31 March 2023

Guiding principles for uncertainty analysis in Annex XV Restriction Reports

– a proposal based on EFSA's guidance material

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1. Introduction

Analysts aim to use the best available data to give the best advice possible. But many factors are uncertain, meaning that there is a range of possible values, and some are more likely than others.

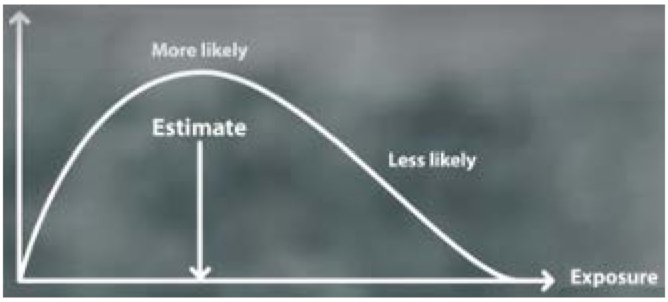

Figure 1. Probability distribution of exposure levels[1]

As shown in the example distribution in Figure 1, there is a chance of exposure being above an estimated level as well as a chance of it being below this estimate. The confidence of the analyst in their conclusions is dependent on the understanding of the possible impacts of what is not known.

Uncertainties can be understood as "all types of limitations in the knowledge available to analysts at the time an assessment is conducted and within the time and resources available for the assessment".

Examples of commonly encountered uncertainties include:

- Limitations in the quality and representativeness of data,
- Comparisons of non-standardised data across countries or categories,
- The choice of one predictive modelling technique over another, or
- The use of default factors (such as the weight of an average adult).

Uncertainties can have an important impact on regulatory decisions. For example, if the probability of exposure exceeding an estimated level is high, decision-makers may put in place (adjusted) regulatory measures to limit exposure. Where decision-makers rely on analysts to provide comprehensive scientific assessments and advice, the information presented to decision-makers should therefore comprise more than a point estimate. Additional information on the range of possible outcomes and their relative likelihood enables the analyst to highlight the impacts of uncertainty on the recommendations made and ensures that decisions are based on robust conclusions.

It is important to emphasise that reporting information on uncertainties of regulatory impact assessment is not a failure but an integral component of better decision making.

The structural use of uncertainty analysis in assessments aims to identify and describe uncertainties and explain the resulting implications for decision-making systematically and transparently. The choice of methodology is relevant because the outcome of the uncertainty analysis will likely affect perceptions about risks and benefits. Hence, in facilitating good practices of uncertainty analysis, it is useful to establish a standardised framework of sound principles and methods as well as guidance on how to communicate

[1] See: https://www.efsa.europa.eu/en/topics/topic/uncertainty-scientific-assessments

uncertainty in a scientific report.

1.1. Context of REACH Restriction

Member States of the European Union or the European Chemicals Agency (ECHA) on request of the European Commission may propose a union-wide restriction of particular substance uses. These actors are also referred to as Dossier Submitters. As for any other scientific assessment, it is important that the proposal of a restriction under REACH includes an analysis of encountered uncertainties and their impacts on the main conclusions of the Restriction Report.

Supported by ECHA's experts, the scientific committees for risk assessment (RAC) and socio-economic analysis (SEAC) form opinions on restriction proposals, including the analysis of uncertainties. These opinions provide scientific advice to the European Commission on regulatory decisions concerning union-wide restrictions of substance uses.

Ultimately, the outcome of an uncertainty analysis will support the Commission in assessing whether regulatory action is warranted on the basis of available information.

1.2. Purpose of this document

This document aims to summarise principles and methods for uncertainty analysis and provide exemplary wording for effective communication of uncertainties in Restriction Reports and opinions. The resulting toolbox is supposed to help the Dossier Submitters to streamline their analysis of uncertainties, ensure equal treatment of uncertainties across cases, and foster public trust in their activities.

Based on this document, Dossier Submitters should be able to identify, clearly characterise, evaluate, and communicate all relevant uncertainties. This requires information on:

- Which elements are uncertain (e.g. hazards and risks, functionalities and uses, emissions and exposure, the availability of alternative substances and technologies, or the estimation of the socio-economic impacts of a restriction),
- Why these elements are uncertain,
- What was done by the Dossier Submitter to reduce a specific element of uncertainty and what needs to be done beyond that to properly address the identified uncertainties,
- How long would it take and how costly would it be to generate sufficient additional information to fill the identified gap(s),
- What is the remaining impact of identified uncertainties on the regulatory action that is being proposed by the Dossier Submitter.

1.3. How to use this document

1.3.1. Methods

This document builds on existing guidance published by the European Food Safety Authority (EFSA) on uncertainty analysis[2] and the communication of uncertainty in scientific assessments[3]. More specifically, the methodology and proposed standard

[2] EFSA's Guidance on Uncertainty Analysis in Scientific Assessments available here: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5123

[3] EFSA's Guidance on Communication of Uncertainty in Scientific Assessments available here: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2019.5520

wording provided in this document aim to apply the findings of EFSA's approach to dealing with uncertainties in the context of REACH Restrictions and thus make EFSA's methods operational in the field of restrictions.

Where more detailed information and guidance on underlying concepts is needed, readers are referred to EFSA's publication on the principles and methods behind their guidance on uncertainty analysis[4].

In line with the existing best practices, the defined methodology for uncertainty analysis conducted by Dossier Submitters aims to use a quantitative or semi-quantitative approach as, according to EFSA, quantitative expressions of uncertainty (e.g. in terms of percentages) tend to be more universally understood and easier to interpret than qualitative expressions. For cases in which uncertainties are not quantifiable at all, an appropriate qualitative approach to uncertainty analysis may be adopted.

1.3.2. Steps and tasks, definitions and standard wording

In the best case, this document may function as a step-by-step manual that walks the reader through the process of implementing an uncertainty analysis for a Restriction Report. Each step is further divided into more detailed tasks that can be followed chronologically and that provide additional information and explanations where useful. Some tasks contain decision trees that are meant to guide the reader in the appropriate direction of further analysis. It should be noted that each assessment is unique and that the Dossier Submitter may find that a modification of the process increases the conclusiveness of the analysis.

The document also contains definitions of key terms and concepts that are relevant to undertaking an uncertainty analysis and that may help the user to better understand the related steps and terminology. Definitions are based EFSA's guidance for uncertainty analysis (see section 1.3.1 of this document) and are presented in the style demonstrated below.

Term	Definition of the term

This document further aims to serve the user with exemplary wording that can be used as standard wording in sections of a Restriction Report. It is important to note that this wording is meant to provide inspiration for how to structure and report the uncertainty analysis and is unlikely to be a perfect fit for every case. It is therefore necessary that Dossier Submitters adjust the detailed reporting of their uncertainty analysis reflecting the context for their assessment. The proposed standard wording is presented in blue font under the following heading.

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This structure is meant to enable efficient work on the Restriction Report more or less in

[4] The principles and methods behind EFSA's Guidance on Uncertainty Analysis in Scientific Assessments available here:
https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5122

parallel to the review of this document.

1.3.3. Fit-for-purpose use of the document

The following points may help to achieve "fit-for-purpose" use by the user of the guiding principles in this document:

- The purpose of the scientific assessment (i.e. the Restriction Report) is to inform the decision maker about different regulatory options, their impacts on EU society and their comparative and overall proportionality. The level of information detail on uncertain elements (i.e. variables and choices) in the assessment that is needed to achieve this objective is likely to vary across different sources of uncertainty and across different Restriction Reports.

- Although this document aims to serve as a step-by-step manual for the analysis that also provides inspiration and building blocks for the text of the uncertainty analysis, it is not meant to be prescriptive, and the Dossier Submitter should always feel encouraged to adjust the approach of the analysis as to better fit the unique context of each assessment.

In more concrete terms this means:

- The number and type of uncertainties described in the Dossier Submitter's assessment should first and foremost reflect the focus on what the decision maker needs to be informed about.

- In some cases, a targeted consideration of sensitivities and influences on the overall conclusions of the Dossier Submitter's assessment is sufficient to show that the assessment is robust to identified uncertainties.

- If, however, the Dossier Submitter finds that relevant uncertainties do have potential to change the conclusions of their assessment, then targeted investment of resources in the analysis of the likelihood of that happening may be warranted and even desired for the sake of decision making.

- It is the Dossier Submitter who is best positioned to judge the effectiveness of their assessment in serving decision making. Yet, without lowering the objective of the assessment, the use of qualitative uncertainty analysis (without the involvement of quantitative probability judgements) may not necessarily be easier. This is because *simplified* qualitative methods tend to be less effective and knowledge about *advanced* qualitative methods may not be spread as widely as knowledge about standard quantitative approaches. While qualitative approaches are covered in this document, it should be considered whether involvement of experts on qualitative analysis would be more beneficial for the conclusiveness of the uncertainty analysis (especially when action is taken early enough).

- If a Dossier Submitter finds other ways to inform the decision maker about any uncertainties affecting their decision or even ways to reduce the uncertainty, i.e. an approach that is different from the steps covered by this document, it can be good to pursue such a path. The Dossier Submitter may not have run out of opportunities to optimise their scientific assessment and underlying data use, which could remediate causes of uncertainty. Or the Dossier Submitter may become aware of additional approaches of handling remaining uncertainty that are not described yet in this document.

2. Uncertainty analysis in Annex XV Restriction Reports

Uncertainty analysis	The process of identifying and characterising uncertainty about questions of interest and/or quantities of interest in a scientific assessment
Scientific assessment	The work subject to uncertainty analysis, in this context, the Annex XV Restriction Report

2.1. Step 1 – Identify uncertainties

Uncertainty	All types of limitations in the knowledge available to analysts during the assessment (e.g. resulting from time and resources available) that affect the range and probability of possible answers to the assessment question

Task 1.1: Systematically examine every part of the Restriction Report for uncertainties, including inputs to the assessment (e.g. evidence[5] from literature or data bases) and methodologies used in the assessment (e.g. statistical methods, calculations or models, reasoning or expert judgement).

To get an overview of potential uncertainties, check Table 1. Please be alert to any additional types of uncertainty that may not be listed in the table.

Table 1. Non-exhaustive collection of examples of uncertainties[6].

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

When screening for uncertainties, it may be of help to think about what the assessment in the Restriction Report would look like with complete knowledge (i.e. in the absence of

[5] See: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5122 – Page 230ff.

