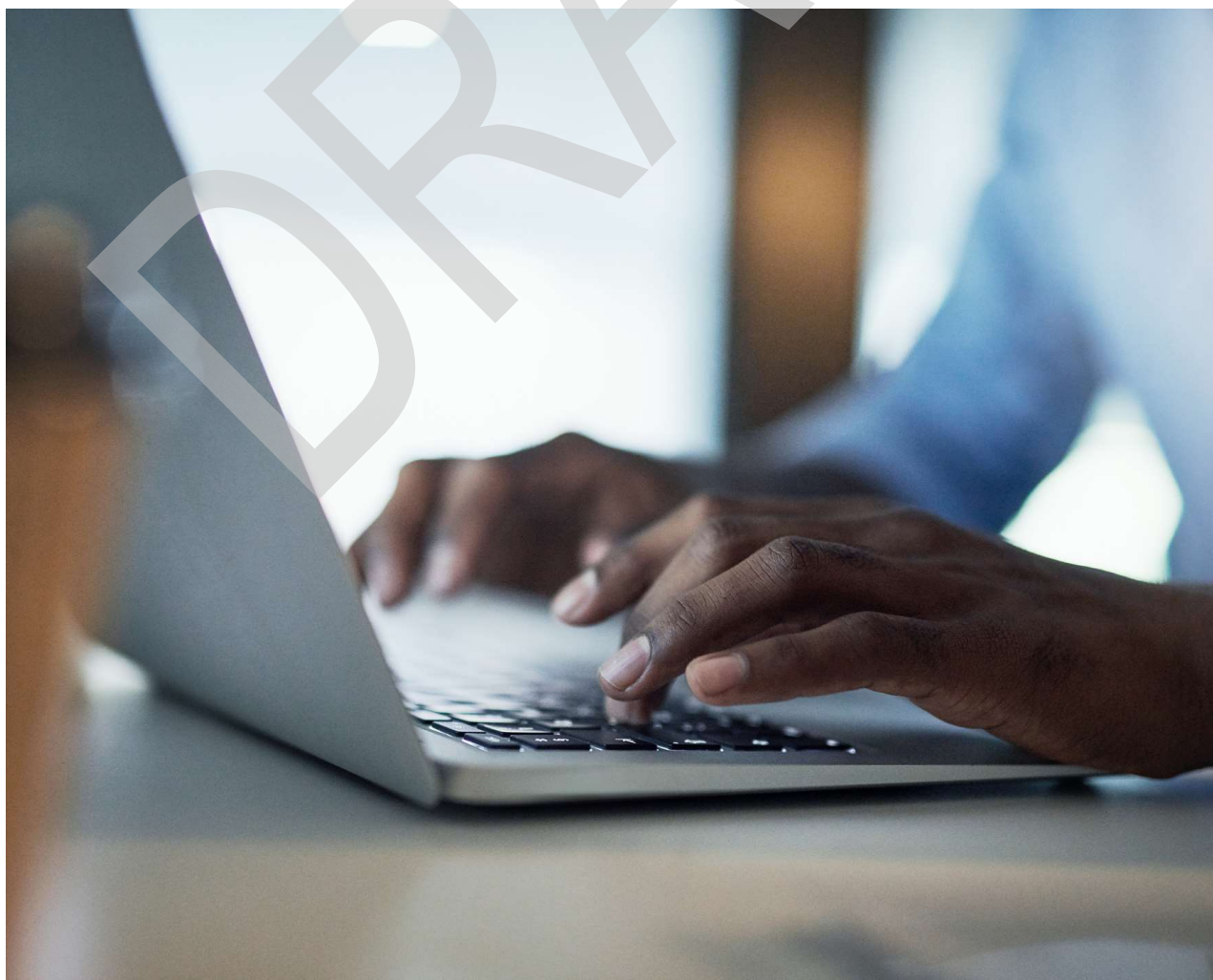


Formulation studies and combined risk assessment in ecotoxicology

Guidance on the need for studies and their
use in risk assessment

April 2021



DRAFT

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1 Introduction

2 For applications considered under Regulation 1107/2009 the formal requirements for
3 Ecotoxicology formulation testing are laid out in Annex, Part A, Section 10, to the
4 Regulation 284/2013. Although formulation data are stated as required in a number of
5 evaluation areas, it may be possible to extrapolate data (toxicity endpoints) between
6 similar formulations and also sometimes to estimate formulation toxicity from studies
7 conducted with the technical active substance.

8 The aim of this document is to provide additional guidance to the above Regulation and
9 hence outline what the key formulation studies might be for a particular product. To
10 achieve this, relevant sections (in *italics*) from the formal requirements in Part A of the
11 Annex to Regulation 284/2013 together with the associated current guidance documents
12 (where relevant), are presented below. HSE's interpretation is provided in the sections
13 headed HSE guidance.

14 As outlined under Points 4 and 8 of the Introduction to Section 10 of Part A of the Annex to
15 Regulation 284/2013, where appropriate formulation studies are submitted, they will be
16 used by HSE in the risk assessment.

17 Section 2 of the guidance sets out some general principles about formulations, including
18 when HSE considers differences in formations to be "major" (generally requiring at least
19 some new data) and "minor" (where it is possible to read across between different
20 formulations.

21 Section 3 covers the data requirements from Annex, Part A, Section 10, to the Regulation
22 284/2013.

23 Section 4 considers issues surrounding both formulations and mixture toxicity that should
24 be considered in the risk assessment.

25 When considering formulation testing it is important to note that vertebrate tests should
26 only be carried out where there is no alternative.

27 Formulations

28 The formulation details of a product/preparation consist of the technical specification and
29 the formulation 'recipe'. The formulation recipe consists of:

- 30 a) The nominal target content for the pure active substance, with acceptable tolerance
31 limits.
- 32 b) The chemical name, trade name and/or CAS number, structure, function and
33 quantity of all other components (the co-formulants) in the formulation.

34 Some of the solvents and surfactants included in formulated products may be directly toxic
35 to non-target species and/or may enhance the toxicity of the active substance to some of
36 these species (e.g. through aiding dispersion, coverage and/or penetration). For some
37 formulations, such as baits (e.g. slug pellets), granules, or those used as seed treatments,
38 co-formulants may influence the level of attractiveness and palatability of the formulation to
39 non-target species and hence the potential level of exposure and risk. There is also the
40 possibility of synergistic effects between active substances or other chemicals in the
41 formulation.

State	Type	Code
Liquid	Soluble Concentrate	SL
	Suspension Concentrate	SC
	Capsule Suspensions	CS
	Emulsifiable Concentrate	EC
	Oil in Water Emulsions	EW
Solid	Granules	GR
	Water Dispersible Granules	WG
	Water Soluble Granules	SG
	Wettable Powders	WP
Seed treatments	Flowable Concentrate	FS
	Solutions for Seed Treatment	LS
	Emulsions for seed treatment	ES
Miscellaneous	Smoke Generate	FU
	Gels	GD, GL, GW

State	Type	Code
	Baits	CB
	Ready to use Baits	RB

42

43 There is strong evidence to indicate that certain formulation types, particularly those
 44 containing emulsifiers and organic solvents, can result in significant increases in toxicity to
 45 some organisms compared with that predicted based on active substance toxicity data
 46 alone. This can result in the acute risk from the formulation being much greater than that
 47 posed by the active substance. However, it is currently not possible to accurately predict
 48 such occurrences.

49 **Changes in formulations**

50 **Minor changes**

51 For the purposes of this document a minor formulation change is defined as one where the
 52 formulation type remains the same and there is:

- 53 • Any change of less than 0.1% w/w¹
- 54 • No more than a 10% change (\pm) in the concentration of the active substance(s)
- 55 • No more than a 20% change (\pm) in the concentration of the solvents, emulsifiers
 56 and other surfactants

57 **Major Changes**

58 For the purposes of this document a major formulation change is defined as one or more
 59 of the following:

- 60 • Change in the formulation type (e.g. SC to WP, SL to EC)
- 61 • Changes in the concentration of active substance(s) of more than 10% (\pm) or in the
 62 concentration of solvents, emulsifiers and other surfactants of more than 20% (\pm) of
 63 previously approved content unless the change is <0.1% w/w
- 64 • Replacement or addition of a solvents, emulsifiers and other surfactants unless the
 65 addition is <0.1% w/w
- 66 • Changes to the base for baits/pellets/granules

¹ 0.1% w/w relates to a change in absolute terms of 0.1 percent or more. If the substance is of known very high toxicity, further consideration may be required.

