

TECHNICAL GUIDANCE DOCUMENT FOR PREPARING THE CHEMICAL SAFETY ASSESSMENT

Chapter R.5: Special factors affecting information requirements and testing strategies

**“Technical Guidance Documents in support of the New EU Chemicals Legislation (REACH) –
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CONTENTS

R.5 SPECIAL FACTORS AFFECTING INFORMATION REQUIREMENTS AND TESTING STRATEGIES....	2
R.5.1 Adaptations under Annex XI	2
R.5.1.1 Testing does not appear scientifically necessary	2
R.5.1.1.1 Use of existing data	2
R.5.1.1.2 Weight of evidence.....	3
R.5.1.1.3 Non-testing methods.....	3
R.5.1.1.4 <i>In vitro</i> methods.....	4
R.5.1.2 Testing is technically not possible	5
R.5.1.3 Substance-tailored exposure-driven testing	5
R.5.2 Other factors influencing further information needs	6
R.5.2.1 Toxicokinetics	6
R.5.2.2 Substances requiring special considerations during testing	7
R.5.2.2.1 Metals and Inorganics.....	7
R.5.2.2.2 Petroleum Substances	8
R.5.3 References for chapter 5	10

R.5 SPECIAL FACTORS AFFECTING INFORMATION REQUIREMENTS AND TESTING STRATEGIES

The REACH Regulation outlines a number of general rules for the adaptation of the standard information requirements. In general terms, Annexes VII-X provide the standard information requirements in column 1, whereas column 2 specifies adaptation possibilities for the specific endpoints. Further guidance on their interpretation may be found in the Integrated Testing Strategies (ITS) for specific endpoints in the relevant subsections of chapter R.7.

In addition to these specific rules, the required standard information set may also be adapted according to the general rules contained in Annex XI of the REACH Regulation; it should be noted that although this guidance will provide assistance in developing the reasoned justification for asking for derogations/waiving from the standard testing regime, in certain cases available data showing hazardous effects could trigger the need for additional information, including testing.

In REACH Annex XI the three main areas defined for adaptation of information requirements are:

- Testing does not appear scientifically necessary;
- Testing is technically not possible;
- Substance-Tailored Exposure-driven Testing.

Many of the concepts relevant to these adaptations are described in greater depth in chapter 4 hence in chapter 5.1 guidance for these is limited to their specific application to the Annex XI provisions. Guidance is also provided in chapter 5.2 on a number of other factors that can be used to justify adaptation of the information requirements; these include toxicokinetic considerations, certain substance properties e.g. complex mixtures and poorly soluble materials.

R.5.1 Adaptations under Annex XI

R.5.1.1 Testing does not appear scientifically necessary

The standard testing regime may be adapted when testing does not appear scientifically necessary according to the rules set out in REACH Annex XI section 1.

R.5.1.1.1 Use of existing data

Section 1.1.1 (physico-chemical properties) and 1.1.2 (data on human health and environmental properties) of REACH Annex XI on the use of existing data enable the use of non-GLP non-Guideline information, under certain conditions. These include the demonstration that such information covers the essential elements of the internationally accepted test method, provided documentation is sufficient and the information is adequate for the purpose of C&L and/or risk assessment.

Section 1.1.3 of REACH Annex XI considers the opportunity of evaluating historical human data, such as epidemiological studies on exposed population, accidental or occupational exposure data and clinical studies.

These approaches were used to a large extent for filling information requirements under the Existing Chemicals Regulation (EU Regulation 793/93). They were also used extensively for C&L of existing substances under the Dangerous Substance Directive (EU Directive 67/548/EEC). Whilst the criteria for classification in that Directive were based on test results generated by

40 applying internationally accepted test methods under GLP, data for existing substances is often
41 available for studies carried out before these internationally accepted methods were adopted, and, as
42 a result, an element of scientific judgement is needed in evaluating these non-standard data.

43 These examples above fall under the traditional application of these approaches previously to
44 REACH implementation, but other examples have been applied successfully, such as:

- 45 - The use of *QSAR* for environmental hazard assessment for classification and risk assessment
46 purposes;
- 47 - The use of *grouping* in the classification of petroleum products and other, mainly inorganic,
48 groups of compounds;
- 49 - The use of *read-across* and *grouping* for both classification and risk assessment purposes and
50 notification of new substances;
- 51 - The use of *non-validated in vitro* test results for risk assessment purposes.
- 52 - The use of $\log K_{ow}$ ¹ as a surrogate for the fish bio-concentration factor for classification and risk
53 assessment purposes.