[6] See: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5122 – Page 44ff.

uncertain elements).

Note that it is not the goal of the screening to find uncertainty in all inputs or selected approaches to the assessment (applying the mindset “nothing is certain”). The selection of a list of relevant uncertainties is linked to the (realistic) expectation that the commissioner of assessment has towards the outcome of the scientific assessment. The exercise of identifying uncertainties should result in a basic list of elements that an objective reader would be interested to be informed about before using the outcome of the Restriction Report. At the same time, it is important to note that further prioritisation and in-depth analysis will follow in later steps of the uncertainty analysis. Hence, it is not recommended either to narrow down the list of considered elements prematurely (based on “gut feeling”).

To read more about the distinction between uncertainties and potential ambiguity in the objectives of the assessment, the reader is referred to Appendix A.

Task 1.2: Present and describe identified uncertainties.

Once the Dossier Submitter has obtained a clear picture of uncertain elements, the aim of this step is to describe the identified uncertainties in a way that allows the readers of the report to gain a good understanding of the sources of uncertainty. It should cover the nature and causes of uncertainty for instance.

It is recommendable to number identified uncertainties and use invariable numbering to refer to individual uncertainties throughout the analysis. For a clear overview, provide a short summary of all identified uncertainties in an overview table and then elaborate further on the description and explanation of each uncertainty below the table.

See the following example wording and tables for use in the Restriction Report.

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3. ASSUMPTIONS, UNCERTAINTIES AND SENSITIVITIES

3.1 IDENTIFICATION OF UNCERTAINTIES

In this section, the Dossier Submitter assesses how uncertainties related to the key assumptions of the impact assessment presented in the Annex XV Restriction Report would affect the conclusions about the restriction options. The analysis of uncertainties is based on EFSA’s guidance on uncertainty analysis and the communication of uncertainty in scientific assessments[7].

Based on the examination of every part of the previous assessment, a list of identified uncertainties was compiled. Both uncertainties associated with the assessment inputs (e.g. data, estimates, other evidence) and uncertainties related to the methodologies (e.g. statistical methods, calculations or models, reasoning, expert judgement) applied to the scientific assessment were considered. Table 2 summarises the identified uncertainties.

[7] See: https://www.efsa.europa.eu/en/topics/topic/uncertainty-scientific-assessments

Table 2. Identified uncertainties in the assessment

Section of the Restriction Report	Identified uncertainties		Source of uncertainty	
	No.	Description of the uncertainty	Assess-ment input	Assess-ment metho-dology
[Section 1.4, Baseline]	1	[..., e.g.: Quantity of Product X placed on the EU market is unknown and difficult to approximate.]	[X]	
	2	[..., e.g.: The calculation of the cost of lost jobs lacks required information about the real gross wages of dismissed employees. A variety of different positions within a company are affected.]		[X]
[...]	[...]	[...]	[X]	[X]

Section [X] of the Restriction Report uses [...] as an input to the assessment. This results in uncertainty about [...] because [...].

Section [X] of the Restriction Report uses [Methodology X] to carry out the assessment of [...]. This results in uncertainty about [...] because [...].

Uncertainty No. [X] in Table 2 results from the assumption that [...] in section [X] of the Restriction Report. This assumption is subject to uncertainty about [...] because [...].

Task 1.3: Determine which of the identified uncertainties are standard uncertainties and which are other (non-standard) uncertainties.

Standard uncertainties	Uncertainties that are explicitly or implicitly addressed by the provisions of a standardised procedure/assessment element, i.e. should have been assessed when the standardised procedure was established (if not, the uncertainty is a non-standard uncertainty)
Non-standard uncertainties	Uncertainties that are not addressed by any standardised procedure/assessment element and are thus not covered by any allowances for uncertainty that would be built into the standard procedure (e.g. doubt about applicability of default values)

In case some of the identified uncertainties represent standard uncertainties, it is useful to comment on the distinction between standard and non-standard. This is because there is a potential to take a shortcut in the analysis of standard uncertainties because they are by definition inputs or methodological elements which are already sufficiently addressed by the standardised procedure which they are part of. In practice this means that, after explaining clearly why they are considered to be standard uncertainties and how the standard procedure has taken care of them, the subsequent analysis of uncertainties can be focused on the remaining non-standard uncertainties.

Decision tree 1: Based on your screening, are there any standard uncertainties that can be separated from the rest of the analysis?

No: Continue with Step 2.

Yes: Communicate the handling of standard uncertainties in the Restriction Report. Review the following example wording and tables for the distinction of standard uncertainties in order to complete the identification of uncertainties in section 3.1 of the Restriction Report.

Note that the information in Table 3 (categorisation of uncertainties as standard and non-standard uncertainties; see below) can be merged with Table 2 (description of identified uncertainties; see Task 1.2) for a leaner analysis. The following example wording is kept separately in this document because, in line with the decision tree above, documentation of conclusions on standard uncertainties in the Restriction Report can be skipped when all uncertainties are considered non-standard.

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3.1 Identification of uncertainties (continued)

The identified uncertainties in Table 2 were further categorised into standard[8] and non-standard uncertainties (see Table 3).

Table 3. Categorisation of identified uncertainties

Identified uncertainties		Standard (S) vs. non-standard (NS) uncertainties
1	[..., e.g.: Unknown quantity of Product X placed on the EU]	[NS]
2	[..., e.g.: Uncertainty about the cost of lost jobs]	[S]
[...]	[...]	[S/NS]

The described uncertainty about [..., e.g. the cost of 500 000 jobs lost in Restriction Option 2 and 3] represents a standard uncertainty because it is [explicitly/implicitly] provided for

[8] Standard uncertainties are considered to be explicitly or implicitly addressed by the provisions of a standardised procedure or standardised assessment element. Normally, standard uncertainties do not need to be re-evaluated in each assessment that follows the defined standard procedure because they should have been assessed when the standard procedure was established. If this is not the case, the uncertainty is a non-standard uncertainty.

by the standardised procedure used for assessing [Element X].

This is done by [...]

- ☐ using specified criteria for [..., *e.g. the gathering of appropriate/robust data*]
- ☐ using defined standard assessment factors or default values that address [..., *e.g. data limitations*]
- ☐ [...].

The procedure put in place by the standardised assessment method can therefore be considered to incorporate adequate provision for these standard uncertainties and the result of the assessment should be sufficiently robust to corresponding sources of uncertainty. Standard uncertainties are not analysed further in this uncertainty analysis.

The rest of the identified uncertainties can be considered non-standard uncertainties. As they are not addressed by any standardised assessment procedures, the identified non-standard uncertainties must be analysed in a case-specific way. This is done in the subsequent steps of the uncertainty analysis.

2.2. Step 2 – Prioritise uncertainties

Prioritisation of uncertainties	The process of evaluating the relative importance of different sources of uncertainty to guide decision on how to treat them in the uncertainty analysis or to guide decisions on gathering further data with the aim of reducing uncertainty
Sensitivity analysis	A qualitative or quantitative study of how the variation in the outputs of a model can be attributed to different sources of variability or uncertainty – how does model output change when model inputs are changed in a structured way
Model	An analytical construct used as a simplified representation of information or a process in order to estimate or predict certain outputs, e.g. a mathematical formula or statistical construct in an assessment or the structure of a reasoned argument or qualitative assessment
Influence analysis	Analysis of the extent to which plausible changes in the overall structure, parameters and assumptions used in an assessment produce a change in the results and conclusions

Task 2.1: Analyse sensitivities of intermediate results (e.g. of the output of a model used for calculation) to the uncertain elements, i.e. to the possible range of inputs and/or methodological choices that were reported as identified uncertainties.

At this stage, sensitivity analysis aims to show the consequence of using other possible inputs and/or methodological choices than those used in the main part of the Restriction Report. This is done separately for each identified uncertainty by:

1. Defining the range of values or choices that are considered possible,

2. Repeating relevant calculations under consideration of the full range of different possible inputs and/or methodological choices, and

3. Comparing the differences in the intermediate results of the relevant models.

When determining the range of different possible inputs and/or methodological choices to be tested for each identified uncertainty, it is recommended to select at minimum the best and worst case. Additionally, any other deviating inputs and/or methodological choices that can be considered particularly relevant should be included in the sensitivity analysis (e.g. mean or median).

If a quantitative sensitivity analysis is not possible, the different scenarios for each uncertain element and the consequences for a part of the assessment should at least be analysed qualitatively based on expert judgment.

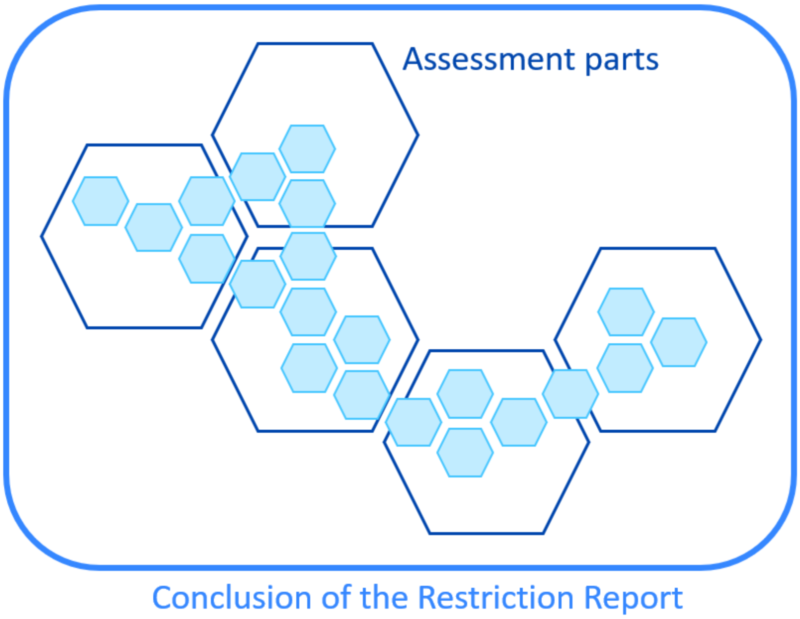
Avoid repetitions of the general descriptions of the uncertainties (Step 1) and instead focus the analysis on:

- The circumstances under which the assumptions about each uncertain element differ and how they would differ

- The knock-on effects on other relevant variables or choices (e.g. chain of reasoning) in the same part of the assessment

- The different outcomes for a relevant part of the assessment that may be expected as a consequence

Note that Task 2.1 looks at sensitivities between several elements in a relevant part of the assessment, whereas the impact on the overall results and conclusions of the Restriction Report are covered in Task 2.2.



