

# TECHNICAL GUIDANCE DOCUMENT FOR PREPARING THE CHEMICAL SAFETY ASSESSMENT

## Chapter R.2: General Decision-Making Framework

**“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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## CONTENTS

R.2 GENERAL DECISION MAKING FRAMEWORK.....	2
R.2.1 REACH Information requirements - Annexes VI – X.....	2
R.2.2 Introduction to the GDMF .....	3
R.2.3 Substances manufactured or imported in quantities between 1 and 10 tonnes per year.....	4
R.2.3.1 Explanatory notes Scheme IA .....	6
R.2.3.1.1 STEP 1 Gather and share existing information .....	6
R.2.3.1.2 STEP 2 Consider information needs .....	6
R.2.3.1.3 STEP 3a Identify information gaps on physico-chemical properties .....	6
R.2.3.1.4 STEP 3b Examine whether phase-in substances meet criteria in Annex III.....	7
R.2.3.1.5 STEP 3c Conclude on further information requirements (i.e. on toxicological and ecotoxicological properties) .....	8
R.2.3.1.6 STEP 4 Generate new information.....	8
R.2.3.2 Explanatory notes on Scheme IIA .....	9
R.2.3.2.1 Box 1: Conclude on what exactly is unclear or insufficient to fulfil the requirements.....	9
R.2.3.2.2 Box 2: Is testing technically possible? .....	9
R.2.3.2.3 Box 3: Is waiving of the test possible considering rules in column 2?.....	10
R.2.3.2.4 Box 4: Consider if in vitro testing may be adequate.....	10
R.2.3.2.5 Box 6: Select appropriate test from the data requirements in Annex VII.....	10
R.2.4 Substances manufactured or imported in the tonnage band $\geq 10$ per year .....	10
R.2.4.1 Explanatory notes on Scheme IB.....	12
R.2.4.1.1 STEP 1 Gather and share existing information .....	12
R.2.4.1.2 STEP 2 Consider information needs .....	13
R.2.4.1.3 STEP 3 Identify information gaps .....	13
R.2.4.1.4 STEP 4: Generate new information or propose a testing strategy .....	14
R.2.4.2 Explanatory notes on Scheme IIB .....	15
R.2.4.2.1 Box 1: Conclude on what exactly is unclear or insufficient to fulfil the requirements.....	15
R.2.4.2.2 Box 2: Is testing technically possible? .....	15
R.2.4.2.3 Box 3: Is exposure-based waiving possible?.....	15
R.2.4.2.4 Box 4: Consider if in vitro testing may be adequate.....	15
R.2.4.2.5 Box 5: Conduct or propose an appropriate in vivo test .....	15

## FIGURES

Figure R.2-1: Scheme IA.....	5
Figure 2-2: Scheme IIA .....	9
Figure R.2-3: Scheme IB .....	11
Figure B.2-4: Scheme IIB.....	14

## 1 **R.2 GENERAL DECISION MAKING FRAMEWORK**

### 2 **R.2.1 REACH Information requirements - Annexes VI – X**

3 Under REACH, registrants are obliged to collect all available relevant information on the intrinsic  
4 properties of a substance, regardless of the quantity manufactured or imported. However, the type  
5 and quantity of information on the intrinsic properties of a given substance that will be required as a  
6 minimum to meet the obligations of the regulation depends on the quantity of that substance that is  
7 manufactured or imported into the EU. Annexes VI-X of REACH specify these minimum data  
8 requirements for a given substance according to its tonnage for registration purposes (REACH  
9 Article 12), which however may be adapted as appropriate.

10 Column 1 of REACH Annexes VII-X lays down the standard information requirements for  
11 substances produced or imported in quantities of  $\geq 1$  tpa (tons per annum),  $\geq 10$  tpa,  $\geq 100$  tpa, and  
12  $\geq 1000$  tpa, respectively. For physico-chemical properties and each of the health and environmental  
13 endpoints, more detailed specific guidance on meeting these information requirements is given in  
14 the appropriate subchapters of chapter R.7

15 For the lowest tonnage band, the information required is that specified in Column 1 of REACH  
16 Annex VII, comprising certain physico-chemical data, toxicological information and  
17 ecotoxicological information. However, under the terms of Article 12 (1b) and Annex III of  
18 REACH, if the substance does not have a dispersive or diffuse use and it is predicted not to be  
19 likely to meet the criteria for classification for any human health or environmental hazard, the  
20 required minimum information is confined to the physico-chemical data.

21 As each new tonnage level is attained, the requirements of the next corresponding REACH Annex  
22 must be addressed. These standard requirements may, however, be adapted (waived or increased)  
23 when appropriately justified (REACH Annexes III and VI-XI). Thus, for each individual substance  
24 the precise information requirements will differ, depending on tonnage, use and exposure, and the  
25 properties of the substance. The Annexes should thus be considered as a whole, and in conjunction  
26 with the overall requirements of registration and the duty of care. Further guidance on the  
27 information requirements for each individual endpoint is given in the appropriate subchapters of  
28 chapter R.7.

29 For each of the REACH Annexes VII to X, Column 2 lists specific rules for adaptation of  
30 information requirements, e.g. exposure or hazard characteristics, according to which the required  
31 standard information requirements for individual endpoints may be modified (adapted) (i.e.  
32 specifying possibilities for waiving the requirement for certain information, or in certain cases,  
33 defining the need for additional information). If the conditions for adaptation in Column 2 are met  
34 and applied, the fact that an adaptation has been made, together with its justification, must be  
35 indicated clearly in the registration. Further guidance on the possibilities for adaptation of the  
36 information requirements for the individual endpoints is given in the appropriate subsections of  
37 chapter R.7.