54 **R.5.1.1.2 Weight of evidence**

55 In the evaluation process of all available information according to Annex I section 3.1.1 of the
56 REACH Regulation, there will be cases where data from sources other than tests specifically
57 addressing an endpoint can provide valuable information. In addition, it is reasonable to expect that
58 there will be cases where several *inadequate* studies on a given endpoint may exist (tests not
59 included in the test methods referred to in REACH Article 13 (3)). If a rationale can be presented to
60 show that such tests adequately describe the endpoint of concern, a further test for that particular
61 endpoint may not be necessary. The pooling of several such studies to satisfy a specific endpoint is
62 a way that an evidence based analysis can be used.

63 *Weight of evidence* is closely linked to *testing/information strategies*, in that the available evidence
64 can help to determine the possible subsequent testing steps. Results from such subsequent tests will
65 have an impact on the evidence based decision, which might lead to a substantiated judgement on
66 whether there is any need for further testing.

67 Further guidance is provided in section R.4.4 on the application of an evidence based approach for
68 the evaluation of information of different types and quality.

69 **R.5.1.1.3 Non-testing methods**

70 Non-testing methods, i.e. (Q)SARs and grouping methods (read-across and category approaches)
71 can be used directly to fulfil information requirements in REACH, provided that they are shown to
72 be adequate for the regulatory purpose (classification and labelling and/or risk assessment)
73 according to the general conditions specified in Annex XI. The assessment of adequacy for non-
74 testing data has to be judged on a case-by-case basis, taking into account the regulatory context in
75 which the result is being proposed.

¹ EU Method A.8 (OECD 117) Partition coefficient even allows calculation methods to be used as a surrogate for experimental derivation of log K.

76 In principle, all types of non-testing methods can be used to indicate the presence or absence of a
77 particular property (or hazard), and to replace test data or to provide supplementary data on non-
78 tested endpoints.

79 The determination of whether a (Q)SAR result may be used can be broken down into three main
80 steps:

- 81 - an evaluation of the scientific validity of the model
- 82 - an assessment of the applicability of the model to the chemical of interest and the reliability of
83 the individual model prediction
- 84 - an assessment of the adequacy of the information for making the regulatory decision, including
85 an assessment of *completeness*, i.e. whether the information is sufficient to make the regulatory
86 decision, and if not, what additional (experimental) information is needed.

87 To be used as a full replacement of an experimental test, all three conditions need to be fulfilled. In
88 cases where some information elements are missing, (Q)SAR results may still be used in the context
89 of a *Weight of Evidence* approach. Appropriate documentation must be given e.g. in the form of
90 QMRFs and QPRFs. Detailed guidance is given in sections R.6.1.9 and R.6.1.10.

91 Grouping approaches (analogue and category approaches) can be performed according to stepwise
92 procedures described in section R.6.2, which also describes a number of considerations useful for
93 assessing the adequacy of the analogue or category approach. The results and regulatory
94 conclusions obtained must be documented according to the appropriate reporting format for the
95 analogue read-across or category (see section R.6.2).

96 The grouping of substances is a scientific exercise, but its successful implementation also has a
97 number of practical and organisational implications. For example, REACH will facilitate the
98 grouping of similar substances as, during pre-registration of a substance, companies can also
99 indicate other substances for which the data are relevant. In this process, a dialogue between the
100 registrant and the authorities will be important.

101 Furthermore, REACH Annex XI states that *the Agency, after consulting with relevant stakeholders*
102 *and other interested parties, shall issue guidance on technically and scientifically justified*
103 *methodology for the grouping of substances sufficiently in advance of the first registration deadline*
104 *for phase-in substances.*

105 The category approach, applied in its fullest extent, should enable the establishment of categories
106 covering all possible chemicals (across company portfolios, across production volume bands, across
107 legislative scopes and even covering substances which are no longer produced or have not (yet)
108 been produced) and establishing through the category approach multiple relationships (the
109 *relational features*) between the category members and their properties.

110 **R.5.1.1.4 *In vitro* methods**

111 REACH Annex XI makes provision for adapting the standard testing regime by suggesting
112 consideration of waiving (because *testing does not appear scientifically necessary*) the standard test
113 provided the following conditions are met:

- 114 - The test has been validated according to internationally agreed validation principles
- 115 - The results are adequate for the purpose of C&L and/or risk assessment (including PBT-

116 assessment) and

117 - There is adequate and reliable documentation of the method.