Task 2.2: Analyse the influence of uncertainties on the results and conclusions of the Restriction Report.

Influence analysis builds on the performed sensitivity analysis by reviewing the pathways and thresholds for different inputs and/or methodological choices in the assessment to affect other parts of the assessment and ultimately the overall results and conclusions of the Restriction Report (not only the intermediate output variables). Hence, the analysis of influences covers the whole cascade of effects that could start with a variation in an uncertain value or choice. This is done by:

1. Describing the cascade of effects triggered by a change in an uncertain element,

2. Measuring the impacts of assuming the best- and worst-case scenarios for each uncertainty on the results and conclusions of the Restriction Report (e.g. break even points), and

3. Performing a collective best-case and worst-case analysis demonstrating the change in the results and conclusions of the Restriction Report when all uncertain elements are set equal to their respective best-case assumptions and when set equal to their respective worst-case assumptions.

In the context of Point 3 it is useful to check for the special case in which there is no collective impact of the identified uncertainties on the assessment results and corresponding conclusions of the Restriction Report. In fact, the analysis of uncertainties may be cut short if all main results of the assessment are robust, no matter whether the best-case assumptions or the worst-case assumptions are applied to all uncertainties.

Decision tree 2: Did the collective best-case and worst-case analysis show potential for the uncertainties to change the results and conclusions of the Restriction Report?

No: Conclude the uncertainty analysis.

Yes: Continue with Task 2.3.

If a quantitative influence analysis is not possible, the different paths for each uncertainty to affect the results and conclusion of the Restriction Report should at least be analysed qualitatively based on expert judgment.

Avoid repetitions of Step 1 and Task 2.1 and instead focus the analysis on:

- How connections between different parts of the assessment distribute the effects of uncertainties

- The relevance of changing outcomes of different parts of the assessment for the results and conclusions of the Restriction Report

Task 2.3: Prioritise the identified uncertainties by ranking them according to the relative contribution of each source of uncertainty to the uncertainty of the Restriction Report as a whole.

This contribution is defined by the two elements previously assessed – the magnitude of uncertainty (see sensitivity analysis) and the impact on the results of the assessment (see influence analysis).

Because the prioritisation focuses on the <u>relative</u> contribution, there should not be a situation in which all identified uncertainties are placed in only one of the following categories as a result of the exercise (provided that there is more than one uncertainty).

- **Priority 1:** Uncertainties of largest magnitude and highest potential impact on the result of the Restriction Report
- **Priority 2:** Uncertainties of comparatively small magnitude but comparatively high potential impact on the result of the Restriction Report
- **Priority 3:** Uncertainties of comparatively large magnitude but comparatively low potential impact on the result of the Restriction Report
- **Priority 4:** Uncertainties of smallest magnitude and lowest potential impact on the result of the Restriction Report

One reason why the analysis of sensitivities, influences and resulting priorities is very useful to have in the uncertainty analysis is the benefit of better coordination of subsequent scrutiny of uncertainties. Uncertainties with a comparatively low potential to influence the conclusions of the Restriction Report might be considered to require less intensive analysis while others are more deserving of being in the focus of the more detailed evaluation. It might even be justified that some lower-priority uncertainties are set aside and only briefly mentioned again in the summary of the uncertainty analysis.

Step 3 will cover the process of organising the rest of the analysis in more detail.

For the implementation of Tasks 2.1 through 2.3, consider the following example wording and tables for use in the Restriction Report.

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3.2 Sensitivity and influence analysis

The following step in the uncertainty analysis aims to evaluate the relative importance of different sources of uncertainty.

For each identified uncertainty, first, sensitivity analysis is used to apply different possible inputs and/or methodological choices to the assessment and compare the outcomes to the results of the initial assessment. Then, influence analysis further considers the effects that the analysed sensitivities could exert on the overall outcomes and conclusions of the Restriction Report, both individually and collectively.

3.2.1 Uncertainty 1

Uncertainty about [the number of units of Product X annually sold on the EU market] can be expected to affect the impact assessment of the different Restriction Options by changing the estimation of [foregone producer surplus]. Several sources estimate [the mean quantity of sold units] at [10 million per year] and this value was used as a point estimate in the impact assessment.

However, according to available data, the range of possible values for [this quantity] can be estimated at [1 to 50 million units per year], which provides the lower and upper bound for sensitivity analysis. Using this range, it can be tested how the outcome of [the estimated producer surplus loss] may vary.

Table 4. Uncertainty 1 – Alternative input values and/or methodological choices for sensitivity analysis and corresponding output values

Range of possible values for [the annual quantity of Product X placed on the EU in the baseline scenario]		Range of corresponding values for [foregone producer surplus]
Lower bound	1 million	X million
Upper bound	50 million	Y million
Estimate used [in the baseline scenario]	10 million	Z million

It results that the range of [foregone producer surplus] might be X to Y million [EUR per year] as a consequence of the impact exerted by uncertainty over the [the quantity of sold units]. The estimate of [foregone producer surplus] presented in the baseline scenario (EUR Z million per year) lies at the lower end of the applicable range, implying that there is some risk of underestimating this figure.

Influence analysis can be used to demonstrate the effect of best-case and worst-case assumptions about [the number of sold units per year] on cost-effectiveness of the presented Restriction Options.

Figure 2. Cost-effectiveness of Restriction Options assuming the highest and lowest quantity of units of Product X sold per year

Figure 2 shows that even if the upper bound of [the quantity sold] was the appropriate value, the conclusions about [the comparative cost-effectiveness of the Restriction Options] would [not] be changed by the potential effects of this uncertainty alone. Hence, when holding all other factors constant, the influence of this uncertainty on the assessment result is [zero].

However, other identified uncertainties also have potential to affect the [the comparative cost-effectiveness of the Restriction Options]. Therefore, a best-case and worst-case analysis will be conducted after the individual description of the rest of uncertainties in order to consider the joint influence on the conclusions on [Restriction Options].

3.2.2 Uncertainty [x]

[sensitivity + influence analysis for each individual uncertainty]

3.2.X Collective influence of uncertainties on the restriction proposal

In order to gain an impression of the joint influence of the uncertainties described above this part of the analysis will implement best-case assumptions for all uncertainties and compare the resulting conclusions on [Restriction Options] with the other extreme scenario of implementing only worst-case assumptions for all uncertainties. This best-case and worst-case analysis will thus demonstrate how far all the elements together may shift the conclusion in one or the other direction.

Table 5. Summary of collective best-case and worst-case analysis

Cost per kg of avoided emissions	**RO1**	**RO2**	**RO3**	**RO4**
Collective best case	A EUR	B EUR	C EUR	D EUR
Collective worst case	E EUR	F EUR	G EUR	H EUR
Point estimate used in the previous sections of the Restriction Report (e.g. mean or median)	I EUR	J EUR	K EUR	L EUR

Based on the findings in Table 5, Figure 3 shows the results of the collective best-case and worst-case analysis for this Restriction Report's conclusion about [the cost-effectiveness of reducing emissions] for the different [Restriction Options] and makes a comparison to [previous restriction proposals].

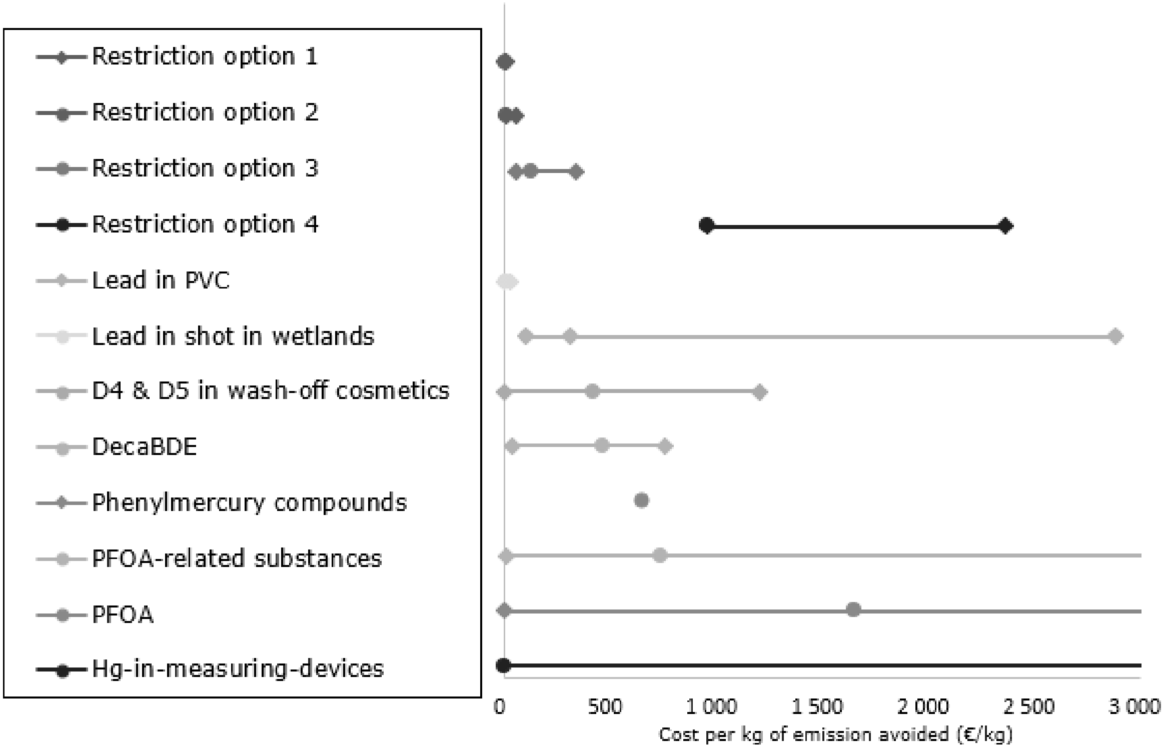

Figure 3. Cost-effectiveness of emission reduction in EUR per kg

It is evident from Figure 3 that RO 4 has the widest range of possible outcomes under uncertainty and that the corresponding cost-effectiveness levels are rather at a higher end of the spectrum. In comparison to this, the effects of uncertainties on the calculations in RO1 and RO2 are of lower concern.

