

TECHNICAL GUIDANCE DOCUMENT FOR PREPARING THE CHEMICAL SAFETY ASSESSMENT

Chapter R.19: Uncertainty analysis in the Chemical Safety Assessment

**“Technical Guidance Documents in support of the New EU Chemicals Legislation (REACH) –
V: Development of a Technical Guidance Document for preparing the Chemical Safety
Assessment (REACH Implementation Project 3.2-2)”**

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Preface

Disclaimer: "The present views expressed are those developed by the RIP 3.2-2 contractor for discussion at the relevant Stakeholder Expert Group meetings and may not in any circumstances be regarded as a final position nor document"

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1 **1 UNCERTAINTY ANALYSIS IN THE CHEMICAL SAFETY ASSESSMENT**

2 **1.1 Introduction**

3 **1.1.1 Objectives of this chapter on uncertainty analysis**

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

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9 Organisation's (WHO) "Draft guidance document on characterizing and communicating uncertainty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

14 Section 1.1.2 of this chapter provides a brief introduction to the role of uncertainty in risk
15 assessment, and explains why it is an important part of the REACH process. Section 1.2 then goes
16 on to outline a number of key concepts in uncertainty analysis, which are aimed to help the reader
17 better understand the nature of uncertainty within risk characterisation under REACH. This outline
18 includes a classification of different sources of uncertainty, distinguishing between uncertainty and
19 variability.

20 Section 1.3 continues by providing a more detailed framework for carrying out a stepwise, tiered
21 approach to uncertainty analysis that may be followed when analysing uncertainty in the chemical
22 safety assessment. It outlines specific techniques for making qualitative, deterministic, and
23 probabilistic uncertainty analyses, and provides criteria for deciding which of these approaches
24 might be suitable under specific circumstances.

25 Section 1.4 suggests approaches for reporting and communicating uncertainty in the chemical safety
26 assessment

27 **1.1.2 Role of uncertainty analysis in the chemical safety assessment**

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

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

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

41 In very general terms, the amount of input required in an uncertainty analysis, and the importance of
42 its contribution to the chemical safety assessment, will depend on the specific circumstances. For
43 example, it would not add any practical value to a chemical safety assessment to provide a detailed
44 probabilistic uncertainty analysis for a substance which has a full data set, few dangerous
45 properties, minimal exposure and a Risk Characterisation Ratio (RCR) which is significantly less
46 than 1.

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

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

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

60 **1.2 Key concepts in uncertainty analysis**

61 **1.2.1 Sources of uncertainty**

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

- 64 • Hazard assessment: how uncertain is the measure of (no) effect,
- 65 • Exposure assessment: how uncertain is the exposure estimate (predicted or based on
66 measurements),
- 67 • Risk characterisation: how uncertain is the risk estimate.

68 These uncertainties can be classified into three categories as indicated in the WHO-IPCS document
69 (2006). It should be noted that the WHO document was written specifically for exposure
70 assessment; however it is possible to broaden its concepts to the chemical safety assessment in
71 general (including the hazard assessment and the risk characterisation). These three broad
72 categories of uncertainties are scenario uncertainty, model uncertainty and parameter uncertainty.

73 Scenario uncertainty

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

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

81 Model uncertainty

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

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

89 Parameter uncertainty

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

94 Parameter uncertainties include:

95 - Measurement errors:

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

98 - Sample uncertainty:

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

102 - Selection of the data used for assessing the risk:

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

106 - Extrapolation uncertainty:

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

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

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

118 **1.2.2 Uncertainty and variability**

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

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

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

- 132 - Inter-species variability;
- 133 - Intra-species variability (e.g. due to age, sensitivity, physiology, behaviour...);
- 134 - Variability in environmental characteristics (e.g. temperature, wind, homogeneity...);
- 135 - Variability in time and space.

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

140 **1.3 uncertainty analysis in the chemical safety assessment**

141 **1.3.1 Qualitative, deterministic and probabilistic analysis: introduction to the tiered** 142 **approach**

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

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

154 1.3.1.1 The risk characterisation ratio

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

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

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

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

168 Therefore, the resulting risk characterisation ratios (RCR) from the comparison of the human and
169 environmental exposure with the corresponding no effect levels are a major driver in risk
170 characterisation and chemical safety assessment, and will also be a contributing factor in deciding
171 whether an uncertainty analysis would be a worthwhile addition to the chemical safety report.

172 It should be noted that under certain circumstances it may not be possible to derive a risk
173 characterisation ratio, for example where the DNEL or PNEC cannot be calculated. Under other
174 circumstances, it may not be necessary to carry out the exposure assessment or risk characterisation
175 because the substance is not classified as dangerous or as a PBT/vPvB, although an exposure
176 assessment would still be required if a case has been made for exposure based waiving. The current
177 paper mainly addresses the situation where a DNEL/PNEC can be derived, but the general
178 principles and the level 1/level 2 uncertainty assessment could also be applied if a qualitative or
179 semi-quantitative risk characterisation is conducted.

180 1.3.1.2 Validated methods *versus* non-standard techniques

181 Another factor which can influence the need to carry out an uncertainty assessment relates to the
182 type of regulatory tools that have been used to derive the input parameters and estimates of effects
183 and exposure. For instance, where standard guideline methods have been followed using
184 internationally recommended defaults, uncertainty can be considered to have been implicitly
185 addressed within the method (although an analysis of uncertainty could still be useful in identifying
186 key parameters for the refinement of risk). On the other hand, if the registrant has developed higher
187 tier methods to generate exposure or effects estimates and novel or non-standard techniques have
188 been used then an uncertainty analysis might be a useful part of the documentation provided to
189 justify the approach within the CSR.

