Guidance on information requirements and chemical safety assessment

Chapter R.19: Uncertainty analysis

November 2012

(Version 1.1)

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Guidance on information requirements and chemical safety assessment

Chapter R19: Uncertainty analysis

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PREFACE

This document describes the information requirements under REACH with regard to substance properties, exposure, use and risk management measures, and the chemical safety assessment. It is part of a series of guidance documents that are aimed to help all stakeholders with their preparation for fulfilling their obligations under the REACH regulation. These documents cover detailed guidance for a range of essential REACH processes as well as for some specific scientific and/or technical methods that industry or authorities need to make use of under REACH.

The guidance documents were drafted and discussed within the REACH Implementation Projects (RIPs) led by the European Commission services, involving stakeholders from Member States, industry and non-governmental organisations. These guidance documents can be obtained via the website of the European Chemicals Agency (http://echa.europa.eu/web/guest/support/guidance-on-reach-and-clp-implementation). Further guidance documents will be published on this website when they are finalised or updated.

This document relates to the REACH Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006[1] and its amendments as of 31 August 2011.

1 Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396, 30.12.2006).

Document History

Version 1	First edition	May 2008
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Convention for citing the REACH regulation

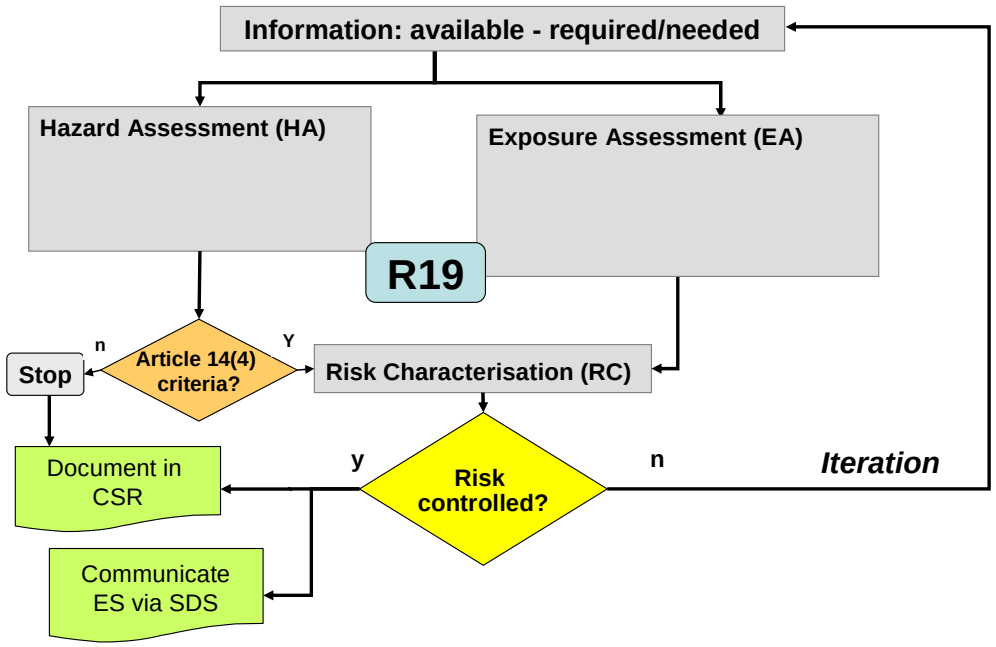
Where the REACH regulation is cited literally, this is indicated by text in italics between quotes.

Table of Terms and Abbreviations

See Chapter R.20

Pathfinder

The figure below indicates the location of Chapter R.19 within the Guidance Document



CONTENTS

TABLES

FIGURES

R.19 UNCERTAINTY ANALYSIS IN THE CHEMICAL SAFETY ASSESSMENT

R.19.1 Introduction

R.19.1.1 Objectives of this chapter on uncertainty analysis

This chapter provides guidance on dealing with uncertainty in the chemical safety assessment and outlines methods for making an uncertainty analysis. The underlying principle is that a tiered approach should be followed and that the amount of detail should be proportionate to the level of uncertainty and its potential impact on the risk characterisation.

The guidance has been written according to the principles outlined in the World Health Organisation's (WHO) "Draft guidance document on characterizing and communicating uncertainty in exposure assessment" (WHO-IPCS, 2006). It is important to note that the WHO document was written specifically for exposure assessment, whereas this chapter necessarily has a broader scope because both exposure and effects data need to be considered in a chemical safety assessment. However, the same general principles apply in terms of the approach to uncertainty analysis.

Section R.19.1.2. of this chapter provides a brief introduction to the role of uncertainty in risk assessment, and explains why it is an important part of the REACH process. Section R.19.2 then goes on to outline a number of key concepts in uncertainty analysis, which are aimed to help the reader better understand the nature of uncertainty within risk characterisation under REACH. This outline includes a classification of different sources of uncertainty, distinguishing between uncertainty and variability.

Section R.19.3 continues by providing a more detailed framework for carrying out a stepwise, tiered approach to uncertainty analysis that may be followed when analysing uncertainty in the chemical safety assessment. It outlines specific techniques for making qualitative, deterministic, and probabilistic uncertainty analyses, and provides criteria for deciding which of these approaches might be suitable under specific circumstances.

Section R.19.4 suggests approaches for reporting and communicating uncertainty in the chemical safety assessment

R.19.1.2 Role of uncertainty analysis in the chemical safety assessment

Each of the main components of chemical safety assessment (hazard assessment, exposure assessment and risk characterisation) involve the derivation or estimation of certain parameters, values, assumption and qualities about the nature of a substance and the situation(s) in which it is used. These include hazard endpoints about intrinsic properties of a substance, estimates used in the prediction or measurement of exposure in the environment or human population, and estimates of risk.

Inevitably, there are uncertainties at each stage of this process. For example there is an inherent degree of uncertainty in the quantification of hazard properties according to experimental method used. There is uncertainty when a series of estimations are used to define an exposure scenario. Wherever mathematical models are used to determine predicted exposure, the specific assumptions also introduce a degree of uncertainty.

Therefore, in order to produce a chemical safety assessment which is robust, reliable and adequate, it is useful to consider the degree of uncertainty in each part of the assessment.

In general terms, the amount of input required in an uncertainty analysis, and the importance of its contribution to the chemical safety assessment, will depend on the specific circumstances (see Section R.19.3.1.3 For example, it would not add much practical value to a chemical safety assessment to provide a detailed probabilistic uncertainty analysis for a substance which has a full data set, few hazardous properties, minimal exposure and a risk characterisation ratio (RCR) which is significantly less than 1.

On the other hand, for a more problematic substance a stepwise and thorough analysis of uncertainty produced and presented in accordance with the principles laid out in this chapter could significantly increase the robustness of the chemical safety assessment. This is discussed further in Section R.19.3.1.3 'Circumstances under which an uncertainty analysis is recommended'.

Ultimately, the importance of uncertainty analysis to each individual chemical safety report will depend on the specific circumstances and will be a matter of judgement for the reports author(s). Section R 19.3 of this Chapter outlines a tiered approach for carrying out an uncertainty analysis, starting with a basic qualitative approach and continuing if appropriate to more complex techniques like deterministic and probabilistic analysis.

Finally, it should be noted that this document may act as a good reference for those developing CSA/CSR tools for conducting (part of) the CSA. The documentation behind such tools should be transparent, including assumptions and uncertainties in the approaches taken in order to clearly communicate the application range of the tool to the user.

R.19.2 Key concepts in uncertainty analysis

R.19.2.1 Sources of uncertainty

As explained in the previous chapter, there are uncertainties at each stage of the chemical safety assessment:

- Hazard assessment: the degree of uncertainty in the measure of (no) effect,
- Exposure assessment: the degree of uncertainty in the exposure estimate (predicted or based on measurements),
- Risk characterisation: the degree of uncertainty in the risk estimate.

These uncertainties can be classified into three categories as indicated in the WHO-IPCS document (2006). It should be noted that the WHO document was written specifically for exposure assessment; however it is possible to broaden its concepts to the chemical safety assessment in general (including the hazard assessment and the risk characterisation). These three broad categories of uncertainties are scenario uncertainty, model uncertainty and parameter uncertainty.

Scenario uncertainty

Scenario uncertainty is the uncertainty in specifying the scenario(s) which is consistent with the identified use(s) of the substance. This uncertainty relates mainly to the level of accuracy of the scenario description.

Scenario uncertainty includes descriptive errors (e.g. wrong or incomplete information), aggregation errors (e.g. approximations for volume and time), errors of assessment (e.g. choice of the wrong model), and errors of incomplete analysis (e.g. overlooking an important exposure pathway).

Model uncertainty

Model uncertainty is the uncertainty in the adequacy of the model used with the scope and purpose of the assessment. In risk assessment, mathematical and statistical models are often applied to represent an exposure or hazard process though a model is always a simplification of reality.

Model uncertainty is principally based upon extrapolation (i.e. use of a model outside the domain for which it was developed), modelling errors (i.e. non-consideration of parameters in the model structure itself, assumption of well-mixed phases etc.) and dependency errors (i.e. lack of consideration of correlations between parameters).

Parameter uncertainty

Parameter uncertainty is the uncertainty involved in the specification of numerical values. Risk assessment involves the specification of values for parameters, either for direct determination of the exposure/effect or as input for mechanistic, empirical or distribution based models which are used. The uncertainties surrounding these values are very common due to lack or insufficiency of data.