If you chose 'No' in Decision tree 2

3.2.X Conclusion about uncertainties

[Explain why there is no potential for the uncertainties to change the results and conclusions of the Restriction Report (e.g. if identified uncertainties mainly affect RO3 and RO4, but the Dossier Submitter is recommending RO1 or RO2 as preferred Restriction Options, then the identified uncertainties do not change the result of the assessment).]

If you chose 'Yes' in Decision tree 2

3.2.X Prioritisation of uncertainties

The performed analysis of sensitivities and influences helps to allocate relative priorities to uncertainties for the benefit of better coordination of the subsequent analysis of uncertainties.

The assignment of priority levels to uncertainties accounts for two factors, the relative magnitude of the uncertainty itself and the relative impact on the results of the Restriction Report:

- **Priority 1:** Uncertainties of largest magnitude and highest potential impact on the result of the Restriction Report
- **Priority 2:** Uncertainties of comparatively small magnitude but comparatively high potential impact on the result of the Restriction Report
- **Priority 3:** Uncertainties of comparatively large magnitude but comparatively low potential impact on the result of the Restriction Report
- **Priority 4:** Uncertainties of smallest magnitude and lowest potential impact on the result of the Restriction Report

Different levels of priority were assigned to the identified uncertainties as shown in Table 6.

Table 6. Prioritisation of identified uncertainties

Identified uncertainties		**Priority**
1	[..., e.g.: Unknown quantity of Product X placed on the EU]	Priority 4
3[9]	[...]	Priority 2
4	[...]	Priority 3
5	[...]	Priority 2
[...]	[...]	Priority 1

[Insert any further explanations about the chosen priorities below the table]

2.3. Step 3 – Grouping of uncertainties

When the Dossier Submitter has attained a better awareness of the possible dynamics that various uncertainties can have on the outcome of the assessment, the remainder of the uncertainty analysis has the objective to evaluate in more detail those effects that were found to have the potential to change the conclusions of the Restriction Report and are thus highest on the priority list.

Unless there is only one source of uncertainty, grouping uncertainties and creating several separate parts for the subsequent uncertainty analysis can improve the reliability of the results by allowing better focus.

However, when dividing the uncertainty analysis into several parts, the Dossier Submitter

[9] In the context of the previous examples, Uncertainty 2 was identified as a standard uncertainty and thus excluded from the scope of the subsequent detailed uncertainty analysis.

also needs to consider that more detailed findings of the uncertainty analysis in each part will eventually need to be combined again to conclude about the overall uncertainty. Hence, grouping uncertainties into many different parts may add complexity to the task. The choice about the number of parts should be fit for purpose and aim for the delivery of reliable outcomes with minimal complexity and appropriate resource investment.

Moreover, the analyst's decision on how to group uncertainties for subsequent analysis should take into consideration the following elements:

- important connections or dependencies between specific uncertainties that are not applicable to other uncertainties,
- different priorities of uncertainties,
- different areas of expertise required to analyse uncertainties, and
- any other applicable circumstances.

In case the Dossier Submitter identified one or several uncertainties that have only a minor potential to influence the conclusions of the Restriction Report and are of low enough relevance to be set aside, these uncertainties should be disregarded during grouping.

Task 3.1: Take a moment to consider how to group uncertainties and how to later combine the findings of the analysis in each part to characterise overall uncertainty.

The combination of results can be based on expert judgement or, where possible, on quantifications if the uncertainty in each part can be quantified and an appropriate quantitative or logical model to combine outcomes of the parts can be specified.

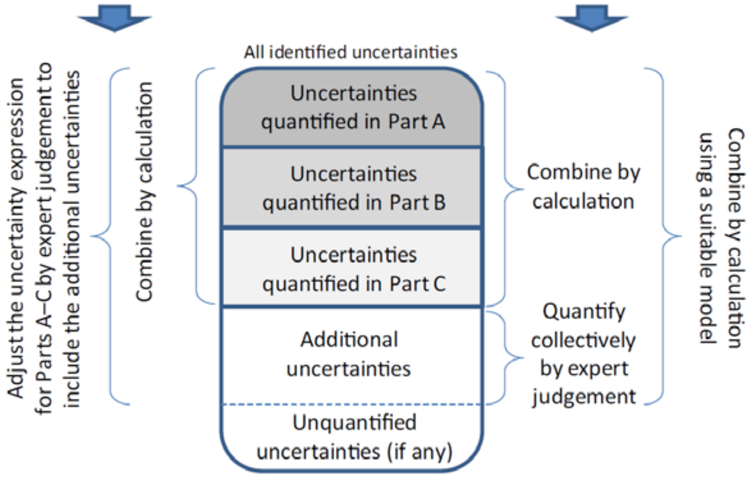

Figure 4. Grouping of uncertainties and combination of the analyses in different parts

More details on the combination of information on uncertainties are covered in Step 5. If you have doubts about grouping and later combination of information, it may help you to first review the rest of section 2 before proceeding with your uncertainty analysis.

Task 3.2: Divide the uncertainty analysis into an appropriate number of parts and communicate the structure.

For the implementation of Tasks 3.1 and 3.2, consider the following example wording and tables for use in the Restriction Report:

3.3 Structure of the subsequent uncertainty analysis

Based on the identification and prioritisation of uncertainties the following more detailed evaluation of the impacts of relevant uncertainties on the conclusions of the report is divided into [2/3/X] parts. The chosen structure balances conflicting objectives of providing sufficient focus in the subsequent analysis and controlling the complexity of the analysis.

The grouping of uncertainties into parts takes account of

- ☐ dependencies between specific uncertainties
- ☐ the above identified priority scale and treats each priority group separately. The analysis of priority-4 uncertainties is set aside for now but will be considered later as part of the characterisation of overall uncertainty
- ☐ different areas of expertise required to analyse uncertainties
- ☐ the chronological appearance throughout the previous sections of the Annex XV Restriction Report
- ☐ [...]

Table 7 summarises the resulting structure.

Table 7. Structure of the uncertainty analysis

Identified uncertainties		Part of the uncertainty analysis
1	[..., e.g.: Unknown quantity of Product X placed on the EU]	Set aside with minor impacts on the outcome, but discussed in the summary section
3	[...]	Part A
4	[...]	
5	[...]	Part B
[...]	[...]	[...]

[Insert any further explanations about the chosen structure below the table]

2.4. Step 4 – Estimate probabilities of the effects of uncertainties

For uncertainties that were found to have concrete potential to change the conclusions of the Restriction Report, the decision maker should receive as much information as possible on the likelihood with which a change of the end result would occur.

The following overview of ways to express the degree of uncertainty outlines some methods for the further evaluation of uncertainties[10]. In general, it is recommended to express uncertainty **quantitatively** whenever possible and use qualitative terms in combination with a quantitative measure. However, there may be cases in which a quantitative evaluation cannot be carried out, meaning that uncertainties must be described solely qualitatively.

Frequently used qualitative expressions of uncertainty use words (descriptive expressions of uncertainty in the form of narrative text without any quantitative definition) and ordinal scales (ordered categories, where the magnitude of the difference between categories is not quantified). More methods are described in Appendix B. Using qualitative forms of expressions, the analyst describes different levels of weight of evidence, relevance, reliability or consistency. Unfortunately, these are most of the time ambiguous and tend to be interpreted differently by different people.

The most commonly used quantitative measure of uncertainty is probability, expressed as a value on a continuous scale ranging from 0 to 1 or as a percentage value between 0% to 100%. The next few paragraphs explain how probabilities can be expressed in the following cases:

i. when analysing a question of interest (e.g. a yes/no questions),
ii. when analysing a non-variable quantity of interest (has **only one** true value),
iii. when analysing a variable quantity of interest (has **multiple** true values, e.g. body weight of different people in a population or the same person across different points in time), and
iv. when analysing dependencies between quantities of interest (direct or indirect relationships between variable quantities, e.g. exposure and body weight).

i. Uncertainty about the answer to a question of interest

To describe uncertainty about a question of interest we express the **probability** with which a given answer is the true answer. In the context of a yes/no question, we define the probability of the answer being 'yes'. A probability of 0% means one is certain that the answer is 'no', and 100% means the answer is certainly 'yes'. 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'.

When the exact probability cannot be estimated, uncertainty about the answer to a question of interest can be expressed using an **approximate probability**, that is a range for the probability with which the answer is 'yes'. An approximate probability of less than 25% means the probability of the answer being 'yes' lies somewhere between 0% and 25%, i.e. the answer is at least three times more likely to be 'no' than 'yes'.

ii. Uncertainty about a non-variable quantity of interest

A full expression of uncertainty about a non-variable quantity of interest uses a **probability distribution** to show the relative probability of different values being the true value. The range of values for the quantity of interest that is described by the probability distribution includes all values that could possibly be the true value, or at least divides the range of possible values into classes of values (sometimes called 'probability bins') to each of which a probability can be assigned. In the latter case, the Dossier Submitter might be able to derive a simplified probability distribution to approximate the real one.

[10] See: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5122 – Page 17ff.

Typical functional forms that could be assumed to apply to cases where data availability is low include the following distributions: uniform, normal or triangular, log-normal or Weibull. See Appendix C on **Bayesian inference** for more information on how to derive a probability distribution based on both expert assumptions and available data.

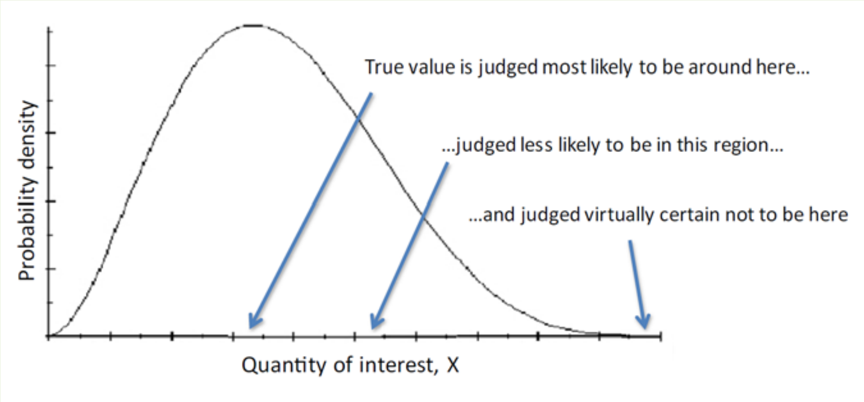

Figure 5. Example of a probability distribution, quantifying uncertainty about a non-variable quantity X

The probability distribution also shows the probability that the true value of the quantity of interest lies in a certain range of possible values. The probability of the true quantity lying inside a specific range of interest corresponds to the area under the curve between the two endpoints of that range.