190 1.3.1.3 Circumstances under which an uncertainty analysis is recommended

191 Uncertainty analysis is of most potential benefit in situations where there is a high level of
192 uncertainty in the risk characterisation and/or the RCR is above the regulatory trigger value. It
193 might also be of benefit in some situations where the RCR is below the trigger value but non-

194 standard methods have been used to derive the relevant values, or where the registrant simply wants
195 to carry out their own uncertainty analysis to improve their characterisation of the risk.

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

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

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

202 ▪ RCR > 1. Where the RCR exceeds 1, it will clearly be necessary to refine the assessment.
203 Under these circumstances, uncertainty assessment can help the registrant to identify and
204 target the main sources of uncertainty in the chemical safety assessment for subsequent
205 refinement in higher tier approaches. Additionally, the assessment can be used to improve
206 the characterisation of the risk.

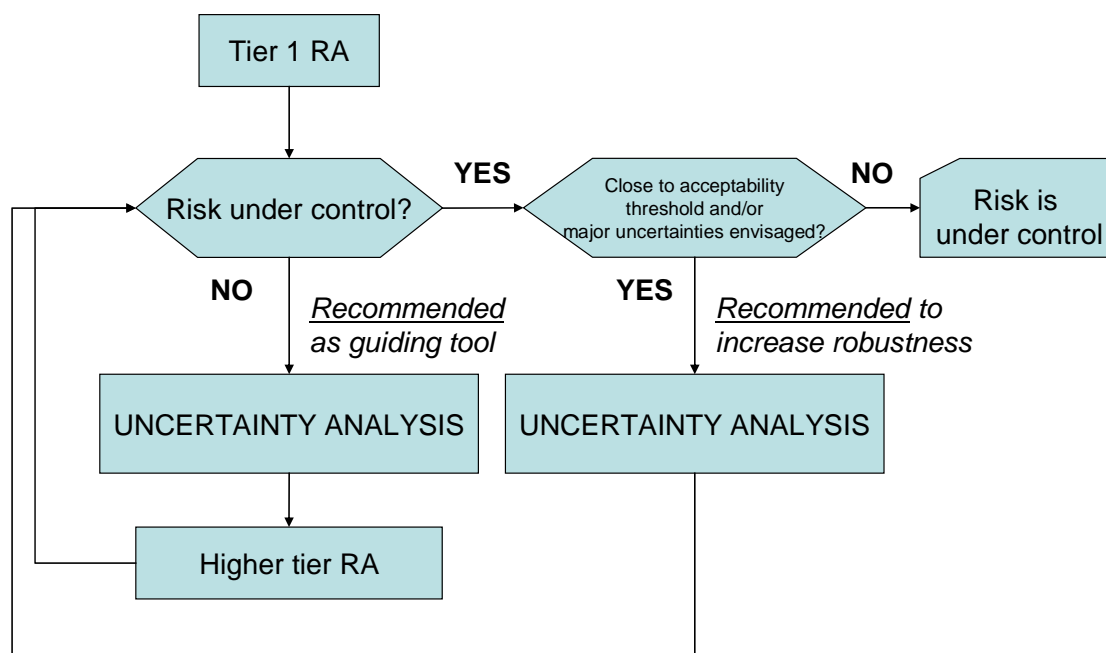
207 ▪ RCR < 1 but non-standard, non-guideline approaches have been used. Under these
208 circumstances, a registrant might include an uncertainty analysis as part of the supporting
209 documentation justifying the use and applicability of a non-standard risk characterisation
210 method.

211 In addition, even where the RCR is less than but close to 1 and standard approaches have been used
212 in accordance with the TGD, a registrant might choose to carry out a qualitative uncertainty analysis
213 to help satisfy themselves that their chemical safety assessment is robust and adequate.

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

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

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225

226 **Figure R.1.1: Circumstances where an uncertainty analysis is recommended.**227 **1.3.1.4 The stepwise approach**

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

232 At the most basic level, the standard chemical safety assessment accounts for uncertainty by using
 233 conservative assumptions and default values, for instance following specific methods recommended
 234 in the TGD. Where this results in the risks being clearly and robustly addressed, this is sufficient
 235 and no further analysis is considered necessary.

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

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

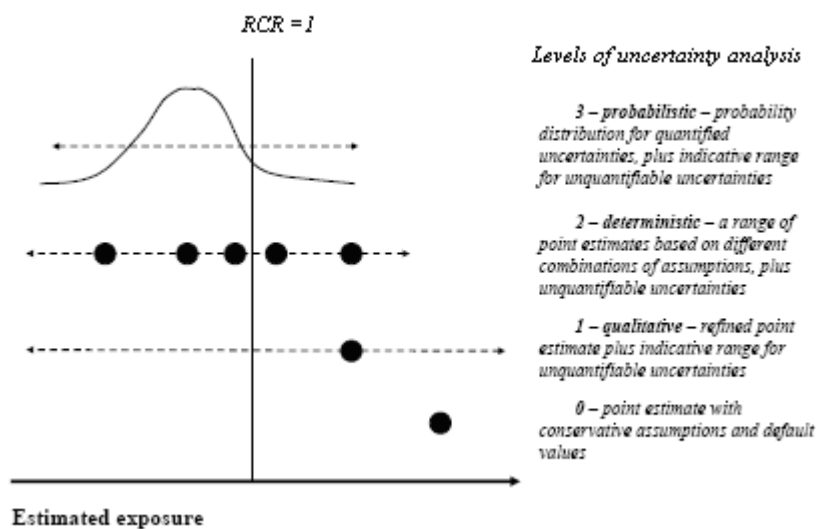
243 The benefits of progressing from lower to higher levels of uncertainty analysis are illustrated for a
 244 hypothetical example in Figure 1. Higher tiers of uncertainty analysis lead to better understanding
 245 and characterisation of uncertainty; this may show that the uncertainty is less than was assumed at