- Addition of another active substance at more than 0.1% w/w
- Addition of a biocide active substance at more than 0.1% w/w

Implication of a major formulation change

If a formulation change is determined to be “major” it will be necessary to demonstrate the toxicity of the new product. This could be by:

- Proving a complete new product data package according to Annex, Part A, Section 10, to the Regulation 284/2013.
- Providing a combination of new studies and a comparison of the toxicity of the new product to the existing product to demonstrate that there is not increase in toxicity. This needs to be comprehensive enough to cover all groups.
- If the major change relates to the addition of a biocide active substance it might be possible to use the ECHA Assessment Report on that active substance to address concerns for some groups. This needs to be considered on a case by case basis.

The following data requirement will be set if a new formulation is not considered to be equivalent to an existing formulation:

In order to allow authorisation of this product from an ecotoxicology perspective, it is necessary to meet all applicable formulation data requirements and to provide an assessment for the proposed uses of the product conducted to Uniform Principles, demonstrating acceptable risks to non-target organisms. Formulation data requirements (see <https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32013R0284> for the latest formulation data requirements) can be addressed through either provision of studies conducted with the product or via an appropriate case, e.g. extrapolation of data from a comparable formulation. In the case of this application the HSE ecotoxicology team has concluded that the proposed formulation is not comparable to the reference product cited. As such all ecotoxicology product data requirements are judged to be outstanding.

Further information on data requirements for ecotoxicology can be found on the HSE website along with [ecotoxicology formulation guidance](#). This guidance includes the ecotoxicology criteria for comparability between two formulations, along with possibilities for extrapolation of data from other sources (on a per-organism group basis).

97 Data requirements

98 This section lists the data requirements for each group and where the guidance
99 documents provide additional useful information this has also been included. Each sub
100 section finishes with the HSE interpretation of the requirements.

101 Terrestrial Vertebrates (Annex points 10.1.1 & 10.1.2)

102 Requirements outlined in Section 10 of Part A of the Annex to Regulation 284/2013:

103 10.1.1.1(birds):

104 “The acute oral toxicity of the PPP shall be investigated if toxicity cannot be
105 predicted on the basis of the data for the active substance, or where results from
106 mammalian testing give evidence of a higher toxicity of the PPP compared to the
107 active substance, unless the applicant shows that it is not likely that birds are
108 exposed to the plant protection product itself”.

109 10.1.2.1 (terrestrial vertebrates other than birds):

110 “If exposure to the formulation is considered possible and the toxicity cannot be
111 predicted on the basis of the data for the active substance, data on the acute oral
112 toxicity of the PPP from the mammalian toxicological assessment shall also be
113 considered (see point 5.8 of Part A of the Annex to 283/2013)”.

114 Relevant EFSA Bird and Mammal guidance (EFSA Journal 2009; 7 (12):1438):

115 In Appendix B it is stated that:

116 “The basic concept of the risk assessment for birds and mammals is that animals
117 are exposed to residues of active substances in the environment, e.g. via their food.
118 Thus, the following steps do not refer to an assessment of formulation toxicity as
119 such, but of the expected effects from exposure to a mixture of active substances
120 (and possibly also toxic co-formulants) in the environment resulting from use of that
121 formulation.”

122 HSE guidance:

123 In relation to effects on terrestrial vertebrates (birds and mammals), the toxicity of pesticide
124 residues in food and drinking water from spray applications is considered unlikely to be
125 affected by the formulated product and because of this, the risk assessment can currently

126 be based on toxicity studies conducted with the technical active substance(s), formulation
127 studies are not usually required.

128 For seed treatments, granules and bait formulations, where there is a greater potential for
129 direct ingestion of the formulated product, it *may* be appropriate to assess the potential
130 palatability/attractiveness of the formulation. The need for such data should be considered
131 in relation to the risk assessment and should not be undertaken as a matter of routine. If
132 an avoidance study is considered relevant, then Applicants are requested to discuss this
133 issue with HSE.

134 For granular formulations, if the initial risk assessment indicates concern, then the refined
135 assessment should, amongst other factors, include consideration of the nutritive value of
136 the base material and its attractiveness as a grit source for birds (e.g. size and hardness),
137 prior to carrying out any additional toxicity testing. If additional formulation toxicity studies
138 are considered relevant, then Applicants are requested to discuss the issue with HSE.

139 For reasons of animal welfare every effort should be made to avoid unnecessary tests on
140 vertebrate species. Applicants are strongly advised to contact HSE prior to commissioning
141 such studies.

142 **Aquatic Organisms (Annex point 10.2)**

143 Requirements outlined in Section 10 of Part A of the Annex to Regulation 284/2013:

144 10.2.1 Acute toxicity to fish, aquatic invertebrates, or effects on algae and macrophytes

145 “Testing shall be performed where:

146 (a) the acute toxicity of the plant protection product cannot be predicted on the
147 basis of the data for the active substance; or

148 (b) the intended use includes direct application on water; or

149 (c) extrapolation on the basis of available data for a similar plant protection product
150 is not possible.

151 *Tests shall be carried out on one species from each of the three/four groups of*
152 *aquatic organisms, that is to say fish, aquatic invertebrates, algae and, where*
153 *relevant, macrophytes as referred to in point 8.2 of Part A of the Annex to*
154 *Regulation (EU) No 283/2013, if the plant protection product itself may contaminate*
155 *water.*

However, where the available information permits to conclude that one of these groups is clearly more sensitive, tests on only the relevant group shall be performed.

If the plant protection product contains two or more active substances, and the most sensitive taxonomic groups for the individual active substances are not the same, testing on all three/four aquatic groups, that is to say fish, aquatic invertebrates, algae and, where relevant macrophytes, shall be required.”

10.2.2 Additional long-term and chronic toxicity studies on fish, aquatic invertebrates and sediment dwelling organisms

“The studies referred to in points 8.2.2 and 8.2.5 of Part A of the Annex to Regulation (EU) No 283/2013 shall be conducted for particular plant protection products, where it is not possible to extrapolate from data obtained in the corresponding studies on the active substance (for example the plant protection product is more acutely toxic than the active substance as manufactured by a factor of 10), unless it is demonstrated that exposure will not occur.

If chronic toxicity studies with the plant protection product are required, the type and conditions of the studies to be provided shall be discussed with the national competent authorities.”

10.2.3 Further testing on aquatic organisms

“The studies referred to in point 8.2.8 of Part A of the Annex to Regulation (EU) No 283/2013 may be required for particular plant protection products where it is not possible to extrapolate from data obtained in the corresponding studies for the active substance or another plant protection product.”

Relevant EFSA aquatic guidance (EFSA Journal 2013; 11 (7): 3290):

7.5. Specific requirements for formulated products

7.5.1. Requirements/triggers for formulated products – acute toxicity

“In principle, acute or short-term exposure tests should be carried out on one species from each of the groups of tier 1 aquatic organisms (fish, aquatic invertebrates, algae and/or macrophytes) if the preparation itself may contaminate water. However, where the available information for an a.s. permits the conclusion that one of these groups is clearly more sensitive (factor of 10 difference), only a test using a species of the relevant group needs to be performed.

In addition, in the case of herbicides and plant growth regulators and other substances where there is reason to suspect effects on plants, tests should be carried out on one aquatic macrophyte species (in case several species have been tested, test on the most sensitive), if the preparation itself can contaminate water.

If the preparation contains two or more a.s., and the most sensitive taxonomic groups for the individual a.s. are not the same, testing on all tier 1 aquatic groups is required – unless a robust scientific reasoning regarding the to-be-expected mixture toxicity allows for a waiving of formulation (see section 10.3). In order to minimise fish testing, a threshold approach should be considered for testing acute toxicity in fish (see sections 7.2.3 and 11.4)."

7.5.2. Requirements/triggers for formulated products – long-term (chronic) toxicity

"According to the data requirements (Commission Regulation (EU) No 284/2013), chronic studies on fish and invertebrates for formulations should only be conducted where it is not possible to extrapolate from data obtained in the corresponding studies on the a.s. (i.e. the PPP is more acutely toxic than the a.s. by a factor of 10), unless it is demonstrated that exposure will not occur. However, if the applicant demonstrates that the increased acute toxicity of the preparation is a result of co-formulants that will rapidly disappear and latency of effects is not to be expected, the RA can be based on the data for the a.s. and a chronic study with the PPP is deemed not necessary.