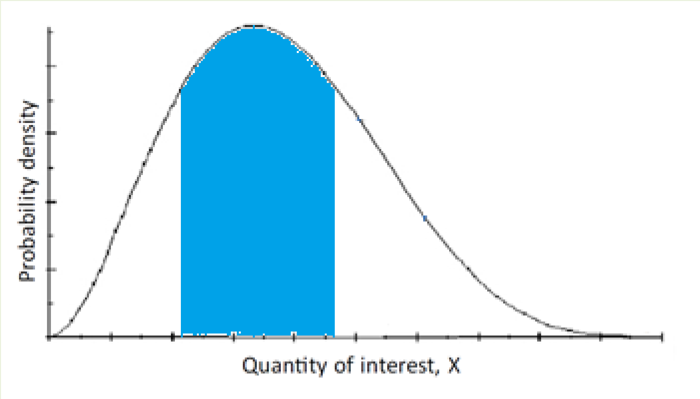

Figure 6. Probability that a specific range of the quantity of interest includes the true value

When sufficient knowledge about the probability distribution is not available, a partial expression of uncertainty may be enough to characterise the probability with which a selected range of values includes the true value. Applying the concept of approximate probabilities to this case results in the concept of a **probability bound**. A probability bound indicates a range of probability values with which a specified range of values of the quantity of interest includes the true value. A probability bound of less than 15% implies that the probability of the true value lying inside a specified (incomplete) range of possible values for quantity X is between 0% and 15%. Another form of probability bound is the range of probability values with which the true value of the quantity of interest exceeds rather than includes a specific value (this is sometimes called 'exceedance probability').

iii. Uncertainty about a variable quantity of interest

A variable quantity must always be seen in a certain context of interest, i.e. a population or time interval. In this context the variable quantity has a **distribution of variability**, that is the relative frequency with which different values of the quantity of interest occur in that population or time interval. One could express distribution variability in a histogram if the value of the variable is known for each individual in the population or each time unit in the interval. However, most of the time, the distribution variability is not perfectly known, and thus, uncertain. Taking the mean of the quantity, or a percentile of variability, converts the variable quantity into a non-variable quantity.

By focusing on the mean or a certain percentile of variability we can express uncertainty about the variable quantity in the same manner as in the case of uncertainty about a non-variable quantity of interest (i.e. a probability distribution or probability bound).

Using a probability bound can simplify the analysis when the uncertainty analysis covers several variable quantities (i.e. several sources of uncertainty). In this case **probability bound analysis** can be used to combine several expressions of uncertainty in the characterisation of overall uncertainty.

The use of distributions to quantify both uncertainty and variability for several variable quantities of interest is a more complex task, requiring a statistical model for variability. Uncertainty about parameters in the statistical model can be quantified using probability distributions.

Where suitable data is available, **statistical methods** such as maximum likelihood fitting (perhaps combined with expert judgement) is the preferred choice of analysis and should be used to derive a measure of uncertainty and/or variability. For more information on how to use statistical analysis to define probabilities see Appendix C.

iv. Uncertainty about dependent quantities of interest

Variable quantities of interest can be dependent on each other. Sources of uncertainty are dependent when learning more about one variable alters the uncertainty about another. It is important to consider whether dependencies may be present and, if so, take them into account because they can have an impact on the assessment conclusion.

Potential dependencies affecting variability or uncertainty are easiest to address by using **probability bound analysis** because it does not require specification of dependencies. However, this approach accounts for all possible dependencies, so the resulting approximate probability often covers a wide range of probabilities.

Narrower bounds or precise probabilities and distributions can be obtained if information on dependencies can be explicitly included in the analysis. If it is reasonable to assume that there are no dependencies, the analysis is obviously simpler.

Task 4.1: Decide how to express uncertainty about the elements that have potential to change the conclusions of the Restriction Report.

As explained in the overview above, uncertainty can be expressed using

- probability,
- probability distributions,

- approximate probability and probability bounds, or
- qualitative expressions (least preferred option due to inherent ambiguity).

Other than in the context of uncertainty, **probability** is also often used to express variability, frequency, incidence or risk. This is why, in the communication of probability judgements for uncertainty, it is useful to explain clearly that that the probability refers to uncertainty about a specific element and/or report a probability as X% certainty to highlight that it is an expert judgement about uncertainty.

The same applies to ranges of probabilities. It is recommendable to communicate explicitly when ranges represent uncertainty (not e.g. variability of a variable quantity). When ranges of probabilities are used, the approximate probability scale in Table 8 can serve as a harmonised framework to express uncertainty.

Table 8. Approximate probability scale recommended for harmonised use in EFSA[11]

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% Report as 'inconclusive', 'cannot conclude', or 'unknown'
Extremely likely	95–99%		
Very likely	90–95%		
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%		

Please note that an **approximate** probability must be a range of probability. Often words like 'approximately', 'about' or 'up to' are used as hedging words in all kinds of situations, but this is not the intention here and an expression such as 'approximately 80%' should be strictly avoided to reduce ambiguity. The correct approximate probability for this example would be to say, 'it is considered to be 66-90% certain that [...]'. If you use the approximate probability scale in your analysis, consider introducing the table in the analysis and do not forget to add a reference to EFSA's publication: "The principles and methods behind EFSA's Guidance on Uncertainty Analysis in Scientific Assessment"[12].

When using a qualitative probability term such as 'extremely likely', make sure that you **first** provide the corresponding quantitative probability range (95%-99% certainty in this case) as an unambiguous indication of approximate probability. As explained before, people tend to interpret qualitative terms differently and thus qualitative descriptions cause ambiguity, if used primarily or even without any quantitative expression.

When using **qualitative** approaches to analyse uncertainties without quantitative probability expressions attached, please comment on the limitations that prevent a quantitative (or semi-quantitative) analysis and, if possible, on the kind and amount of resources needed to extend the uncertainty analysis by quantitative elements. If analysts must resort to purely qualitative expression of uncertainty, it should be clearly stated that the probability of different answers is unknown. In that case, the analyst should be careful with the use of language in their descriptive text that could be misinterpreted as a

[11] See: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5123

[12] See: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5122

probability statement (e.g. 'likely', 'unlikely') and any verbal expressions that have risk management connotations, such us 'negligible'. When used without further definition, the latter kind of expressions can easily be misunderstood as a judgement about the probability of adverse effects and even a judgement about the acceptability of that probability. This makes clear that using qualitative expressions of uncertainties (allowing free choice of language to characterise uncertainty) is not necessarily easier and presents the analyst with the challenge of describing different levels of weight of evidence, relevance, reliability or consistency of information without providing implicit and misleading statements about probability. In fact, EFSA's scientific committee involved in capacity building for uncertainty analysis states that it is "unaware of any well-developed or rigorous theoretical basis for qualitative approaches, which rely instead on careful use of language and expert judgement"[13]. Aside from the use of descriptive text, the analyst may rank the magnitudes of different uncertainties or magnitudes of impact on the assessment's conclusion in order to facilitate a comparison of different uncertainties. If used in rankings, numbers obviously stand for the ordering of categories, not for the quantification of uncertainty nor the quantification of the difference between the categories. As an alternative to the use of numeric ordinal scales, the analyst may use labelling of different categories; for example, 'high', 'medium' or 'low' uncertainty. It is desirable to provide a definition for each category, so that they can be used and interpreted in a consistent manner.

More qualitative methods are listed in Appendix B.

Task 4.2: Evaluate each uncertainty by assigning a probability judgement to the different possible outcomes for an uncertain element (i.e. the range of possible answers or values) or, alternatively, by utilising appropriate qualitative techniques.

For the implementation of Tasks 4.1 and 4.2, consider the following example wording and tables for use in the Restriction Report.

ANNEX XV RESTRICTION REPORT

3.4 Estimation of probabilities

The next step in the uncertainty analysis aims to evaluate each uncertainty in more detail by assigning a probability judgement to the different possible outcomes for an uncertain element.

3.4.1 Part A

First the uncertainties grouped together in Part A will be evaluated in more detail.

3.4.1.1 Uncertainty 3

In the context of the performed sensitivity analysis, the range of possible [values/choices/answers] for [the quantity/question of interest] has been reported as 0 to 1 and the corresponding [values] of [the dependent output variable] have been calculated for each [quintile]. Since uncertainty about which [value/choice/answer] is [correct/applicable/true] [together with other uncertainties affecting the Restriction Report] has been shown to have potential to change the main results and conclusions of

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[13] See: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5122 – Page 50

the Restriction Report, it is important to gain a more detailed understanding of the probability of these effects.

Table 9 shows the outcomes of sensitivity analysis for Uncertainty 3 and makes an estimation of the probabilities attached to different possible outcomes.

Table 9. Estimated certainty of possible [values/choices/answers] of [the quantity/question of interest] (Uncertainty 3)

Range of possible [values/choices/answers] for [the quantity/question of interest]	**Corresponding [values] of [the dependent output variable]**	**Estimated certainty of the different possible outcomes**
0-0.02	A	20%
0.02-0.04	B	30%
0.04-0.06	C	25%
0.06-0.08	D	15%
0.08-1	E	10%

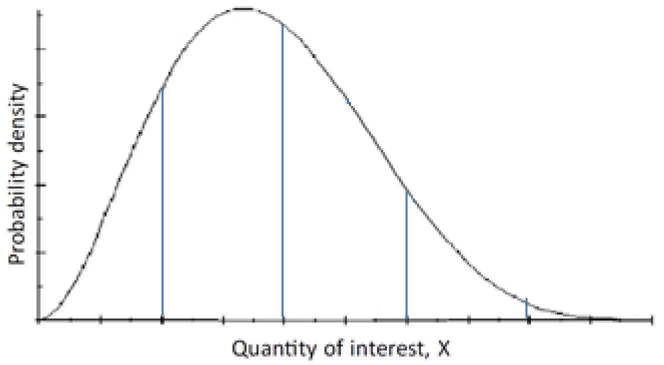


Figure 7. Probability distribution (Uncertainty 3)

Based on this, the certainty with which the [correct/applicable/true] [value/choice/answer] for [the quantity/question of interest] lies in [the 2nd quintile] (as assumed in the baseline scenario of this Restriction Report) is estimated to be [30%].