118 Furthermore, REACH Annex XI permits the use of results from *in vitro* methods that have not yet
119 been scientifically validated provided that they are identified as being *suitable* (see section R.4.3.1
120 and Table R.5-2).

121 In addition, *in vitro* methods can play an important role in the development and use of Integrated
122 Testing Strategies (ITS), which provide the appropriate approach for hazard assessment. *In vitro*
123 information as such or together with information generated by other components of the ITS may be
124 used for meeting the information requirements of REACH through the application of an evidence
125 based approach.

126 **R.5.1.2 Testing is technically not possible**

127 REACH Annex XI section 2 states that testing for a specific endpoint may be omitted if it is
128 technically not possible to conduct the study as a consequence of the properties of the substance.

129 The physico-chemical characteristics of a chemical may limit the possibility for performing certain
130 (eco)toxicity assays. Depending on the endpoint, certain properties of the considered chemical
131 might exclude testing; such properties include solubility, high volatility, colour (e.g. masking a
132 response such as contact irritation or sensitisation), reactivity with water resulting immediately in a
133 substance with known properties, mixing of substances that may present a danger of fire or
134 explosion, high reactivity and impossibility of radio-labelling of substances required in certain
135 studies.

136 The physico-chemical characteristics may also prevent administration of precise and consistent
137 doses of the chemical for both *in vitro* studies and *in vivo* studies. E.g the following needs to be
138 scrutinised: testing of gases for oral toxicity, testing of non-water soluble compounds for fish
139 toxicity, and testing of non-water soluble compounds in submerged cell cultures, and low volatility
140 substances for inhalation testing.

141 For poorly water soluble substances (e.g. below the detection limit of the analytical method of the
142 test substance) it may neither be possible nor relevant to try and conduct certain ecotoxicological
143 tests, as it is difficult to maintain a high enough and constant concentration of the substance in the
144 water. For these types of substances, different test duration and alternative test methods need to be
145 considered. As the amount in solution will be low, instead of acute aquatic toxicity studies chronic
146 studies may be relevant (see chapter 7.8), for bioaccumulation assessment a fish dietary
147 bioaccumulation test may be more relevant than the normal BCF study (see chapter 7.10.1). Also
148 special environmental compartments may be relevant to consider and hence testing with sediment-
149 dwelling species may be both possible and more relevant, for which the details are given in (see
150 chapter 7.10.12). Issues like this have to be considered on a case-by-case basis for the individual
151 substance and individual endpoint. In particular the physico-chemical properties of the substance
152 will have a decisive influence on whether testing is technically possible. In all circumstances where
153 proposals for waiving of testing are based on such grounds, a detailed justification should be
154 provided in writing.

155 **R.5.1.3 Substance-tailored exposure-driven testing**

156 This adaptation possibility pertains to the information requirements in Annex VIII sections 8.6 and
157 8.7, Annex IX and Annex X of REACH. Column 1 of these Annexes specifies the standard
158 information requirements for the given endpoints. The information requirements may be omitted,

159 triggered, replaced or adapted in accordance with the rules in these Annexes as stated in column 2.
160 In addition REACH Annex XI contains more general adaptation criteria also to be taken into
161 consideration.

162 The adaptation possibilities in REACH Annex XI section 3 shall be based on an exposure
163 assessment in accordance with REACH Annex I section 5 (i.e. exposure scenarios for manufacture
164 and identified uses and subsequent exposure estimates). Consideration of exposure should be placed
165 within the context of a risk-based decision-making framework. If the available data is insufficient to
166 derive a DNEL value, the concept of the Threshold of Toxicological Concern (TTC, see chapter
167 8.1) may provide suitable threshold values necessary for a risk-based assessment. Several threshold
168 levels have been proposed and a careful consideration of the chemical structure and use pattern is
169 necessary to decide whether the concept of Threshold of Toxicological Concern might be
170 applicable.

171 For environmental endpoints, cut off criteria for testing as well as non-testing, for example on the
172 basis of physico-chemical characteristics, should be considered. Specific criteria for individual
173 endpoints have been given in the relevant endpoint specific guidance. These criteria are aimed at
174 providing guidance on whether exposure of a particular environmental compartment can be
175 excluded and thus hazard testing does not need to be carried out.

