. Identify words that are ambiguous (e.g. high), or imply a risk management judgement (e.g. negligible, safe). Replace or define them with words that are, as far as possible, unambiguous and free of risk management connotations or, where appropriate, with numbers.
- 4) Sometimes the Terms of Reference for an assessment are very open, e.g. requesting a review of the literature on an area of science. In such cases, assessors should seek to ensure the conclusions they produce either refer to well-defined quantities, or contain well-defined statements that can be considered as answers to well-defined questions, in one of the three forms listed above (point 2, options a–c). This is necessary both for transparency and so that assessors can evaluate and express the uncertainty associated with their conclusions.

11. Qualitative expression of uncertainty

- 1) Qualitative expressions of uncertainty use words or ordinal categories, without quantifying either the range of possible answers or values for the question or quantity of interest, or their probabilities.
- 2) Qualitative expressions are inevitably ambiguous unless accompanied by a quantitative definition. It is therefore recommended to use quantitative expressions when characterising overall uncertainty [[SO4.2](#) and [14](#)]. Nevertheless, qualitative expression is useful in uncertainty analysis, and recommended for use in the following situations:
 - a) As a simple approach for prioritising uncertainties (Section [8](#)).
 - b) At intermediate steps in uncertainty analysis, to describe individual sources of uncertainty as an aid to quantifying their combined impact by probability judgement (Section [12.6](#)). This may be useful either for individual parts of an assessment (Section [9](#)), or as a preliminary step when characterising the overall uncertainty of the conclusion (Section [16.1](#)).
 - c) When quantifying uncertainty by expert judgement, and when communicating the results of that, it may in some cases be helpful to use an approximate probability scale with accompanying qualitative descriptors (Section [12.3](#)).
 - d) At the end of uncertainty analysis, for describing uncertainties that the assessors are unable to include in their quantitative evaluation: see Section [16.2](#) for further guidance on this.
 - e) When reporting the assessment, for expressing the assessment conclusion in qualitative terms when this is required by decision-makers or legislation [[SO3.5](#)].
- 3) For the situations identified in 2b above, it is recommended to describe the individual sources of uncertainty with one or more ordinal scales. This will aid consistency and transparency, and help assessors make a balanced overall evaluation of multiple uncertainties when forming a probability judgement about their combined impact. One or more scales may be used (e.g. in weight of evidence, one option could be to define scales

for relevance, reliability and consistency, EFSA Scientific Committee, 2017), and they should be defined as part of planning the assessment (EFSA, 2015). Evaluations using the scales could be done more or less formally, using a range of options similar to those for expert elicitation of probability judgements, depending on what is proportionate to the needs of the assessment (see Section 12.6).

- 4) It is recommended that qualitative expressions obtained as in point 3 above are used to inform a quantitative probability judgement of their combined impact on the assessment. They should not be combined by any form of calculation, matrix or fixed rule, unless there is an explicit, reasoned basis for the specific form of calculation, matrix or rule that is chosen [see SO10.3].

12. Quantifying uncertainty using probability

The Scientific Committee recommends that assessors express in quantitative terms the combined impact of as many as possible of the identified uncertainties [SO4.2]. This Guidance uses probability for this purpose [SO5.10]. Probabilities can be specified fully (Section 12.1) or partially (Sections 12.2, 12.3), and obtained from data (Section 12.5) or expert judgement (Section 12.6), as appropriate for the assessment in hand. When data are available, they should be used, and via a statistical analysis if possible. However, there is always some expert judgement involved, even if it is only to choose a *statistical model*. Uncertainty of variable quantities and dependencies can also be addressed (Sections 12.4, 12.7). The combined impact of two or more sources of uncertainty may be quantified either by direct expert judgement (Section 12.6) or by calculation after quantifying each individual source of uncertainty (Sections 13, 14, 15).

12.1. Probability and probability distributions

- 1) Probability is a continuous scale ranging from 0 to 1. It can also be expressed as a percentage, ranging from 0% to 100%, and the latter is used in this Guidance.
- 2) For a yes/no question (including whether a *non-variable quantity* of interest exceeds a specified value), 0% probability means that the answer is certainly no, 100% probability means it is certainly yes, while probabilities between 0% and 100% represent increasing degrees of certainty that it is yes. For example, a probability of 50% means the answer is equally likely to be yes or no, and 75% means it is three times more likely to be yes than no.
- 3) Uncertainty about the value of a non-variable quantity can be expressed fully by a probability distribution, which shows the relative probability of different values. An example is shown in Figure 13. A probability distribution determines the probability that any specified range of possible values includes the *true value* of the quantity of interest.
- 4) Sometimes a partial expression of uncertainty about the value of a non-variable quantity is sufficient: the probability that a specified range of possible values includes the true value of the quantity of interest, e.g. the probability that 'mean exposure exceeds 10 mg/kg bw per day'. Although in the past it has often been implicit that a range contains the true value of a quantity with close to 100% probability, for example when reporting lower and upper bound estimates for exposure, the probability for the range should be specified explicitly.

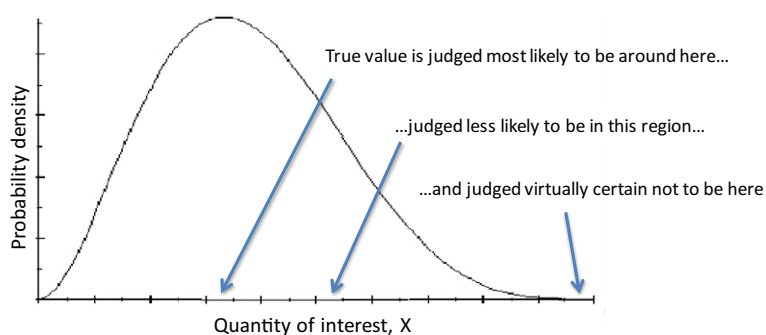


Figure 13: Example of probability distribution, quantifying uncertainty about a non-variable quantity X

12.2. Approximate probabilities and probability bounds

- 1) When probabilities are obtained by expert judgement rather than from statistical analysis of data, it may be easier to specify a probability approximately by giving a range for the probability. For example, one might specify only that the probability is less than 5%, i.e. between 0% and 5%. The meaning of such a range is that it is judged that the probability would lie in the range if more time was taken to specify the probability precisely.
- 2) Combining points 12.1.4 and 12.2.1 yields a probability bound: an approximate probability, specified as a range, that an uncertain non-variable quantity lies in a specified range of possible values or exceeds a specified value. For example, one might specify that 'there is less than 10% probability that mean exposure exceeds 10 mg/kg bw per day'. Probability bounds analysis (Section 14.1) can then be used to combine uncertainties expressed in this way.