246 lower tiers, but variation may be greater. Higher levels progressively refine the characterisation of
 247 uncertainty, and enable the assessor to give a more realistic estimate of the likelihood of the RCR
 248 being exceeded. This approach is outlined in Figure 1. At level 0, a point estimate is derived using
 249 agreed conservative assumptions and default values, for instance following specific methods
 250 recommended in the TGD. As has been previously described, the impact of uncertainty is
 251 considered to be implicitly built in to this estimate by the use of these conservative assumptions.
 252 However, in this example the RCR is greater than one and so further work is clearly required to
 253 refine the risk assessment.

254 At Level 1 a qualitative uncertainty analysis has been used to identify the make a refined estimate
 255 of exposure and estimate an indicative range of unquantifiable uncertainties. Again, in this example,
 256 the point estimate and the upper end of the indicative range do not demonstrate adequate control of
 257 the risk.

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

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



264

265 **Figure R.1.2: Graphical illustration of the benefits of progressing from lower to higher**
 266 **levels of uncertainty analysis.**

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

269 Level 1 – Qualitative assessment

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

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

278 Level 2 – Deterministic assessment

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

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

288 Level 3 – Probabilistic assessment

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

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

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

300 More detailed information on the use of probabilistic uncertainty analysis is provided in Section
301 1.3.4.

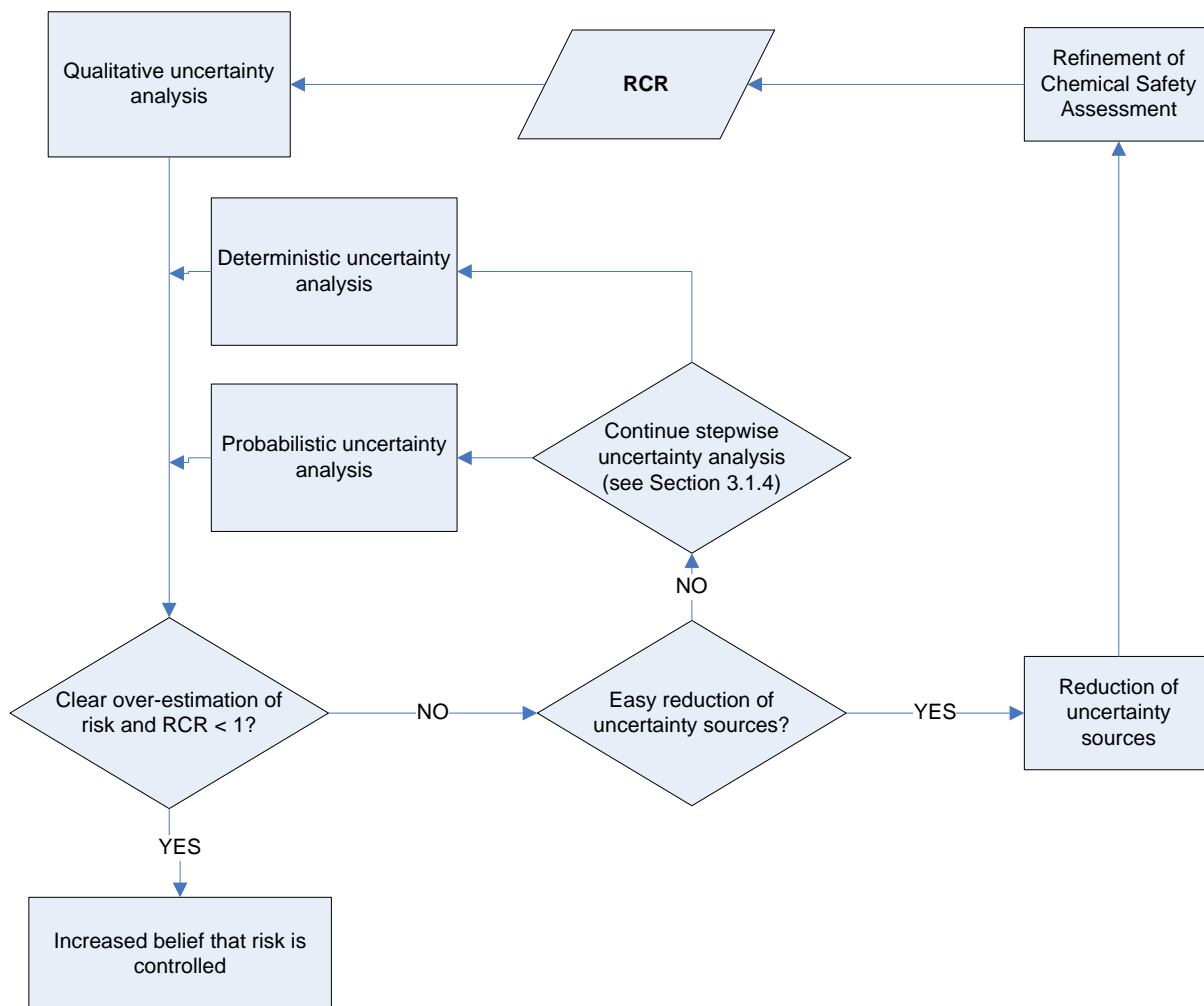
302 **1.3.1.5 How to use the results of the uncertainty analysis**

303 As discussed in Section 1.3.1.3, the need to carry out an explicit uncertainty analysis is related to
304 the degree of uncertainty in the risk characterisation and the RCR value. If an uncertainty analysis is
305 considered needed, it can be carried out according to the tiered approach outlined in Section 1.3.1.4
306 and using the specific methods in Sections 1.3.2 - 1.3.4.