176 Similarly, for human health, testing may not be necessary if exposure by the relevant route of
177 exposure can be excluded or if the risk management measure already in place are sufficient to
178 protect against any risk which would be identified by a positive test result (See RIP 3.2 for further
179 guidance on exposure based waiving).

180 **R.5.2 Other factors influencing further information needs**

181 In addition to the different factors set out in Annex XI for the adaptation of the testing necessary to
182 meet the requirements of REACH, there are other considerations for modifying or adapting the
183 testing strategy for completing the information needed to comply with the regulation.

184 **R.5.2.1 Toxicokinetics**

185 REACH does not contain a mandatory requirement to generate toxicokinetic information. REACH
186 Annex I section 1.0.2 states “the human health hazard assessment shall consider the toxicokinetic
187 profile (i.e. absorption, metabolism, distribution and elimination) of the substance”. Furthermore,
188 REACH states in Annex VIII section 8.8.1 that the registrant should perform “assessment of the
189 toxicokinetic behaviour of the substance to the extent that can be derived from the relevant
190 available information”.

191 Toxicokinetics (TK) information is not a toxicological endpoint in itself; however, such information
192 might make some further testing unnecessary in terms of predictability of other properties. TK
193 information can also assist in the development of testing strategies, contribute significantly to the
194 interpretation of information from toxicodynamic (TD) studies, providing the basis for adaptation of
195 the standard REACH testing requirements by identifying the optimal study type and design
196 including dose setting.

197 Information on mode of action and metabolism derived from TK data also provides the basis for
198 read-across and grouping approaches, and consequent adaptation of chemical testing strategies.
199 Further guidance on such approaches is given in section R.6.3.

200 Along with other approaches, TK can contribute to reduction of animal use under REACH.

201 In section R.6.3. of this document the general principles of TK are addressed and the relevant
202 parameters necessary to describe and assess the absorption and bioavailability, distribution,
203 metabolism and excretion (so-called ADME) of a substance dependent on the various exposure
204 scenarios are discussed. The use of physico-chemical (PC) parameters for default assumptions
205 regarding TK parameters, and the impact of the TK behaviour of a substance on hazard and risk
206 characterisation, are also addressed.

207 **R.5.2.2 Substances requiring special considerations during testing**

208 Standard approaches for hazard and risk characterisation rely on the premise that human and/or
209 environmental exposure to a certain substance is adequately represented by the exposure of the test
210 substance used in standard test protocols. However, there may be situations where the composition
211 of a substance to which human and/or environmental exposure occurs, could be different from that
212 tested in the laboratory studies. For example substances with variability in composition may result
213 in a similar variation in the exposure profile of the different components over time. Also the
214 composition of a liquid that is a complex mixture might be very different from that of its associated
215 vapour phase or the Water Accommodated Fraction (WAF) and it is therefore necessary to develop
216 a specific testing strategy to ensure that the composition of the sample to be tested in the laboratory
217 reflects fully the composition of the likely human or environmental exposure. Such substances are
218 designated as *Non-standard substances*, *Complex Substances* or *Substance of Unknown or Variable*
219 *composition*, *Complex reaction products* or *Biological material* (UVCB substances) and have
220 generally the following characteristics:

- 221 - they contain numerous chemicals (typically closely related isomers and/or chemical classes with
222 defined carbon number or distillation ranges), and cannot be represented by a simple chemical
223 structure or defined by a specific molecular formula
- 224 - they are not intentional mixtures of chemicals.
- 225 - many are of natural origin (e.g., crude oil, coal, plant extracts) and cannot be separated into their
226 constituent chemical species.
- 227 - the concept of *impurities* typically does not apply to complex substances.
- 228 - they are produced according to a performance specification related to their physico-chemical
229 properties.

230 This class of substances requires a case-by-case consideration of the approach to define the
231 appropriate information and methods necessary for meeting the requirements of REACH. Pigments,
232 surfactants, antioxidants, and complex chlorine substances are examples of classes of substances,
233 which may require special considerations to take into account the testing requirements for complex
234 substances. Additional examples are presented in section R.5.2.1 and R.5.2.2, metal and inorganic
235 substances and petroleum products).