12.3. Approximate probability scale

- 1) When probability judgements are made by semi-formal expert knowledge elicitation (EKE) procedures or by less formal methods (see Section 12.6), assessors may find it helpful to refer to a standard scale of probability ranges. The approximate probability scale shown in Table 2 is recommended for this purpose in EFSA, and was adapted from a similar scale used by the Intergovernmental Panel on Climate Change [SO11.3.3].
- 2) When using Table 2, assessors should consider which of the tabulated ranges expresses their judgement of the probability that is required. This could be either the probability of an answer to the question of interest, or the probability that the quantity of interest lies in a specified range. It is emphasised that Table 2 is intended for quantifying uncertainty and not variability. For example, it may be used to express the probability that a specified percentile of exposure exceeds a specified value, but not the proportion of the population who do so. Similarly, it should not be used to express the incidence (risk) of an effect in a population but, if incidence was assessed, Table 2 could be used to express the probability that incidence exceeds a specified level. It can also be used to express the probability that an uncertain qualitative conclusion is true.
- 3) Assessors are not restricted to the tabulated ranges: they may use a different range than those listed, if it would better describe their judgement, or give a precise probability if they can.
- 4) If assessors are unable to select a single range from the second or third columns of Table 2, they can use more than one range to express their judgement. If assessors feel very uncertain, it may be easier to start with the full set of ranges (i.e. a total range of 0–100%) and then omit any ranges they would not regard as credible, given the available evidence. If they are unable to omit any part of the probability scale, this implies they are unable to make any statement about the probability of the answers or values of interest and should report them as inconclusive or unknown (see Section 16.2 for the implications of this).
- 5) The verbal probability terms in Table 2 may be used to aid communication. Assessors' judgements should be based on the probability ranges, not on the verbal terms. To avoid ambiguity, the verbal terms shown in Table 2 should always be accompanied by the quantitative range in brackets, e.g. 'Likely (66–90% probability)', and should not be used for other ranges.

Table 2: Approximate probability scale recommended for harmonised use in EFSA. See text above for guidance

Probability term	Subjective probability range	Additional options	
Almost certain	99–100%	More likely than not: > 50%	Unable to give any probability: range is 0–100%
Extremely likely	95–99%		
Very likely	90–95%		Report as 'inconclusive', 'cannot conclude', or 'unknown'
Likely	66–90%		
About as likely as not	33–66%		
Unlikely	10–33%		
Very unlikely	5–10%		
Extremely unlikely	1–5%		
Almost impossible	0–1%		

12.4. Quantifying uncertainty for a variable quantity

- 1) Any variable quantity should have a specified context of interest for an assessment. For example, the context of interest might be a specified population at a specified time. The context defines a distribution of *variability*: the relative frequency of occurrence of different values for the quantity. For example, the exposure to or intake of a specified substance during a specified period of time will vary from individual to individual and the variability distribution could be summarised using a histogram if the intake of all individuals was known. However, it is nearly always the situation that there are individuals/cases/places for which the value of the quantity is not known, so the variability distribution is not known exactly and is therefore uncertain. Then quantities such as the mean, or percentiles of variability, are non-variable but uncertain and uncertainty about them can be expressed using probability.
- 2) One approach to expressing uncertainty for a variable quantity is to focus on a specified percentile of variability. That percentile is then an uncertain quantity and uncertainty about it can be expressed using a probability distribution or probability bounds (a range with a probability or approximate probability). If there is more than one variable quantity, then it is recommended to begin by using probability bounds, because it may then be possible to use probability bounds analysis to combine the uncertainties (Section 15.1).
- 3) If the assessment uses a quantitative model involving more than one variable and probability bounds analysis does not provide sufficient information for decision-making, it will be necessary to quantify both uncertainty and variability using distributions (see Sections 12.4 and 15.2, SO5.3 and SO11.1). This requires a statistical model for the variability. Parameters in the statistical model are then uncertain quantities and uncertainty about them can be quantified using probability distributions. Statistical expertise is needed (Section 1.7). Section 15.2 provides further detail, including some principles for how to combine uncertainties expressed in this way.

12.5. Obtaining probabilities from data

- 1) Where suitable data are available, statistical analysis should be used to derive estimates for the quantity of interest, together with a measure of uncertainty [SO11.2].
- 2) Statistical methods for quantifying uncertainty include confidence and prediction intervals, the bootstrap and Bayesian inference [see SO11.2.1–3]. Choosing and applying a suitable method may require assistance from a statistician (Section 1.7). Bayesian inference using prior distributions based on expert judgement directly expresses uncertainty about parameters using probabilities which can be combined with other probabilities deriving directly from expert judgement. Traditional non-Bayesian statistical methods can also be used: confidence and prediction intervals [SO Annex B.10] and output from the bootstrap [SO Annex B.11] can be used as the basis for expert judgements expressed as probabilities. For example, a 95% confidence interval for a parameter might become an expert judgement that there is 95% probability that the true value of the parameter lies in the

range given by the confidence interval. [SO11.2.1](#) discusses when it is reasonable to make such a judgement and when some adjustment of either the interval or its probability might be needed.

- 3) Statistical analysis of a data set using a single statistical model quantifies only part of the uncertainty that is present: that part which is reflected in the variability of the data and the sampling scheme which is assumed in the model. Selection of data and statistical model involves additional uncertainty, which must be taken into account. Some of this may be partly addressed within the statistical analysis, e.g. by assessing goodness of fit or using model averaging techniques [[SO11.5.2](#)]. Any uncertainties that are not quantified within the statistical analysis must be taken into account later, by expert judgement, when characterising overall uncertainty (Section 16); this could be facilitated by conducting scenario analysis of alternative statistical models.

12.6. Obtaining probabilities or distributions by expert judgement

- 1) All assessments will require expert judgements of probability for at least some uncertainties, except for standard assessments with no non-standard uncertainties (Section 3.1).
- 2) Expert judgement is subject to psychological biases, e.g. over-confidence (EFSA, 2014a). EFSA's (2014a) guidance describes formal methods of EKE that are designed to counter those biases: these maximise rigour, but require significant time and resource. Semi-formal EKE [[SO11.3.1](#)] is more streamlined, and probability judgements can also be made by 'minimal assessment' (EFSA, 2014a), '*expert group judgements*' and '*individual expert judgement*' [[SO9](#)].
- 3) Most methods are described for eliciting distributions, but can be adapted to elicit probabilities or probability bounds, for both yes/no questions and quantities of interest.
- 4) Required steps in all methods include ensuring the question or quantity of interest is well-defined (Section 10), selecting experts with appropriate expertise, deciding how to express the probability judgement (probability, distribution or probability bounds (Sections 12.1 and 12.2), reviewing the available evidence, conducting the elicitation in a manner that mitigates psychological biases, and recording the experts' rationale for their judgements. All participants should have basic training in making probability judgements (Section 1.7). The methods and results should be documented transparently, including the evidence considered and the experts' identities, reasoning and judgements, but not who said what.
- 5) Formal and semi-formal EKE should be led by people trained in the elicitation method that is used (Section 1.7). Probability judgements by minimal assessment and expert group judgement can be carried out as part of normal Working Group meetings with little or no specialist support. However, it is recommended that Working Groups seek support (Section 1.7) when first making probability judgements, to help choose methods appropriate for their work.
- 6) It is recommended to use less formal methods to prioritise uncertainties (Section 8), and then apply more formal methods to elicit those with most impact on the assessment conclusions. Any limitations in the methods used, e.g. due to time constraints, will make probability judgements more approximate, and should be taken into account when characterising overall uncertainty (Section 16).
- 7) All expert judgements, including probability judgements, must be based on evidence and reasoning. Some assessors have concerns about using probability judgements in their assessments, for various reasons. Those concerns are recognised and addressed by this Guidance (see Box 2 and [SO4.2](#)).
- 8) Most expert judgements will be made either by members of the Working Group conducting the assessment, or by external experts participating in a formal EKE procedure, or a combination of Working Group members and additional experts, depending on what is appropriate in each case. However, for assessments that are to be adopted by a Panel or Scientific Committee, the final assessment is the responsibility and Opinion of the Panel or Committee, who therefore have an important role in peer reviewing and the judgements it includes. It is therefore important to inform and/or consult the Panel or Committee at key steps in the EKE process (EFSA, 2014a). In addition, those conducting an EKE may consider involving Panel or Committee members who have particular expertise in the question at hand.