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

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

317 Figure 2 outlines a possible iterative approach for using the tiered uncertainty approach in the
 318 chemical safety assessment.



319

320 **Figure R.1.3 : Possible approach to uncertainty analysis in the Chemical Safety**
 321 **Assessment.**

322 1.3.2 Level 1 - Qualitative uncertainty analysis

323 *Baseline approach*

324 The Level 1 - qualitative evaluation of uncertainty consists of the identification of uncertainty
 325 sources and their qualitative characterisation. It aims at providing a comprehensive view of main
 326 uncertainties as a basis for the risk assessment refinement or the application of quantitative
 327 uncertainty evaluations in Level 2 (deterministic) and/or Level 3 (probabilistic). Various methods
 328 for the qualitative evaluation of uncertainties have been developed, all of them consisting in a
 329 systematic screening and classification of all uncertainty sources (e.g. EFSA, 2006; WHO/IPCS,
 330 2006; Van der Sluijs et al. 2003, Petersen et al., 2003). A baseline approach to the qualitative
 331 assessment of uncertainty is described below and structured into six points. It is based on principles

332 of maximum simplicity and workability, but should not stop the risk assessor from considering
333 more structured and detailed assessment methods as reported in the fore mentioned guidelines and
334 scientific papers.

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

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

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

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

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

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

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

368 E) Evaluation of the overall uncertainty. In this scope the mathematical combination of magnitude
369 estimates (e.g. scores) for each source of uncertainty would be misleading, while a subjective
370 consideration of the assessor would be preferred with account of correlation and dependencies
371 among uncertainty sources (EFSA, 2006).

372 F) Final outcomes. The final result of the qualitative uncertainty assessment should be the
373 identification of most relevant sources of uncertainty and technical means for reducing them, as
374 well as the evaluation of the overall effect of uncertainty sources on the risk estimate. In the case

375 that the risk quotient is close to, but below limits of acceptability ($RCR < 1$), the potential outcomes
376 of the qualitative uncertainty analysis are the following:

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

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

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

388 *Checklist of sources of uncertainty*

389 The systematic identification of potential sources of uncertainty can be supported by the use of
390 checklists. For the sake of example, a rough checklist of main sources of uncertainty in the most
391 general case is reported in Table 2 and Table 3. More detailed checklists can be developed with
392 specific regard to the type of considered risk (e.g. environmental, occupational, consumer),
393 exposure category and type of considered effects (e.g. PBT assessment).

394 **Table R.1-1: Major sources of uncertainty related to effect assessment.**

395 It should be noted that the adequacy of assessment factors is a source of uncertainty that has been
396 addressed in the development of the TGD based on scientific state of art and agreed levels of
397 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: <ul style="list-style-type: none"> - oversimplification - dependency errors - use out of the validity domain
Parameter uncertainty (physicochemical and hazard properties)	Measurement uncertainties, e.g.: <ul style="list-style-type: none"> - Low sample size - Measurement errors
	Selection of data, e.g.: <ul style="list-style-type: none"> - Choice of the dose descriptor - Default values
	Extrapolation uncertainties, e.g.:

	- QSAR, QSPR, Read-across, in-vitro test
	Adequacy of assessment factors associated to uncertainty, e.g.: <ul style="list-style-type: none"> - Interspecies (from animal to human) - Acute to chronic - Route to route - Lab to field
	Adequacy of assessment factors associated to variability, e.g.: <ul style="list-style-type: none"> - intraspecies due to age, sensitivity, etc. - interspecies due to sensitivity etc.

398

Table R.1-2: Major sources of uncertainty related to exposure assessment

Uncertainty group	Sources of uncertainty
Scenario uncertainty	Adequacy of exposure scenario assumptions, e.g.: <ul style="list-style-type: none"> - 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.: <ul style="list-style-type: none"> - oversimplification - dependency errors - application out of the validity domain
Parameter and data uncertainty	Measurement uncertainties, e.g.: <ul style="list-style-type: none"> - low sample size - measurement error

	<p>Selection of data, e.g.:</p> <ul style="list-style-type: none"> - 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
	<p>Extrapolation, e.g.:</p> <ul style="list-style-type: none"> - read across for similar substances/scenarios
	<p>Variability, e.g.:</p> <ul style="list-style-type: none"> - Environmental variability (temperature, wind, homogeneity etc.) - Variation in behaviour (related to exposure potential) - Variation in time and space, relating to any of the above

399

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

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

403 As far the physico chemical data are concerned:

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

410 As far the hazard information is concerned:

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

421 In the exposure assessment, main uncertainties can be hidden behind the assumptions made in the
422 exposure scenario or the measurements used. In the exposure scenario the main sources of

423 uncertainty to be considered are linked to the emission of the substance, the pathway / route of
424 exposure and the exposed population, which in turn mainly depend on operational conditions and
425 efficiency of risk management measures.