38 In addition to these specific rules, the required standard information set may also be adapted  
39 according to the general rules contained in Annex XI of the REACH Regulation e.g. in cases where  
40 testing is not technically possible, or testing does not appear scientifically necessary, or based on  
41 exposure consideration. In such cases the fact and the reasons for each adaptation should be clearly  
42 indicated in the registration. Further guidance on these rules/conditions is detailed below in chapter  
43 R.5. It should be noted that although this guidance will provide assistance in developing the  
44 reasoned justification for asking for derogations/waiving from the standard testing regime, in

45 certain cases available data showing hazardous effects could trigger the need for additional  
46 information including testing.

47 In general terms, REACH Annexes VII-X provide the standard information requirements and  
48 columns 1 and 2 specify adaptation possibilities for the specific endpoints. Different descriptors for  
49 exposure considerations are used in these Annexes varying from *limited* to *no relevant* exposure.  
50 These descriptors may not always be easily interpretable and difficult to define in operational terms,  
51 indeed their application requires practical experience and expert judgement applied on a case-by-  
52 case basis taking account of all the relevant supporting information (see RIP 3.2, EBW workshop).  
53 Further guidance on their interpretation may be found in the Integrated Testing Strategies (ITS) for  
54 specific endpoints in the relevant subsections of chapter R.7.

## 55 **R.2.2 Introduction to the GDMF**

56 Annex VI of the REACH Regulation describes a general scheme embodying four steps to be  
57 followed by the registrant to fulfil the information requirements detailed above for a given  
58 substance:

59 Step 1: Gather and share existing information

60 Step 2: Consider information needs

61 Step 3: Identify information gaps

62 Step 4: Generate new information or propose a testing strategy

63 To illustrate more clearly this information gathering and evaluation process and elaborate on the  
64 procedures to be followed in steps 1 to 4, two General Decision Making Frameworks (GDMFs)  
65 have been developed<sup>1</sup>, i.e:

66 - One for substances manufactured or imported in quantities  $\geq 1$  tonnes per year  
67 (REACH Annex VII)

68 - A second one for substances manufactured or imported in quantities  $\geq 10$ ,  $\geq 100$ ,  
69 and  $\geq 1000$  tonnes per year (REACH Annex VIII-X)

70 These GDMFs provide an overview on how all available existing information should be gathered,  
71 assessed and what new data may be needed for the assessment of the properties of substances under  
72 the REACH legislation. More specific guidance for each endpoint is given in chapter R.7 including  
73 an Integrated Testing Strategy (ITS) developed specifically for each endpoint.

74 Each of the GDMFs is illustrated in two schematic diagrams: Scheme I illustrates the first three  
75 steps of REACH Annex VI. Scheme II provides a more detailed illustration of the fourth step: the  
76 process for completing the information requirements. Further detail on the GDMF is provided in  
77 this section and in subsequent chapters of this Guidance Document (GD).

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<sup>1</sup> The data-gathering step in either GDMF is based on a substance specific approach. In case the substance is member of a well defined group for which substantial category information is available, a different information gathering strategy may be needed.

78 **R.2.3 Substances manufactured or imported in quantities between 1 and 10 tonnes per**  
79 **year**

80 Taking into account Article 12 (a) and (b) Annex VII covers all substances produced or imported in  
81 quantities between 1 and 10 tpa. Column 1 of this Annex establishes the standard information  
82 requirements for

83 - non-phase-in substances (i.e. new substances) [Non-phase-in substances, however, should  
84 follow steps 1, 2, and 3a and 3c in any case] and

85 - phase-in substances meeting one or both of the criteria in Annex III [Phase-in substances should  
86 follow the described order of steps 1, 2, 3a, 3b and if necessary 3c of the following GDMF. Step  
87 4 may not be necessary, dependent on the outcome of steps 1- 3].

88 For substances manufactured or imported in quantities  $\geq 1$  tpa all relevant physico-chemical,  
89 toxicological and ecotoxicological information that is available to the registrant shall be provided.

90 The criteria given in REACH Annex III are met if:

91 (a) Substances are predicted (i.e. by application of (Q)SARs or other evidence) to be likely to meet  
92 the criteria for category 1 or 2 classification for carcinogenicity, mutagenicity or reproductive  
93 toxicity or the criteria in Annex XIII (i.e. PBT or vPvB)

94 or

95 (b) Substances

96 i. have dispersive or diffuse use(s) particularly where such substances are used in consumer  
97 preparations or incorporated into consumer articles; and