Box 2: Some common concerns about probability judgements (*italics*), and how this Guidance addresses them (plain). This is a subset of a longer list, which may be found in [SO4.2](#).

- *Quantifying uncertainty requires extensive data:* uncertainty can be quantified by expert judgement for any well-defined question or quantity [[SO5.10](#)], provided there is at least some relevant evidence.
- *Data are preferable to expert judgement:* this Guidance recommends use of relevant data where available [see [SO5.9](#)].
- *Subjectivity is unscientific:* All judgement is subjective, and judgement is a necessary part of all scientific assessment. Even when good data are available, expert judgement is involved in evaluating and analysing them, and when using them in risk assessment.
- *Quantitative judgements are over-precise:* EFSA's methods produce judgements that reflect the experts' uncertainty – if they feel they are over-precise, they should adjust them accordingly.
- *Quantitative judgements cannot be made from qualitative assessments:* Probability judgements can be made for any well-defined conclusion [[SO5.1](#)], and all EFSA conclusions should be well-defined.
- *It is not valid to combine probabilities derived from data with probabilities derived by expert judgement:* there is a well-established theoretical basis for using probability calculations to combine probability judgements elicited from experts (including probability judgements informed by non-Bayesian statistical analysis) with probabilities obtained from Bayesian statistical analysis of data [[SO5.10](#) and [SO11.2.1](#)].

12.7. Dependencies

- 1) Many variable quantities are interdependent, e.g. food intake and body weight.
- 2) Sources of uncertainty are dependent when learning more about one would alter the assessors' uncertainty about the other. For example, getting better data on the toxicity of one chemical may reduce the assessors' uncertainty about toxicity of a closely related chemical (see [[SO5.4](#)]).
- 3) Assessors should always consider whether dependencies may be present and, if so, take them into account, because they can have a large impact on the assessment conclusion.
- 4) Potential dependencies affecting variability or uncertainty are most easily addressed by probability bounds analysis, because it does not require specification of dependencies (Sections [14.1](#) and [15.1](#)). However, it accounts for all possible dependencies, so the resulting approximate probability often covers a wide range of probabilities.
- 5) Narrower bounds, or precise probabilities or distributions, can be obtained if information on dependencies can be included in the analysis. Calculations with probabilities (Section [13](#)) or distributions (Sections [14.2](#), [15.2](#)) require specification of all potential dependencies. If there is good reason to believe all dependencies are negligible, assuming independence makes calculation much simpler (Section [14.2](#)). When there is reason to believe non-negligible dependencies may be present, they should be estimated from data or by expert judgement; this will require specialist expertise (Section [1.7](#)).

13. Combining uncertainties for yes/no questions using a logic model

- 1) A logic model expresses a yes/no conclusion as a logical deduction from the answers to a series of yes/no questions. When the answers to these questions are uncertain, the conclusion is also uncertain.
- 2) The simplest logic models are the 'and' and 'or' models. In the 'and' model, the conclusion is 'yes' only if each question has the answer 'yes'. In the 'or' model, the conclusion is 'yes' if any of the questions has the answer 'yes'. More complex models combine 'and' and 'or' hierarchically to build a tree of reasoning leading to a conclusion, for example taking the output of an 'or' submodel for some questions as one input to an 'and' model, which might also include other input questions or submodel outputs.
- 3) When uncertainty about the answer to each question is expressed using probability, the mathematics of probability can be used to calculate a probability for the conclusion. If precise probabilities are specified for the answers to each question, the result is a precise probability for the conclusion. If an approximate probability is specified for any of the questions, the result is an approximate probability for the conclusion. Calculations are fairly straightforward [[SO Annex B.18](#)] when uncertainties about answers to questions are independent; otherwise seek specialist advice (Section [1.7](#)).

14. Combining uncertainties by calculation for a quantitative model involving only non-variable quantities

14.1. Uncertainties expressed using probability bounds

- 1) If uncertainty for each input to the model has been quantified using a probability bound (Section 12.2), the method of Probability Bounds Analysis [SO Annex B.13] can be used to deduce a probability bound for the output: an approximate probability that a particular range includes the output value that corresponds to the true values of the inputs.
- 2) Two simple versions of the calculation are described in SO Annex B.13. In the first, the output range consists of all possible output values from the model corresponding to input values in the ranges specified for the inputs as part of the probability bounds. The approximate probability for the output range is straightforwardly obtained, using a calculator, from the approximate probabilities for input ranges. The second version applies when the model output is monotonic with respect to each input, i.e. each input either always increases or always decreases the output when the input is increased. The calculation uses approximate probabilities that inputs exceed specified values to compute an approximate probability that the output exceeds the value obtained by using the specified values in the model. If neither simple version is useful, seek specialist advice (Section 1.7). As an example of a simple application, suppose that the model multiplies an uncertain concentration times an uncertain consumption to obtain an uncertain intake and that the probability that concentration exceeds 10 mg/kg is judged to be less than 10% and that the probability that consumption exceeds 0.2 kg/day is judged to be less than 5%. Then, probability bounds analysis concludes that the probability that intake exceeds $0.2 \times 10 = 2$ mg/day is less than $(10 + 5) = 15\%$.
- 3) The calculation is robust in the sense that it is not affected by possible dependence between uncertainties about inputs. All possible forms of dependence have been taken into account when computing the probability bound for the output.

14.2. Uncertainties expressed using probability distributions

- 1) If uncertainty about each input to the model has been expressed using a probability distribution (Section 12.1) and there is no dependence between the uncertainties, the mathematics of probability leads to a probability distribution expressing the combined uncertainty about the output of the model.
- 2) The simplest method for computing the probability distribution for the output is one-dimensional Monte Carlo simulation [SO Annex B.14] which is easily implemented in freely available software or, in some simple cases, in a spreadsheet.
- 3) If assessors are not confident about how to express or elicit uncertainty using probability distributions or are not confident about how to carry out one-dimensional Monte Carlo, seek advice (Section 1.7).
- 4) If dependence between uncertainties about inputs (Section 12.7) is considered to be an issue, seek advice (Section 1.7).

15. Combining uncertainties by calculation for a quantitative model involving variable quantities

15.1. Probability bounds analysis for both uncertainty and variability

- 1) Probability Bounds Analysis [SO Annex B.13] can be applied to quantitative models which have variable inputs. This is most straightforward when the model output increases when any variable input is increased. For models which are monotonic but with some inputs causing increases and others decreases, the inputs can be redefined so that the model output increases with respect to each input [SO Annex B.13]. It may be possible to apply the method to other models but specialist advice is likely to be needed (Section 1.7).