426 As far the exposure models are concerned, it is recognized that in general the default models will
427 only be replaced by higher tier models in exceptional cases. Some specific considerations are the
428 following:

- 429 - a qualitative risk assessment is especially important for empirical/knowledge-based models.
430 The model structure of an empirical model is not in the form of equations, and errors in the
431 equations that are important sources of uncertainty in mechanistic models will not occur.
432 However, the model structure of an empirical model can also be flawed, e.g. when an
433 important parameter is not considered in the model, or the influence of a parameter is
434 substantially over- or underestimated.
- 435 - a large portion of uncertainty in modelling cannot be evaluated in a strict quantitative
436 manner. The uncertainties of qualitative input parameters and of the logical structure of the
437 model can in general only be discussed qualitatively.

438 As far the input parameters are concerned:

- 439 - uncertainties can arise in measurements. For example, not all of a physical sample during
440 the chemical analysis may be recovered, which may lead to underestimated exposures. Some
441 of the measurements may be below the limit of detection of the applied method and will
442 therefore underestimate exposure if recorded as zero, or overestimate it if recorded as equal
443 to the limit of detection. There may also be uncertainties in the reading of laboratory
444 measuring devices and uncertainties as a result of some other aspect of laboratory process
445 (e.g. sample preparation). The applied sampling protocols (e.g. EN 689) and good laboratory
446 practice minimise these uncertainties.
- 447 - most of the measured data received on exposure estimation are small data sets, and less than
448 12 data points are not uncommon. For small sets of data points, statistical sampling
449 uncertainties need to be considered when properties are estimated (e.g. the median or the
450 90th percentile) for exposure data. The smaller the number of observations, the larger the
451 uncertainties associated with any inferences that may be derived from them.
- 452 - the most relevant question to ask is whether the data obtained are appropriate for the
453 purposes of exposure assessments. The main question whether the data set is representative
454 for the exposed population or natural community. Qualitative information on the data set
455 will affect the interpretation of any inferences made from it.
- 456 - Uncertainties can arise as a result of the method by which measurements are selected for
457 inclusion in the data set, particularly if data are pooled before or during the risk assessment
458 process. A random or stratified sampling strategy would give different percentile values,
459 averages and spread in the data than the pooled data sets. If measurement data are pooled, it
460 should be done in a transparent way.
- 461 - When quality measured data are not available for a particular scenario, it may be possible to
462 extrapolate from data from analogues using expert judgement. Due to the extrapolation
463 process, the uncertainty in the estimation will increase.
- 464 - It may seem that measurements always give more reliable results than model estimations.
465 However, measured concentrations can have a considerable uncertainty associated with
466 them, due to temporal and spatial variations. Therefore, the availability of adequate

467 measured data does not imply that PEC calculations are unnecessary. Both approaches
468 complement each other in the complex interpretation and integration of the data.

469 *Example of qualitative evaluation of uncertainty*

470 An example for the qualitative assessment of uncertainties is reported in Table 4, where sources of
471 uncertainty are grouped into scenario, model and input parameters uncertainties, each source of
472 uncertainty is further classified into variability or uncertainty and then evaluated for direction and
473 magnitude. The symbols + and – indicate overestimation and underestimation, respectively, and the
474 scales from + to +++ and from – to --- indicate the magnitude (e.g. in a scale from 1 to above 3
475 orders of magnitudes). As it can be noted in Table 4, in many cases the direction of the uncertainty
476 is not known and therefore expressed as +/-.

477 **Table R.1-3: 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 ...			

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

480 *Communication of the qualitative evaluation of uncertainty*

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

484 1.3.3 Level 2 - Deterministic uncertainty analysis

485 *Baseline approach*

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

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

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

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

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

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

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

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

517 *Selection of uncertainty sources*

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

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

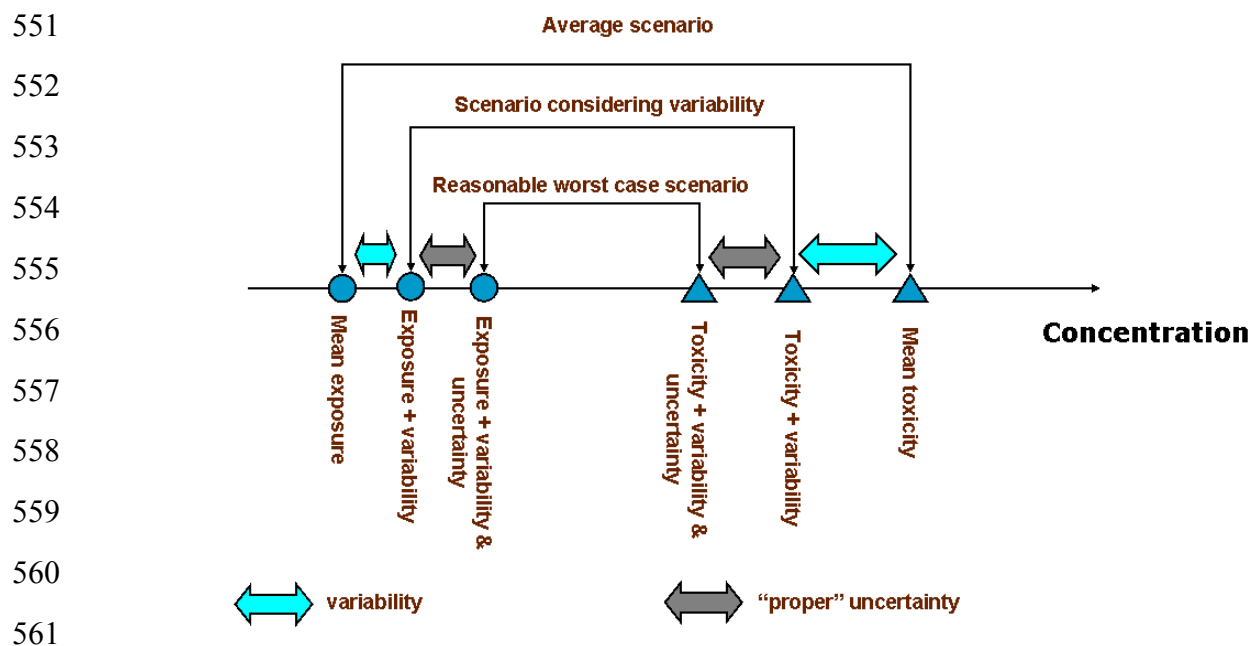
526 lipophilicity (K_{ow}) and volatility. The availability of further sensitivity studies on updated version of
527 EUSES and sensitivity studies on other exposure scenarios (e.g. occupational exposure) would be
528 useful.