Parameter uncertainties include:

- Measurement errors:

  e.g. influence of the methodology used, errors in the analytical method used to measure chemical concentration, technical inadvertence;

- Sample uncertainty:

  representativeness of the data set, e.g. a small sample may not give the entire range of values found in reality; the sample may be biased towards lower or higher values as a result of the selection criteria used to take the sample; averaging methodologies;

- Selection of the data used for assessing the risk:

  i.e. use of default data (e.g. TGD (technical guidance document) default data are frequently used for exposure assessment) or choice of the dose descriptor (i.e. uncertainty in choosing one data among others for risk assessment purpose);

- Extrapolation uncertainty:

  i.e. use of alternative methods (e.g. QSAR, in-vitro test, read-across for similar substances) or use of assessment factors (e.g. inter-species, intra-species, acute to chronic, route to route, lab to field extrapolation).

Classification using the three categories defined above is not as strict as it may seem. In some cases, uncertainties may in practice arise in overlapping areas. For instance, numerical values of model parameters are often determined from the calibration of a model against some dataset. In this case, the parameter values may be uncertain both to the extent that this calibration dataset suffers uncertainty in measurement (parameter uncertainty) and that the model which is calibrated is not adequate for the situation (model uncertainty).

In order to identify the main sources of uncertainty involved in the chemical safety assessment, a checklist is provided in Section R.19.3.2.

R.19.2.2 Uncertainty and variability

In many recent uncertainty studies, the difference between variability and uncertainty in the risk assessment is emphasised (Jager et al. 2001a, Verdonck et al., 2005).

Uncertainty can be caused by limitations in knowledge (e.g. limited availability of empirical information), as well as biases or imperfections in the instruments, models or techniques used. An example is an emission estimate that is based on a reasonable-worst case assumption. The limited knowledge about this factor could be improved (and uncertainty decreased) by site-specific knowledge or measurements. This matters because the real emission (and associated exposure) can differ from the presumed worst-case emission. Consequently, as the quality of data and models improves, the amount of uncertainty decreases. Thus, uncertainty can be reduced by developing an improved knowledge base.

Variability, on the other hand, refers to variation that exists in the real world. It is an inherent property of a system that can not actually be reduced thanks to further information. There are various sources of variability such as:

- Inter-species variability;

- Intra-species variability (e.g. due to age, sensitivity, physiology, behaviour…);

- Variability in environmental characteristics (e.g. temperature, wind, homogeneity…);

- Variability in time and space.

Therefore one of the main differences between uncertainty and variability is the fact that uncertainty is often reducible through further information, whereas variability is not. However, what can be done is to reduce the uncertainty in our knowledge about the actual variability (Jager et al. 2001a, EUFRAM 2005).

R.19.3 Uncertainty analysis in the chemical safety assessment

R.19.3.1 Qualitative, deterministic and probabilistic analysis: introduction to the tiered approach

Section R.19.1.2 introduced the concept that uncertainty analysis can be a useful tool for increasing the robustness, reliability and adequacy of the chemical safety assessment. This section provides further details on uncertainty analysis, and discusses the circumstances under which it would be worthwhile to include the detailed results of an uncertainty assessment in the chemical safety report. The section goes on to introduce the concept of a tiered approach to uncertainty analysis, starting with basic qualitative assessment and continuing, if appropriate, to more detailed deterministic and probabilistic techniques. Subsequent sections (Sections R.19.3.2 to R.19.3.4) provide more detailed guidance on how to carry out each of these types of uncertainty analysis.

Two important factors that can influence the need for uncertainty analysis are (i) the risk characterisation ratio and (ii) the techniques that have been used to derive it. This is discussed further in the following subsections.

R.19.3.1.1 The risk characterisation ratio

Fundamentally, uncertainty is important in the chemical safety assessment because of its potential impact on the outcome of the risk characterisation. In Part E of the Guidance risk is usually characterised by means of a deterministic quotient of exposure and effects:

- a comparison of the exposure of each exposed human population (whether measured or calculated) with the appropriate derived no-effect level (DNEL)
- a comparison of the predicted environmental concentration (PEC) in each environmental compartment with the corresponding predicted no-effect concentration (PNEC)

The REACH regulation states that for any exposure scenario, the risks to humans and the environment can be considered to be adequately controlled, throughout the lifetime of the substance that results from manufacture or identified uses, if:

- the exposure levels do not exceed the appropriate DNEL or PNEC
- the likelihood and severity of an event occurring due to the physicochemical properties of the substance is negligible

Therefore, the resulting risk characterisation ratios (RCR) from the comparison of the human and environmental exposure with the corresponding no effect levels are a major driver in risk characterisation and chemical safety assessment, and the RCR uncertainty will also be an important output of uncertainty analysis.

It should be noted that under certain circumstances it may not be possible to derive a risk characterisation ratio, for example where the DNEL or PNEC cannot be calculated. Under other circumstances, it may not be necessary to carry out the exposure assessment or risk characterisation because the substance does not meet the criteria for any of the Article 14(4) hazard classes, categories or properties[2], although an exposure assessment would still be required if a case has been made for exposure based waiving. The current paper mainly addresses the situation where a DNEL/PNEC can be derived, but the general principles could also be applied if a qualitative or semi-quantitative risk characterisation is conducted.

R.19.3.1.2 Validated methods *versus* non-standard techniques

Another factor which can influence the need to carry out an uncertainty assessment relates to the type of regulatory tools that have been used to derive the input parameters and estimates of effects and exposure. If the registrant has developed higher tier methods to generate exposure or effects estimates and novel or non-standard techniques have been used then an uncertainty analysis might be a useful part of the documentation provided to justify the approach within the CSR.

2

- hazard classes 2.1 to 2.4, 2.6 and 2.7, 2.8 types A and B, 2.9, 2.10, 2.12, 2.13 categories 1 and 2, 2.14 categories 1 and 2, 2.15 types A to F
- hazard classes 3.1 to 3.6, 3.7 adverse effects on sexual function and fertility or on development, 3.8 effects other than narcotic effects, 3.9 and 3.10
- hazard class 4.1:
- hazard class 5.1;
- or PBT, vPvB properties.

R.19.3.1.3 Circumstances under which an uncertainty analysis is recommended

Uncertainty analysis is of most potential benefit in situations where RCR is close to the regulatory trigger value (above or below a RCR of one), and more insight is needed in the robustness of the risk characterisation. It might also be of benefit in some situations where the RCR is close to the trigger value but non-standard methods have been used to derive the relevant values, or where the registrant simply wants to carry out their own uncertainty analysis to improve their characterisation of the risk.

For example, in situations where the RCR has been derived by non-standard methods and is below but close to the regulatory trigger, then the inclusion of an uncertainty analysis within the chemical safety report could considerably increase the robustness of the chemical safety assessment.

Therefore, the need to consider uncertainty depends on a range of circumstances related to the absolute value of the RCR; its method of calculation; and the level of uncertainty in the assessment.

Uncertainty analysis is recommended for use in the following types of situations:

- RCR > 1. Where the RCR exceeds 1, it will clearly be necessary to refine the assessment. Under these circumstances, uncertainty assessment can help the registrant to identify and target the main sources of uncertainty in the chemical safety assessment for subsequent refinement in higher tier approaches. Additionally, the assessment can be used to improve the characterisation of the risk.
- When non-standard, non-guideline approaches have been used. Under these circumstances, a registrant might include an uncertainty analysis as part of the supporting documentation justifying the use and applicability of a non-standard risk characterisation method.
- Even where the RCR is less than but close to 1 and standard approaches have been used in accordance with the TGD, a registrant might choose to carry out a qualitative uncertainty analysis to help satisfy themselves that their chemical safety assessment is robust and adequate.

Figure R. 19-1 below outlines the general circumstances under which an uncertainty analysis would be recommended. In the first pathway of the diagram the initial chemical safety assessment shows that the risks are not adequately controlled (e.g. the RCR > 1). Under these circumstances, uncertainty analysis is recommended as a useful guiding tool to help target identify which parameters in the chemical safety assessment possess the greatest uncertainty or might be resulting in an exaggerated overestimation of risk.

In the second pathway, the risk is considered to be under control but either the RCR is close to 1 and/or major uncertainties are envisaged (for example due to the use of non-standard approaches to the chemical safety assessment) and so the uncertainty analysis is recommended to test the robustness of the RCR and as a way of demonstrating a low likelihood that the risk has been underestimated and that the RCR might exceed 1.