236 **R.5.2.2.1 Metals and Inorganics**

237 Metals and inorganic metal compounds have properties which require specific considerations when
238 assessing their hazards and risks. These considerations may include:

- 239 - The occurrence of metals as natural elements in food, drinking water and all environmental
240 compartments

- 241 - The essentiality of some of the metals for humans and organisms living in the environment and
 - 242 their general relationship with the natural background
 - 243 - The speciation of metals influencing bioavailability and for some even the hazard profile
 - 244 - The short and long term bioavailability of metals and differing degrees of availability to humans
 - 245 and other organisms in the environment
- 246 The classical (eco-)toxicity tests do not necessarily consider the above properties and the results
247 obtained may, therefore, be difficult to interpret. Taking specific considerations into account when
248 testing metals and inorganic metal compounds could often prevent these. Extensive experience on
249 hazard and risk assessment of metals was gathered under the Existing Substances Regulation
250 programme and the technical and scientific knowledge with regard to metals has advanced
251 significantly. These have been described in detail by Van Gheluwe *et al* (2006) for the environment
252 and Battersby *et al* (2006) for human health. Specific guidance on testing and data interpretation for
253 the hazard and risk assessment of metals and inorganic metal compounds is given in the chapters
254 related to the individual endpoints.

255 **R.5.2.2.2 Petroleum Substances**

256 Petroleum substances belong to the group of UVCB substances: complex mixtures of hydrocarbons,
257 often of variable composition, due to their derivation from natural crude oils and the refining
258 processes used in their production. Many petroleum substances are produced in very high tonnages
259 to a range of technical specifications, with the precise chemical composition of particular
260 substances, rarely if ever fully characterised. Since complex petroleum substances are typically
261 separated on the basis of distillation, the technical specifications usually include a boiling range.
262 These ranges correlate with carbon number ranges, while the nature of the original crude oil and
263 subsequent refinery processing influence the types and amount of hydrocarbon structures present.
264 The CAS definitions established for the various petroleum substance streams generally reflect this,
265 including details of final refinery process; boiling range; carbon number range and predominant
266 hydrocarbon types present.

267 For most petroleum substances, the complexity of the chemical composition is such that it is beyond
268 the capability of routine analytical methodology to obtain complete characterisation. Typical
269 substances may consist of predominantly mixtures of straight and branched chain alkanes, single
270 and multiple naphthenic ring structures (often with alkyl side chains), single and multiple aromatic
271 ring structures (often with alkyl side chains). As the molecular weights of the constituent
272 hydrocarbons increase, the number and complexity of possible structures (isomeric forms) increases
273 exponentially.

274 Similar to the petroleum substances are the hydrocarbon solvents; they also consist of variable,
275 complex mixtures of hydrocarbons and are described by EINECS numbers that are also used for
276 petroleum refinery streams. Hydrocarbon solvents usually differ from petroleum refinery streams in
277 the following ways:

- 278 - they are more highly refined;
- 279 - they cover a narrower range of carbon number;
- 280 - they contain virtually no substances of concern (e.g. benzene)
- 281 - they contain virtually no olefins.

282 Although compositionally somewhat better defined than the corresponding petroleum streams,
283 hydrocarbon solvents require special consideration of the testing strategies similar to that of the
284 petroleum substances.

285 Toxicity is defined via a concentration response and is dependant on the bioavailability of the
286 individual constituents in a UVCB test substance. This may make interpretation for some
287 substances very difficult. For example the physical form may prevent the dissolution of the
288 individual constituents of such a substance to any significant extent where the whole substance is
289 applied directly to the test medium. The consequence of this would be that toxicity may not be seen
290 in such a test system (e.g. coal tar pitch). This would thus not allow for the toxicity assessment of
291 these constituents to be addressed, were they to be released into the environment independent of the
292 original matrix.

293 Testing strategies for environmental effects of petroleum substances necessarily reflect the
294 complexity of their composition. Reflecting the properties of the constituent hydrocarbons,
295 petroleum substances are typically hydrophobic and exhibit low solubility in water. However,
296 reflecting the range of structures, constituent hydrocarbons will exhibit a wide range of water
297 solubility. When adding incremental amounts of a complex petroleum substance to water, a point
298 will be reached where the solubility limit of the least soluble component is exceeded and the
299 remaining components will partition between the water and the undissolved hydrocarbon phases.
300 Consequently, the composition of the total dissolved hydrocarbons will be different from the
301 composition of the parent substance. This water solubility behaviour impacts on both the conduct
302 and interpretation of aquatic toxicity tests for these complex substances, whilst the complex
303 composition and generally low water solubility impacts on the choice and conduct of
304 biodegradation studies.