If chronic toxicity studies with the PPP are required, generally, studies similar to those conducted for an a.s. are required. It can be used as a higher tier option in the RA to construct an ETR using the fraction of PEC_{sw} originating from spray drift if the applicant shows that the co-formulants are not present in the other routes of exposure (i.e. run-off and drainage). However, this RA cannot be used to overrule an ETR constructed using chronic data for the a.s. and PEC_{sw} integrating all routes of exposure (i.e. the normal 'PEC_{sw} or PEC_{max}). This may not be applicable when the formulation contains multiple a.s. (see guidance provided in section 10.3). An alternative is to conduct a specific microcosm study with the PPP to investigate long-term risks."

HSE guidance:

There is strong evidence to indicate that certain formulation types, particularly those containing emulsifiers and organic solvents, can result in significant increases in acute toxicity to aquatic life compared with that predicted based on active substance toxicity data alone. This can result in the acute risk from the formulation being much greater than that posed by the active substance. However, it is currently not possible to accurately predict such occurrences. It is therefore recommended that toxicity data should be provided for formulations which include significant levels of emulsifiers and solvents. Where the toxicity

of the active substance is 10 times lower than the toxicity to another group of aquatic organisms testing with the formulation is not required. This is particularly the case for fish where testing should not be conducted if another group of aquatic organisms is 10 times more sensitive than fish.

For some formulations it may be possible to present a scientifically reasoned case to explain why it should not be more acutely toxic than would be predicted due to the presence of the active substance alone, although this is only likely to be possible for very simple formulations.

Extrapolation of aquatic acute toxicity data between similar formulations may be possible – particularly where the existing formulation data indicates that there is a high margin of safety to aquatic life from the proposed use(s).

Minor formulation changes (see Section 2.1) do not require new formulation studies.

Major formulation changes (see Section 2.1), such as a change in formulation type would usually require supporting formulation data, unless a convincing case can be made that the proposed change would not be likely to increase its toxicity to aquatic life.

When Applicants are carrying out formulation studies, they are encouraged to make full use of the threshold approach and hence potentially reduce the number of fish toxicity studies and/or the number of fish tested. Further guidance is provided in Creton *et al.* (2014).

Products containing more than one active substance

The toxicity of the product should be compared to the toxicity predicted from the active substances assuming additive toxicity in accordance with EFSA (2013) section 10.3. The Model Deviation Ratio (MDR) should be calculated.

- If the MDR is between 0.2 and 5 the observed and calculated mixture toxicities are considered in agreement and additive toxicity can be concluded.
- In the MDR is greater than 5 the toxicity is more than additive so there is potential synergy between the active substances, however since it is also likely that not all relevant chemicals in the product have been taken into account further steps (see below) are required.
- If the MDR is less than 0.2 then the toxicity is less than additive (i.e. antagonistic).

When the MDR is greater than 5 it is important to try to determine the cause of this because if synergy is concluded further testing and assessment is likely to be required (in the case of fish and aquatic invertebrates this could lead to the need for chronic product testing).

261 The first step is to look at the details of the formulation. If a solvent is present at a large
262 proportion of the product it is likely that this could be contributing to the overall toxicity. If
263 toxicity data are available include this substance in the MDR calculation and determine if
264 the mixture now meets the requirements for additive toxicity. If it does then no further
265 testing is required, but the additional substance should be included in the risk assessment.
266 If additive toxicity has not been demonstrated additional components in the formulation
267 can be added to the mixture assessment. The most important components should be
268 identified, because everything considered in the mixture combination to conclude additive
269 toxicity needs to be included in the risk assessment so including substances that do not
270 contribute to the overall toxicity will make the risk assessment stage more complicated.

271 If it is not possible to demonstrate additive toxicity when additional substances in the
272 product are considered synergy must be considered.

273 For UK national registrations HSE would not normally require the assessment of chronic
274 toxicity formulation studies - since formulations would not be expected to remain intact
275 over chronic timescales, however if the toxicity of the product is greater than predicted by
276 its components then this should be considered.

277 **Bees (Annex point 10.3)**

278 Requirements outlined in Section 10 of Part A of the Annex to Regulation 284/2013:

279 “The possible effects on bees shall be investigated except where the PPP is for exclusive
280 use in situations where bees are not likely to be exposed such as:

281 (a) food storage in enclosed spaces;

282 (b) non-systemic plant protection products for application to soil, except granules;

283 (c) non-systemic dipping treatments for transplanted crops and bulbs;

284 (d) wound sealing and healing treatments;

285 (e) non-systemic rodenticidal baits;

286 (f) use in greenhouses without bees as pollinators.

287 Testing shall be required if:

288 — the plant protection product contains more than one active substance,

289 — the toxicity of a plant protection product cannot be reliably predicted to be either the
290 same or lower than the active substance tested, in accordance with the requirements set
291 out in points 8.3.1 and 8.3.2 of Part A of the Annex to Regulation (EU) No 283/2013.

292

293 For seed treatments the risk from drift of dust during drilling of the treated seed shall be
 294 taken into account. As regards granules and slug pellets the risk from drift of dust during
 295 application shall be taken into account. If the plant protection product is systemic and to be
 296 used on seeds, bulbs, roots, applied directly to soil, for example sprayed on to soil,
 297 granules/pellets applied to soil, irrigation water, or applied directly to or into the plant, for
 298 example by spraying or stem injection, then the risk to bees foraging those plants shall be
 299 assessed, including the risk deriving from residues of the plant protection product in
 300 nectar, pollen and water, including guttation.

301 Where bees are likely to be exposed, testing by both acute (oral and contact) and chronic
 302 toxicity, including sub-lethal effects, shall be conducted.

303 Where exposure of bees to residues in nectar, pollen or water resulting from systemic
 304 properties of the active substance may occur and where the acute oral toxicity is < 100
 305 µg/bee or a considerable toxicity for larvae occurs, residues concentrations in these
 306 matrices shall be provided and the risk assessment shall be based on a comparison of the
 307 relevant endpoint with those residue concentrations. If this comparison indicates that an
 308 exposure to toxic levels cannot be excluded, effects shall be investigated with higher tier
 309 tests”.

310 10.3.1.1. Acute toxicity to bees

311 Where bee acute testing with the plant protection product is required, both acute
 312 oral and contact toxicity tests shall be conducted.

313 10.3.1.2. Chronic toxicity to bees

314 Circumstances in which required

315 The test shall be carried out where bees are likely to be exposed.

316 10.3.1.3. Effects on honey bee development and other honey bee life stages

317 A bee brood study shall be conducted to determine effects on honey bee
 318 development and brood activity.

319 The bee brood test shall provide sufficient information to evaluate possible risks
 320 from the plant protection product on honey bee larvae.

321 10.3.1.4. Sub-lethal effects

322

Tests investigating sub-lethal effects, such as behavioural and reproductive effects, on bees and, where applicable, on colonies may be required.

10.3.1.5 Cage and tunnel tests

The test shall provide sufficient information to evaluate:

- possible risks from the plant protection product for bee survival and behaviour, and

- impact on bees resulting from feeding on contaminated honey dew or flowers.

Sub-lethal effects shall be addressed, if necessary, by carrying out specific tests (for example foraging behaviour).

Circumstances in which required

“When acute or chronic effects on colony survival and development cannot be ruled out, further testing shall be required especially if effects are observed in the honeybee brood feeding test (see point 8.3.1.3 of Part A of the Annex to Regulation (EU) No 283/2013) or if there are indications for indirect effects such as delayed action, effects on juvenile stages, or modification of bee behaviour; or other effects such as prolonged residual effects; in those cases cage/tunnel tests shall be carried out and reported”.

Relevant guidance: Information is provided in SANCO (2002), however this is not in line with the current data requirements.

HSE guidance:

Formulation studies are required where the formulation contains more than one active substance unless extrapolation from a similar formulation is possible.

The acute oral and contact toxicity to bees of an active substance may be increased by formulations containing significant quantities of organic solvents and/or surfactants such as emulsifiable concentrates (EC). Therefore, the acute toxicity of EC formulations should be assessed using standard laboratory acute toxicity studies conducted with the proposed or a similar EC formulation. For such formulations the risk assessment should take account of the formulation toxicity endpoints. For other formulation types (providing they only contain a single active substance), an extrapolation of the results of acute toxicity studies conducted with the technical active substance may be possible where a well-reasoned case can be provided to demonstrate that the co-formulants will not increase the toxicity to bees.