529 *Scenarios analysis*

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

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

540 The outcomes of this approach are represented in Figure 3, where PEC and PNEC outcomes of the
541 three scenarios are reported on the Concentration axis. In the hypothetical case represented in Fig. 3
542 PNECs are always higher than PECs, even in the reasonable worst case scenario; this outcome of
543 the deterministic uncertainty assessment would corroborate the belief that the risk is adequately
544 controlled. In other cases the worst case scenario might show PNEC higher than PEC. In those
545 cases the analysis of the plausibility of the worst case scenario provides an insight on the feasibility
546 of uncertainty reduction options. The development of average, typical and worst case scenarios
547 allows the distinction between uncertainty and variability: the difference in risk outcomes between
548 the reasonable worst-case and typical scenario can be considered as a measure for uncertainty,
549 while the difference between the typical and average scenario can be considered as a measure for
550 variability.



562 **Figure R.1.4 : Outcomes of the application of deterministic risk assessment to average,**
 563 **typical and reasonable worst case scenarios.**

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

575 *Communication of the deterministic evaluation of uncertainty*

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

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

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

589 **1.3.4 Level 3 - Probabilistic Uncertainty Assessment**

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

604 A variety of approaches exist for probabilistic analysis of the risk (and associated uncertainty),
605 including 1D and 2D Monte Carlo simulations, bootstrapping and Bayesian analysis, fuzzy
606 arithmetic and probability bounds (e.g. European Commission 2003, Cullen and Frey 1999, US
607 EPA 1997, IPCS/WHO 2006). For a detailed description of these techniques the reader is referred
608 to the sources cited above. Moreover, the uncertainty analysis of EUSES (Jager et al. 1997, 2000,
609 2001a,b, Vermeire 2001, Lessmann et al., 2005) can serve as a template for such an analysis.

610 The following sections 1.3.4.1 and 1.3.4.2 present general methodological aspects and an example
611 of simplified method for the probabilistic risk assessment, respectively.

612 **1.3.4.1 General methodological aspects of the probabilistic risk assessment**

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

616 *Probabilistic approach to hazard assessment*

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

- 619 - for human effect data, the benchmark dose concept (Slob and Pieters, 1998; Vermeire 2001)
620 can be used to determine the dose-response relationship for the most critical endpoint(s);
- 621 - for ecotoxicological data, the SSD concept (Aldenberg and Jaworska, 2000; Aldenberg et al.,
622 2002) can be applied to fit the available ecotoxicological data of different species.

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

626 The outcome of the probabilistic estimation of the hazard can be expressed by a cumulative
627 distribution similar to the red curve represented in Figure 4.

628 Confidence intervals can be also calculated for the cumulative distribution (not represented in Fig.
629 4). While the cumulative distribution mainly represents the variability (e.g. inter-species variability
630 in SSD), the width of confidence intervals mainly indicate the contribution of uncertainty sources.

631 *Probabilistic approach to exposure assessment.*

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

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

- 637 • Based on the knowledge obtained by the qualitative and/or quantitative deterministic
638 uncertainty analysis, parameters to be treated in a probabilistic approach should be
639 identified.
- 640 • Uncertainty and variability of model input parameters should be described by appropriate
641 distributions. This usually involves the collection of data, expert judgement and fitting
642 distribution functions to data. Dependencies among model input parameters should be also
643 taken into account.
- 644 • Computations (e.g. Monte Carlo simulations) should be carried out to estimate the
645 propagation of variability and uncertainty through the model. The model output will be also
646 a probabilistic distribution shaped by uncertainty and variability.
- 647 • The estimated exposure can be expressed by a probability distribution (e.g. the exposure
648 concentration distribution, also indicated with ECD) similar to the bell shaped blue curve
649 represented in Figure 4.
- 650 • Confidence intervals can be also calculated for the cumulative distribution (not represented
651 in Fig. 4). While the cumulative distribution mainly represents the variability (e.g. spatial
652 and temporal variability of exposure), the width of confidence intervals mainly indicate the
653 contribution of uncertainty sources.