- 2) For each variable input, a percentile of interest should be chosen and a probability bound be provided, expressing uncertainty about the percentile. The result of the calculation is a probability bound for a percentile of the output; the output percentile is determined by doing a probability bounds analysis of the kind described in Section 14.1 but applied to variability rather than uncertainty. For models where output increases with respect to each input, the calculation does not require specialist software or expertise. For details, see [SO Annex B.13](#) which includes a worked example. Otherwise, seek advice (Section 1.7).
- 3) The calculation is robust in the sense that it is not affected by possible dependence between the variables and it is also not affected by possible dependence between uncertainties about the chosen percentiles. All possible forms of dependence have been taken into account when computing the probability bound for the output.

15.2. Probability distributions for both variability and uncertainty

- 1) As indicated in Section 12.4, a full expression of uncertainty about variability uses probability distributions in two roles: (i) as statistical models of variability; (ii) to express uncertainty about parameters in such models. Using probability to express uncertainty is fundamentally Bayesian and leads naturally to the use of Bayesian inference [[SO Annex B.12](#)] and Bayesian graphical models [[SO11.5.2](#)] to provide a full analysis of variability and uncertainty about variability using data and expert judgement.
- 2) A full expression of uncertainty about variability is required if the quantitative model has more than one variable input and a probability distribution is needed expressing uncertainty about either: (i) one or more specified percentiles of variability of the model output; or (ii) the proportion of individuals/cases exceeding a specified value of the model output.
- 3) In situations where randomly sampled data are available for all variable inputs to a model, the bootstrap [[SO Annex B.11](#)] may be used to quantify uncertainty, due to sampling, about variability of model outputs. Alternatively, where uncertainty about all parameters in a statistical model of variability is expressed by expert judgement, possibly informed by data, probability distributions and two-dimensional Monte Carlo [[SO Annex B.14](#)] may be used to compute consequent uncertainty about variability of model output. Where data are available for some inputs and expert judgements for others, Bayesian modelling and inference provide the best solution.
- 4) Possible dependence between variables can usually be addressed by an appropriate choice of statistical model for the variability. Dependence between uncertainties relating to parameters in a statistical model may arise simply as a consequence of applying the model to data, in which case Bayesian inference directly quantifies the dependence without need for judgements from experts about dependence. An example of this is the dependency between uncertainty of the mean and variance estimated from a sample of data [[SO5.4](#)]. If dependence between uncertainties relating to parameters arises because learning more about one would change the assessors' judgement of the other, it needs to be addressed by specialist EKE methods (Section 1.7).
- 5) Any analysis of the kind described in this section is likely to benefit from specialist statistical expertise, especially in Bayesian modelling and computation (Section 1.7).

16. Characterising overall uncertainty

All assessments must report clearly and unambiguously the impact of uncertainty on the assessment conclusion (Section 1.2). In assessments where the impact of one or more uncertainties cannot be characterised, it must be reported that this is the case and that consequently the assessment conclusion is *conditional* on assumptions about those uncertainties, which should be specified (see Sections 16.2 and 17).

In standardised assessments where there are no non-standard uncertainties, these requirements are met simply by reporting that non-standard uncertainties were checked for and none were found (Section 3.1). For all other assessments, the Scientific Committee recommends that assessors express in quantitative terms the combined impact of as many as possible of the identified uncertainties [[SO4.2](#)]. Any uncertainties that the assessors are unable to include in their quantitative evaluation must be described qualitatively [[SO4.2](#), 14 and 15] and presented alongside the quantitative evaluation, so that together they characterise the assessors' overall uncertainty (note this refers to the overall impact of the

identified uncertainties, and does not include 'unknown unknowns', See Section 16.2). Three options for this are depicted diagrammatically in Figure 14. In option 1, all identified uncertainties are evaluated collectively in one step: methods for this are, for convenience, described in the earlier sections and flow charts where this approach is used (Figures 2, 6, 7 and 11). In options 2 and 3, uncertainties for some parts of the assessment are quantified and combined separately, and other, additional uncertainties are taken into account when characterising overall uncertainty.

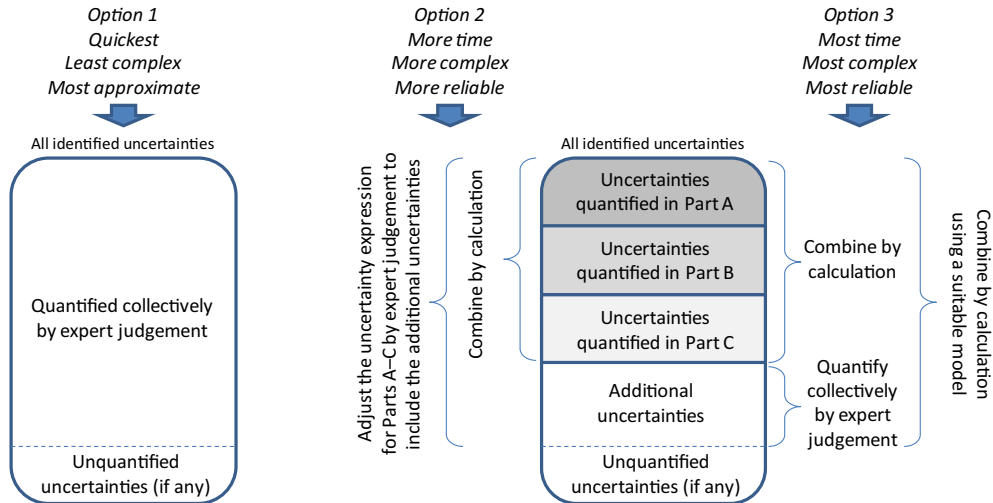


Figure 14: Illustration of options for characterising overall uncertainty. See [SO14] for detailed explanation

16.1. Taking account of additional uncertainties

This section describes the approach for taking account of additional uncertainties in assessments where at least some uncertainties have been quantified separately and combined by calculation earlier in the assessment (in Figures 3, 4, 8, 9 and 10). In urgent assessments and assessments using the simpler options for uncertainty analysis, no uncertainties are quantified separately and, for simplicity and speed of use, the approach to overall uncertainty characterisation for those cases (Option 1 in Figure 14) is described in the relevant Sections and Figures earlier in this Guidance (Figures 2, 6, 7 and 11). For all other assessments, where some uncertainties are quantified separately, the earlier Figures will have directed the user to this section, and the user should continue their uncertainty analysis with Figures 15–17 (below).

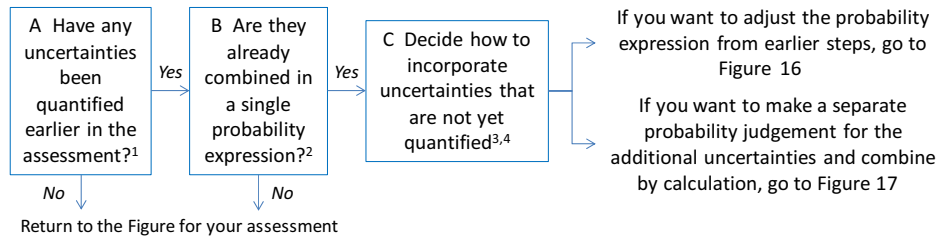


Figure 15: Deciding on approach for taking account of additional uncertainties

Text notes for Figure 15:

¹ The answer to this question should always be yes, as some parts should already have been quantified in the earlier Figures that direct the user to this Figures 3, 4, 8, 9 and 10. If not, return to the Figure for your assessment, combine the parts according to the guidance there, and return here if/when indicated.