For the other studies listed in Regulation 284/2013, a case may be made regarding the potential to read across from the data on the active substance to the proposed formulation.

357 Minor formulation changes (see Section 3.1) would not be required to be addressed
358 further.

359 For major formulation changes (see Section 3.2) the following advice is given:

360 Extrapolation of bee toxicity data between products of the same formulation type will often
361 be possible, provided any major (>10% w/w) organic solvents present in the formulation
362 are unchanged or can be demonstrated to be of no greater toxicity.

363 Extrapolation of data between formulation types may also be possible where a convincing
364 case can be provided to justify that the 'new' formulation will not be of any greater toxicity
365 (see Section 5 for possible examples).

366 For semi field and field studies the relevant formulation should be used and if there is
367 reliance on data from another formulation a case should be provided to justify the
368 extrapolation.

369 **Arthropods other than bees (Annex point 10.3.2)**

370 Requirements outlined in Section 10 of Part A of the Annex to Regulation 284/2013:

371 10.3.2 Effects on non-target arthropods other than bees:

372 "Effects on non-target terrestrial arthropods shall be investigated for all plant
373 protection products except where plant protection products containing the active
374 substance are for exclusive use in situations where non-target arthropods are not
375 exposed such as:

376 (a) food storage in enclosed spaces that preclude exposure;

377 (b) wound sealing and healing treatments;

378 (c) enclosed spaces with rodenticidal baits.

379 Testing shall be required if:

380 — the plant protection product contains more than one active substance,

381 — the toxicity of a plant protection product cannot be reliably predicted to be either
382 the same or lower than the active substance tested, in accordance with the
383 requirements set out in point 8.3.2 of Part A of the Annex to Regulation (EU) No
384 283/2013.

385 For plant protection products, two indicator species, the cereal aphid parasitoid
386 *Aphidius rhopalosiphi* (Hymenoptera: Braconidae) and the predatory mite

Typhlodromus pyri (Acari: Phytoseiidae) shall be tested. Initial testing shall be performed using glass plates, and both mortality and effects on reproduction (if assessed) shall be reported. Testing shall determine a rate-response relationship and LR 50², ER 50³ and NOEC endpoints shall be reported for assessment of the risk to these species in accordance with the relevant risk quotient analysis.

For a plant protection product containing an active substance suspected of having a special mode of action (for example insect growth regulators, insect feeding inhibitors) additional tests involving sensitive life stages, special routes of uptake or other modifications, may be required. The rationale for the choice of test species used shall be provided.

Testing shall provide sufficient information to evaluate the toxicity (mortality) of the plant protection product to arthropods in the in-field as well as in the off-field area.

10.3.2.2 Extended laboratory testing, aged residue studies with non-target arthropods

Circumstances in which required

Further testing shall be required where effects are seen following laboratory testing in accordance with the requirements set out in point 10.3.2.1 and where the relevant risk quotient analysis indicates a risk to the standard indicator non-target arthropod species.

Firstly, the indicator species affected in standard Tier 1 laboratory testing (point 10.3.2.1) shall be tested. In addition, where an in-field risk is indicated to one or both standard indicator species, testing of one additional species shall be required. Where an off-field risk to the standard indicator species is indicated, testing of one further additional species shall be required.

An aged residue study shall be conducted with the most sensitive species to give information on the time scale needed for potential re-colonisation of treated in-field areas.

10.3.2.3. Semi-field studies with non-target arthropods

Circumstances in which required

Where effects are seen following laboratory testing in accordance with the requirements set out in point 8.3.2 of Part A of the Annex to Regulation (EU) No

² LR50 = "Lethal Rate 50%" that is to say the application rate required to kill half the members of a tested population after a specified test duration

³ ER50 = "Effect Rate 50%" that is to say the application rate required to cause an effect on half the members of a tested population after a specified test duration

283/2013 or point 10.3.2 of this Annex (for example relevant trigger values are breached), semi-field testing shall be required.

10.3.2.4 Field studies with non-target arthropods

Circumstances in which required

Where effects are seen following testing in accordance with the requirements set out in point 8.3.2 of Part A of the Annex to Regulation (EU) No 283/2013 or in accordance with points 10.3.2.2 or 10.3.2.3 of this Annex, and where the relevant risk quotient analysis indicates a risk to non-target arthropods, field testing shall be required.

10.3.2.5 Other routes of exposure for non-target arthropods

Where for particular arthropods (such as pollinators and herbivores) testing conducted in accordance with points 10.3.1 and 10.3.2.1 to 10.3.2.4 is not appropriate, additional specific testing shall be required, where there are indications that exposure by routes other than by contact occur (for example plant protection products containing active substances with systemic activity). Before undertaking such testing, the proposed design to be used shall be discussed with the relevant competent authorities”.

Relevant guidance:

SANCO (2002): Does not add useful information as it was produced prior to the change in data requirements which are significant for soil organisms.

Candolfi *et al* (2001) provides recommendations about which species to test at tier 2:

- *Orius laevigatus*
- *Chrysoperla carnea*
- *Coccinella septempunctata*
- *Aleochara bilineata*

HSE guidance:

Formulation studies are required where the formulation contains more than one active substance unless extrapolation from a similar formulation is possible.

The inclusion of co-formulants in a formulation may increase toxic effects to non-target arthropods due, for example, to improvements in spray coverage and/or by enhancing cuticular

448 penetration/uptake of the active substance. Also, occasionally co-formulants may be directly toxic
449 to non-target arthropods, although such effects are considered to be infrequent.

450 Given the potential for co-formulants to increase the effects of a product on non-target
451 arthropods, toxicity tests to address the data requirements outlined above, should be
452 conducted using the relevant formulated product. Such formulation data would also usually
453 be sufficient to address the active substance data requirements.

454 It should be noted that it may be possible to extrapolate from one formulation to another, –
455 although the extent of ‘acceptable’ differences between the ‘new’ and previously tested
456 formulation(s) will vary depending on the potential for adverse effects (see below).

457 Where changes in formulation are ‘minor’ (as defined in Section 2.1), no further
458 consideration is required.

459 Where formulation changes from that originally evaluated are ‘major’ (as defined in Section
460 2.1), an assessment of the ‘acceptability’ of the risk to non-target arthropod from the ‘new’
461 formulation is required. For major changes in formulation the following advice is given:

462 Where the formulation type of the ‘new’ formulation is the same as that previously tested in
463 higher tier studies, it may be possible to make a case for the extrapolation of the “higher
464 tier” data, with this including a comparison of the previously tested and proposed
465 formulation.

466 Where the formulation type of the ‘new’ formulation is different from that previously tested
467 in higher tier studies, some additional studies conducted with the new formulation may be
468 required, unless a well-reasoned and convincing case can be provided as to why the
469 change will not pose a greater risk to non-target arthropods. Major formulation changes,
470 particularly those involving significant increases in organic solvent and/or surfactant
471 concentrations are amongst those considered most likely to increase the toxicity to non-
472 target arthropods. It is suggested that new higher tier formulation toxicity studies are
473 initially conducted with the previously identified most sensitive indicator test species.
474 Further toxicity testing with other species would usually only be required where the results
475 of this initial testing indicated a potential for increased toxic effects.

476 **Non-target soil meso- and macrofauna (Annex point 10.4)**

477 Requirements outlined in Section 10 of Part A of the Annex to Regulation 284/2013:

478 10.4.1: Earthworms

479 “The possible impact on earthworms shall be reported unless the applicant shows
480 that it is not likely that earthworms are exposed, directly or indirectly.

481 10.4.1.1: Sub-lethal effects:

482 The test shall provide information on the effects on growth and reproduction of the
483 earthworm.

484 Circumstances in which required

485 The sub-lethal toxicity of a plant protection product to earthworms shall be
486 investigated if the relevant criteria as defined in point 8.4.1 of Part A of the Annex to
487 Regulation (EU) No 283/2013 are met, and the toxicity of the plant protection
488 product cannot be predicted on the basis of the data for the active substance,
489 unless the applicant shows that no exposure occurs.