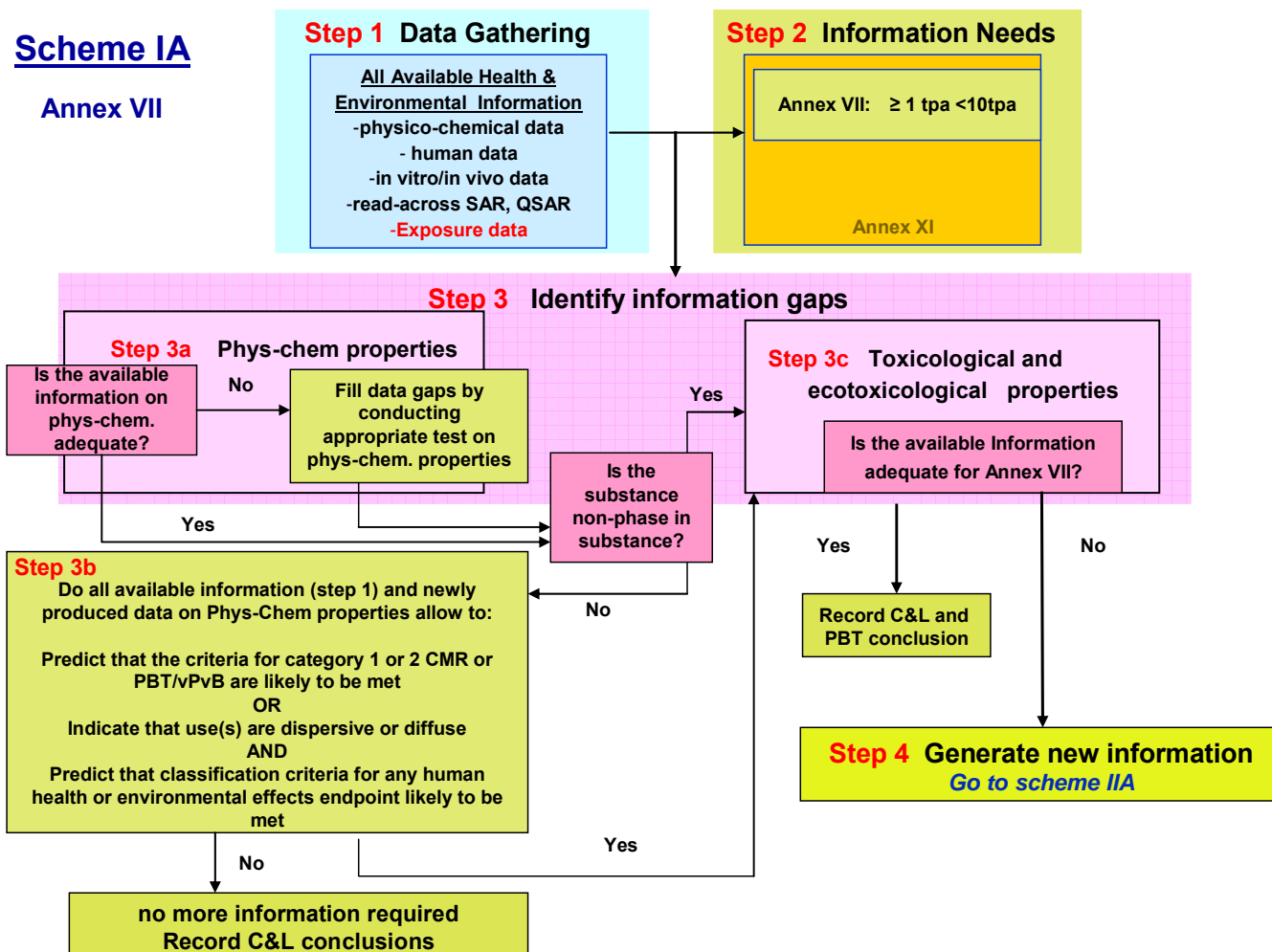
98 ii. for which it is predicted (i.e. by application of (Q)SARs or other evidence) that they are  
99 likely to meet the classification criteria for any human health or environmental effects  
100 endpoint under Directive 67/548/EEC.

101 For phase-in substances not meeting the criteria, only the information on physico-chemical  
102 properties as set out in section 7 of the REACH Annex VII are required.

103 The GDMF is illustrated in two schematic diagrams; Scheme IA (Figure R.2-1) illustrates the first  
104 three steps of REACH Annex VI. Scheme IIA (Figure R.2-2) provides a more detailed illustration  
105 of the fourth step: the process for completing the information requirements.

106

Figure R.2-1: Scheme IA



107

### 108 **R.2.3.1 Explanatory notes Scheme IA**

#### 109 **R.2.3.1.1 STEP 1 Gather and share existing information**

110 First, all existing available data on the intrinsic properties of the substance should be gathered, i.e.:

- 111 • Physico-chemical data
- 112 • Human data
- 113 • Testing data: i.e. all *in vitro* and *in vivo* testing data
- 114 • Non-testing data: i.e. data obtained with (Q)SAR models, and obtained by grouping of
- 115 substances and read-across etc.
- 116 • Exposure information

117 Such information may be obtained from a variety of sources such as in-house data of companies,  
118 from other manufacturers and importers of the substance by cooperation in a SIEF (REACH Article  
119 29), or from the Agency upon request (REACH Article 26) or from databases or other sources in the  
120 open literature or accessible on the internet – see chapter R.3.

121 This information gathering step may also include the establishment of membership of the substance  
122 in a chemical category and the information this generates (incl. read-across to other substances), as  
123 well as the information that is retrievable from computational tools, i.e. (Q)SAR models.

124 Acquiring of results from non-testing methods would be especially important for substances for  
125 which testing data set is limited or non-existent. For details on gathering of non-testing information  
126 see sections R.6.1 and R.6.2.

127 Also information on exposure should be gathered in accordance with REACH Annex VI, sections 3,  
128 5, and 6. This information will be used to conclude on *dispersive use* and *diffuse use* of the  
129 substance (see RIP 3.2 for further explanation of *dispersive and diffuse use*).

130 All these data gathering activities should be well documented to allow a proper assessment of the  
131 completeness of the data.

#### 132 **R.2.3.1.2 STEP 2 Consider information needs**

133 Column 1 of REACH Annex VII specifies information requirements that include data on physico-  
134 chemical, toxicological and ecotoxicological properties. Only information on physico-chemical  
135 properties has to be provided for all substances covered by Annex VII. Information requirements on  
136 toxicological and ecotoxicological properties should be provided for all non-phase-in substances  
137 and for phase-in substances meeting the criteria specified in REACH Annex III.

138 There may be different ways of guiding through Annex VII of REACH. A procedure here specified  
139 proposes as a first stage to comply with information requirements on physicochemical properties as  
140 generation of these data may be very helpful in evaluation of existing information on toxicological  
141 and ecotoxicological properties. These data may also be used directly in the classification schemes  
142 (e.g. pH for irritation and log  $K_{ow}$  in environmental hazard classification).

#### 143 **R.2.3.1.3 STEP 3a Identify information gaps on physico-chemical properties**

##### 144 **(I) Evaluate available information on physico-chemical properties**

145 Before examination of data gaps can be possible all available information on physico-chemical  
146 properties of the substance (collected in step 1) should be assessed for its reliability and adequacy

147 (i.e. whether it can be considered as equivalent to data generated by the corresponding test method  
148 (chapter R.3 and section R.7.1).