² The answer to this question should always be yes, as some parts should already have been combined in the earlier Figures that direct the user to this Figure. If not, return to the Figure for your assessment, combine the parts according to the guidance there, and return here if/when indicated.

³ Even when uncertainties are quantified separately and combined earlier in the assessment, there will nearly always be additional uncertainties that need to be taken into account at this step, for example uncertainties about the structure of the model used for the combination step, or unquantified dependencies between the uncertainties. In addition, there may be other uncertainties that the assessors chose not to quantify earlier in the analysis, and left to be considered collectively here.

⁴ Two options are described for incorporating the additional uncertainties. Revising the probability expression from earlier steps by expert judgement (Figure 16, and Option 2 in Figure 14) is simpler and takes less time, but more approximate because it requires the assessors to make a subjective judgement about how the additional uncertainties will alter it. Making a separate probability judgement for the additional uncertainties and combining this with the earlier probability expression by calculation (Figure 17, and Option 3 in Figure 14) is more rigorous if an appropriate model can be specified.

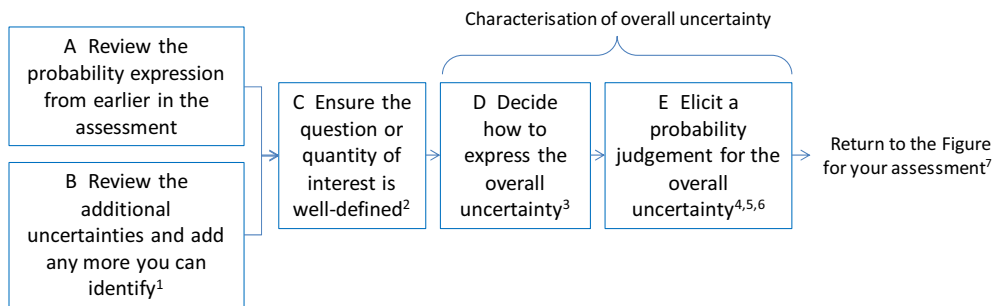


Figure 16: Revising a probability expression from earlier steps to take account of additional uncertainties

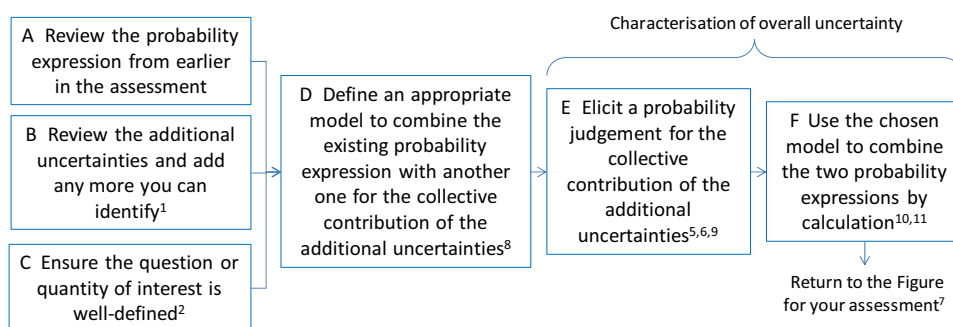


Figure 17: Evaluate additional uncertainties then combine with an earlier probability expression by calculation

Text notes for Figures 16 and 17 (presented together to avoid duplication of common items):

¹ See Section 7. For standardised assessments, only non-standard uncertainties need be considered, because other uncertainties (including the applicability of the standardised procedure and all its elements) are considered to be accepted as being adequately covered by the standardised procedure. For all other assessments, all identifiable sources of uncertainty must be considered, i.e. anything that contributes to the uncertainty of the question or quantity of interest. This includes all uncertainties affecting the inputs to the assessment or the methods used in the assessment, including (but not limited to) the types of uncertainty listed in Table 1 (Section 7.2). It includes, for example, the relevance, reliability and consistency of all the evidence used (EFSA, 2017), the suitability of any conceptual, logical, mathematical or statistical models or experimental models (e.g. model species or system) that were used, and the rigour of the methods used for making probability judgements (less formal methods are more approximate, see Section 12.6). It is recommended that assessors make a list or table of all the uncertainties they identify, indicating which are included in the probability expression from earlier in the assessment and which remain to be added. The latter will include most or all uncertainties relating to assessment methods.

Note that, if the question or quantity of interest is well-defined (Section 10) and has been accepted by decision-makers as a suitable basis for decision-making, then uncertainties about the assessment of the question or quantity of interest must be evaluated but uncertainties about the relevance of that question or quantity to decision-making are outside the scope of the uncertainty analysis, since the decision-makers have accepted it as relevant. This applies to all standardised assessments and to those case-specific assessments where the above condition is met. For example, if decisions are to be made about an EU-wide issue but decision-makers have accepted that an assessment for a specified subset of EU Member States is a suitable basis for their decision, uncertainties about extrapolation from the subset of Member states to the whole EU are outside the scope of the assessment.

² See Section 10. Here the question or quantity of interest is that for the assessment as a whole, not for one of its parts.

³ When additional uncertainties are incorporated by revising a probability expression from earlier in the assessment, this does not imply the revised expression must be in the same form as the earlier one. For example, if the earlier expression was a probability for a yes/no question or a probability distribution (Section 12.1) for a quantity of interest, it may be sufficient for decision-making – and easier for assessors – to use probability bounds (Section 12.2) or the approximate probability scale (Section 12.3).

⁴ Elicit the probability judgement using an appropriate method (Section 12.6). If the additional uncertainties are expected to be minor relative to those represented by the existing probability judgement, a less formal elicitation method may be sufficient. If the additional uncertainties are larger, a more formal method should be considered, especially if the overall uncertainty might have substantial implications for decision-making. When revising a probability expression from earlier in the assessment, special care must be taken to guard against the psychological bias of anchoring and adjustment (EFSA, 2014a) – which will tend to cause excessive anchoring on the earlier probability

expression and underestimation of the degree of adjustment needed to account for the contribution of the additional uncertainties. Assessors should be aware of this issue and take explicit steps to mitigate it in whatever elicitation method is chosen, e.g. make an initial assessment, then challenge it by discussing what sources of uncertainty might cause a larger adjustment to be needed, and revise it if appropriate. The reasoning for the final judgement should be documented.

⁵ Note that uncertainties relating to choices about models may be included in the probability judgement by considering how the true answer for the question or quantity of interest might differ from the result given by the chosen model. It is not necessary (and not possible) to specify or consider all other possible model choices. This applies to all types of models (conceptual, mathematical, statistical, experimental, etc.).

⁶ It is normal for assessors to feel uncertain about their probability judgements, even though precise subjective probabilities can in theory be given for any well-defined question or quantity of interest [SO5.10]. It is sometimes suggested that this leads to an 'infinite regress' where each probability judgement requires a further probability judgement. The approach in this Guidance is to take the uncertainty of the judgement into account when expressing the judgement. When using probability bounds (Section 12.2) or an approximate probability scale (Section 12.3), the assessors should choose an approximate probability that accommodates their uncertainty about their judgement. When expressing judgements as a precise probability or distribution, a practical approach is to make an initial judgement by whatever method has been chosen (Section 12.6), and then add an extra round of discussion or elicitation for assessors to consider whether their initial judgement needs adjustment to represent their additional uncertainty in making the judgement. Ultimately, the key consideration for assessors is whether they consider the final judgement to be an appropriate representation of what they can say about the question or quantity of interest, given the available evidence [see SO14].