[IF AVAILABLE USE EXISTING DATA TO SUPPORT THE MODELLING OF PROBABILITIES -> can combine own best guess and available data with Bayesian inference, see Appendix C and an example in Rheinberger et al. (2009)[14]]

[14] See: Rheinberger et al. 2009, 29(1):76-94, Risk Analysis (wiley.com) – Figure 3

3.4.1.2 Uncertainty 4

[...]

3.4.2 Part B

Next, the uncertainties allocated to Part B will be evaluated in more detail.

3.4.2.1 Uncertainty 5

[...]

2.5. Step 5 – Combine uncertainties to characterise overall uncertainty

In the final step of the uncertainty analysis, quantitative probability judgements and any non-quantifiable uncertainties elicited in the previous steps need to be combined into a characterisation of overall uncertainty about the results and conclusions of the Restriction Report. This means that the characterisation of uncertainties needs to be brought into a consolidated form that can be discussed in view of the proportionality of different restriction options and the final conclusions of the Restriction Report.

The following overview will outline some methods for the characterisation of overall uncertainty. In general, it is recommended to combine uncertainty **by calculation** whenever possible and only use expert judgement where no calculation of combined uncertainty is feasible. This is recommended because even minor uncertainties in multiple parts of the assessment may result in significant overall uncertainties if their relationship is multiplicative or exponential. It is often difficult to express such uncertainty propagations in qualitative terms.

The next paragraphs explain how uncertainties can be combined in the following cases:

i. using a logical model for yes/no questions,
ii. using a quantitative model involving only non-variable quantities, and
iii. using a quantitative model involving variable quantities.

i. Logical model for yes/no questions

The model expresses a yes/no conclusion as a logical deduction from the answers to a series of yes/no questions.

'And'-model: The conclusion is 'yes' only if each question has the answer 'yes'. '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'-sub model for some questions as one input to an 'and'-model, which might also include other input questions or sub model outputs.

When uncertainty about the answer to each question is expressed using probability, the mathematics of probability can be used to calculate a joint 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[15] are fairly straightforward when uncertainties about answers to questions are independent but do get more involved if they are not.

ii. Discrete variables

Sometimes it is possible to describe a variable as a set of exhaustive and mutually exclusive distinct outcomes. This might be the case when a variable is reduced to a yes/no question or even when the variability in a continuous variable can be sufficiently described as a number of contingencies so that the defined discrete choices can still be considered fairly representative of the range of possible outcomes.

If the analyst was able to assign **probabilities** to all possible answers or values of a discrete variable (non-negative probabilities that sum up to 100%), it is possible to calculate expected values for these variables and take them forth as an average over the possible outcomes. This approach is called **expected value analysis**. For example, if the analyst assigns a probability of 50% that a parameter value is 20, and a 50% that it is 30, then the expected value equals 50%*20 + 50%*30 = 25.

iii. Quantitative model for non-variable quantities

A simple form of analysis using **probability** expressions for only the most important uncertainties is **partial sensitivity analysis**. It analyses how the conclusions of an assessment change as only one uncertain element is changed, but all other factors are held constant.

If uncertainty for each input to the model has been quantified using a **probability bound**, the method of **Probability Bounds Analysis**[16] can be used to deduce a probability bound for the output: one seeks an approximate probability of a particular range including the output value that corresponds to the true values of the inputs. 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.

If uncertainty about each input to the model has been expressed using a **probability distribution** and there is no dependence between the uncertainties, the mathematics of probability lead to a probability distribution, expressing the combined uncertainty about the output of the model. The simplest method for computing the probability distribution for the output is **Monte Carlo simulation**[17] which can be easily implemented in freely available software or, in some simple cases, in a spreadsheet.

A Monte Carlo simulation derives a distribution for the assessment result/conclusion by drawing randomly and repeatedly from the probability distributions of the different uncertain variables in a model. The analyst should then provide information about the simulations, e.g. in form of a histogram, and report at a minimum the mean and variance of the simulated variable of interest. This will allow to make inference about the overall probability of certain results and conclusions. For example, if in a simulation of 10 000 draws a specific exposure value is exceeded only 300 times, this can be

[15] See: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5122 – Page 64f & Annex B.18

[16] See: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5122 – Page 65 & Annex B.13

[17] See: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5122 – Page 65f & Annex B.14

interpreted to mean that the exceedance probability is in a bound of 0-5%.

If analysts are not confident about how to express or elicit uncertainty using probability distributions or are not confident about how to carry out Monte Carlo simulations or have issues addressing the dependence between uncertainties about inputs they should seek expert advice.

iv. Quantitative model for variable quantities

Probability Bounds Analysis for both uncertainty and variability can also be applied to quantitative models which have variable inputs (and are based on **probability bounds**).

A full expression of uncertainty about variability uses **probability distributions** in two roles: (a) as statistical models of variability; (b) to express uncertainty about parameters in such models. When using probability distributions for variable quantities, a **Monte Carlo simulation** can be applied. Some of these methods for combining uncertainties require more background information[18] and advice from experts.

Task 5.1: Decide how to combine quantified uncertainty to arrive at a quantitative characterisation of overall uncertainty.

As explained above, uncertainty can be combined into a characterisation of overall uncertainty about the results and conclusions of the Restriction Report using:

- a logical model,
- expected value analysis (/decision analysis),
- partial sensitivity analysis,
- Probability Bounds Analysis, or
- Monte Carlo simulation.

Note that the consideration of unquantifiable uncertainties is covered in Task 5.4.

Task 5.2: Combine all quantified uncertainties (i.e. probabilities) to characterise overall uncertainty about the results and conclusions of the Restriction Report.

For the implementation of Tasks 5.1 and 5.2, consider the following example wording and tables for use in the Restriction Report.

ANNEX XV RESTRICTION REPORT

3.5 Combination of evaluated uncertainty and characterisation of overall uncertainty

3.5.1 Details about the process of combining evaluated uncertainties

[18] See: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5122 – Annex B.11, 12, 14

[*Example for the use of a Monte Carlo simulation from a previous Restriction Report (lead compounds used as stabilisers in PVC articles):*

The model used for estimating releases is outlined in Figure 3.

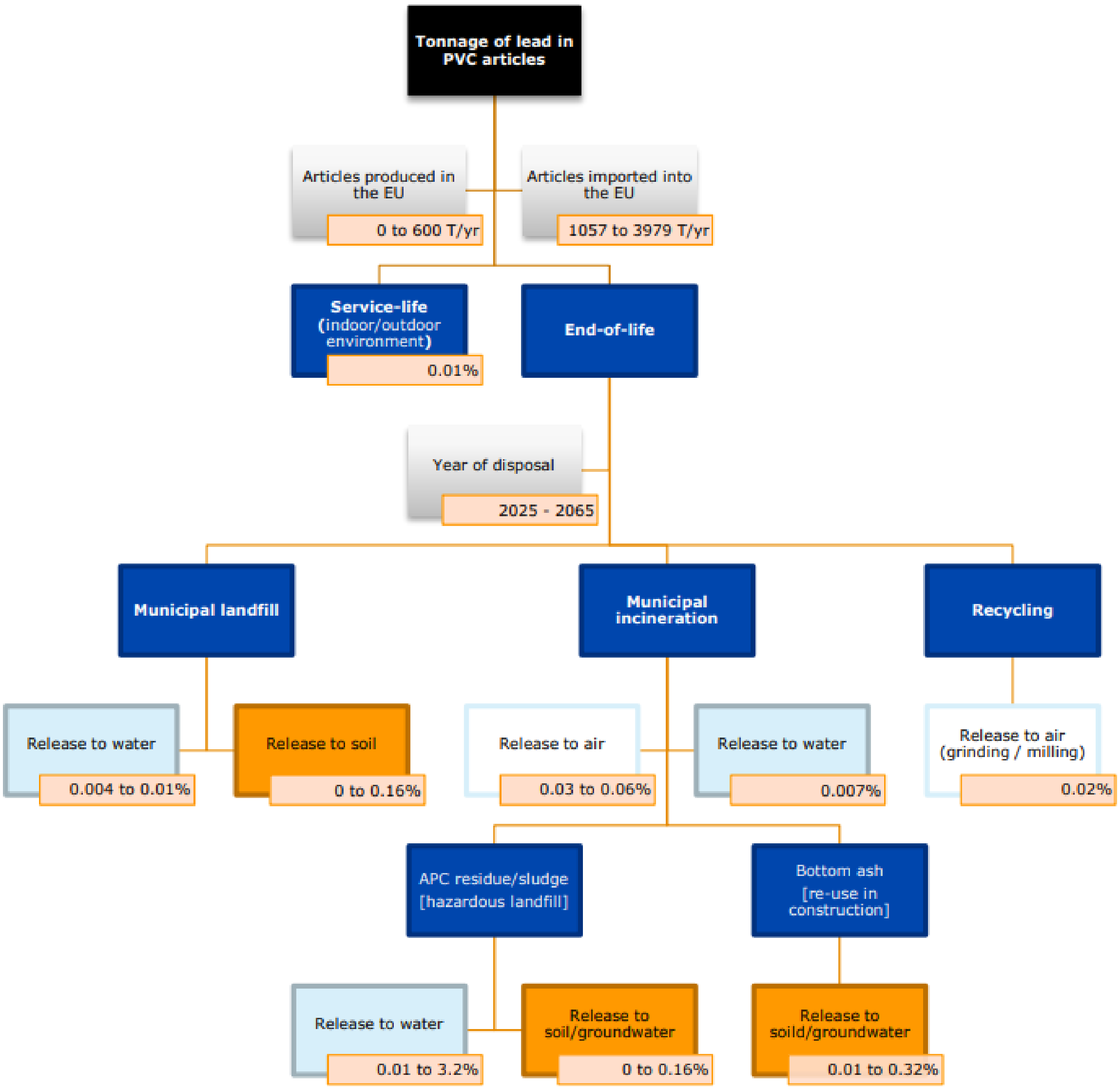


Figure 3. Overview of probabilistic model used to estimate release of lead to the environment

The model estimates releases from the service life and waste life cycle based on tonnage data (from industry) and release factors found in the literature, ECHA guidance or empirically derived from measurement data.