149 **(II) Identify information gaps on physico-chemical properties and perform testing if**  
150 **necessary**

151 If the reliable available information does not correspond to the information requirements specified  
152 in REACH Annex VII perform relevant test(s) (in accordance with the specific guidance provided  
153 in chapter 7.1).

154 Phase-in substances should proceed to Step 3b; non-phase in substances to step 3c.

155 **R.2.3.1.4 STEP 3b Examine whether phase-in substances meet criteria in Annex III**

156 (I) Evaluate *all* available information

157 At this stage *all* available information on physical-chemical and environmental fate properties,  
158 toxicity and ecotoxicity of the substance should be assessed for its reliability, relevance, and  
159 completeness. Although the reliability criteria are of a general nature, decision on whether a single  
160 piece of information is reliable (i.e. how to assigned it a specific level of reliability, e.g. Klimish  
161 score) is endpoint specific and should thus be treated within the relevant endpoint. Therefore the  
162 single subchapters of chapter R.7 on *Evaluation of available information* developed as a part of  
163 guidance for all endpoint(s) should be consulted.

164 Guidance on how to evaluate and integrate non-testing results is provided in section R.6.1.7.2. This  
165 may be of particular importance in cases when testing data are scarce and (only) non-testing data  
166 are available/have been retrieved.

167 (II) Conclude on *likely to be classified*

168 Here an overall assessment of the *reliable* data should be performed and used in estimation on  
169 whether:

170 a. a substance is likely to meet the criteria for CMR category 1 or 2 or PBT/vPvB, or

171 b. a substance is:

172 (1) likely to be classified for any health or environmental hazard and

173 (2) has a dispersive or diffuse use

174 All available information should be used in the evaluation of the toxicity and ecotoxicity of the  
175 substance including information from non-testing methods. In case no testing (eco)toxicity data are  
176 available predictions from non-testing methods would exclusively provide the basis for the  
177 assessment. The available and reliable information should be compared with the classification  
178 criteria for any human health and environmental effects' endpoints under Directive 67/548/EEC. If  
179 based on available information it could be predicted that the substance would be likely to meet  
180 classification criteria for any effect or the criteria for CMR category 1 or 2; or the criteria for PBT  
181 or vPvB then the substance should be considered as meeting the requirement (a) or (b) (ii)  
182 according to REACH Annex III. In general any results (both testing and non-testing) assessed as  
183 reliable (i.e. meeting the validity criteria) would be sufficient to predict that the substance would be  
184 likely to meet these criteria (see RIP 3.2/PBT and 3.6).

185 According to REACH Annex III if *dispersive use* or *diffuse use* (particularly where such substances  
186 are used in consumer preparations or incorporated into consumer articles) may be demonstrated, the  
187 criterion (b) (ii) should be considered as fulfilled (see RIP 3.2 for further explanation of *dispersive*  
188 and *diffuse use*).

189 In the case, when based on the available information, the substance is likely to meet the criteria  
190 specified in REACH Annex III, other information requirements on REACH Annex VII are also  
191 required: i.e. in that case proceed to Step 3c.

192 However, if the substance is not likely to meet the criteria for CMR category 1 or 2 or PBT/vPvB or  
193 for any other classification endpoint (i.e. health and the environmental) or has not a dispersive or  
194 diffuse use, no further information generation on this substance is required at the  $\geq 1$  tpa level. In  
195 this case all the gathered available and produced information should be provided in the registration  
196 dossier. Also classification of the substance based on the available data should be recorded.

#### 197 **R.2.3.1.5 STEP 3c Conclude on further information requirements (i.e. on toxicological and** 198 **ecotoxicological properties)**

199 Identify data gaps for other information required on REACH Annex VII (for all non-phase-in  
200 substances, and for phase-in substances that meet the criteria of step 3b)

201 The main task here is to identify data gaps for other information required by Annex VII (i.e. in  
202 addition to the physico-chemical properties). Since data required on this Annex would be used in  
203 C&L for decision on whether available information is adequate for purpose of classification see the  
204 relevant endpoint specific guidance in chapter R.7, i.e. acute toxicity (7.4), sensitisation (7.3), skin  
205 and eye irritation (7.2), mutagenicity (7.7), aquatic toxicity (7.8), degradation (7.9), and  
206 bioaccumulation (7.10).

207 A decision on *adequacy* relies often on *Weight of Evidence* (WoE) approaches for the various  
208 endpoints (also mentioned in REACH Annex XI, section 1.2), see chapter. Further details on the  
209 *adequacy of data* can be found in chapter R.4 on *Evaluation of available information*, chapter R.5  
210 *Special factors affecting information requirements and testing strategies*, and in chapter R.7 on  
211 endpoint specific guidance.