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

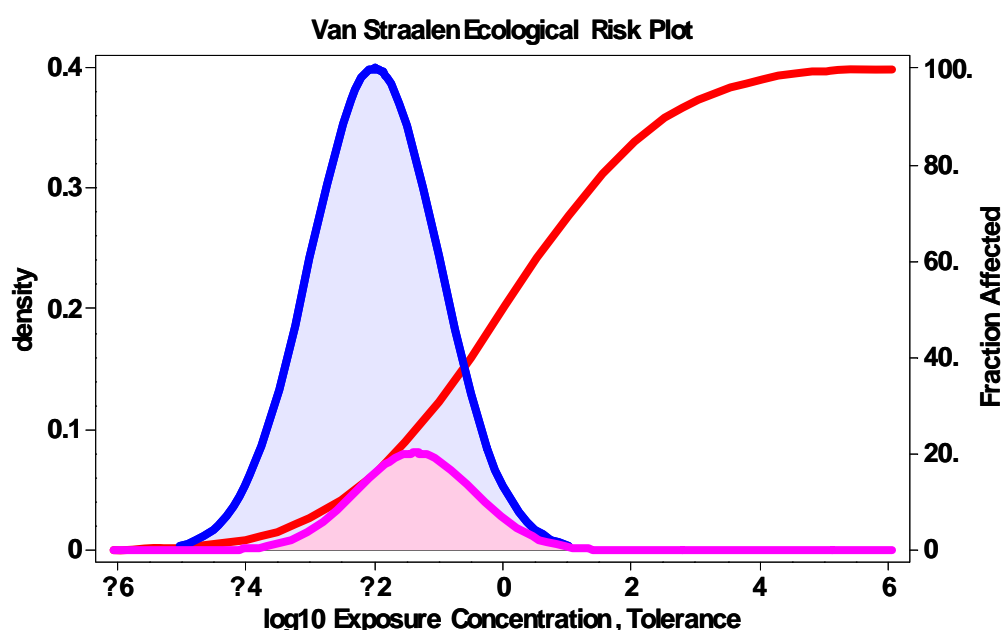
659 *Probabilistic estimation of risk*

660 The risk characterization ratio is no longer a deterministic estimate, but a distribution from which
661 the probability that an RCR of one is exceeded can be calculated. Since the risk is assumed to be
662 not adequately controlled when the exposure predicted concentration exceeds the predicted no
663 effect concentration (PNEC or DNEL for the environmental and the human health risk,
664 respectively), the probabilistic risk estimation is based on the overlapping of the exposure and the
665 effect distributions. In Figure 4 the area under the curve of this distribution is the expected risk,
666 given the fact that both exposure and effect are distributed. The only number that needs to be
667 communicated is the expected risk, which is a single number. In some cases it will be possible to

668 assume mathematical forms for the distribution of both effects and exposure, and to estimate
 669 parameters for both distributions. Exposure and effects distributions can then be combined
 670 mathematically to derive expressions of risks (an example is given in section 19.3.4.2). In other
 671 cases the combination of effects and exposure distributions can be calculated numerically by means
 672 of a Monte Carlo analysis.

673 Probabilistic risk assessment models yield distributions of model output that can be interpreted as a
 674 probability distribution of risk for predefined endpoints (Suter, 1993; Aldenberg et al, 2002). The
 675 correct interpretation of the risk prediction depends on the dimensions and units of both exposure
 676 and effect measures. This means that if the interest is the risk of acute mortality, both the ecological
 677 effect function and the exposure data distribution should be based on a relevant time scale, e.g. a
 678 48-hour exposure. This compatibility should be extended to aspects of time and space, to assure that
 679 the predicted risk is a realistic and relevant event.

680



681

682 **Figure R.1.5 : Distribution of overlap. (Aldenberg, et al., 2002, Van Straalen, 1990, 2002)**
 683 **between exposure distribution (normal distribution on the left) and (no-) effect**
 684 **distribution (cumulative normal distribution on the right). The smaller shaded curve**
 685 **results from multiplying exposure and effect functions. The area under the smaller**
 686 **curve is equal to the expected risk, when both exposure and effect are distributed: here**
 687 **18.6%.**

688

689 *Different approaches to the probabilistic analysis*

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

692 If the interest is the probability that a no-effect level (PNEC or DNEL) is exceeded given
 693 uncertainty in exposure, the exposure concentration distribution (ECD) is compared to the no-effect
 694 level. The probability that the PNEC or DNEL is exceeded can then be read from the cumulative

695 distribution function. In this case, the output of the probabilistic CSA reflects our uncertainty that a
696 specific no-effect level is exceeded.

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

701 A more sophisticated assessment is possible when both the no-effect level and the exposure are
702 expressed as probability distributions, as represented in Figure 4. This type of analysis was
703 pioneered by Van Straalen (1990) and Cardwell et al. (1993) and has since then been refined and
704 internationally proposed as the standard framework for probabilistic risk assessment. In 3.4.2
705 below, we will show, how the three cases can be united.

706 *Sensitivity analysis*

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

715 *Variability and uncertainty propagation*

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

722 *The cut-off probability*

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

729 *Communication of the uncertainty in the CSA*

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

¹ 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.