There are relatively large uncertainties in the input parameters for the model (e.g. the release factors to environmental compartments, tonnage of lead stabiliser used, proportion of waste disposed via different routes in the future). Therefore, a probabilistic modelling approach (using Monte Carlo simulation) was adopted (a) to integrate the variability apparent in the input parameters and (b) to estimate the most likely releases from within the theoretical minimum and maximum extremes of the model. For example, the release factor to water from municipal landfill was reported to vary, dependent on the source of the factor, from 0.0001 to 0.032.

Lower and upper bound release factors for the exposure estimates were selected from ECHA R.18 guidance, a technical report (TNO 2001) and REACH registration dossiers (Arche, 2013). The model was re-run 100 000 times with different values for the input parameters selected from within the lower and upper bound ranges on each occasion. Estimates of releases are reported as the interquartile range of estimates and the median estimate.

The assessment also considers that the proportion of PVC waste disposed via different routes will vary in the future. On each model run a year of disposal was selected from between 2025 to 2065, which corresponds to a proportion of PVC waste disposed in landfill and going to incineration and recycling (based on industry predictions). The model was weighted such that a year of disposal is 10 times more likely to be from the later part of the range, than the earlier part, recognising that PVC articles have a relatively long service life and are therefore more likely to be disposed in 50 years, than in 10.

Estimated lead releases were found to be between 4.3 and 10.3 tonnes, with a median value of 6.8 tonnes (Table 5). These values reflect total lead emissions expected to be released from PVC articles placed on the EU market for 2016 (both EU manufactured and imported in the EU/from both service life and disposal stages).

Table 5. Lead releases from PVC articles placed on the EU market in 2016 (estimated via Monte Carlo analysis)

Lead releases to the environment (tonnes) 2016 tonnage			
Life cycle stage	**25th percentile**	**Median**	**75th percentile**
Service Life	0.19	0.26	0.34
Recycling of articles	0.16	0.23	0.30
Municipal landfill	0.07	0.14	0.22
Municipal incineration[1]	3.29	6.11	9.88
Total[2]	**4.3**	**6.8**	**10.3**

1: Releases from municipal incineration include those associated with long-term disposal of fly-ash and from the re-use of incinerator bottom ash in construction projects.
2: Due to the characteristics of the Monte Carlo simulation the sum of the estimates for the different life-stages at 25th percentile, median and 75th percentile are not necessarily consistent with corresponding estimates of total releases

In this example, the Monte Carlo simulation was carried out using the software "Crystal Ball" in Excel]

3.5.2 CHARACTERISATION OF OVERALL UNCERTAINTY

For a question of interest:

The main question of the Restriction Report is [..., *e.g. whether the benefits of restricting the use outweigh the costs*].

Taking into account all the identified uncertainties, the conclusion of the previous assessment that [...] is estimated to be true

☐ with an overall approximate probability of xx-xx%.

☐ with an overall probability of less / more than X%.

Therefore,

☐ despite the combined impact of the identified uncertainties in the Restriction Report, it is [likely/very likely/extremely likely/almost certain] that [the question of interest X] yields the same answer upon clarification of the knowledge limitations.

☐ given the combined impact of the identified uncertainties in the Restriction Report, it must be deemed [likely/very likely/extremely likely/almost certain] that [the question of interest X] yields a different answer upon clarification of the knowledge limitations.

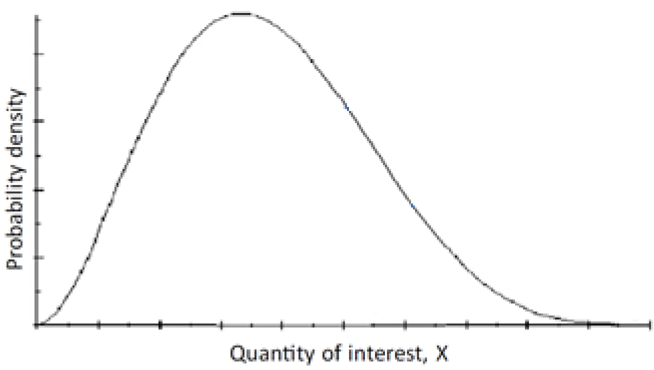
☐ given the combined impact of the identified uncertainties in the Restriction Report, it is expected to be approximately as likely as not that [the question of interest X] yields a different answer upon clarification of the knowledge limitations.

For a quantity of interest:

The main objective of the Restriction Report is to find [..., *e.g. the net benefit of restricting the use*]. According to the conducted impact assessment in section 2 of this report, [..., *e.g. the net benefits of restricting the use were estimated to be in the range of X to Y million EUR*].

☐ Based on the evaluation of all uncertainties, it is expected that the true value of [the quantity of interest, X] [still] lies inside the estimated range with a probability of less / more than X%. Therefore, due to the combined impact of the identified uncertainties, the estimated value of [the quantity of interest, X] can / cannot be deemed robust to the identified uncertainties.

☐ Based on the evaluation of all uncertainties, it is expected that the resulting value of [the quantity of interest, X] [still] lies inside a range of [...]. The following probability distribution shows the probabilities modelled for the values in this range.



[..., describe further conclusions one can make based on the analysis of the probability distribution of the result/conclusion of the Restriction Report, e.g. information about the mean and variance of the variable that describes the result/conclusion of the assessment and about the overall probability of certain results/conclusions]

The previous tasks have focused on the combination of particularly relevant and quantifiable uncertainties. However, there will nearly always be additional uncertainties that need to be considered at this step, for example uncertainty about the structure of the model used for the combination of quantified uncertainties, or dependencies between the uncertainties. If judged decisive for the recommendations/conclusions arrived at in the Restriction Report, these uncertainties should be included in the combined uncertainty assessment. In addition, there may be other uncertainties that the analysts chose not to quantify earlier in the analysis and left to be considered jointly here.

Task 5.3: Take account of the contribution of any additional uncertainties.

There are two options for incorporating additional uncertainties:

1. Revise the probability expression from earlier steps to include additional uncertainties by expert judgement. This is simpler and takes less time, but less rigorous because it requires the analysts to make a subjective judgement about how the additional uncertainties will alter the probability expression.

2. Define a separate quantitative probability expression for the additional uncertainties (can be based on expert judgement), but then combine this with the earlier probability expression by calculation. This is more rigorous if an appropriate model can be specified.

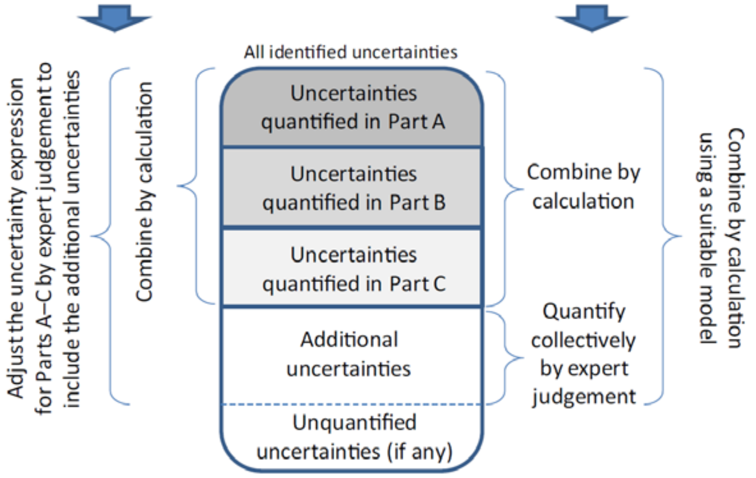


Figure 8: Illustration of options for incorporating additional uncertainties

It is important to make sure that all uncertainties have been accounted for before concluding the uncertainty analysis and the Restriction Report to avoid the impression that the conclusion is undermined by the uncertainties.

Task 5.4: Check for any unquantified uncertainties and, if applicable, describe them qualitatively.

Unquantified uncertainties	An identified source of uncertainty in a scientific assessment that the analysts are unable to include, or choose not to include, in a quantitative expression of overall uncertainty for that assessment
Unknown unknowns	A limitation of knowledge that one is unaware of

Any uncertainties not included in the quantitative evaluation must be described qualitatively and be presented alongside the quantitative evaluation so that, together, they characterise overall uncertainty, i.e. the overall impact of identified uncertainties on the result of the Restriction Report.

If applicable, it should be specified on which assumptions about uncertainty the assessment's conclusion is consequently conditional. Be aware that this analysis does not include 'unknown unknowns' (see Kaplan and Garrick, 1981, for a pertinent discussion)[19].

For the implementation of Task 5.4, consider the following example wording and tables for use in the Restriction Report.

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3.5.2 CHARACTERISATION OF OVERALL UNCERTAINTY (CONTINUED)

As the analysis of uncertainties and their combined impact on the outcome of the Restriction Report did not include the identified uncertainty about [...], there remain[s an] unquantified uncertaint[y/ies] to be considered. The uncertaint[y/ies] [is / are] unquantified because [...]. It results that the above presented quantitative analysis of overall uncertainty is conditional on the following assumptions:

- [...]
- [...]

In addition, it is useful to be aware that any conclusion on the uncertainty analysis might be limited by 'unknown unknowns' which represent limitations one is unaware of.

Task 5.5: Evaluate whether the result of the uncertainty analysis is sufficient for the discussion of proportionality of restriction options and ultimately for decision making.

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

[19] See: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1539-6924.1981.tb01350.x

with decision-makers, unless analysts have an understanding of what level of certainty decision-makers consider appropriate or acceptable for this type of assessment.

Decision tree 3: Is the result expected to be sufficient for decision-making?

No: Go back to the start of Step 4 and conduct another iteration of the analysis.

If the answer is no, the first (and simpler) option is to return to Step 4 and, for some or all parts of the analysis, 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.

Still no: After re-iterating Step 4 and Step 5, if the answer is still no, the second option is to return to Step 4 but, in doing so, use fully specified probabilities, probability distributions and dependencies to characterise the impact of uncertainties on the assessment conclusion. This requires more complex calculations, but usually decreases uncertainty about the answer to the question of interest.

Yes: Great. You have completed the uncertainty analysis.