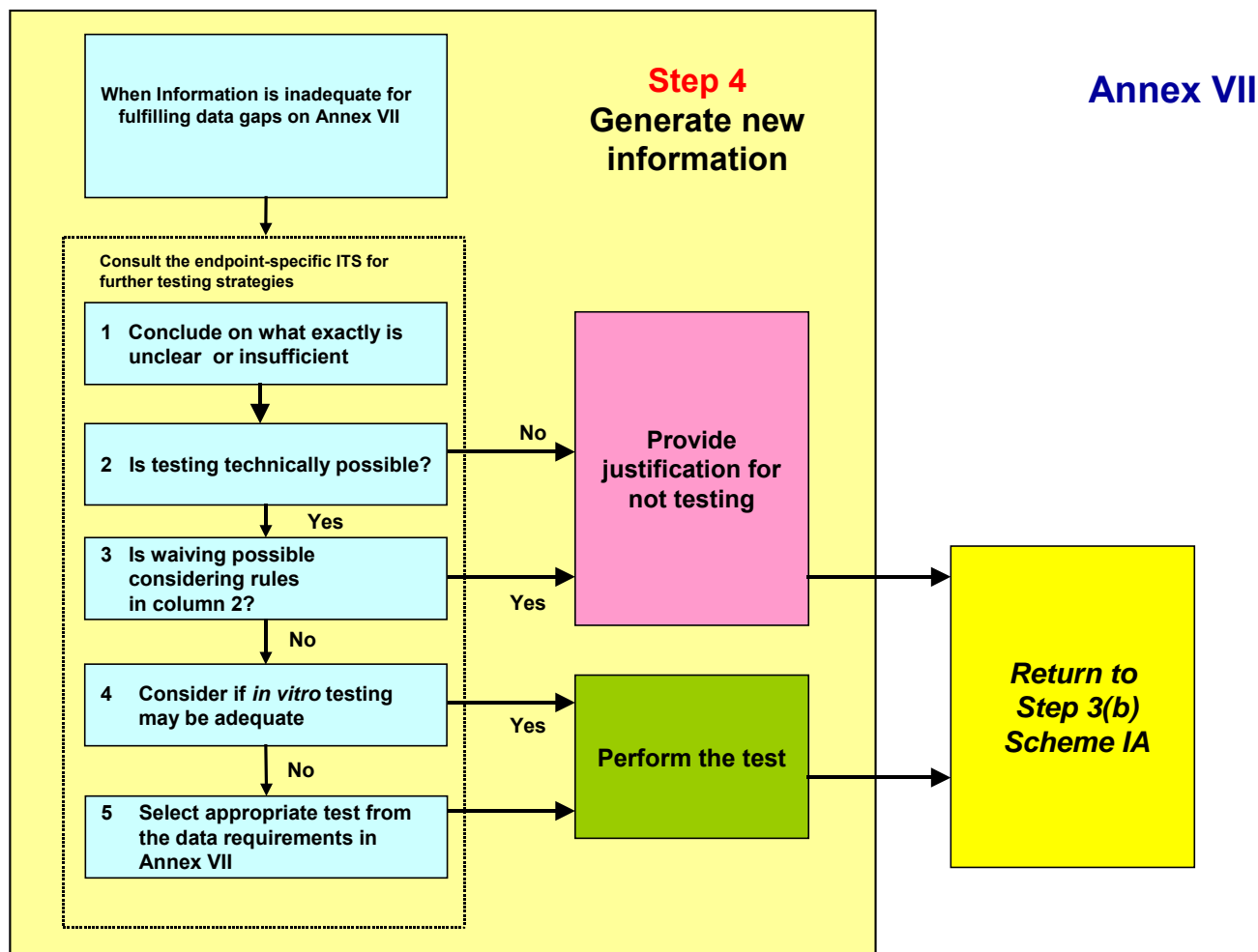
212 If reliable data are not adequate to fill data gaps, acquire relevant information following the  
213 guidance in Scheme IIA (Figure R.2-2).

#### 214 **R.2.3.1.6 STEP 4 Generate new information**

215 Scheme IIA (Figure R.2-2) comprises a general strategy on how to proceed when available data are  
216 not adequate to fill data gaps.

217

Figure R.2-2: Scheme IIA



218

### 219 R.2.3.2 Explanatory notes on Scheme IIA

#### 220 R.2.3.2.1 Box 1: Conclude on what exactly is unclear or insufficient to fulfil the requirements

221 In general the data gaps would require generation of data according to the information requirements  
 222 specified in Column 1 of REACH Annex VII. However, in the cases, when available (and reliable)  
 223 information exists it is important to develop a clear idea about exactly what is needed to arrive at  
 224 the conclusion that with the new information the available information may be regarded as  
 225 adequate.

#### 226 R.2.3.2.2 Box 2: Is testing technically possible?

227 In accordance with REACH Annex XI section 2 testing for specific endpoints may be omitted if it  
 228 is technically not possible to conduct the study as a consequence of the properties of the substance,  
 229 e.g. very volatile, highly reactive or unstable substances (specific cases can be found in Column 2  
 230 of REACH Annex VII). Any omission of testing should be justified and the technical limitations  
 231 explained.

232 **R.2.3.2.3 Box 3: Is waiving of the test possible considering rules in column 2?**

233 Column 2 includes specific rules for adaptation of the information requirements in REACH Annex  
234 VII. Based on intrinsic properties some test may be waived or replaced by other, better suited for  
235 the substance. These adaptation rules should thus be carefully considered before performance of a  
236 new test.

237 **R.2.3.2.4 Box 4: Consider if *in vitro* testing may be adequate**

238 At present, with the exception of the endpoints skin corrosion and skin irritation, it is only possible  
239 in specific cases to conclude on a classification according to the existing EU or GHS criteria on the  
240 basis of *in vitro* studies alone, e.g. for identification of severe eye irritants using organotypic  
241 methods. See chapter R.7 on specific endpoints.

242 However, the combination of various pieces of evidence, including *in vitro* test data, may provide  
243 adequate information for a decision on classification and/or risk assessment, when applied in an  
244 integrated manner.

245 **R.2.3.2.5 Box 6: Select appropriate test from the data requirements in Annex VII**

246 The registrant should perform the test, unless appropriate justification for waiving, as explained in  
247 the previous steps, can be provided. Test results should be used at this stage (i.e. for substances  
248 manufactured or imported from  $\geq 1$  tonnes per year) for the purpose of classification and labeling  
249 (chapter R.7 for individual endpoint specific guidance and the RIP 3.6).