490 10.4.1.2: Field studies:

491 The test shall provide sufficient data to evaluate effects on earthworms under field
492 conditions.

493 Circumstances in which required

494 Where the relevant risk quotient analysis indicates a chronic risk to earthworms a
495 field study to determine effects under practical field conditions shall be conducted
496 and reported as an option for refined risk assessment”.

497 **HSE guidance:**

498 According to Regulation 284/2013, a formulation study with the plant protection product is,
499 as stated above, required when the toxicity of the product cannot be predicted from the
500 data on the active substance.

501 Whilst it is not specified that data are always required for formulations that contain more
502 than one active substance it is unlikely that it will be possible to predict the toxicity of a
503 product containing more than one active substance without at least a test that includes
504 both active substances (the same formulation or a similar formulation).

505 Extrapolation is usually possible for minor formulation changes. HSE considers that it may
506 also be possible to extrapolate from certain formulation types and hence reduce the need
507 for a study with every formulation.

508 As indicated above, it is considered that significant quantities of organic solvents and/or
509 surfactants such as emulsifiable concentrates (EC) may increase the toxicity of the
510 product. Therefore, if data are available on an EC formulation then it is likely that this can
511 be used to cover other formulation types. As for other formulations, HSE considers that it
512 is acceptable to extrapolate between formulation types.

513 Where we have data for a product containing >1 a.s. in the formulation, if this is an EC
514 formulation, then HSE considers that an extrapolation can be made from this data to other
515 EC formulations – and non-EC formulations – if these contain the same a.s. in the same or
516 similar proportions.

517 If the mixed active formulation tested is not an EC, then HSE proposes that it may be
518 possible to extrapolate to other formulation types – and a case can be made. For example,
519 if we have a wettable powder (WP) with a.s. A and B then we can read that across to other
520 formulation types – if these contain the same a.s. in the same or similar proportions.

521 10.4.2. Effects on non-target soil meso- and macrofauna (other than earthworms)

522 Circumstances in which required

523 “Effects on soil organisms (other than earthworms) shall be investigated for all plant
524 protection products, except in situations where soil organisms are not exposed such
525 as:

526 (a) food storage in enclosed spaces that preclude exposure;

527 (b) wound sealing and healing treatments;

528 (c) enclosed spaces with rodenticidal baits.

529 Testing shall be required if:

530 — the plant protection product contains more than one active substance,

531 — the toxicity of a plant protection product cannot be reliably predicted to be either
532 the same or lower than the active substance tested in accordance with point 8.4.2
533 of Part A of the Annex to Regulation (EU) No 283/2013.

534 For plant protection products applied as a foliar spray, data on the relevant two non-
535 target arthropod species might be taken into account for a preliminary risk
536 assessment. If effects do occur on either species, testing on *Folsomia candida* and
537 *Hypoaspis aculeifer* shall be required (see point 10.4.2.1). If data on *Aphidius*
538 *rhopalosiphii* and *Typhlodromus pyri* are not available then the data outlined in point
539 10.4.2.1 shall be required.

540 For plant protection products applied as soil treatments directly to soil either as a
541 spray or as a solid formulation, then testing shall be required on both *Folsomia*
542 *candida* and *Hypoaspis aculeifer* (see point 10.4.2.1).

543 10.4.2.2. Higher tier testing

The tests shall provide sufficient information to evaluate the risk of the plant protection product for soil organisms (other than earthworms) using a more realistic test substrate or exposure regime.

Circumstances in which required

Further testing shall be required where significant effects are seen following laboratory testing in accordance with the requirements set out in point 8.4.2.1 of Part A of the Annex to Regulation (EU) No 283/2013 or in accordance with point 10.4.2.1 of this Annex and where risk is indicated following the relevant risk quotient analysis.

The need to perform such studies and the type and conditions of the studies to be performed shall be discussed with the national competent authorities”.

HSE guidance:

Data on the two standard soil invertebrates (*Folsomia candida* and *Hypoaspis aculeifer*) will usually be required unless one of the following apply:

- the studies can be waived due to data on the two standard NTA species giving tier 1 Hazard Quotients below 2 (for foliar sprays)
- the toxicity of a single active substance formulation can be reliably predicted on the basis of the active substance
- data on a similar formulation are available for read across

It will be necessary to provide a case for the second and third of the above bullet points (see NTA and earthworm sections for more information).

Soil non-target micro-organisms (annex point 10.5)

Requirements outlined in Section 10 of Part A of the Annex to Regulation 284/2013:

10.5 Effects on soil nitrogen transformation (Annex point 10.5)

“The test shall provide sufficient data to evaluate the impact of the plant protection products on soil microbial activity in terms of nitrogen transformation.

Circumstances in which required

The effects of plant protection products on soil microbial function shall be investigated if the toxicity of the plant protection product cannot be predicted on the

573 basis of data for the active substance, unless the applicant shows that no exposure
574 occurs”.

575 **HSE guidance:**

576 Whilst it is not specified that data are always required for formulation that contain more
577 than one active substance it is unlikely that it will be possible to predict the toxicity of a
578 product containing more than one active substance without at least a test that includes
579 both active substances (the same formulation or a similar formulation).

580 Given that formulations are unlikely to remain ‘intact’ in soil over chronic timescales, long-
581 term effects from the formulation on soil micro-organism activity are considered unlikely.
582 Therefore, specific formulation testing is not usually required for products that only contain
583 one active substance. In most cases it should be possible to extrapolate effects data from
584 studies conducted in support of the active substance data requirements.

585 **Effects on terrestrial non-target higher plants (annex point**
586 **10.6)**

587 Requirements outlined in Section 10 of Part A of the Annex to Regulation 284/2013:

588 Summary of screening data

589 “The effects of plant protection products on non-target plants shall be reported, if
590 the toxicity of the plant protection product cannot be predicted on the basis of the
591 data for the active substance, unless the applicant shows that no exposure occurs.

592 Circumstances in which required

593 Screening data shall be required for plant protection products other than those
594 exhibiting herbicidal or plant growth regulator activity, and if the toxicity cannot be
595 established from data on the active substance (point 8.6.1 of Part A of the Annex to
596 Regulation (EU) No 283/2013). The data shall include testing from at least six plant
597 species from six different families including both mono- and dicotyledons. The
598 tested concentrations/rates shall be equal or higher than the maximum
599 recommended application rate. If screening studies do not cover the specified range
600 of species or the concentrations/rates necessary, then tests in accordance with
601 point 10.6.2 shall be carried out.

602 Data are not required, where exposure is negligible, for example in the case of
603 rodenticides, active substances used for wound protection or seed treatment, or in
604 the case of active substances used on stored products or in glasshouses where
605 exposure is precluded.

606 10.6.2. Testing on non-target plants

607 The test shall provide the ER 50 values of the plant protection product to non-target
608 plants.

609 Circumstances in which required

610 Studies of effects on non-target plants shall be required for herbicide and plant
611 growth regulator plant protection products and for other plant protection products,
612 where risk cannot be predicted from screening data (see point 10.6.1) or when the
613 risk cannot be reliably predicted on the basis of the active substance data
614 generated in accordance with point 8.6.2 of Part A of the Annex to Regulation (EU)
615 No 283/2013.

616 For all granules risk from drift of dust during time of application shall be considered.

617 Data shall not be required, where exposure is not likely (such as in the case of
618 rodenticides, active substances used for wound protection or seed treatment, or in
619 the case of active substances used on stored products or in glasshouses where
620 exposure is precluded).

621 10.6.3 Extended laboratory studies on non-target plants

622 If as a result of conducting studies in accordance with points 10.6.1 and 10.6.2 and
623 carrying out a risk assessment, a high risk has been identified, an extended
624 laboratory study on non-target plants addressing lower tier concerns may be
625 required by the national competent authorities. The study shall provide information
626 regarding the potential effects of the plant protection product on non-target plants
627 following a more realistic exposure.

628 The type and conditions of the study to be performed shall be discussed with the
629 national competent authorities.

630 10.6.4 Semi-field and field tests on non-target plants

631 Semi-field and field tests to study effects observed on non-target plants following
632 realistic application may be submitted as a basis for a refined risk assessment.
633 Testing shall address effects on plant abundance and biomass production at
634 varying distances from the crop or at exposure levels representing varying
635 distances from the crop.

636 The type and conditions of the study to be performed shall be discussed with the
637 national competent authorities".

HSE guidance:

Given that co-formulants may have a large impact on a product's phytotoxicity – particularly in relation to post-emergence exposure – potential effects on non-target plants should be assessed using the formulated product.