3. Appendices

3.1. Appendix A: Definition of questions or quantities of interest

Question of interest	A categorical question (asking for a choice between two or more answer categories, e.g. yes/no or low/medium/high) that is the subject of a scientific assessment as a whole, or of a part of such an assessment (may refer to a given quantity, e.g. asking whether exposure to X is below threshold value Y)
Quantity of interest	A quantity (numerical property or characteristic) that is the subject of a scientific assessment as a whole, or of a part of such an assessment (e.g. asking to quantify exposure to X)

In the evaluation of uncertainty, it may help to make sure that the questions and/or quantities of interest for the Restriction Report are well-defined. This is the case if, at least in theory, the assessment conducted as part of the restriction proposal could deliver a true and certain answer on which one can be sure to agree.

Any ambiguity in the definition of questions or quantities of interest will add extra uncertainty and make the evaluation of the list of identified uncertainties more difficult.

3.1.1. Overall objective of the report

Task A.1: Describe what the result of the assessment would be without any uncertainties present (i.e. if all the existing uncertainties were resolved). If available, you may refer to the Terms of References (ToR) for the assessment for the defined objective of the assessment.

Possible answer:

"Without uncertainties, the result of the scientific assessment would clearly indicate

- For question of interest:

  whether [..., *e.g. presence/absence of 1/2/X clearly defined states, conditions, mechanisms, etc. that is/are of interest for the assessment*] at the time of [...] for [population/location X] and under [condition X, e.g. status quo or with specified management actions]."

- For quantity of interest:

  a well-defined measure for [..., *e.g. quantity X that is of interest for the assessment*] at the time of [...] for [population/location X] and under [condition X, e.g. status quo or with specified management actions]."

Task A.2: Does the defined question or quantity of interest include ambiguous words, such as 'high', or an implied risk management judgement, such as 'negligible' or 'safe'?

If yes: Replace or define them with words that are, as far as possible, unambiguous and free of risk management connotations or, where appropriate, with numbers.

This can help to allow proper evaluation and expression of uncertainty associated with the conclusion of the analysis.

3.1.2. Objective of the main sections in the report

Task A.3: For each main section of the report, describe what the result of the section would be without uncertainties (i.e. if all the existing uncertainties were resolved).

Possible answer:

"Without uncertainties in Section X, the result of the scientific study/procedure/calculation would clearly indicate

- For question of interest

  whether [..., *e.g. presence/absence of 1/2/X clearly defined states, conditions, mechanisms, etc. that is/are of interest for the assessment*] at the time of [...] for [population/location X] and under [condition X, e.g. status quo or with specified management actions].

- For quantity of interest

  a well-defined measure for [..., *e.g. quantity X that is of interest for the assessment*] at the time of [...] for [population/location X] and under [condition X, e.g. status quo or with specified management actions].

Task A.4: Do the defined questions or quantities of interest include ambiguous words, such as 'high', or an implied risk management judgement, such as 'negligible' or 'safe'?

If yes: Replace or define them with words that are, as far as possible, unambiguous and free of risk management connotations or, where appropriate, with numbers. This can help to allow proper evaluation and expression of uncertainty associated with the conclusion of the analysis.

3.2. Appendix B: More information on qualitative expressions of uncertainty

Qualitative methods described by the EFSA guidance[20] include the following:

- **Descriptive methods (covered in section 2)**, using text to describe uncertainties.
- **Ordinal scales (covered in section 2)**, characterising uncertainties using an ordered scale of categories (e.g. high, medium or low uncertainty).
- **NUSAP method**, using a set of ordinal scales to characterise different dimensions of each source of uncertainty, and its influence on the assessment conclusion, and plotting these together to indicate which sources of uncertainty contribute most to the uncertainty of the assessment conclusion.
- **Uncertainty tables for quantitative questions**, a template for listing sources of uncertainty affecting a quantitative question and assessing their individual and combined impacts on the uncertainty of the assessment conclusion.
- **Uncertainty tables for categorical questions**, a template for listing lines of evidence contributing to answering categorical questions (including yes/no questions), identifying their strengths and weaknesses, and expressing the uncertainty of answers to the questions.
- **Structured tools for evidence appraisal**, which include templates for identifying and evaluating sources of uncertainty affecting validity of a single study and the whole body of evidence retrieved from the literature and can also be adapted to evaluate studies submitted to EFSA for the assessment regulated products.

According to EFSA, the first four methods can be applied to either quantitative or categorical questions of interest. The fifth and sixth are specific to quantitative questions and categorical questions, respectively. Finally, the seventh method represents a family of structured tools for evidence appraisal.

For more detailed descriptions of these methods, refer to section 10 and the corresponding Annexes of EFSA's publication of the principles and methods behind their guidance on uncertainty analysis in scientific assessments (see footnote above).

[20] See: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5122 – Page 50ff. & Annex B.1, B.2, B.3, B.4, B.5, B.6 and B.19

3.3. Appendix C: Use of statistical analysis of data to define probabilities

In order to become more familiar with the use of statistical analysis to derive probability from existing data, it is useful to take a close look at "The principles and methods behind EFSA's Guidance on Uncertainty Analysis in Scientific Assessment", in the following also referred to as guidance on principles and methods.

It requires some expert judgement to follow the subsequent steps, but most analysts will have some pre-existing knowledge about the topics.

Task B.1: Define the statistical model to be used

The use of statistical methods requires that a statistical model is chosen. This model specifies:

1. The kind of distribution to be used to describe variability of the quantity of interest

2. If relevant, the mathematical form of dependencies between variables (e.g. for regression models or dose–response functions)

3. If relevant, the experimental design and/or sampling scheme

Task B.2: Find data to describe uncertain elements

It is best to select data that may be considered to have arisen from the model.

Task B.3: Choose a method of statistical analysis

Section 11.2 of EFSA's guidance on principles and methods for uncertainty analysis discusses three statistical inference methodologies for quantifying uncertainty about parameters in statistical models based on analysis of data:

1. Confidence intervals

2. The bootstrap

3. Bayesian inference

3.3.1. Confidence intervals[21]

Most people remember confidence intervals from the context of p-values and hypothesis tests. However, these do not quantify uncertainty.

Confidence intervals also provide a form of statistical inference and represent a method for quantifying uncertainty about parameters in a statistical model on the basis of available data. They are often used in literature to report uncertainty.

The prediction interval in linear and multiple regression modelling is a confidence interval for an individual value of the response. For statistical models having more than one parameter, it is possible to construct a confidence region which addresses dependence in the uncertainties about parameters (see Annex B.10 in EFSA's guidance on principles and

[21] See: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5122 – Annex B.10

methods).

The method returns a range of values for a parameter, which has a specified level of confidence. By varying the confidence level, it is possible to build a bigger picture of the uncertainty.

The correct interpretation of a 95% confidence interval is a frequency property: 95% of confidence intervals computed from repetitions of the experiment or study would include the true value of the uncertain parameter. It does not mean that the probability that the uncertain parameter lies in the interval is 95%. However, it is often reasonable to reinterpret a reported confidence interval in this way provided some conditions are met:

1. Analysts do not have knowledge, from sources other than the data being analysed, which gives them significant information about the value of the parameter. If they have such information, it should be used as the basis for a prior distribution in a Bayesian inference.

2. The reported confidence interval does not itself convey information that would lead to a different probability (e.g. it includes parameter values that analysts judge to be impossible or extremely unlikely).

3. Other information reported along with the confidence interval (e.g. concerning the reliability of the experiments or their relevance to the assessment) would not lead analysts to assign a different probability.

These reinterpretations require judgement and so the resulting probability is subjective rather than frequentist. Other weaknesses of this method include the following:

- It does not quantify uncertainty using a probability distribution

- It does not easily address dependence between parameters

The mathematical justification of the confidence interval procedure is usually based on assuming a large sample size (and balanced experimental design in more complex models).

3.3.2. The bootstrap[22]

The bootstrap uses a statistical model based on random sampling and, besides data, requires a choice of one or several statistical estimators to be applied to the data. An estimator is a statistical calculation such as a sample mean or median which can be applied to a data set of any size.

The output of the bootstrap is a sample of possible values for the estimator(s), i.e. a sample from a probability distribution for the estimator(s). This provides a measure of the sensitivity of the estimator(s) to the sampled data.

It works by applying the estimator(s) to hypothetical data sets which are of the same size as the original data set and are obtained by resampling the original data with replacement. The method does not require advanced mathematics and is often implemented using Monte Carlo simulation.

Other methods can be applied to the basic output of the bootstrap to obtain a confidence interval for the 'true' value of an estimator after all. As for all confidence intervals, they

[22] See: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5122 – Annex B.11

have the weakness that the confidence interval probability needs reinterpretation.

Although the basic output from the bootstrap is a sample from a probability distribution for the estimator, that distribution does not directly represent uncertainty about the true value of the estimator using and is subject to a number of biases which depend on the model, data and estimator used. However, in many cases, it may be reasonable to make an expert judgement that the distribution does approximately represent uncertainty. In doing so, analysts would be adopting the distribution as their own expression of uncertainty. If this is the case, the bootstrap can be used to evaluate uncertainty for non-standard estimators, even in non-parametric models and the output might be used as an input to subsequent calculations to combine uncertainties.

3.3.3. Bayesian inference[23]

In Bayesian inference, a statistical model for some form of variability of relevant uncertain parameters is used as a prior distribution for the parameters. The prior distribution estimates uncertainty about the values of the parameters in the model *prior* to observing the data and is preferably obtained by expert knowledge (i.e. experts estimate the probabilities of different possible values of the relevant parameters).

For some models, there exist standard choices of prior distributions (e.g. a triangular distribution) which are intended to compensate to some degree a lack of knowledge. However, the primary reliance on expert judgement can be considered the preferred option. When using a standard choice, it should at least be verified that the probability statements it makes are acceptable to relevant experts for the parameter in question.

Bayesian inference combines the information provided by the prior distribution and the information provided by data and finds a (joint) probability distribution for the parameters (i.e. quantities of interest[24]) of the statistical model. This distribution is called the posterior distribution and it represents uncertainty about the values of the relevant parameters. A good thing is that the posterior distribution from a Bayesian inference can be combined with subjective probability distributions representing other uncertainties because it is itself a subjective probability distribution.

However, it is a good idea to check the sensitivity of the posterior distribution to the choice of prior distribution, especially if a standard prior distribution was used, rather than a prior elicited from experts. The main weakness of the method might be limited familiarity of analysts with Bayesian inference; however, the related code is not very difficult to implement in statistical software given some familiarisation with the topic.

[23] See: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5122 – Annex B.12

[24] When the subject of the model is a question of interest (rather than a quantity of interest) Bayesian inference returns a probability (rather than a probability distribution).