250 **R.2.4 Substances manufactured or imported in the tonnage band  $\geq 10$  per year**

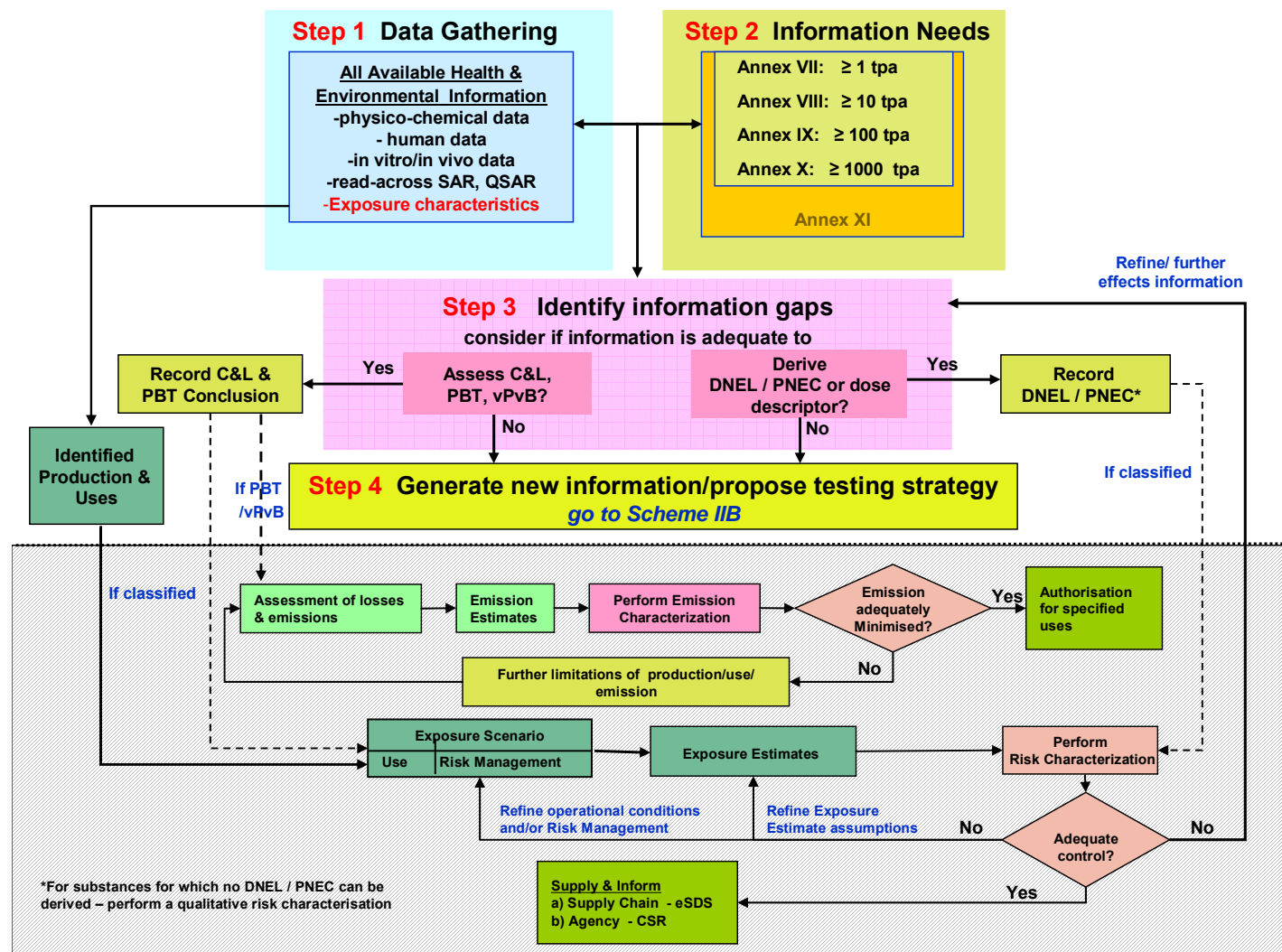
251 REACH Annexes VI to XI specify the information that shall be submitted for registration and  
252 evaluation purposes. For the lowest tonnage level, the standard information requirements are in  
253 REACH Annex VII, and every time a new tonnage level is reached, the requirements of the  
254 corresponding annex have to be added. This section describes the GDMF for substances that have to  
255 be registered for REACH Annexes VIII to X.

256 The GDMF is illustrated in two schematic diagrams; Scheme IB illustrates the first three steps of  
257 Annex VI. The lower half of the Scheme, shown as the hatched area below the horizontal dotted  
258 line, illustrates the application of the information for Classification and Labelling, PBT and vPvB  
259 assessment and chemical safety assessment, detailed guidance for which is given in other RIP  
260 outputs. Scheme IIB provides a more detailed illustration of the fourth step: the process for  
261 completing the information requirements.

262

263

Figure R.2-3: Scheme IB



264

## 265 **R.2.4.1 Explanatory notes on Scheme IB**

### 266 **R.2.4.1.1 STEP 1 Gather and share existing information**

267 At this stage *all* available information on physical-chemical and environmental fate properties,  
268 toxicity and ecotoxicity of the substance should be assessed for its reliability, relevance, and  
269 completeness. Although the reliability criteria are of a general nature, decision on whether a single  
270 piece of information is reliable (i.e. how to assigned it a specific level of reliability, e.g. Klimish  
271 score) is endpoint specific and should thus be treated within the relevant endpoint. Therefore the  
272 single subchapters of chapter R.7 on *Evaluation of available information* developed as a part of  
273 guidance for all endpoint(s) should be consulted.

274 First, all existing available data on the intrinsic properties of the substance should be gathered, i.e.:

- 275 - Physico-chemical data
- 276 - Human data
- 277 - Testing data: i.e. all *in vitro* and *in vivo* testing data
- 278 - Non-testing data: i.e. data obtained with (Q)SAR models, and obtained by  
279 grouping of substances and read-across etc.
- 280 - Exposure characteristics

281 Such information may be obtained from a variety of sources such as in-house data of companies,  
282 from other manufacturers and importers of the substance by cooperation in a SIEF (REACH Article  
283 29), or from the Agency upon request (REACH Article 26) or from databases or other sources in the  
284 open literature or accessible on the internet.