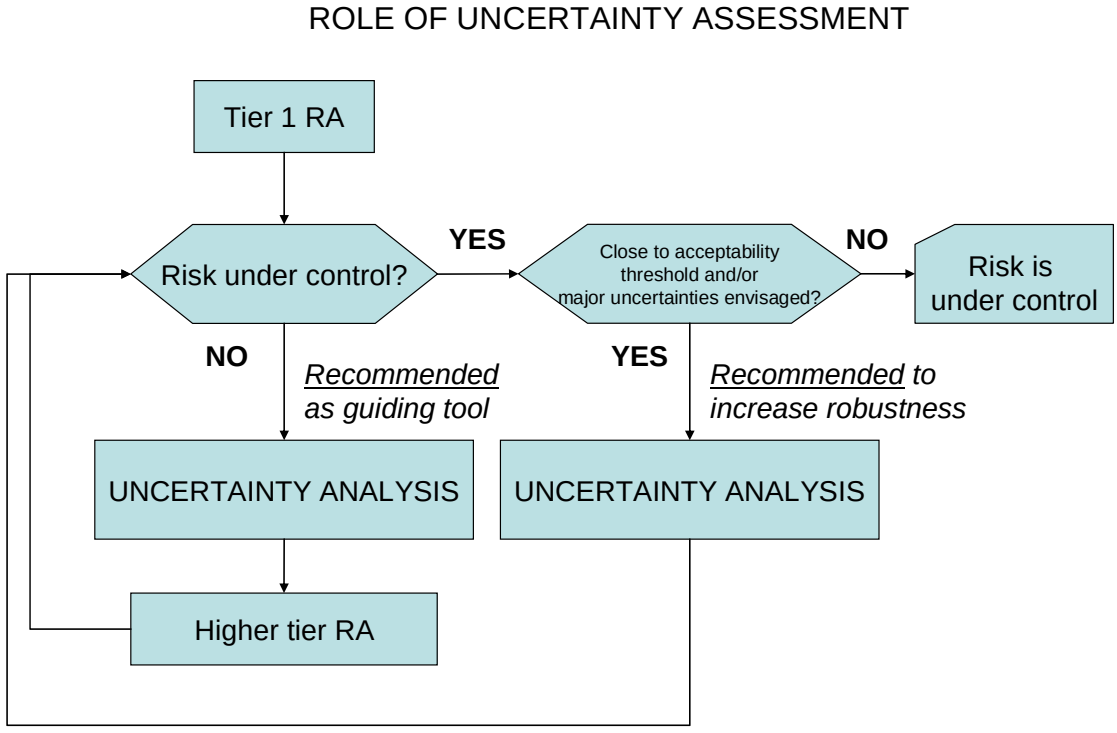


Figure R. 19-1 Circumstances where an uncertainty analysis is recommended.

R.19.3.1.4 The stepwise approach

It should now be clear that it is not practical or necessary to conduct a detailed analysis of uncertainties in every chemical safety assessment. On the contrary, the amount of effort and detail should be proportionate to the needs. For these reasons, a stepwise approach to uncertainty analysis is recommended, as follows.

At the most basic level the standard chemical safety assessment accounts for uncertainty by using conservative assumptions and default values, for instance following specific Tier 1 methods recommended in the exposure estimation Chapters R.14 to R.18. Where this results in the risks being clearly and robustly addressed, this is sufficient and no further analysis is considered necessary.

At the next level (Level 1), all significant parameters are considered at least qualitatively. To gain additional insights, sensitive input parameters may be treated both deterministically (Level 2) and probabilistically (Level 3) (WHO-IPCS, 2006).

Therefore, the stepwise approach to uncertainty analysis may begin at Level 1 by treating all uncertainties qualitatively; this may be sufficient, if the outcome is clear enough for risk managers' purposes. Otherwise, those uncertainties which appear critical to the outcome may be analysed quantitatively; this can be done deterministically or, if necessary and feasible, probabilistically.

The benefits of progressing from lower to higher levels of uncertainty analysis are illustrated for a hypothetical example in Figure R.19-2. Higher tiers of uncertainty analysis lead to better

understanding and characterisation of uncertainty; this may show that the uncertainty is less than was assumed at lower tiers, but variation may be greater. Higher levels progressively refine the characterisation of uncertainty and variability, and enable the assessor to give a more realistic estimate of the likelihood of the RCR being exceeded. This approach is outlined in Figure R.19-2. At level 0, a point estimate is derived using agreed conservative assumptions and default values, for instance following specific methods recommended in the TGD. As has been previously described, the impact of uncertainty is considered to be implicitly built into this estimate by the use of these conservative assumptions. However, in this example the RCR is greater than one and so further work is clearly required to refine the risk assessment.

At Level 1 a qualitative uncertainty analysis can be used to refine the estimate of exposure and estimate an indicative range of unquantifiable uncertainties. In this specific example, the point estimate and the upper end of the indicative range do not demonstrate adequate control of the risk.

At Level 2, a deterministic approach uses different combinations of assumptions to make a range of point estimates, which in this example fall around the RCR value of 1 and provide more quantitative information about the sensitivity of the RCR to specific parameterisation.

Finally, at Level 3 a probability distribution is derived which provides statistical information about the likelihood that the RCR will be exceeded under specific circumstances and according to the parameterisation used.

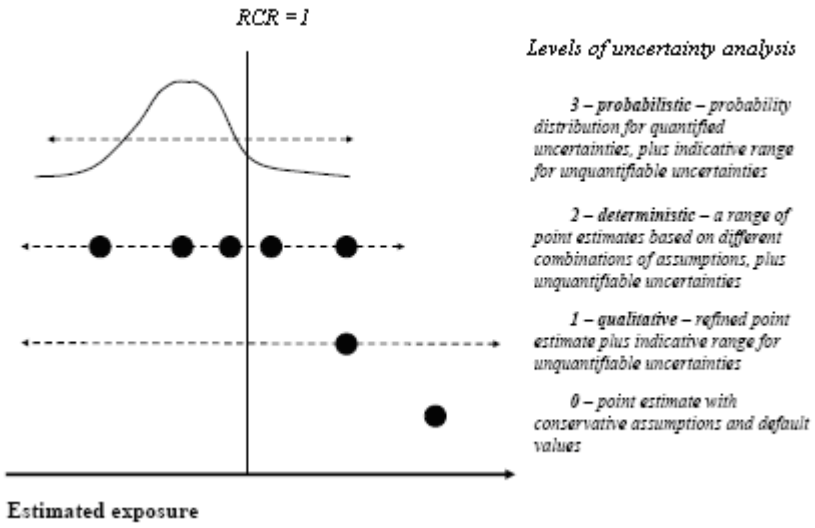


Figure R.19-2 Illustration of the benefits of progressing from lower to higher levels of uncertainty analysis.

The solid circles represent point estimates of exposure. The dotted lines represent the indicative range of exposure (after EFSA, 2006)

Level 1 – Qualitative assessment

Level 1 treats all uncertainties qualitatively. For qualitative analysis, it is proposed to list the different sources of uncertainty and or variability. These sources can be classified in order to identify the main uncertainties and ways to refine the CSA. Uncertainties assessed at Level 1 may be communicated by listing or tabulating them, together with an indication of their direction and magnitude (see part C of Section R.19.3.2 for the definitions of direction and magnitude). In

addition, it will generally be desirable to give a more detailed discussion in the text of the more important uncertainties, and of their combined effect on the assessment outcome. Further details and possible formats for this are given in Section R.19.3.2.

Level 2 – Deterministic assessment

Uncertainties assessed at Level 2 (deterministic) generate alternative point estimates, by making a series of reasonable worst-case assumptions for the determination of the exposure and by the use of varying factors for the determination of the hazard. Reasonable worst case assumptions can be incorporated in different ways, e.g. built into the exposure model, based on expert judgment ('I have never observed a factor X lower than Y) or on a quantitative measure (e.g. 95th percentile estimates for use as input data for modelling of environmental exposure).

Deterministic approaches can be thought of as a simplified sensitivity analysis. Further information on deterministic approaches and their application in the chemical safety assessment is given in Section R.19.3.3.

Level 3 – Probabilistic assessment

Uncertainties assessed at level 3 (probabilistic) include a probabilistic assessment of those uncertainties which appear critical to the outcome of the chemical safety assessment. Probabilistic approaches enable variation and uncertainty in effects and/or exposure and the resulting risk to be quantified, mainly by using probability distributions instead of fixed values in risk assessment.

- The results of a probabilistic risk assessment (PRA) are also shown as distributions. This allows the assessor to see the most likely impact (expressed as the RCR), but also within which ranges. This could potentially provide a better basis for making decisions about further iterations of the CSA.

In addition, output from a probabilistic assessment will often include a sensitivity analysis, identifying major contributors to variability and uncertainty in the estimated exposure. Note however that Assessment Factors will be derived and fixed according to the TGD.

More detailed information on the use of probabilistic uncertainty analysis is provided in Section R.19.3.4.

R.19.3.1.5 How to use the results of the uncertainty analysis

As discussed in Section R.19.3.1.3 the need to carry out an explicit uncertainty analysis is related to the degree of uncertainty in the risk characterisation and the RCR value. If an uncertainty analysis is considered needed, it can be carried out according to the tiered approach outlined in Section R.19.3.1.4 and using the specific methods in Sections R,19.3.2. to R.19.3.4 .

Where the application of a tiered uncertainty analysis gives a clear indication that the risk is adequately controlled (e.g. an increased belief that the (distribution of the) RCR is less than 1), it would be sufficient to present the results of the analysis according to the recommended method. However, another possible outcome is that the uncertainty analysis simply provides evidence that in fact the RCR is 'marginal' or even that it might exceed 1 under specific realistic circumstances. In such a case, the results of the uncertainty assessment strongly indicate that the chemical safety assessment needs to be refined.

It is important to note that the uncertainty analysis may not only help to determine the degree of confidence in the RCR, but it can also help to identify which specific parameters should be targeted in a refined risk assessment.

Figure R. 19-3 outlines a possible iterative approach for using the tiered uncertainty approach in the chemical safety assessment.