Where the 'tier 1' screening data indicates a potential for adverse phytotoxic effects (i.e. more than 50% effect for one or more species at the maximum application rate), and the proposed formulation differs significantly from that assessed in 'tier 2' tests, a well-reasoned supporting case and/or further (bridging) data should be provided for the extrapolation of the 'tier 2' post-emergence data.

In relation to pre-emergence effects (in which exposure arises from soil uptake), formulation differences are considered unlikely to affect the level of phytotoxicity of spray applied formulations. Therefore, it is acceptable to extrapolate data in relation to pre-emergence effects between different spray applied formulations containing the same active substance(s), without the need for additional evidence.

For those active substances which might be expected or are known to be able to move in the vapour phase, additional field data may be required to demonstrate that the potential movement via post-application volatilisation does not pose an unacceptable risk.

The above relates to the plant protection product, where the product may contain one or more active substances.

657 **Adjuvants**

658 For some products use of an additional adjuvant is required or recommended as part of
659 the product's directions for use. Extra ecotoxicological information may be required to
660 support approval of products in some cases. The guidance in this section only applies
661 where the additional adjuvant is not incorporated into the product, as supplied to the end
662 user.

663 Further guidance on this topic will be added to a future version of this document.

Product risk assessment (multiple active substances)

In order to grant approval to a product, there has to be an appropriate risk assessment underpinning it, therefore for those products that contain more than one active substance there is a need to consider the risk from the product, i.e. the combined risk from the active substances present in that formulation and the influence of any co formulators.

The following section considers the comparison between toxicity endpoints derived from studies conducted with mixed active formulations and the predicted toxicity, and which endpoints should be used in the subsequent risk assessment.

General Simplified Approach

The first consideration is whether the toxicity of the mixture is largely explained by the toxicity of a single a.s., if so, it may well be possible to make a case that a sufficient level of protection should be achieved by basing the risk assessment on the toxicity data for the active substance which is driving the risk assessment.

An example of this approach is detailed below:

Formulation 'Test1' contains two active substances, A (20 %w/w) and B (30 %w/w). Studies on *Daphnia magna* are available for both active substances and the formulation. All studies were conducted to OECD 202 and were considered valid and suitable for use in the risk assessment.

Since all three studies are on the same species and to the same guideline the toxicity can be compared. The toxicity endpoints are:

Substance	Toxicity	Units
A	0.5	mg a.s./L
B	67	mg a.s./L
'Test1'	2.7	mg formulation/L

Active substance A is clearly more toxic than Active substance B so to determine whether active A explains the toxicity of the formulation the endpoint from the formulation study can be expressed in terms of active A alone:

689 'Test1' contains 20% w/w so an endpoint of 2.7 mg formulation/L is equivalent to 0.54 mg
690 a.s. (A only)/L.

691 This is slightly higher than the endpoint for A, so it is considered that the formulation
692 toxicity is driven by active A,

693 The following example shows where the toxicity is not driven by one of the active
694 substances:

695 Formulation 'Test2' contains two active substances, C (20 %w/w) and D (30 %w/w).
696 Studies on *Daphnia magna* are available for both active substances and the formulation.
697 All studies were conducted to OECD 202 and were considered valid and suitable for use in
698 the risk assessment.

699 Since all three studies are on the same species and to the same guideline the toxicity can
700 be compared. The toxicity endpoints are:

Substance	Toxicity	Units
C	6.2	mg a.s./L
D	9.7	mg a.s./L
'Test2'	14.9	mg formulation/L

701

702 C is slightly more toxic than D, but D is present in greater concentration so the formulation
703 will be expressed in terms of each active.

704 'Test2' contains 20% w/w of C so an endpoint of 14.9 mg formulation/L is equivalent to
705 2.98 mg a.s. (C only)/L.

706 'Test2' contains 30% w/w of D so an endpoint of 14.9 mg formulation/L is equivalent to
707 4.47 mg a.s. (D only)/L.

708 The formulation endpoint is lower than the toxicity of each active substance when
709 expressed in terms of that active alone.

710 In this example toxicity is additive:

Active	EC50	proportion w/w	p1/EC50	
active C	6.2	0.2	0.032258	
active D	9.7	0.3	0.030928	
			0.063186	sum
			15.82632	EC50 mix

711

712 The endpoint predicted using the Finney equation is very similar to the tested toxicity,
713 demonstrating additive toxicity, so a risk assessment covering both actives together is
714 required.

715 **Aquatic organisms**

716
717 For aquatic organisms, guidance on combinations of active substances in formulations is
718 given in section 10.3 of the EFSA Journal 2013; 11 (7): 3290.

719 The guidance recommends counterchecking calculated and measured mixture toxicity
720 using the Concentration Addition (CA) method.

- 721 • The observed and calculated mixture toxicities are considered in agreement if the
722 MDR (Model Deviation Ratio) is between 0.2 and 5.0.
- 723 • More-than additive (i.e. synergistic) mixture toxicity is indicated if the MDR is > 5. If
724 synergistic effects cannot be excluded, the assessment should preferably be based
725 on measured values.
- 726 • Less-than additive toxicity mixture toxicity is indicated if the MDR is < 0.2. If less-
727 than additive toxicity (i.e. antagonistic) mixture toxicity is indicated and no plausible
728 toxicological explanation for this apparent antagonism can be provided (e.g. special
729 feature of the formulation type), the RA should be based on the calculated mixture
730 toxicity.

731 Section 10.3.11 (p153) of EFSA (2013) provides a decision scheme for whether to use the
732 measured or calculated mixture toxicity.

733 **CRD guidance for combined aquatic risk assessments**

734 The MDR calculation should always be provided for mixed active substance products.

735 NOTE: This section is split into two sections based on the standard formulation data
736 available:

- 737 • Formulation data available - acute risk from spray drift
- 738 • Formulation data are not available
 - 739 ○ Chronic risk to fish and aquatic invertebrates
 - 740 ○ Risk from drainflow to all groups

741

742 **Spray drift (acute risk)**

743 A formulation risk assessment for exposure via spray drift using the measured formulation
744 endpoints should be presented, even if less-than additive toxicity is indicated. If reliable
745 formulation data have been provided it is not considered appropriate to disregard these
746 data.

747 In the rare case that the MDR is < 0.2 then a combined assessment of the acute risk via
748 drift based on calculated mixture toxicity (unless antagonism is plausible – see point 9 in
749 the EFSA (2013) decision scheme) should be included.

750 Options for refining the acute risk via spray-drift include use of drift reduction technology
751 ([http://www.pesticides.gov.uk/guidance/industries/pesticides/topics/pesticide-](http://www.pesticides.gov.uk/guidance/industries/pesticides/topics/pesticide-approvals/pesticides-registration/data-requirements-handbook/Active-substance-PECsw-calculations-for-UK-specific-authorisation-requests)
752 [approvals/pesticides-registration/data-requirements-handbook/Active-substance-PECsw-](http://www.pesticides.gov.uk/guidance/industries/pesticides/topics/pesticide-approvals/pesticides-registration/data-requirements-handbook/Active-substance-PECsw-calculations-for-UK-specific-authorisation-requests)
753 [calculations-for-UK-specific-authorisation-requests](http://www.pesticides.gov.uk/guidance/industries/pesticides/topics/pesticide-approvals/pesticides-registration/data-requirements-handbook/Active-substance-PECsw-calculations-for-UK-specific-authorisation-requests)), more acute data (excluding the
754 generation of further vertebrate data) to enable geomean/SSD approach, higher tier data.

755 **Spray drift (chronic risk) and drainflow**

756 The risk from the whole product also needs to be considered for the chronic risk from
757 spray drift and from drainflow.

758 The MDR calculations will have provided the mixture to be considered for the product risk
759 assessment. This could be:

- 760 • Only the single active substance in a 1 active substance product (as this explained
761 the toxicity of the product).
- 762 • Two or more active substances in a product (if these actives explained the toxicity
763 of the product).
- 764 • One or more active substances and one or more other co formulants if these were
765 needed to explain the toxicity of the product.

766 It is important that all substances needed to explain the toxicity of the product (See section
767 3.2) are included in the risk assessment. If it was not possible to explain the toxicity of the
768 product using additive toxicity a more detailed consideration is required and we
769 recommend you seek advice before making your application.