285 This information gathering step should if possible also include the establishment of membership of  
286 the substance in a proper chemical category and the information this provides (incl. read-across to  
287 other substances), as well as the information that is retrievable from computational tools, i.e.  
288 (Q)SAR models.

289 It may well be that the available information on these intrinsic properties of the substance go  
290 beyond the tonnage triggered requirements of test data (referred to in Step 2): it is a requirement of  
291 REACH Article 12, that “*The technical dossier referred to in Article 10(a) shall include [...] all*  
292 *physico-chemical, toxicological and ecotoxicological information that is relevant and available to*  
293 *the registrant [...]”.*

294 For some chemicals the data available may be quite abundant and exceed the minimum information  
295 requirements of REACH; guidance is given in chapter R.3 how to proceed for such cases.

296 With respect to the exposure characteristics, information on the manufacture (if within EU), use,  
297 handling and disposal of the substance (i.e. covering its whole life cycle) or of articles containing  
298 the substance, should be gathered to obtain insight into the populations and compartments exposed,  
299 as well as the nature of the exposures, i.e. routes, frequency and duration (see REACH Annex VI,  
300 sections 3, 5, and 6); this information will guide further information requirements: e.g. if limited  
301 and well controlled human exposure is only taking place at the workplace during a few days a  
302 month, chronic toxicity studies may not be needed.

303 The further elaboration of these data on exposure characteristics in terms of deriving associated  
304 exposure estimates is required under REACH only when available and/or required information

305 indicates that the substance should be classified as dangerous or meets the PBT/vPvB criteria (see  
306 Step 3, Box 4), as only under these conditions a full risk assessment is requested.

307 All these data gathering activities should be well documented, to allow a proper assessment of the  
308 completeness of the chemical safety report. Further details on this first step can be found in chapter  
309 R.3 of this document.

#### 310 **R.2.4.1.2 STEP 2 Consider information needs**

311 The tonnage-triggered information-requirements for REACH on physico-chemical, toxicological  
312 and ecotoxicological properties are described in column 1 of Annexes VII-X. Specific rules for  
313 adaptation are provided in column 2 of these Annexes, whereas general rules for adaptation of these  
314 standard requirements are provided in Annex XI.

315 Further details on this step can be found in chapter R.3 of this document.

#### 316 **R.2.4.1.3 STEP 3 Identify information gaps**

317 In this step for each endpoint an assessment must be made of the adequacy of the available  
318 information for arriving at conclusions on hazard assessment, i.e. C&L, and PBT/vPvB assessment,  
319 and identification of (a) dose descriptor(s) enabling the derivation of (a) DNEL(s) and (a) PNEC(s).  
320 DNEL(s)/PNEC(s) are subsequently to be used in the risk characterisation when a substance is  
321 classified as dangerous and a full risk assessment is required.

322 The term *adequate* refers to the ability to meet the defined information requirements (Annexes VII-  
323 XI), and to allow a conclusion on the above mentioned aspects in hazard assessment. This  
324 evaluation of the adequacy of available information is further explained in chapter R.4.

325 In this step, three main conclusions can be obtained:

- 326 - the information available is considered *adequate* for the objectives mentioned (C&L, PBT/  
327 vPvB assessment, and DNEL/PNEC derivation), and there is
  - 328 ○ no need for any classification: then there is no REACH requirement for any  
329 further information or any safety assessment;
  - 330 ○ need for classification: further information requirements on exposure  
331 conditions are needed for assessing the associated exposures (see Box 4) that  
332 subsequently allow a chemical safety assessment to be performed (see RIP  
333 3.2);
- 334 - the information available is considered *inadequate* for at least one of the objectives and further  
335 information is needed; for this situation, Scheme IIB (Figure R.2-4) provides guidance.

336 It is possible that the data may be adequate for C&L and PBT (or vPvB), but not for DNEL and/or  
337 PNEC derivation, or vice versa, as data requirements for these conclusions may differ.