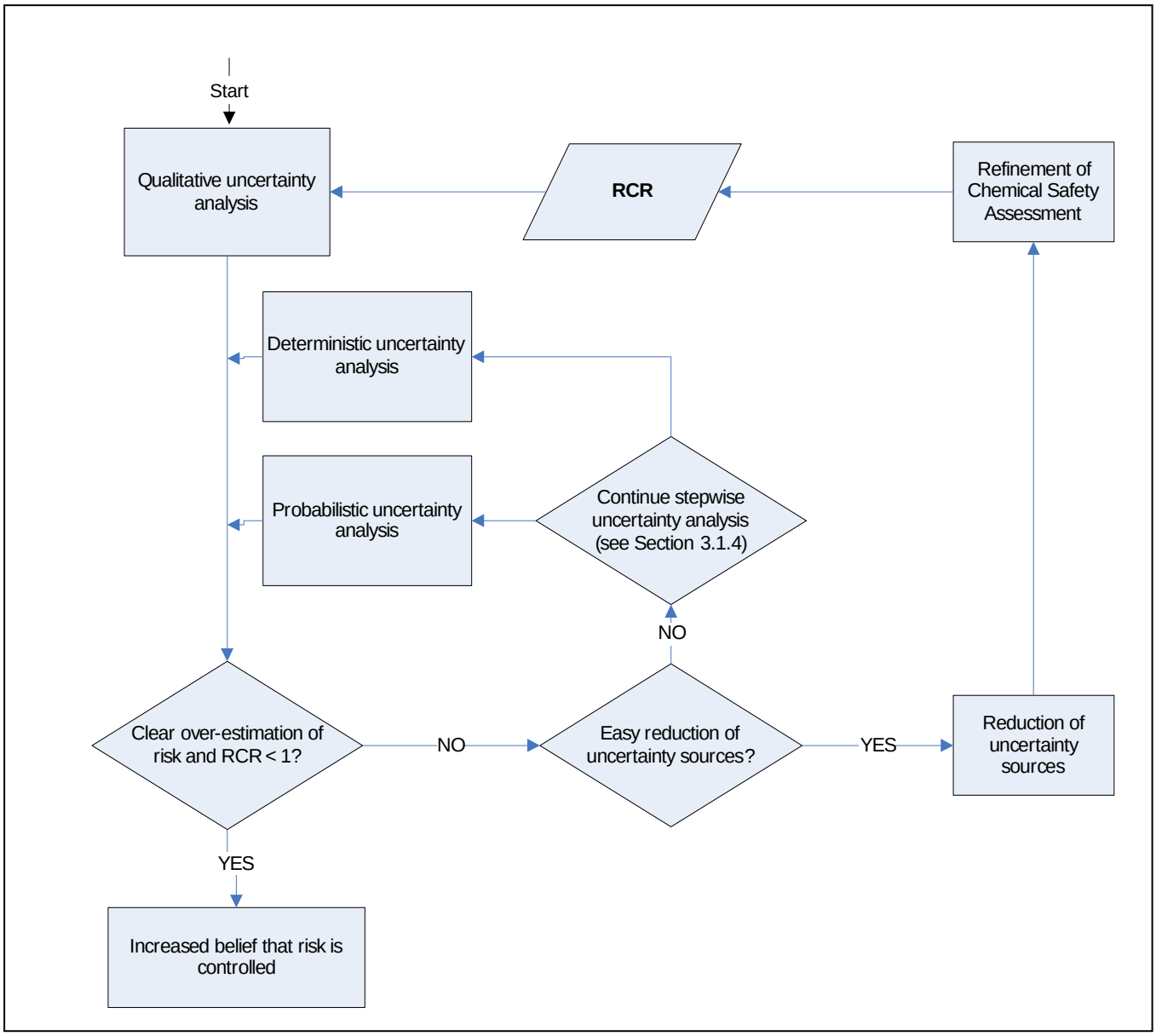


Figure R. 19-3 Possible approach to uncertainty analysis in the chemical safety assessment.

R.19.3.2 Level 1 - Qualitative uncertainty analysis

Baseline approach

The Level 1 - qualitative evaluation of uncertainty consists of the identification of uncertainty sources and their qualitative characterisation. It aims at providing a comprehensive view of main

uncertainties as a basis for the risk assessment refinement or the application of quantitative uncertainty evaluations in Level 2 (deterministic) and/or Level 3 (probabilistic). Various methods for the qualitative evaluation of uncertainties have been developed, all of them consisting in a systematic screening and classification of all uncertainty sources (e.g. EFSA, 2006; WHO/IPCS, 2006; Van der Sluijs et al. 2003, Petersen et al., 2003). A baseline approach to the qualitative assessment of uncertainty is described below and structured into six points. It is based on principles of maximum simplicity and workability, but should not stop the risk assessor from considering more structured and detailed assessment methods as reported in the fore mentioned guidelines and scientific papers.

A) Systematic identification of uncertainties. Uncertainties can be separately assessed in the hazard assessment and the exposure assessment phases, and the assessment of the overall uncertainty be performed in the risk characterization phase.

B) Uncertainties classification. As mentioned in the introduction chapter, sources of uncertainties can be aggregated into three groups, i.e. scenarios, model and input parameters, respectively. Moreover, two types of uncertainties should be distinguished, i.e. uncertainty and variability.

C) Uncertainties evaluation. The risk assessor needs to know whether identified uncertainties potentially lead to underestimate or overestimate the risk, and to which extent. Therefore, each individual uncertainty source can be characterised in terms of direction and magnitude. "Direction" refers to any directional influence of an uncertainty on the assessment outcome (EFSA, 2006), i.e. the inclination for overestimation or underestimation of the risk. For example, if the uncertainty source implies the use of a conservative assumption, it tends to overestimate the risk. "Magnitude" refers to how much the specific uncertainty source potentially affects (underestimates or overestimates) the risk outcome. The main interest is not the uncertainty source itself (e.g. percent uncertainty of the input parameter) rather than the effect on the risk estimate (e.g. percent impact on the risk outcome).

D) Criteria and scaling for evaluation. Indication of magnitude can be expressed using a simple qualitative scale, e.g. low, medium and high. Three useful ways of defining the magnitude scale are the following:

i) the magnitude scale can be referred to the potential of that uncertainty source to increase the estimate above the level of concern (if known). This type of scale allows considering whether the combined uncertainties are large enough to affect the decision making based on the risk evaluation (EFSA, 2006);

ii) the magnitude scale can be defined in relation to the magnitude of specific sources of uncertainties; for example, the smallest and largest contributors could be classified as "low" and "high" and all other uncertainties could be expressed relative to these (EFSA, 2006). While this scale supports a comparative assessment of source of uncertainty, it does not allow considering the combined effect of uncertainty sources on the risk outcome;

iii) the magnitude scale can be defined with reference to the estimated variation of the risk outcome in terms, e.g., of orders of magnitude; for example, sources of uncertainty marked as "low", "moderate" and "high" may affect risk estimates by less than one order of magnitude, less than two orders of magnitude and more than two orders of magnitude, respectively (US-EPA, 1989).

E) Evaluation of the overall uncertainty. In this scope the mathematical combination of magnitude estimates (e.g. scores) for each source of uncertainty would be misleading, while a subjective

consideration of the assessor would be preferred with account of correlation and dependencies among uncertainty sources (EFSA, 2006).

F) Final outcomes. The final result of the qualitative uncertainty assessment should be the identification of most relevant sources of uncertainty and technical means for reducing them, as well as the evaluation of the overall effect of uncertainty sources on the risk estimate. In the case that the risk quotient is close to, but below limits of acceptability (RCR < 1), several potential outcomes of the qualitative uncertainty analysis are possible:

i) there is clear evidence that risk is over-estimated, therefore there is increased belief that risk may be adequately controlled,

ii) there is no clear evidence that risk is over-estimated, therefore a more detailed (e.g. quantitative) uncertainty analysis or a refinement of the risk assessment by reduction of uncertainties are recommended.

The feasibility of reducing uncertainty sources depends on the type of uncertainty, the possibility of gaining further data and applying more reliable assessment methods. The application of quantitative uncertainty assessment (tier 2 and tier 3) is generally recommended in order to overcome judgmental biases. However, the qualitative uncertainty assessment should be always performed in order to out point the uncertainty sources to address in the quantitative evaluation and to consider those uncertainties that can not be quantified.

Checklist of sources of uncertainty

The systematic identification of potential sources of uncertainty can be supported by the use of checklists. For the sake of example, a rough checklist of main sources of uncertainty in the most general case is reported in Table R. 19-1 and Table R.19-2. More detailed checklists can be developed with specific regard to the type of considered risk (e.g. environmental, occupational, consumer), exposure category and type of considered effects (e.g. PBT assessment).

Table R. 19-1 Major sources of uncertainty related to effect assessment.

It should be noted that the adequacy of assessment factors is a source of uncertainty that has been addressed in the development of the TGD based on scientific state of art and agreed levels of conservatism, and is not expected to be re-considered on a case by case basis.