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

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

743 **1.3.4.2 A simplified probabilistic analysis**

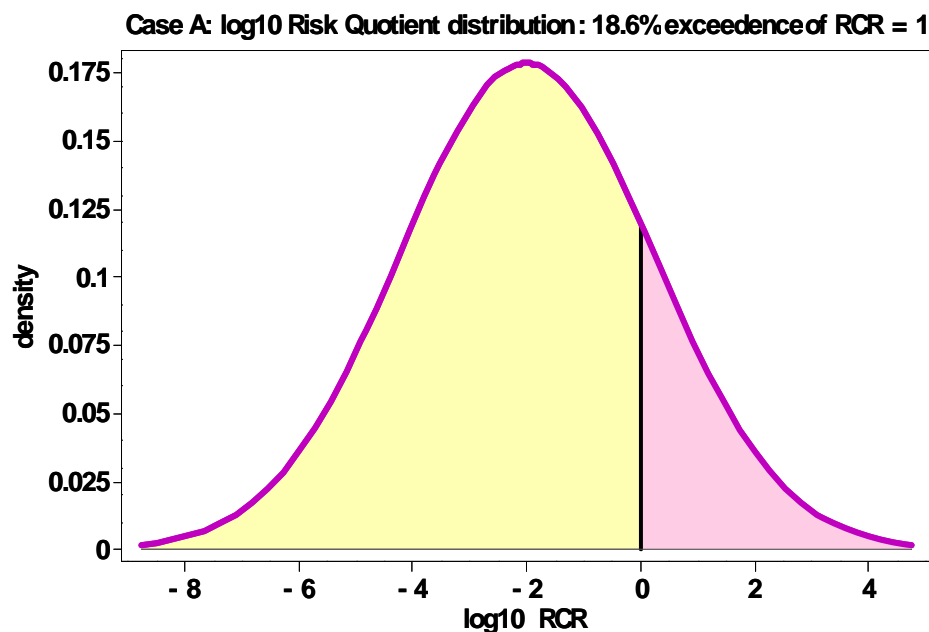
744 When both exposure and (no-) effect level are normally (Gaussian) distributed, a simplified method
745 for the probabilistic assessment of the risk can be performed without the need for a full probabilistic
746 analysis. The method for this was developed and documented and is already applied in
747 ecotoxicology (Van Straalen (1990), Cardwell *et al.* (1993), Aldenberg *et al.* (2002), Van Straalen
748 (2002), Verdonck (2003), and Verdonck *et al.* (2003)). One implementation of this theory is
749 available within ETX 2.0 (Van Vlaardingen *et al.*, 2004) and is being tested in the framework for
750 probabilistic risk assessment for pesticides (EUFAM, 2005). There is also a simple spreadsheet
751 for calculating expected risk in case of normal \log_{10} exposure and normal \log_{10} response, or no-
752 effect (Aldenberg, 2007). One can show that the three different approaches to probabilistic risk
753 analysis (section 19.3.4.1) are all covered by the expected risk equation (5.16) in Aldenberg *et al.*
754 (2002, p. 72). A fixed exposure or (no-) effect level can be implemented as a normal distribution
755 with standard deviation equal to 0, which reduces to the appropriate cumulative value.

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

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

763 The expected risk estimate is a measure of the probability that exposure values exceed effect
764 (hazard) values. The expected risk value can also be calculated from the RCR distribution (Figure
765 5). The chance that species in the environment are not adequately protected, i.e. the probability that
766 the $RCR \geq 1$, is given by the probability of \log_{10} RCR exceeding 0 (Aldenberg *et al.*, 2002, and
767 Verdonck *et al.*, 2003). In the simplified case of both normal \log_{10} exposure and normal \log_{10}
768 effect, the \log_{10} RCR distribution is also normal. Figs 4 and 5 refer to the same case A in Aldenberg
769 (2005).

770



771

772 **Figure R.1.6 : A probability distribution of the log₁₀ RCR (x-axis), with the probability**
 773 **that the RCR of 1 is exceeded**

774 (darker area on the right of the log₁₀(RCR) = 0, i.e. RCR = 1, line). A simple procedure is available
 775 to calculate this probability, and is equal to the expected risk.

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

782 Again, the risk outcome is nothing else than the probability that the exposure distribution can
 783 overlap the effect (hazard) distribution. The risk outcome is recalculated to a RCR distribution
 784 (Figure 5) and is the chance that the (sensitive) human target population (worker, consumer or
 785 general population) is not adequately protected (i.e., the probability that the RCR ≥ 1).

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

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

791 *Step 1a.* For human effect data, the dose-response relationship for the most critical endpoint(s) shall
 792 be used (e.g., by applying the benchmark dose concept (cf. Slob and Pieters, 1998). The entire fitted
 793 dose-response curve can be used to derive the DNEL uncertainty which is calculated using the
 794 standard assessment factors (whose uncertainty is ignored for the time being).²

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

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

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

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

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

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

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

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

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

823 For communicating the risk of the simplified joint probability method, previous work in both the
824 literature (Verdonck et al, 2003) and in the context of risk communication (Frewer et al. 2005) has
825 shown that the current graphical presentation as output of software (Van Vlaardingen et al., 2004) is
826 confusing. By keeping the current way or risk characterisation, it is proposed to present the risk that
827 the RCR is exceeded as the output of the assessment. An example of this approach is given in Table
828 5.

829

830 **Table R.1-4 : 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 %

831

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

837 **1.4 General recommendations for communicating uncertainty in the chemical safety** 838 **assessment**

839 Specific formats for reporting qualitative, deterministic and probabilistic uncertainty analyses are
 840 recommended in their respective sections. This section briefly discusses where and how these
 841 should be incorporated in the chemical safety report and provides a list of more general
 842 considerations when reporting uncertainty analysis (Frewer et al., 2005).

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

850 Some general considerations for the presentation of uncertainty analysis include:

851 *Setup, limitations of approach*

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

857 *Presentation of methods*

- 858 ▪ Specialist jargon should be avoided whenever possible
- 859 ▪ Novel ideas should be introduced one at a time rather than all at once
- 860 ▪ Explanations should be started with familiar assessment methodologies and subsequently
 861 move to unfamiliar assessment approaches

- 862 ▪ For decision-makers, inclusion of a “positive control”, the effects of which were already
863 well understood by those involved in the risk analysis process, facilitates communication
864 about new methods (e.g. deterministic and probabilistic side by side)
- 865 ▪ Graphs with frequencies on both axes are generally difficult to understand and communicate
866 to non-experts.

867 *Communicating the results of the assessment*

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

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