770 The risk assessment for the individual substances in the product (active substances and
771 possibly co formulants that contribute to the toxicity of the products) will provide ETRs for
772 each groups. These could be from first tier risk assessments or higher tier risk
773 assessments.

774 In order to conduct the combined risk assessment for the chronic risk to fish and
775 invertebrates from spray drift and the risk from drainflow to all groups based on lower tier

776 drainflow PECs for all groups add the ETRs for each substance. If the total is less than 1
777 the combined risk is acceptable.

778 **Example**

779 Product X contains two active substances (a and b) and when compared to formulation
780 data for fish, aquatic invertebrates and algae the MDRs were all between 0.2 and 5.

781 Combined risk assessment:

782 Spray drift

Group / timescale	ETR active a	ETR active b	Sum ETR	Risk acceptable?
Fish / acute	Covered by formulation assessment ETR = 0.75			Yes
Fish / chronic	0.35	0.41	0.76	Yes
Invertebrate / acute	Covered by formulation assessment ETR = 0.62			Yes
Invertebrate / chronic	0.59	0.11	0.70	Yes
Algae	Covered by formulation assessment ETR = 0.97			Yes

783

784 Drainflow

Group / timescale	ETR active a	ETR active b	Sum ETR	Risk acceptable?
Fish / acute	0.35	0.55	0.9	Yes
Fish / chronic	0.42	0.53	0.95	Yes
Invertebrate / acute	0.67	0.12	0.79	Yes
Invertebrate / chronic	0.72	0.25	0.97	Yes
Algae	0.61	0.54	1.15	No

785

786 **HSE guidance for exposure via drainflow where higher tier assessment is required**

787 The consideration of combined drainflow when a higher tier assessment is required does
788 not necessarily require a numerical combined drainflow assessment. This requirement will
789 depend on several factors including the fate and behaviour of the individual active
790 substances and therefore is best considered in conjunction with the fate and behaviour
791 specialist.

792

793 There are several different situations where a combined higher tier drainflow assessment
794 needs to be considered:

- 795 a) One active substance required a higher tier drainflow assessment, but the other
796 active substance(s) did not.
- 797 b) None of the active substances required a higher tier drainflow assessment but when
798 combined the sum of the first tier ETRs is above 1.
- 799 c) More than one active substance required a higher tier drainflow assessment.

800 In the first situation if one of the active substances contributes $\geq 90\%$ to the combined risk
801 (based on the toxic unit approach, using the lower tier drainflow PEC_{sw} values as the
802 concentrations) then it can be concluded that this component drives the overall mixture
803 toxicity and no further consideration of the combined risk is needed. Only this active
804 substance requires further consideration via a higher tier drainflow assessment. If this is
805 not the case, then a combined drainflow assessment is required. A simple and
806 conservative approach is to combine the single lower tier drainflow PEC_{sw} value for the
807 lower risk substance with each of the maximum annual concentrations from the higher tier
808 assessment for the higher risk substance. Option 1 or option 2 below can be followed to
809 calculate the combined risk. If an acceptable risk cannot be demonstrated, additional
810 higher tier drainflow modelling will be required for the lower risk substance and combined
811 with the higher tier drainflow modelling for the higher risk substance following options 1, 2
812 or 3 below.

813 In the second situation if one of the active substances contributes $\geq 90\%$ to the combined
814 risk (based on the toxic unit approach, using the lower tier drainflow PECs as the
815 concentrations) then it can be concluded that this component drives the overall mixture
816 toxicity and no further consideration of the combined risk is needed. If this is not the case,
817 then a combined higher tier drainflow assessment is required. Higher tier drainflow
818 modelling can be provided for one substance and combined with the single lower tier
819 drainflow PEC_{sw} value as outlined above. If an acceptable risk cannot be demonstrated,
820 additional higher tier drainflow modelling will be required for both (all) substances, and
821 combined following option 1, 2 or 3 below.

822 In the third situation a combined higher tier assessment is required because it is clear that
823 both (all) the active substances contribute to the combined risk.

824 Toxic unit approach

825 The toxic unit approach is described in section 10.3.3 of EFSA (2013) and is described
826 in equation 14 reproduced below:

827

$$\sum_{i=1}^n TU_i = \sum_{i=1}^n \frac{C_i}{ECx_i}$$

828

829

830

For the drainflow assessment C_i is the concentration of each active substance in drainflow (PEC drainflow) and ECx_i is the toxicity endpoint for that active substance and species under consideration.

831

832

833

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835

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837

Section 10.3.7 of EFSA (2013) states that “Furthermore, if the toxicity of the mixture is largely explained by the toxicity of a single a.s., a sufficient protection level might be achieved by simply basing the RA on the toxicity data for that single ‘driver’. Hence, where CA provides a reliable estimate of the toxicity of the given mixture (ECx_{PPP}) and the largest part of the sum of toxic units (i.e. $\geq 90\%$) calculated for the measured mixture toxicity (ECx_{PPP}) by Equation 14 comes from a single a.s., it can be concluded that this component drives the overall mixture toxicity”.

838

839

So, for each active substance the percentage contribution can be calculated by dividing the C/ECx for that active substance by the sum of TU and expressing it as a percentage.

840

841

842

843

If a combined higher tier drainflow assessment is required, this can be done using either the preferential flow model (MACRO) or the web-based risk assessment tool Webfram. NOTE: At the time of writing Webfram is unavailable, so this version of the guidance will only consider MACRO.

844

845

846

There are three options for combined exposure from higher tier drainflow modelling with MACRO. They progress in refinement from option (1) to option (3) and once the relevant criteria are met then no further assessment is required.

847

Criteria for acceptable risk using MACRO

848

Criteria for algae and aquatic plants:

849

850

851

852

For aquatic plants and algae, there must be no more than 60% of exceedance years in each scenario. The risk is acceptable if there are no more than 18 years out of 30 exceeding the RAC based on first tier toxicity data. You do not need to provide any further information in this case.

853

Criteria for fish and aquatic invertebrates:

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855

856

857

For aquatic invertebrates and fish there is a lower limit threshold value. The risk is acceptable if there are no more than 10% of exceedance years in each scenario. This equates to no more than 3 years out of 30 exceeding the RAC. You do not need to provide any further information in this case

If the exceedance years are above 10% for any scenario it may still be possible to show an acceptable risk. This will need a more detailed case-by-case assessment. This should consider the size, frequency and the duration of exceedance events. Applicants must consider all scenarios where exceedances are above 10%. Use the following metrics:

- The size of the maximum exposure peak in relation to the RAC
- Duration of exceedance events
- The number of exposure peaks above the RAC within each year

Option 1

Combine the annual maximum PEC_{sw} value from drainflow for each substance for each of the thirty years (Equation 1) and compare against the lowest RAC value to determine the number of exceedance years. Carry out this procedure for each of the twelve soil and climate combinations.

Equation 1

$$\text{PEC}_{\text{sw}} (\text{combined, drainflow}) = \text{PEC}_{\text{sw}}(\text{A}) + \text{PEC}_{\text{sw}}(\text{B}) + \dots$$

where: $\text{PEC}_{\text{sw}}(\text{X})$ is the PEC_{sw} (drainflow) for substance X

Option 2

Determine the combined toxicity RAC value of the mixture for each of the 30 years from the Finney equation (Equation 2) using the maximum annual PEC_{sw} value from drainflow of each substance. There is an exceedance year where the sum of the maximum annual drainflow concentrations exceeds the combined toxicity RAC value. Carry out this procedure for each of the twelve soil and climate combinations.

Equation 2 (Finney equation)

$$\frac{1}{\text{RAC}(\text{A} + \text{B} + \dots)} = \frac{f(\text{A})}{\text{RAC}(\text{A})} + \frac{f(\text{B})}{\text{RAC}(\text{B})} + \dots$$

where:

$\text{RAC}(\text{A} + \text{B} + \dots)$ is the combined regulatory acceptable concentration

$\text{RAC}(\text{X})$ is the regulatory acceptable concentration of substance X

$f(\text{X})$ is the fraction of substance X in the mixture calculated from:

$$f(X) = \frac{PEC_{sw}(X)}{PEX_{sw}(\text{combined, drainflow})}$$

Option 3

Determine the combined toxicity RAC value of the mixture for each of the 30 years from the Finney equation (Equation 2) using the daily PEC_{sw} value from drainflow of each substance. Where the sum of the daily drainflow concentrations for any day in a calendar year exceeds the daily combined toxicity RAC value, an exceedance year is recorded. Carry out this procedure for each of the twelve soil and climate combinations.