Uncertainty group	**Sources of uncertainty**
Model uncertainty	Adequacy of the model, e.g. QSAR, toxicokinetic and mechanistic models of effects: - oversimplification - dependency errors - use out of the validity domain
Parameter uncertainty (physicochemical and hazard	Measurement uncertainties, e.g.: - Low sample size - Measurement errors

properties)	Selection of data, e.g.: - Choice of the dose descriptor - Default values
	Extrapolation uncertainties, e.g.: - QSAR, QSPR (quantitative structure property relationships), Read-across, in-vitro test
	Adequacy of assessment factors associated to uncertainty, e.g.: - Interspecies (from animal to human) - Acute to chronic - Route to route - Lab to field

Table R.19-2 Major sources of uncertainty related to exposure assessment

Uncertainty group	**Sources of uncertainty**
Scenario uncertainty	Adequacy of exposure scenario assumptions, e.g.: - emission sources, (i.e. disregarding a relevant source of release during the manufacturing/use processes or the life-cycle) - exposed population (e.g. consumers, children) or ecological community - spatial and temporal setting (e.g. local, regional, short- or long-term) - environment of exposure (e.g. conceptual model of working place or natural environment) - Exposure pathway(s) / route (s) (e.g. disregarding an important exposure pathway / route) - Exposure event(s) (e.g. magnitude and frequency of the event) - Assumed efficacy of risk management measures (e.g. usage)
Model uncertainty	Adequacy of the model used, e.g.: - oversimplification - dependency errors - application out of the validity domain
Parameter and data	Measurement uncertainties, e.g.:

uncertainty	- low sample size - measurement error
	Selection of data, e.g.: - conservativeness in estimation of emissions - choice of the exposure concentration used for the exposure assessment - adequacy of default values - assumed effectiveness of risk management measures
	Extrapolation, e.g.: - read across for similar substances/scenarios
	Variability, e.g.: - Environmental variability (temperature, wind, homogeneity etc.) - Variation in behaviour (related to exposure potential) - Variation in time and space, relating to any of the above

A brief explanation of the sources of uncertainty included in the checklist is provided below.

In the effect assessment major sources of uncertainty appear to be the estimation of physico-chemical and hazard information.

As far the physico chemical data are concerned:

- it can be expected that uncertainty is most important when properties have to be estimated from QSPRs or other alternative estimation methods,
- uncertainty may also be due to the selection of test data, test methods employed or to sample size (see "sampling and measurement uncertainties" later),
- uncertainty in these parameters can (under selected, well-defined, chemical-specific conditions) be reduced considerably by more precise determination if considered critical (e.g., log K_{ow} to estimate bioaccumulation potential).

As far the hazard information is concerned:

- although, in principle, the adequacy of assessment factor is a relevant source of uncertainty, it should be noted that assessment factors proposed by the TGD are the result of the analysis of the state of knowledge and widely agreed level of conservatism. It follows that the modification of assessment factors is not a generally accepted practice and should only possible based on the same TGD principles regulating the assessment factors derivation,
- the analysis of uncertainty is especially recommended when hazard information is based on alternative test methods, because the relevance of their results has to be evaluated on a case by case basis,

- it is important to have a comprehensive understanding of the conservatism behind the assessment factor.

In the exposure assessment, main uncertainties can be hidden behind the assumptions made in the exposure scenario or the measurements used. In the exposure scenario the main sources of uncertainty to be considered are linked to the emission and exposure of the substance, efficiency of risk management measures, and the pathway / route of exposure,

Some specific considerations are the following:

- a qualitative risk assessment is especially important for empirical/knowledge-based models. The model structure of an empirical model is not in the form of equations. However, the model structure of an empirical model can also be flawed, e.g. when an important parameter is not considered in the model, or the influence of a parameter is substantially over- or underestimated.

- a large portion of uncertainty in modelling cannot be evaluated in a strict quantitative manner. The uncertainties of qualitative input parameters and of the logical structure of the model can in general only be discussed qualitatively.

As far the input parameters are concerned:

- uncertainties can arise in measurements. For example, not all of a physical sample during the chemical analysis may be recovered, which may lead to underestimated exposures. Some of the measurements may be below the limit of detection of the applied method and will therefore underestimate exposure if recorded as zero, or overestimate it if recorded as equal to the limit of detection. There may also be uncertainties in the reading of laboratory measuring devices and uncertainties as a result of some other aspect of laboratory process (e.g. sample preparation). The applied sampling protocols (e.g. EN 689) and good laboratory practice minimise these uncertainties.

- most of the measured data received on exposure estimation are small data sets, and less than 12 data points are not uncommon. For small sets of data points, statistical sampling uncertainties need to be considered when properties are estimated (e.g. the median or the 90th percentile) for exposure data. The smaller the number of observations, the larger the uncertainties associated with any inferences that may be derived from them.

- the most relevant question to ask is whether the data obtained are appropriate for the purposes of exposure assessments. The main question whether the data set is representative for the exposed population or natural community. Qualitative information on the data set will affect the interpretation of any inferences made from it.

- Uncertainties can arise as a result of the method by which measurements are selected for inclusion in the data set, particularly if data are pooled before or during the risk assessment process. A random or stratified sampling strategy would give different percentile values, averages and spread in the data than the pooled data sets. If measurement data are pooled, it should be done in a transparent way.

- When quality measured data are not available for a particular scenario, it may be possible to extrapolate from data from analogues using expert judgement. Due to the extrapolation process, the uncertainty in the estimation will increase.

- It may seem that measurements always give more reliable results than model estimations. However, measured concentrations can have a considerable uncertainty associated with

them, due to temporal and spatial variations. Therefore, the availability of adequate measured data does not imply that PEC calculations are unnecessary. Both approaches complement each other in the complex interpretation and integration of the data.

Example of qualitative evaluation of uncertainty

An example for the qualitative assessment of uncertainties is reported in Table R. 19-3, where sources of uncertainty are grouped into scenario, model and input parameters uncertainties, each source of uncertainty is further classified into variability or uncertainty and then evaluated for direction and magnitude. The symbols + and – indicate overestimation and underestimation, respectively, and the scales from + to +++ and from – to --- indicate the magnitude (e.g. in a scale from 1 to above 3 orders of magnitudes). As it can be noted in Table R. 19-3, in many cases the direction of the uncertainty is not known and therefore expressed as +/-.

Table R. 19-3 Example of table for the qualitative assessment of uncertainties

	SOURCES OF UNCERTAINTY		VARIABILITY OR UNCERTAINTY	DIRECTION & MAGNITUDE
HAZARD ASSESSMENT	Model	Source 1	VAR	-
	Input parameters	Source 2	UNC	+++
		Source n	UNC	++/--
	Overall effect on hazard estimate E.g.: Mainly affected by overestimation from Source 2, which is uncertainty that may be reduced by…			
EXPOSURE ASSESSMENT	Scenario	Source 1	UNC	++
	Model	Source 2	VAR	+
		Source 3	UNC	+/-
	Input parameters	Source 4	UNC	-
		Source M		--
	Overall effect on exposure estimate E.g.: Mainly affected by overestimation from Source 1 and Source 2. Source 1 can be reduced by means…. Data on variability of Source 2 out line that adopted conservative assumptions are plausible only if…			
RISK CHARACTERIZATION	Overall effect on risk estimate E.g.: The risk estimate appears to be overestimated mainly based on assumptions in exposure assessment, that may be revised on the basis of further investigation …			

Legend: +, ++, +++ = low, moderate and high overestimates; -, --, --- = low, moderate and high underestimates; VAR= variability; UNC= uncertainty

Communication of the qualitative evaluation of uncertainty

The reporting of the qualitative evaluation of uncertainties does not pose relevant problems of communication, since checklists, tables or matrices applied for the systematic analysis of uncertainty sources can be presented and easily interpreted by the reader.

R.19.3.3 Level 2 - Deterministic uncertainty analysis

Baseline approach

When a qualitative assessment indicates a sufficient likelihood that single or combined uncertainties could alter the risk management decision, then it may be useful to examine them quantitatively. This can be done by performing a scenarios analysis, i.e. by changing critical assumptions and/or input parameters and calculating the effect on the assessment outcomes. The aim is to evaluate whether the main uncertainties identified in the qualitative assessment might be large enough to alter the assessment outcome and change the risk management decision. Therefore, the deterministic uncertainty analysis can be seen as a simple sensitivity analysis method, with limited capability as far the number of parameters and the combined effects that can be considered.

The outcome of the deterministic uncertainty assessment is the confirmation of robustness of the risk evaluation or the indication for the further reduction of uncertainty and refinement of the risk evaluation.

The baseline procedure for the deterministic assessment of uncertainties can be the following:

A) Selection of uncertainty sources. Based on the qualitative uncertainty assessment (Level 1), a limited group of uncertainty sources to be analysed in quantitative terms should be selected.

B) Scenarios analysis. For the selected uncertainty sources a scenario analysis should be performed. It consists of defining two (e.g. use a worst case and an average case) or more scenarios differing for the most uncertain input parameters/assumptions according to various degrees of conservatism. The risk is then estimated for each scenario.

C) Comparative analysis of risk estimates. In the case scenarios vary for one single assumption or parameter, the relevance of the uncertainty on that assumption or parameter will be investigated. In a combined scenario analysis where multiple uncertainty sources are varied in the best-case / worst case, the comparison of risk estimates may show the overall and the relative influence of the individual sources.

D) Outcomes of the uncertainty analysis. Using the knowledge gained from the deterministic assessment of uncertainties, it should be decided whether additional information may significantly reduce the uncertainty and improve the accuracy of the RCR. Options are to collect more hazard information, more exposure information or better define the variability in the exposure scenarios. It should be considered that variability itself cannot be reduced, only better characterized. If necessary, additional RMMs can be considered to demonstrate adequately controlled risks.

E) Reporting. The uncertainty analysis should be reported in the CSA outlining the main points of the assessment and its key results.

Selection of uncertainty sources

Selecting the uncertainty sources to be addressed (Step A) and how they can be combined in different representative scenarios (Step B) is often difficult.