305 For petroleum derived UVCBs, the lethal loading test procedure, also known as the WAF procedure
306 provides the technical basis for assessing the short term aquatic toxicity of complex petroleum
307 substances (Girling et al. 1992). Test results are expressed as a lethal or effective loading that
308 causes a given adverse effect after a specified exposure period. The principal advantage of this test
309 procedure is that the observed aquatic toxicity reflects the multi-component dissolution behaviour
310 of the constituent hydrocarbons comprising the petroleum substance at a given substance to water
311 loading. In the case of petroleum substances, expressing aquatic toxicity in terms of lethal loading
312 enables complex substances comprised primarily of constituents that are not toxic to aquatic
313 organisms at their water solubility limits to be distinguished from petroleum substances that contain
314 more soluble hydrocarbons and which may elicit aquatic toxicity. As a consequence, this test
315 procedure provides a consistent basis for assessing the relative toxicity of poorly water soluble,
316 complex substances and has been adopted for use in environmental hazard classification (UNECE,
317 2003). Complex substances that exhibit no observed chronic toxicity at a substance loading of 1
318 mg/l indicate that the respective constituents do not pose long term hazards to the aquatic
319 environment and, accordingly, do not require hazard classification (CONCAWE, 2001; UNECE
320 2003).

321 There are two possible approaches for generating new information or interpreting existing
322 information, bearing in mind the limitations on interpretation of the results mentioned above:

- 323 - First for petroleum substances, a model, PETROTOX, has been developed (Redman et al,
324 2006), based on previous work assuming a non-polar narcosis mode of action (McGrath et al,
325 2004, 2005). This model, which was developed to predict the ecotoxicity of petroleum
326 substances and hydrocarbon blocks, could be used to address individual structures where no

327 experimental data is available.

- 328 - The WAF loading concept may be used for environmental hazard classification (GHS 2005),
329 but should not be used for PBT assessment (see RIP 3.2).

330 The complex composition and generally low water solubility also impacts the choice and conduct of
331 biodegradation studies.

332 A further complication impacting both the choice of test method and interpretation of results is the
333 volatility of constituent hydrocarbons, which shows a wide variation across the range of carbon
334 numbers and hydrocarbon structures present in petroleum substances. It has been the practise to
335 assess the inherent hazards of petroleum substances by conducting testing in closed systems (going
336 to great lengths to ensure that volatile losses are minimised), even though under almost all
337 circumstances of release into the environment, there would be extensive volatilisation of many of
338 the constituent hydrocarbons.

339 Health effects testing strategies for petroleum substances also reflect the complexity of their
340 composition and their physico-chemical properties. Key factors impacting both the choice of test
341 method and interpretation of results are:

- 342 - the vapour pressure of constituent hydrocarbons, which show a wide variation across the range
343 of carbon numbers and hydrocarbon structures present in petroleum substances. This will
344 influence the physical nature of the material to which exposure occurs
- 345 - the lipid solubility of constituent hydrocarbons, which show a wide variation across the range of
346 carbon numbers and hydrocarbon structures present in petroleum substances. This will influence
347 the potential for uptake into body tissues
- 348 - the viscosity of the complex petroleum substance which can significantly impact on potential
349 for dermal absorption
- 350 - the presence of small amounts of individual *hazardous* constituents in complex petroleum
351 substances eg Poly Aromatic Hydrocarbons (PAH's), which may or may not be relevant to the
352 toxicity of the complex petroleum substance
- 353 - the presence of other constituents in the complex mixture which may modify (inhibit or
354 potentiate) the toxicity of hazardous constituents.

355 Toxicological evaluation of complex petroleum substances has normally been based on results of
356 testing of the complete mixture, using OECD Guideline methods. Using this approach it has been
357 possible to take account of the complex interactions that occur between individual constituents of
358 the mixture and the various physico-chemical properties that influence potential for exposure and
359 uptake. In some cases however it has been necessary to adopt modified or non-standard test
360 methods to provide a more reliable indication of the toxicity of certain petroleum fractions. The use
361 of non-standard methods to evaluate the health and environmental effects of petroleum substances
362 is described in more detail in the endpoint specific chapters.

363 **R.5.3 References for chapter 5**

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