⁷ Return to the Figure you were using in Sections 3, 4, 5 or 6.

⁸ The output of this step should comprise (a) specification of a well-defined scale for elicitation of the collective contribution of the additional uncertainties, and (b) a specified model for combining this with the probability expression from earlier in the assessment. Specifying these requires consideration of how the additional uncertainties would influence the uncertainty of the question or quantity of interest, and what dependencies (see Section 12.7) might exist between these uncertainties and those represented by the existing probability expression. If the dependencies were negligible, a simple model for a non-variable quantity of interest might be to elicit a probability distribution for how much the additional uncertainties might change the result of the assessment, expressed as a ratio. This distribution could then be multiplied with the existing probability expression by Monte Carlo simulation (Section 14.2) to produce a distribution representing the overall uncertainty. If non-negligible dependencies are thought to be present they will need to be specified and included in a more complex model (Section 14.2) or accommodated by using probability bounds analysis, which takes account of all possible forms of dependence (Section 14.1).

⁹ Elicit a probability judgement for the additional uncertainties on the scale defined in the preceding step, using appropriate forms of probability expression (Sections 12.1 or 12.2) and an appropriate elicitation method (Section 12.6). If the additional uncertainties are expected to be minor relative to those represented by the existing probability judgement, a less formal elicitation method may be sufficient. If the additional uncertainties are larger, a more formal method should be considered, especially if the overall uncertainty might have substantial implications for decision-making.

¹⁰ Combine the probability judgement from the preceding step with the probability expression from earlier in the assessment, using the model that was specified two steps before this one. The method for this will depend on the forms of the two probability expressions (which may differ).

¹¹ After combining the two probability expressions, assessors must consider whether there is an additional uncertainty (not yet quantified) about the form of the model they used to combine them. In particular, assessors should consider whether potential dependencies between the uncertainties are adequately described by the model. If they are uncertain about this, they should review the probability expression produced in this step and consider whether and how to adjust it to account for the extra uncertainty (this can be done by following the process in Figure 16, then returning to here). This procedure also offers a pragmatic solution if assessors expect dependencies but find it difficult to specify a model for them.

16.2. Uncertainties that remain unquantified

- 1) The Scientific Committee recommends that assessors express in quantitative terms the combined impact of as many as possible of the identified uncertainties, because this avoids the ambiguity of qualitative expression and therefore provides better information for decision-making [SO4.2]. In theory, probability judgements can be made for any well-defined question or quantity of interest [SO5.10].

- 2) However, it is recognised that in some assessments, there may be some uncertainties that assessors are unable to include in a probability judgement [SO5.12]. In such cases, assessors should produce a probability expression representing the uncertainties that they are able to include, and a qualitative description of the uncertainties that remain unquantified.
- 3) If any uncertainties remain unquantified, the quantitative evaluation of uncertainty will be conditional on whatever assumptions have been made about those unquantified uncertainties [SO5.13]. Assessors must choose what assumptions to make: making no explicit assumptions will result in implicit assumptions, often that the *unquantified uncertainty* has no effect on the question or quantity of interest.
- 4) If the assessors are unable to include the unquantified uncertainties in their probability expression, this implies that they can say nothing, even approximately, about how much those unquantified uncertainties might change the assessment conclusion. Therefore, assessors must avoid implying any judgement about this in their qualitative description of the unquantified uncertainties, for example that they are negligible, minor, large, likely, unlikely, etc. If the assessors feel able to use such words this implies that, based on expert judgement, they are in fact able to say something about the impact of those uncertainties. If so, they should return to and revise the probability judgement to include them, at least approximately.
- 5) It follows that any uncertainties that remain unquantified, and the assumptions made about them, must be documented explicitly in the assessment and summarised alongside the *quantitative expression of uncertainty*. This is essential, to provide a proper characterisation of the overall uncertainty. The body of the assessment should include a more detailed description of each unquantified uncertainty, without implying any judgement about their magnitude or likelihood. Assessors should state which parts of the assessment they affect, describe their causes, explain why it was not possible to include them in the quantitative evaluation, state what assumptions have been made about them, and identify any options for reducing them or making them quantifiable [SO5.13].
- 6) All scientific assessments, whoever they are done by, are conditional on the expertise of assessors and the scientific knowledge available to them. EFSA addresses this by using appropriate procedures to select experts for participation in assessments, and additional procedures to select experts for participation in expert knowledge elicitation (EFSA, 2014a). In addition, uncertainty analysis represents those uncertainties that the assessors are able to identify and cannot, by definition, include 'unknown unknowns'. Decision-makers should be aware that these forms of conditionality are general, applying to all scientific assessment, and it is therefore not necessary to specify them in each assessment report.

17. Addressing uncertainty in conclusions and reporting

- 1) For standard assessments where no case-specific sources of uncertainty have been identified, the EFSA output must at minimum state what standardised procedure was followed and report that non-standard uncertainties were checked for and none were found (Section 3.1). If the applicability of the standardised procedure to the case in hand is not self-evident, then an explanation of this should be provided. If non-standard uncertainties are found, the assessors should report that standard uncertainties in the assessment are accepted to be covered by the standardised procedure and the uncertainty analysis is therefore restricted to non-standard uncertainties that are particular to this assessment, the analysis of which should then be reported as described below.
- 2) In all other assessments, the uncertainty analysis should be reported as described below, although the level of detail may be reduced due to time constraints in *urgent assessments*.
- 3) Uncertainty analysis is part of scientific assessment; so in all cases, it should be reported in a manner consistent with EFSA's general principles regarding transparency (EFSA, 2007b, 2009) and reporting (EFSA, 2014b, 2015). In particular, it is important to list the sources of uncertainty that have been identified and document how they were identified, how each source of uncertainty has been evaluated and how they have been combined, where and how data and expert judgement have been used, what methodological approaches have been used (including models of any type) and the rationale for choosing them, and what

the results were. Where the assessment used methods that are already described in other documents, it is sufficient to refer to those.

- 4) The location of information on the uncertainty analysis within the assessment report should be chosen to maximise transparency and accessibility for readers. This may be facilitated by including one or more separate sections on uncertainty analysis, which are identifiable in the table of contents.
- 5) The Scientific Committee has stated that EFSA's scientific assessments must report clearly and unambiguously what sources of uncertainty have been identified and characterise their overall impact on the assessment conclusion, in a form compatible with the requirements of decision-makers and any legislation applicable to the assessment in hand [SO1.4].
 - a) In some types of assessment, decision-makers or legislation may stipulate a specified form for reporting assessment conclusions. In some cases, this may comprise qualitative descriptors such as 'safe', 'no concern', 'sufficient evidence', etc. To enable these to be used by assessors without implying risk management judgements requires that assessors and decision-makers have a shared understanding or definition of the question or quantity of interest and level of certainty associated with each descriptor.
 - b) In other cases, decision-makers or legislation may require that conclusions be stated without qualification by probability expressions. This can be done if assessors and decision-makers have a shared understanding or definition of the level of probability required for *practical certainty* about a question of interest, i.e. a level of probability that would be close enough to 100% (answer is certain to be yes) or 0% (certain to be no) for decision-making purposes. On issues where practical certainty is not achieved, the assessors would report that they cannot conclude, or that the assessment is inconclusive.