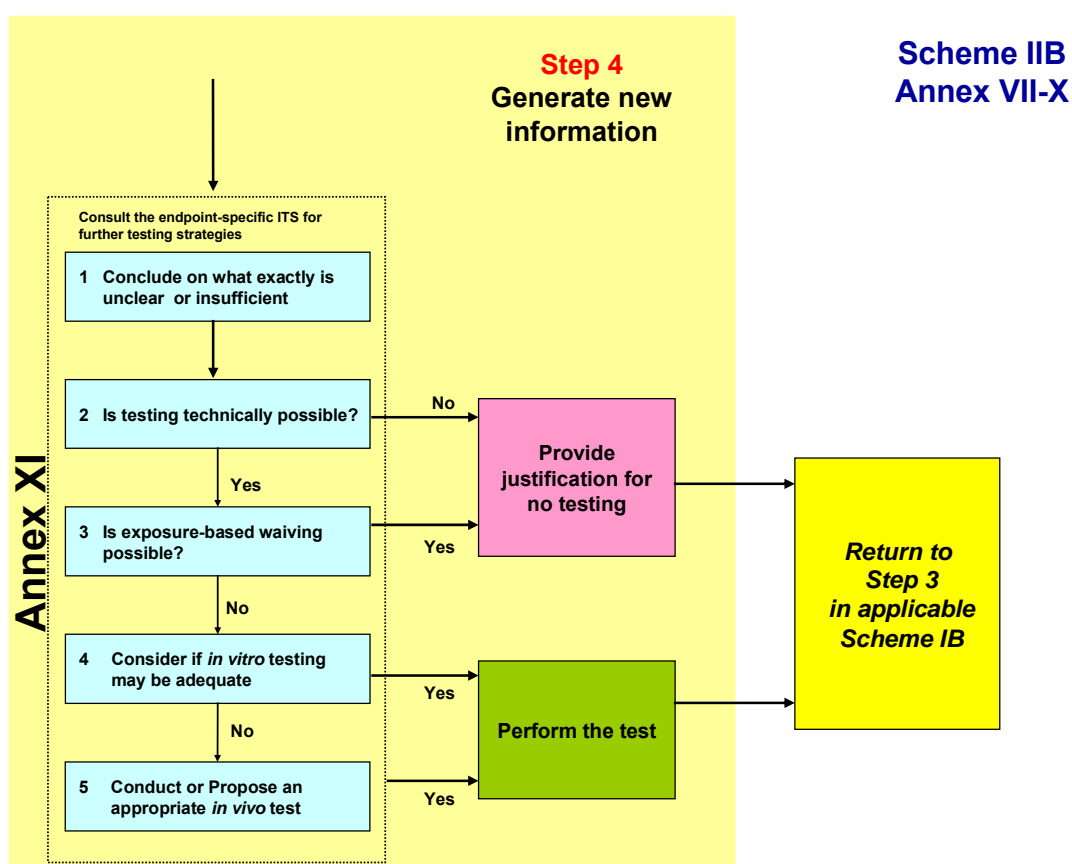
338 It is also emphasised that it may not always be possible to establish a quantitative DNEL for risk  
339 assessment purposes via the identification of a concrete quantitative dose descriptor value, e.g. a  
340 NOAEL etc.; in these situations it may be possible nevertheless to define some quantitative or semi-  
341 quantitative dose descriptor or a qualitative approach that may also allow a conclusion that the use  
342 and handling of the substance may be regarded as adequately controlled.

343 Further details on the adequacy of data can be found in chapter R.4 *Evaluation of available*  
 344 *information*, chapter R.5 *Special factors affecting information requirements and testing strategies*,  
 345 and in chapter R.7 on endpoint specific guidance.

#### 346 R.2.4.1.4 STEP 4: Generate new information or propose a testing strategy

347 In the above assessment in Step 3 of scheme IB (Figure R.2-3) the conclusion may be that the  
 348 available information is inadequate for one or more of the goals of data gathering: C&L, assessment  
 349 of PBT/vPvB, and risk assessment. Scheme IIB (Figure R.2-4) comprises a general strategy on how  
 350 to proceed in such cases. In addition, more specific guidance on addressing inadequacy of  
 351 information has been formulated for each endpoint based on the application of so-called Integrated  
 352 Testing Strategies (ITS), (see chapter R.7).

353 **Figure R.2-4: Scheme IIB**



354

355 As already indicated in Step 1 further information gathering preferably comes from further non-  
 356 testing sources, with the additional *in vivo* testing option only as a last resort. The generic steps of  
 357 scheme IIB (numbered boxes) will be shortly discussed.

**358 R.2.4.2 Explanatory notes on Scheme IIB****359 R.2.4.2.1 Box 1: Conclude on what exactly is unclear or insufficient to fulfil the requirements**

360 It is conceivable that the information gathering has not been as extensive as possible, i.e. further  
361 information gathering could potentially yield further existing data; if so, this should be addressed  
362 following the guidance described and exemplified in Step 1 of Scheme IB (Figure R.2-3). However,  
363 where all possible information sources have been consulted, it is important to develop a clear idea  
364 about exactly what additional information is needed to be able to conclude on hazard and/or risk  
365 assessment (i.e. C&L, and PBT/vPvB assessment, and/or DNEL derivation including identification  
366 of dose descriptors).

**367 R.2.4.2.2 Box 2: Is testing technically possible?**

368 Testing may in certain specific cases not be technically possible. In accordance with REACH  
369 Annex XI section 2 testing for specific endpoints may be omitted if this is the case (e.g. very  
370 volatile, highly reactive or unstable substances; specific cases can be found in Column 2 of REACH  
371 Annex VII). Any omission of testing should be justified and the technical limitations explained.  
372 Case-by-case expert judgement is needed here.

**373 R.2.4.2.3 Box 3: Is exposure-based waiving possible?**

374 If adequate control can be demonstrated the need for completing the information requirements for  
375 some endpoints may be waived: columns 2 of Annexes VIII-X give guidance for what information  
376 requirements exposure levels are critically decisive; evidently, this requires a documented  
377 knowledge of all scenarios and accurate assessment of all associated exposures (see for further  
378 details section R.5.1, and the corresponding endpoints chapters in chapter R.7).

**379 R.2.4.2.4 Box 4: Consider if *in vitro* testing may be adequate.**

380 At present, with the exception of the endpoints skin corrosion and skin irritation, it is only possible  
381 in specific cases to conclude on a classification according to the existing EU or GHS criteria on the  
382 basis of *in vitro* studies alone, e.g. for identification of severe eye irritants using organotypic  
383 methods. See chapter R.7 on specific endpoints.

384 However, the combination of various pieces of evidence, including *in vitro* test data, may provide  
385 adequate information for a decision on classification and/or risk assessment, when applied in an  
386 integrated manner.

**387 R.2.4.2.5 Box 5: Conduct or propose an appropriate *in vivo* test**

388 According to REACH, *in vivo* testing should be regarded only as a last resort when evaluating the  
389 additional information needs. Only appropriate *in vivo* tests taking into account existing reduction  
390 and refinement methods should be used. Clearly, REACH Annex VI indicates that the registrant  
391 should perform the test when REACH Annex VIII applies, unless appropriate justification for  
392 waiving, as explained in the previous steps, can be provided. When REACH Annexes IX and X  
393 apply the registrant should produce a test-proposal and await the approval of the Agency.