Criteria for the selection can be (a) the potential impact of that specific uncertainty on the risk estimation and (b), when the risk refinement is addressed, the possibility of reducing that uncertainty based on further investigations. In this scope, useful indications are provided by previous sensitivity analysis studies performed on the EUSES model. Based on previous studies of Jager et al. (1997, 1998, 2000) Verdonck et al. (2005) indicates that key parameters in EUSES for the estimation of the environmental exposure are tonnage, release scenario, biodegradability,

lipophilicity (K_{ow}) and volatility. The availability of further sensitivity studies on updated version of EUSES and sensitivity studies on other exposure scenarios (e.g. occupational exposure) would be useful.

Scenario analysis

In the most common case two alternative scenarios are defined by selecting best cases and worst cases for assumptions and/or input values. In order to distinguish between variability and uncertainty sources, three scenarios can be developed (MERAG factsheet, 2007):

1. The reasonable worst-case scenario accounts for all worst-case assumptions and parameters caused by both variability and uncertainty;
2. The typical scenario account for the worst-case assumptions and parameters only caused by variability;
3. The average scenario does not account for sources of variability and uncertainty. It is characterized by averages or medians for parameters. In some cases it can be judged not sufficiently protective for the environment and thus not considered.

The outcomes of this approach are represented in Table R. 19-4, where PEC and PNEC outcomes of the three scenarios are reported on the Concentration axis. In this hypothetical case PNECs are always higher than PECs, even in the reasonable worst case scenario; this outcome of the deterministic uncertainty assessment would corroborate the belief that the risk is adequately controlled. In other cases the worst case scenario might show PNEC lower than PEC. In those cases the analysis of the plausibility of the worst case scenario provides an insight on the feasibility of uncertainty reduction options. The development of average, typical and worst case scenarios allows the distinction between uncertainty and variability: the difference in risk outcomes between the reasonable worst-case and typical scenario can be considered as a measure for uncertainty, while the difference between the typical and average scenario can be considered as a measure for variability.

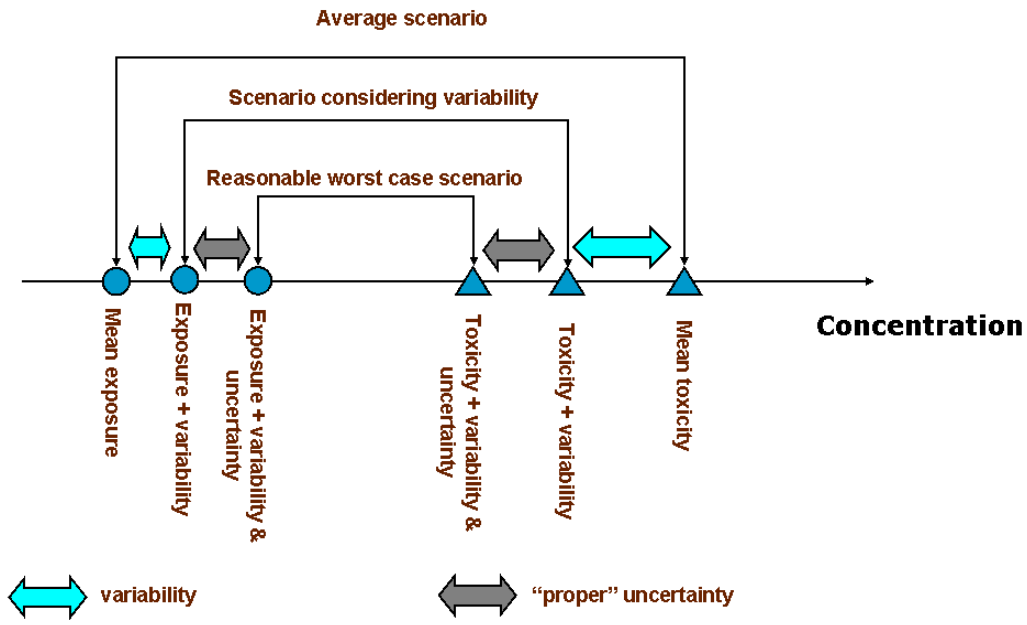


Figure R. 19-4 Deterministic risk assessment related to average, typical and reasonable worst case scenarios.

The development of representative scenarios should be based on available data and expert judgment on the plausibility (or probability) of that assumption/parameter in the reality, with additional consideration of risk management consequences. This is because the plausibility or probability of the scenario determines the probability of the resulting exposure estimate, which in turn determines the level of certainty in managing the risk (EFSA, 2006). Therefore, the assessor should try alternative assumptions and a range of input values and report the resulting risk estimates together with an evaluation of their relative plausibility. Whereas the probabilistic risk assessment (Tier 3) allows quantifying this probability, the deterministic approach implies subjective evaluations only. Terms such as "probable", "low probability" etc. or numerical scales (e.g. a 1 in 10 chance) can be used. It is important to consider that the combination of multiple conservative assumptions can quickly lead to a scenario that is extremely conservative and even beyond the bounds of possibility.

Communication of the deterministic evaluation of uncertainty

The uncertainty evaluation can be reported separately for the effect assessment, the exposure assessment and the risk characterization. The rationale and attributes of different representative scenarios should be clearly reported, together with resulting risk estimates. As a minimum, the reporting of the deterministic uncertainty assessment should:

- identify which uncertainties have been treated at Tier 2,
- if only one uncertainty is quantified, present the alternative input values used, describe their relative plausibilities and give the corresponding exposure estimates,
- if more than one uncertainty is quantified, present the alternative combinations of input values used, their relative plausibilities and the corresponding exposure,
- a comparison of risk estimates should be reported with indication of which sources of uncertainty have most influence on the outcome.

It may be helpful to summarise the results in tables or graphs, showing the relation between input values and the resulting exposure or risk.

R.19.3.4 Level 3 - Probabilistic Uncertainty Assessment

The probabilistic assessment of uncertainty aims at defining the probability that that the RCR is exceeded, given the fact that both the effect and the exposure are probabilistic factors. While deterministic risk assessment methods try to overcome uncertainties by introducing worst case assumptions and lead to an assessment with an unknown degree of conservatism, probabilistic methods try to quantify uncertainties in probabilistic terms. The advantage of the probabilistic risk assessment is that of more accurate risk estimates consistent with the probabilistic nature of risk, whereas the constraints are that of being demanding in terms of data collection/availability, calculation effort and experience of the risk assessor. Other factors limiting the use of probabilistic techniques are the lack of guidance, and difficulties in risk communication. For these reasons, the probabilistic risk assessment is usually undertaken only for substances of high concern and large data availability. The application of probabilistic techniques may increase in the future along with the consolidation of guidance and the availability of simplified methods and software tools. A preliminary tentative of methodological guidance was made in EU within the EUFRAM programme (EUFRAM, 2005).

A variety of approaches exist for probabilistic analysis of the risk (and associated uncertainty), including 1D and 2D Monte Carlo simulations, bootstrapping and Bayesian analysis, fuzzy arithmetic and probability bounds (e.g. European Commission 2003, Cullen and Frey 1999, US EPA 1997, IPCS/WHO 2006). For a detailed description of these techniques the reader is referred to the sources cited above. Moreover, the uncertainty analysis of EUSES (Jager et al. 1997, 2000, 2001a,b, Vermeire 2001, Lessmann et al., 2005) can serve as a template for such an analysis.

The following Section R.19.3.4.1. and R.19.3.4.2 present general methodological aspects and an example of simplified method for the probabilistic risk assessment, respectively.

R.19.3.4.1 General methodological aspects of the probabilistic risk assessment

The probabilistic assessment of the risk (and associated uncertainty) implies the probabilistic estimation of the hazard, the exposure and the risk, as well as the analysis of sensitivity of different input parameters.

Probabilistic approach to hazard assessment

Uncertainty and variability of the effect need to be quantified. The interpretation of hazard is different between man and the environment:

- for human effect data, the benchmark dose concept (Slob and Pieters, 1998; Vermeire 2001) can be used to determine the dose-response relationship for the most critical endpoint(s);
- for ecotoxicological data, the SSD concept (Aldenberg and Jaworska, 2000; Aldenberg et al., 2002) can be applied to fit the available ecotoxicological data of different species.

Even though the standard TGD approach sometimes does not advocate these methods under certain data limitations, these accepted methods do provide the possibility (with standard software) to quickly determine the uncertainty and variability of the hazard assessment, even with limited data.

The outcome of the probabilistic estimation of the hazard can be expressed by a cumulative distribution similar to the red curve represented in Figure R. 19-5.

Confidence intervals can be also calculated for the cumulative distribution (not represented in Figure R. 19-5). While the cumulative distribution mainly represents the variability (e.g. inter-species variability in SSD), the width of confidence intervals mainly indicate the contribution of uncertainty sources.

Probabilistic approach to exposure assessment.

A probabilistic interpretation of measurements data in the environment can be performed. When the exposure is predicted by modelling, probabilistic methods are often used to quantify the propagation of the uncertainty associated to input parameters.

Basic steps for the probabilistic estimation of the effects of uncertainty in model input parameters are the following:

- Based on the knowledge obtained by the qualitative and/or quantitative deterministic uncertainty analysis, parameters to be treated in a probabilistic approach should be identified.
- Uncertainty and variability of model input parameters should be described by appropriate distributions. This usually involves the collection of data, expert judgement and fitting distribution functions to data. Dependencies among model input parameters should be also taken into account.
- Computations (e.g. Monte Carlo simulations) should be carried out to estimate the propagation of variability and uncertainty through the model. The model output will be also a probabilistic distribution shaped by uncertainty and variability.
- The estimated exposure can be expressed by a probability distribution (e.g. the exposure concentration distribution, also indicated with ECD) similar to the bell shaped blue curve represented Figure R. 19-5).
- Confidence intervals can be also calculated for the cumulative distribution (not represented in Figure R. 19-5). While the cumulative distribution mainly represents the variability (e.g. spatial and temporal variability of exposure), the width of confidence intervals mainly indicate the contribution of uncertainty sources.