In such cases, assessors should also comply with any requirements of decision-makers or legislation regarding where and how to document the details of the uncertainty analysis that led to the conclusion.

- 6) In other cases, where the form for reporting conclusions is not specified by decision-makers or legislation, the assessment conclusion should include (a) a clear statement of the overall result for those uncertainties that have been quantified and (b) a clear description of unquantified sources of uncertainty, i.e. those that could not be included in the quantitative analysis. The former will generally express the overall quantified uncertainty about the assessment conclusion using probabilities, probability distributions, probability bounds, or ranges from the approximate probability scale (Sections 12.1–12.3). For each unquantified source of uncertainty, the assessors should describe (either in the conclusion or another section, as appropriate) which part(s) of the assessment it arises in, the cause or reason for it, how it affects the assessment (but not how much), why it is difficult to quantify, what assumptions have been made about it in the assessment and what could be done to reduce or better characterise it. Assessors must avoid using any words that imply a judgement about the magnitude or likelihood of the unquantified sources of uncertainty (Section 16.2).
- 7) In addition to the detailed reporting of the methods and results of the uncertainty analysis, the assessors should prepare a concise summary of the overall characterisation of uncertainty in format and style suitable for inclusion in the executive summary of the assessment report. This should present, in the simplest terms possible, a quantitative expression of the combined effect on the assessment conclusion of those uncertainties that have been quantified, and a brief description of any unquantified sources of uncertainty.
- 8) Assessors must check that there is no incompatibility between the reporting of the uncertainty analysis and the assessment conclusions. In principle, no such incompatibility should occur, because sound scientific conclusions will take account of relevant uncertainties, and therefore should be compatible with an appropriate analysis of those uncertainties. If there appears to be any incompatibility, assessors should review and if necessary revise both the uncertainty analysis and the conclusion to ensure that they are compatible with one another and with what the science will support.
- 9) In many assessments, information on the main contributors to the uncertainty of the question or quantity of interest may be useful to decision-makers, to inform decisions about the need for further work such as data gathering, to support refinement of the assessment. Such information may be generated by methods for prioritising uncertainties (Section 8).

- 10) Communicating uncertainty is discussed in [SO16] and guidance on communication to different target audiences including decision-makers is the subject of another companion document (EFSA, 2018b, in prep.).

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Glossary

Additional uncertainties	Term used when some uncertainties have already been quantified, to refer to other uncertainties that have not yet been quantified and need to be taken into account in the characterisation of overall uncertainty
Ambiguity	The quality of being open to more than one interpretation. A type or cause of uncertainty that may apply for example to questions for assessment, evidence, models or concepts, and assessment conclusions
Approximate probability	A range or bound for a probability
Approximate probability scale	A set of approximate probabilities with accompanying verbal probability terms, shown in Section 12.3 of the Guidance and recommended for harmonised use in EFSA scientific assessments
Assessment factor	A numerical factor used in quantitative assessment, to represent or allow for extrapolation or uncertainty
Assessor	A person conducting a scientific assessment and/or uncertainty analysis
Calibration	Used in the Guidance to refer to the process of evaluating whether a standardised procedure is appropriately conservative and, if necessary, adjusting it to achieve this. More specifically, the process of ensuring a standard procedure provides an appropriate probability of achieving a specified management objective to an acceptable extent

Case-specific assessment	Scientific assessments where there is no pre-established standardised procedure, so the assessors have to develop an assessment plan that is specific to the case in hand. Standardised elements (e.g. default values) may be used for some parts of the assessment, but other parts require case-specific approaches. Both standardised and case-specific assessments are used in Applications Management, one of the core processes in EFSA's Process Architecture
Categorical question	An assessment question that is expressed as a choice between two or more categories, e.g. yes/no or low/medium/high. Many issues that are expressed as categorical questions refer explicitly or implicitly to quantities (e.g. whether exposure is below a threshold value)
Characterising uncertainty	The process of making and expressing an evaluation of uncertainty either for an assessment as a whole or for a specified part of an assessment. Can be performed and expressed either qualitatively or quantitatively
Collective	Used in this document to refer to evaluating the combined impact of two or more uncertainties together
Combine uncertainties	The process of integrating separate characterisations of two or more uncertainties to produce a characterisation of their combined impact on an assessment or part of an assessment. Can be performed by calculation or expert judgement, and in the latter case either quantitatively or qualitatively
Conceptual model	The reasoning developed by assessors in the course of a scientific assessment, which is then implemented as a narrative argument, a logic model, a calculation or a combination of these. Documenting the conceptual model, e.g. as a bullet list, flow chart or graphic, may be helpful to assessors during the assessment and also for readers, if included in the assessment report
Conditional	Used in the Guidance to refer to dependence of the quantitative result of an assessment or uncertainty analysis on assumptions made about sources of uncertainty that have not been quantified
Conservative	Term used to describe assessments, or parts of assessments (e.g. assumptions, default factors, etc.), that tend to overestimate the severity and/or frequency of an adverse consequence (e.g. overestimate exposure or hazard and consequently risk). Can also be used to refer to underestimation of a beneficial consequence. Conservatism is often introduced intentionally, as a method to allow for uncertainty
Decision-maker	A person with responsibility for making decisions; in the context of this document, a person making decisions informed by EFSA's scientific advice. Includes risk managers but also people making decisions on other issues, e.g. health benefits, efficacy, etc
Default value or factor	Pragmatic, fixed or standard value used in the absence of relevant data, implicitly or explicitly regarded as accounting appropriately for the associated uncertainty
Dependency	Variable quantities are dependent when they are directly or indirectly related, such that the probability of a given value for one quantity depends on the value(s) of other quantities (e.g. food consumption and body weight). Sources of uncertainty are dependent when learning more about one would alter the assessors' uncertainty about the other
Distribution	A probability distribution is a mathematical function that relates probabilities with specified intervals of a continuous quantity or values of a discrete quantity. Applicable both to random variables and uncertain parameters
Evidence appraisal	The process of evaluating the internal validity of evidence and its external validity for the question at hand, in addition to other sources of uncertainties such as imprecision
Expert group judgement	The process of eliciting a judgement or judgements from a group of experts without using a formal or semi-formal elicitation procedure

Expert judgement	The judgement of a person with relevant knowledge or skills for making that judgement
Expert knowledge elicitation (EKE)	A systematic, documented and reviewable process to retrieve expert judgements from a group of experts, often in the form of a probability distribution
External validity	Extent to which the findings of a study can be generalised or extrapolated to the assessment question at hand. It is not an inherent property of the evidence
Identifying uncertainties	The process of identifying sources of uncertainty affecting a scientific assessment
Individual expert judgement	The process of eliciting a judgement or judgements from a single expert without using a formal or semi-formal elicitation procedure
Influence analysis	The extent to which plausible changes in the overall structure, parameters and assumptions used in an assessment produce a change in the results
Logic model	A model expressing a yes/no conclusion as a logical deduction from the answers to two or more yes/no questions
Management objective	A well-defined expression of the outcome required by decision-makers from a decision, policy or procedure, specifying the question or quantity of interest and the temporal and spatial scale for which it should be assessed. Applied in the Guidance to the calibration of standardised procedures
Model	In scientific assessment, usually refers to a mathematical or statistical construct, which is a simplified representation of data or of real world processes, and is used for calculating estimates or predictions. Can also refer to the structure of a reasoned argument or qualitative assessment
Monte Carlo: one-dimensional	A method for making probability calculations by random sampling from one set of distributions, all representing uncertainty about non-variable quantities or categorical questions
Monte Carlo: two-dimensional	A method for making probability calculations by random sampling from two sets of distributions, one set describing the variability of variable quantities, and the second set representing uncertainty, including uncertainty about the parameters of the distributions describing variability
Non-standard uncertainties	Any deviations from a standardised procedure or standardised assessment element that lead to uncertainty regarding the result of the procedure. For example, studies that deviate from the standard guidelines or are poorly reported, cases where there is doubt about the applicability of default values, or the use of non-standard or 'higher tier' studies that are not part of the standard procedure
Non-variable quantity	A quantity that has a single real or true value
Ordinal scale	A scale of measurement comprised of ordered categories, where the magnitude of the difference between categories is not quantified
Overall uncertainty	The assessors' uncertainty about the question or quantity of interest at the time of reporting, taking account of the combined effect of all sources of uncertainty identified by the assessors as being relevant to the assessment
Parameter	Parameter is used in this document to refer to quantitative inputs to an assessment or uncertainty analysis, without specifying whether they are variable or not. In most places a non-variable quantity is implied, consistent with the use of parameter in statistics. However, in some places parameter could refer to a variable quantity, as it is sometimes used in biology (e.g. glucose level is referred to as a blood parameter)
Parts of the scientific assessment	Components of a scientific assessment that it is useful to distinguish for the purpose of assessment, e.g. a risk assessment comprises hazard and exposure assessment, and each of these can be subdivided further (e.g. to distinguish individual model parameters, studies, or lines of evidence)

Parts of the uncertainty analysis	Parts of an uncertainty analysis that it is useful to distinguish, evaluating uncertainties within each part collectively, and then combining the parts and any additional uncertainties to characterise overall uncertainty. Not necessarily the same as the parts into which the scientific assessment is divided (see text)
Practical certainty	A level of probability that would be close enough to 100% (answer is certain to be yes) or 0% (certain to be no) for the purpose of decision-making. What levels of probability will comprise practical certainty will vary, depending on the context for the decision including the decision options and their respective costs and benefits
Prioritising uncertainties	The process of evaluating the relative importance of different sources of uncertainty, to guide decisions on how to treat them in uncertainty analysis or to guide decisions on gathering further data with the aim of reducing uncertainty. Prioritisation is informed by influence or sensitivity analysis
Probability	Defined depending on philosophical perspective: (1) the frequency with which sampled values arise within a specified range or for a specified category; (2) quantification of judgement regarding the likelihood of a particular range or category
Probability bound	A probability or approximate probability for a specified range of values
Probability bounds analysis	A method for combining probability bounds for inputs in order to obtain a probability bound for the output of a deterministic model. It is a special case of the general theory of imprecise probability which provides more ways to obtain partial expressions of uncertainty for the output based on more general partial expressions for inputs
Probability judgement	A probability, approximate probability or probability bound obtained by expert judgement
Protection goal	A management objective for protection of an entity of interest
Qualitative assessment	Sometimes refers to the form in which the conclusion of an assessment is expressed (e.g. a verbal response to a question of interest), or to the methods used to reach the conclusion (not involving calculations), or both
Qualitative expression of uncertainty	Expression of uncertainty using words or ordinal scales
Quantitative expression of uncertainty	Expression of uncertainty using numeric measures of the range and relative likelihood of alternative answers or values for a question or quantity of interest
Quantity	A property or characteristic having a numerical scale
Quantity of interest	A quantity that is the subject of a scientific assessment as a whole, or of a part of such an assessment
Question of interest	A categorical question that is the subject of a scientific assessment as a whole, or of a part of such an assessment
Real value	A synonym for true value (q.v.)
Resolved	The actual or hypothetical process of removing an uncertainty by making the measurement or observation needed to obtain the true answer or value for the question or quantity of interest
Risk management judgement	The process or result of weighing policy alternatives in consultation with interested parties, considering risk assessment and other legitimate factors, and, if need be, selecting appropriate prevention and control options
Risk manager	A type of decision-maker, responsible for making risk management judgements
Scientific assessment	The process of using scientific evidence and reasoning to answer a question or estimate a quantity
Scope (for non-standard uncertainties)	The degree to which a standardised procedure was calibrated to be more conservative than required (e.g. by rounding up an assessment factor), which determines how much opportunity there will be to accommodate the presence of non-standard uncertainties in individual assessments
Semi-formal expert knowledge elicitation	A structured and documented procedure for eliciting expert judgements that is intermediate between fully formal elicitation and informal expert judgements

Sensitivity analysis	A study of how the variation in the outputs of a model can be attributed to, qualitatively or quantitatively, different sources of uncertainty or variability. Implemented by observing how model output changes when model inputs are changed in a structured way
Standard uncertainties	Sources of uncertainty that are considered (implicitly or explicitly) to be addressed by the provisions of a standardised procedure or standardised assessment element. For example, uncertainties due to within and between species differences in toxicity are often addressed by a default factor of 100 in chemical risk assessment
Standardised assessment	An assessment that follows a standardised procedure (q.v.)
Standardised procedure	A procedure that specifies every step of assessment for a specified class or products or problems, and is accepted by assessors and decision-makers as providing an appropriate basis for decision-making. Often (but not only) used in scientific assessments for regulated products. Both standardised and case-specific assessments are used in Applications Management, one of the core processes in EFSA's Process Architecture
Statistical model	A probabilistic model of variability, possibly modelling dependence between variables or dependence of one variable on another, for example a family of probability distributions representing alternative possible distributions for a variable or regression or dose-response models. Usually has parameters which control the detail of distributions or dependence
True value	The actual value that would be obtained with perfect measuring instruments and without committing any error of any type, both in collecting the primary data and in carrying out mathematical operations. (OECD Glossary of Statistical Terms, https://stats.oecd.org/glossary/detail.asp?ID=4557)
Uncertainty	In this document, uncertainty is used as a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question. Available knowledge refers here to the knowledge (evidence, data, etc.) available to assessors at the time the assessment is conducted and within the time and resources agreed for the assessment. Sometimes 'uncertainty' is used to refer to a source of uncertainty (see separate definition), and sometimes to its impact on the conclusion of an assessment
Uncertainty analysis	The process of identifying and characterising uncertainty about questions of interest and/or quantities of interest in a scientific assessment
Unknown unknowns	A limitation of knowledge that one is unaware of
Unquantified uncertainty	An identified source of uncertainty in a scientific assessment that the assessors are unable to include, or choose not to include, in a quantitative expression of overall uncertainty for that assessment
Urgent assessment	A scientific assessment requested to be completed within an unusually short period of time. Part of Urgent Responses Management in EFSA's Process Architecture
Variability	Heterogeneity of values over time, space or different members of a population, including stochastic variability and controllable variability. See [SO5.3] for discussion of uncertainty and variability
Variable quantity	A quantity that has multiple true values (e.g. body weight measured in different individuals in a population, or in the same individual at different points in time)
Weight of evidence assessment	A process in which evidence is integrated to determine the relative support for possible answers to a scientific question
Well defined	A question or quantity of interest that has been defined by specifying an experiment, study or procedure that could be undertaken, at least in principle, and would determine the question or quantity with certainty