The uncertainties associated to scenarios and applied models are usually not treated with probabilistic methods. In principle, the probabilistic approach can be applied to different scenarios or models, and associated uncertainties can be evaluated as in the deterministic uncertainty analysis (Level 2). In alternative, different scenarios/models can be also assigned probabilities representing their relative plausibility.

Probabilistic estimation of risk

The risk characterization ratio is no longer a deterministic estimate, but a distribution from which the probability that an RCR of one is exceeded can be calculated. Since the risk is assumed to be not adequately controlled when the exposure predicted concentration exceeds the predicted no effect concentration (PNEC or DNEL for the environmental and the human health risk, respectively), the probabilistic risk estimation is based on the overlapping of the exposure and the effect distributions. In Figure R. 19-5, the area under the curve of this distribution is the expected risk, given the fact that both exposure and effect are distributed. The only number that needs to be

communicated is the expected risk, which is a single number. In some cases it will be possible to assume mathematical forms for the distribution of both effects and exposure, and to estimate parameters for both distributions. Exposure and effects distributions can then be combined mathematically to derive expressions of risks (an example is given in Section R.19.3.4.2.). In other cases the combination of effects and exposure distributions can be calculated numerically by means of a Monte Carlo analysis.

Probabilistic risk assessment models yield distributions of model output that can be interpreted as a probability distribution of risk for predefined endpoints (Suter, 1993; Aldenberg et al, 2002). The correct interpretation of the risk prediction depends on the dimensions and units of both exposure and effect measures. This means that if the interest is the risk of acute mortality, both the ecological effect function and the exposure data distribution should be based on a relevant time scale, e.g. a 48-hour exposure. This compatibility should be extended to aspects of time and space, to assure that the predicted risk is a realistic and relevant event.

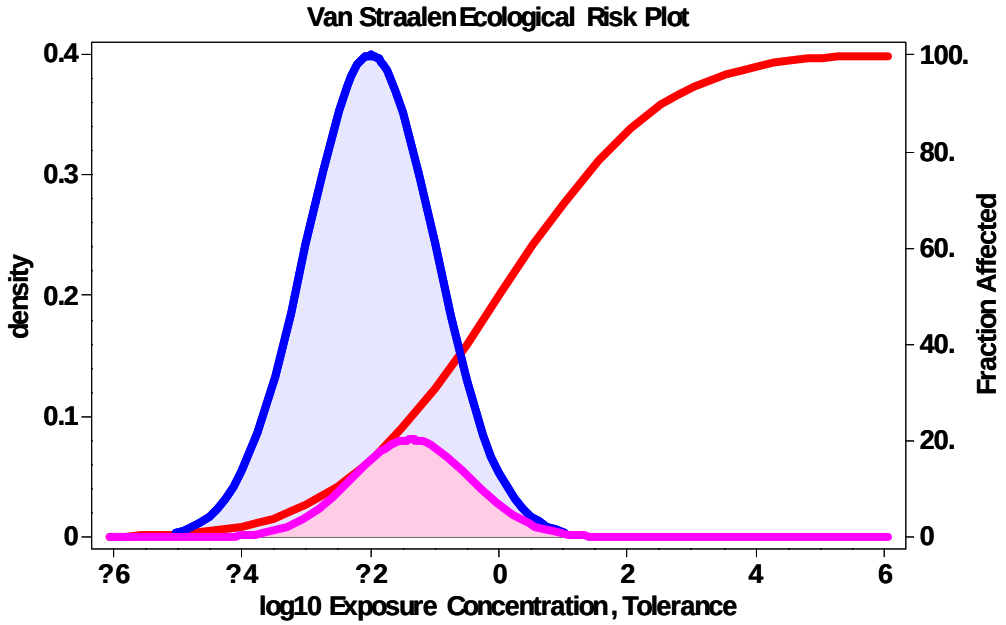


Figure R. 19-5 Distribution of overlap between exposure distribution and (no-) effect distribution

Exposure distribution (normal distribution on the left hand side) and (no-) effect distribution (cumulative normal distribution on the right). The smaller shaded curve results from multiplying exposure and effect functions. The area under the smaller curve is equal to the expected risk, when both exposure and effect are distributed: here 18.6% (Aldenberg, et al., 2002, Van Straalen, 1990, 2002).

Different approaches to the probabilistic analysis

Different probabilistic risk assessment applications are possible that consider uncertainty in the hazard assessment, or the exposure assessment or both.

If the interest is the probability that a no-effect level (PNEC or DNEL) is exceeded given uncertainty in exposure, the exposure concentration distribution (ECD) is compared to the no-effect level. The probability that the PNEC or DNEL is exceeded can then be read from the cumulative distribution function. In this case, the output of the probabilistic CSA reflects our uncertainty that a specific no-effect level is exceeded.

If the interest is the probability that a no–effect level is exceeded at a point estimate of exposure, given uncertainty in the no-effect level (due to inter-or intra species variation), the no-effect level distribution (e.g., SSD in ecotoxicology) is compared to the exposure level. In that case, the output of the probabilistic CSA reflects our uncertainty that a specific exposure leads to an effect.

A more sophisticated assessment is possible when both the no-effect level and the exposure are expressed as probability distributions, as represented in Figure R. 19-5. This type of analysis was pioneered by Van Straalen (1990) and Cardwell et al. (1993) and has since then been refined and internationally proposed as the standard framework for probabilistic risk assessment. In Section R.19.3.4.2. below, we will show how the three cases can be united.

Sensitivity analysis

A sensitivity analysis can be computed to examine the contribution of each model input to variation and uncertainty in the output. Such a sensitivity analysis can provide insight into whether a real world system is sensitive to perturbations of some of its components or processes, assuming that such relationships are adequately represented in the model. This allows a ranking of the input parameters concerning their contribution to the overall uncertainty. Based on the outcome of probabilistic exposure assessment and the sensitivity analysis, uncertainties that can be reduced (e.g. by further investigation or risk management measures). A comprehensive description of sensitivity analysis techniques is provided by Saltelli et al. (2000).

Variability and uncertainty propagation

In principle variability and uncertainty should be treated separately, but it is rarely done in the common practice. For this purpose, a second order or 2-dimenional or embedded Monte Carlo simulation has been developed (Burmaster, 1996; Cullen and Frey, 1999). It simply consists of two Monte Carlo loops, one nested inside the other. The inner one deals with the variability of input variables, while the outer one deals with uncertainty. For each uncertain parameter value in the outer loop a whole distribution is created in the inner loop based only on variability.

The cut-off probability

A major remaining issue is that the cut-off probability for adequately controlled risks needs to be decided. The decisions will probably be different for environmental and for human RA purposes. This is essentially a decision for regulators and not a scientific issue. However, by using the same assumptions and safety factors as in the deterministic case for a PEC/PNEC of 1, a first impression of the residual risk can be made. Since these are the standard assumptions used so far, it seems reasonable to propose the residual risk as the cut-off probability.[3]

Communication of the uncertainty in the CSA

[3] Annex 3 of the RIP3.2 CSA study, Ch. 7 calculates a residual risk of about 1% for the Annex VI data set for the environment, which could be used as a tentative cut-off probability. For human RA, such as residual risk has not yet been determined.

The output of the probabilistic uncertainty assessment may consist in a large number of separate tables and graphs showing distributions and can be difficult to communicate by easy means. Probability distributions can be communicated in many ways, including:

- probability density function, showing the relative probability of different values,
- cumulative distribution, showing the probability of values below any given level,
- exceedance (inverse cumulative) distribution, showing the probability of values above any given level,
- summary statistics, e.g. mean or median estimates for the 97.5th percentile exposure together with one or more confidence intervals (e.g. 75, 90, 95 or 99% intervals); these may be presented numerically or graphically (e.g. box and whisker plots).

Difficulties of interpretation could be partly circumvented by staying as close as possible to accepted output formats of a risk assessment such as the TGD. The reader is referred to Frewer *et al.* (2005) for a more in depth treatment.

R.19.3.4.2 A simplified probabilistic analysis

When both exposure and (no-) effect level are normally (Gaussian) distributed, a simplified method for the probabilistic assessment of the risk can be performed without the need for a full probabilistic analysis. The method for this was developed and documented and is already applied in ecotoxicology (Van Straalen (1990), Cardwell et al. (1993), Aldenberg et al. (2002), Van Straalen (2002), Verdonck (2003), and Verdonck et al. (2003). One implementation of this theory is available within ETX 2.0 (Van Vlaardingen et al, 2004) and is being tested in the framework for probabilistic risk assessment for pesticides (EUFRAM, 2005). There is also a simple spreadsheet for calculating expected risk in case of normal $\log_{10}$ exposure and normal $\log_{10}$ response, or no-effect (Aldenberg, 2007). One can show that the three different approaches to probabilistic risk analysis (Section R.19.3.4.1) (Section R.19.3.4.1.) are all covered by the expected risk equation (5.16) in Aldenberg et al. (2002, p. 72). A fixed exposure or (no-) effect level can be implemented as a normal distribution with standard deviation equal to 0, which reduces to the appropriate cumulative value.

This method was originally developed for environmental risk assessment, but it should be stressed that the concept can be applied equally well to human risk assessment but with a different interpretation of the risk outcome. This will be further explained below.

For risk characterisation of the short-term or long-term environmental risk, the acute or chronic effect data are subjected to the species sensitivity distribution method (SSD) (see [Reference to TGD hazard assessment section in which SSD is described]). The exposure distribution is constructed based on average and reasonable worst-case exposure estimates.

The expected risk estimate is a measure of the probability that exposure values exceed effect (hazard) values. The expected risk value can also be calculated from the RCR distribution (Figure R. 19-6). The chance that species in the environment are not adequately protected, i.e. the probability that the RCR ≥ 1, is given by the probability of $\log_{10}$ RCR exceeding 0 (Aldenberg et al., 2002, and Verdonck et al, 2003). In the simplified case of both normal $\log_{10}$ exposure and normal $\log_{10}$ effect, the $\log_{10}$ RCR distribution is also normal. Figs 4 and 5 refer to the same case A in Aldenberg (2005).

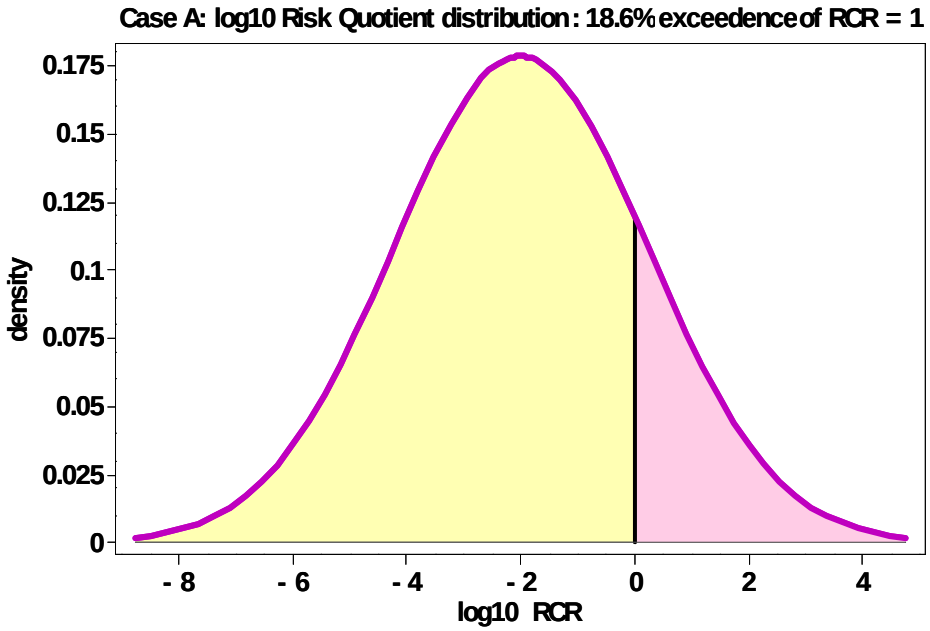


Figure R. 19-6 Probability distribution of the $\log_{10}$ RCR (x-axis), with the probability that the RCR of 1 is exceeded

(darker area on the right of the $\log_{10}$(RCR) = 0, i.e. RCR = 1, line). A simple procedure is available to calculate this probability, and is equal to the expected risk.

For human risk characterisation, the effect data are described by the dose-response curve, as used in the Benchmark Dose Method (BMD). Many types of software are available for dose-response modelling. It should be stressed that the same assessment factors are used as in the normal hazard assessment, but the uncertainty and variation of the toxicity data are taken into account by using the entire dose-response relation based on all available toxicity data (LC50s or NOECs). The exposure distribution is constructed based on the average and the reasonable worst-case exposure estimate.

Again, the risk outcome is nothing else than the probability that the exposure distribution can overlap the effect (hazard) distribution. The risk outcome is recalculated to a RCR distribution (Figure R. 19-6) and is the chance that the (sensitive) human target population (worker, consumer or general population) is not adequately protected (i.e., the probability that the RCR $\geq$ 1).

For application in the CSA, some pragmatic steps are needed to describe the exposure uncertainty. Because this approach is based on a scenario analysis of only an average-case and a worst case estimate of the exposure level, this method is referred to as 'semi-quantitative'.

Step 1. Definition of distributions for the hazard assessment. The interpretation of hazard is different between man and the environment.

Step 1a. For human effect data, the dose-response relationship for the most critical endpoint(s) shall be used (e.g., by applying the benchmark dose concept (cf. Slob and Pieters, 1998). The entire fitted dose-response curve can be used to derive the DNEL uncertainty which is calculated using the standard assessment factors (whose uncertainty is ignored for the time being).[4]

[4] The calculations are fully analogous to those for environmental hazard in Step 2b, however a worked out example is not yet available.

Step 1b. For ecotoxicological data, the SSD concept (cf. Aldenberg et al., 2002) shall be used to fit the data. The entire SSD shall be used to derive the PNEC uncertainty using the standard assessment factors (whose uncertainty is ignored for the time being).

Step 2. Definition of the distributions for the exposure assessment. Depending on the data availability, an average case (median of 50^{th} percentile) and the worst case (90^{th} percentile) of exposure shall be defined. The difference between the two is used to estimate the uncertainty of exposure.

Step 2a. From the measured data set, if it is large, the empirical 50^{th} and 90^{th} percentile of exposure shall be determined. If the data set is small, a statistical model to estimate the 50^{th} and 90^{th} percentile of exposure shall be used.

Step 2b. For a modelled exposure, the worst-case model estimate shall be used as the 90^{th} percentile of exposure. Expert judgment shall be applied to make a scenario analysis for the average-case prediction and this shall be used as the 50^{th} percentile of exposure.

Step 3. Calculation of overlap between the effect and exposure distribution. By applying a few simple scaling steps, the influence of the uncertainty in both distributions on the RCR can be read off easily from specific statistical tables. Although the calculations are relatively simple, its application can be made very easy with the support of statistical software, e.g. Van Vlaardingen et al., 2004.

Step 4. Outcomes of the uncertainty assessment should be used to decide if additional information will improve the knowledge of uncertainty and variability and reduce the probability that the RCR is larger than one. Options are to collect more hazard information, more exposure information or better define the variability in the exposure scenarios. The remaining RCR uncertainty should be considered to either iterate a risk assessment refinement or consider additional RMMs to demonstrate adequately controlled risks.

Step 5. Reporting. The uncertainty analysis should be reported in the CSA in a concise summary report outlining the main points of the assessment and its key results. A technical report annex to the CSA should be made available for those who wish to examine the details.

Communication of the results of a simplified joint probability analysis in the CSA

For communicating the risk of the simplified joint probability method, previous work in both the literature (Verdonck et al, 2003) and in the context of risk communication (Frewer et al. 2005) has shown that the current graphical presentation as output of software (Van Vlaardingen et al., 2004) is confusing. By keeping the current way or risk characterisation, it is proposed to present the risk that the RCR is exceeded as the output of the assessment. An example of this approach is given in Table R. 19-4.

Table R. 19-4 Output of a joint probability analysis in the context of the CSA

Scenario	Probability that RCR of one is exceeded (risk)	Confidence interval
ES 1, no additional RMMs	20%	0.1-60%
ES 2, no additional RMMs	8%	0.2-30%
ES 2, additional RMMs	< 1%	0.2-0.9 %

In this purely hypothetical table, the uncertainty in both effects and exposure in the first iteration of the CSA is substantial, leading to a conclusion of 'risks not adequately controlled'. A closer look at the exposure conditions could reveal substantial uncertainty about duration of exposure. If the arbitrary limit would have been set at 1%, the second iteration would still not be satisfactory leading to additional RMMs that finally lead to a low probability of exceeding the RCR.

R.19.4 General recommendations for communicating uncertainty in the chemical safety assessment

This section provides general considerations when reporting the results of the uncertainty analysis (Frewer et al., 2005) in the CSR.

In many cases the uncertainty analysis will relate to reliability of the risk characterisation ratio (RCR) and so one approach would be to include the uncertainty analysis in the corresponding section of the chemical safety report. However, it would also be possible to have summary tables of the key sources of uncertainty at the end of the hazard assessment sections. In other cases the uncertainty analysis will be functionally used in the risk assessment refinement loop. In these cases the presentation of the uncertainty analysis outcomes might be presented as a track record of technical choices and further refined estimations leading to the final risk estimate.

Some general considerations for the presentation of uncertainty analysis include:

Setup, limitations of approach

- Describe what was done (narrative) and why (motivate)
- Considerations what is and what is not considered
- Considerations of uncertainty and variability
- Narrative forms should be used to explain what is not understood as well as identifying what is understood

Presentation of methods

- Specialist jargon should be avoided whenever possible
- Novel ideas should be introduced one at a time rather than all at once
- Explanations should be started with familiar assessment methodologies and subsequently move to unfamiliar assessment approaches
- For decision-makers, inclusion of a "positive control", the effects of which were already well understood by those involved in the risk analysis process, facilitates communication about new methods (e.g. deterministic and probabilistic side by side)

- Graphs with frequencies on both axes are generally difficult to understand and communicate to non-experts.

Communicating the results of the assessment

- Communicating what is not known as well as what is known, and potential uncertainties
- Use narrative forms backed up with diagrams (where appropriate) to describe the results of assessments and associated uncertainties
- A concise summary report outlining the main points of the assessment and its key results should be produced
- A technical report annex to the CSA should be made available for those who wish to examine the details

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