Guidance on the presentation of higher tier drainflow modelling results for use in aquatic risk assessments can be found on the following link:

<https://www.hse.gov.uk/pesticides/pesticides-registration/data-requirements-handbook/fate/macro.htm>

Guidance for the use of Webfram in a combined risk assessment is not currently available but will be provided if the Webfram tool is reinstated.

Birds and mammals

When a product has more than one active substance, the risks to birds and mammals must also be considered. Active substances may cause the same toxic effects within test organisms. In such cases a combined assessment is required for acute and reproductive effects on birds and mammals. Applicants should note that this is relevant for all formulation types i.e. seed treatments, granules and foliar sprays. A combined assessment might also need to include one or more metabolites.

The Environmental Panel of the Advisory Committee on Pesticides (meeting 108) has proposed the following tiered approach to bird and mammal risk assessments as follows:

- Is one active substance clearly driving the risk assessment?
- Does the Tier I risk assessment for all active substances within the formulation pass with a margin of safety?
- Did the mammalian toxicology assessment identify that a combined assessment was not required?

If the answer to any of these is **yes**, a combined risk assessment is probably not required, and a reasoned case should be presented. Otherwise, further consideration of combined risk is required.

917 **Guidance on how to carry out a combined risk assessment**

918 If, after considering the above, it is deemed that a combined risk assessment is required,
919 then following is proposed as a way forward:

920 The acute risk assessment can be performed using the Finney equation:

921
$$1/T \text{ overall} = P1/T1 + P2/T2 + P3/T3 \text{ etc}$$

922 Where P1/P2 etc are the proportions of the component active substances and T1/T2 etc
923 represent their respective toxicities. This can then be used in the risk assessment using
924 the total amount of active substances applied to calculate the DDD (i.e. if one active is
925 applied at 100 g a.s./ha and the other at 70 g a.s./ha the total application rate for the risk
926 assessment is 170 g a.s./ha).

927 For the long-term risk assessment, HSE will apply the recommendations of Appendix B of
928 EFSA (2009) which uses a toxic unit approach for the Tier I formulation assessment. If the
929 Tier I risk assessment fails, then further refinements will be required. Refinements may
930 involve the standard ecological refinements outlined in EFSA (2009) or may be based on a
931 toxicological argument. In the case of granules, seed treatments, pellets and baits, to
932 which terrestrial vertebrates may be directly exposed, this could include a more detailed
933 consideration of other aspects e.g. nutritive value, attractiveness and availability.

934

935 N.B. HSE do not consider it necessary to conduct additional toxicity studies when making
936 these refinements and applicants are strongly advised to consult with HSE Ecotoxicology
937 experts before commissioning any such studies.

938 An alternative, simple approach, when the TERs are above the trigger, is to calculate the
939 Assessment Factor (AF)/TER for each active substance and add these up. If the total is
940 below 1 the combined risk (assuming additive toxicity) is acceptable (this approach can be
941 used for the acute and reproductive assessment at either the screening or tier 1 step):

Group	Timescale	TER active a	TER active b	AF	Sum AF/TER
Birds (Sc)	Acute	24	69	10	0.56
Birds (Sc)	Reproductive	12	25	5	0.62
Mammals (Sc)	Acute	46	120	10	0.30
Mammals (Sc)	Reproductive	8.5	5.1	5	1.57
Mammals (T1)	Reproductive	11.9	8.7	5	0.99

942 Sc = Screening step

943 T1 = Highest Tier 1 TER

944 Applicants are welcome to contact HSE to discuss possible refinement options (e.g. risk
945 characterisation of each active substance, phase-specific approach (Appendix J of EFSA
946 (2009)) on a case-by-case basis.

DRAFT

What to analyse in aquatic toxicity studies on plant protection products that contain more than one active substance

Please note:

The following section outlines HSE's views as to what to analyse in aquatic toxicity studies for plant protection products that contain more than one active substance.

It is appreciated that there is a lack of guidance on this topic and the following is an attempt to aid Notifiers and Applicants as to what is required.

Anyone wishing to carry out aquatic toxicity studies with a plant protection product that contains more than one product is welcome to discuss either individual studies and/or a testing strategy with HSE. Please contact HSE via CRD.Information.Management@hse.gov.uk.

Key issue

According to Regulation 284-2013, data are required on the toxicity of plant protection products to aquatic life. Whilst the conduct and use of these studies is relatively straightforward when the plant protection product contains one active substance, there is uncertainty when there is more than one active substance. The uncertainty arises due to a lack of clarity regarding the regulatory purpose behind such studies and hence what should be measured and how the endpoint should be presented.

The following section provides some background, outlines why these studies are carried out and what they are used for.

In addition, there is a methodology regarding how to make use of "non-ideal" data in order to reduce the need for repeat testing.

This section only considers plant protection product with more than one active substance.

974 Introduction

975 According to Section 10.2.1 of Regulation 284-2013 data are required on the toxicity of a
976 plant protection product to fish, aquatic invertebrates, aquatic algae and macrophytes.

977 The Regulation highlights that:

978 *Testing shall be performed where:*

979 *a) the acute toxicity of the plant protection product cannot be predicted on the basis of*
980 *the data for the active substance; or*

981 *b) the intended use includes direct application on water;*

982 *c) extrapolation on the basis of available data for a similar plant protection product is*
983 *not possible.*

984 *Tests shall be carried out on one species from each of the three/four groups of aquatic*
985 *organisms, that is to say fish, aquatic invertebrates, algae and, where relevant,*
986 *macrophytes as referred to in point 8.2 of Part A of the Annex to Regulation (EU) No*
987 *283/2013, if the plant protection product itself may contaminate water.*

988 *However, where the available information permits to conclude that one of these groups*
989 *is clearly more sensitive, tests on only the relevant group shall be performed.*

990 *If the plant protection product contains two or more active substances, and the most*
991 *sensitive taxonomic groups for the individual active substances are not the same,*
992 *testing on all three/four aquatic groups, that is to say fish, aquatic invertebrates, algae*
993 *and, where relevant macrophytes, shall be required*

994 The above is relatively straightforward to follow and highlights the “regulatory need” as to
995 what studies are required.

996 In addition to the information in the Regulation, EFSA (2013) provides guidance in Section
997 7.5 regarding which species should be tested. However, this guidance is focused
998 predominately on plant protection products that contain only one active substance. We
999 have presented in **Appendix 1** some potential additional guidance regarding what species
1000 could be tested when the plant protection product contains more than one active
1001 substance.

1002 Whilst Regulation 284-2013 and EFSA (2013) provides guidance on what studies are
1003 required, there is currently little guidance regarding the appropriate chemical analysis that
1004 should be carried out when there is more than one active substance in the plant protection
1005 product.

1006 This section outlines a proposal from HSE regarding a possible approach to assessing the
 1007 toxicity to aquatic life of a plant protection product that contains more than one active
 1008 substance.

1009 Study guidelines

1010
 1011 As outlined above, studies on the toxicity of the plant protection product to aquatic life are
 1012 required; according to Regulation 284-2013, the following studies are key:

1013 Fish:

1014 *OECD Test Guideline 203: Fish, Acute Toxicity Test*

1015 Invertebrates:

1016 *OECD Test Guideline 202: Daphnia sp. Acute Immobilisation Test*

1017 *US EPA OCSPP 850.1035 Mysid Acute Toxicity Test*

1018 Algae and macrophytes:

1019 *OECD Test Guideline 201: Freshwater Alga and Cyanobacteria, Growth*
 1020 *Inhibition Test*

1021 *OECD Test Guideline 221: Lemna sp. Growth Inhibition Test*

1022 *ASTM E1913-04: Standard Guide for Conducting Static, Axenic, 14-Day*
 1023 *Phytotoxicity Tests in Test Tubes with the Submersed Aquatic Macrophyte,*
 1024 *Myriophyllum sibiricum Komarov*

1025 *OECD Test Guideline 238: Sediment-free Myriophyllum spicatum toxicity*
 1026 *test*

1027 *OECD Test guideline 239: Water-sediment Myriophyllum spicatum toxicity*
 1028 *test*

1029 *Development of a proposed test method for the rooted aquatic macrophyte*
 1030 *Myriophyllum sp. In: Maltby L, Arnold D, Arts G,.et al (2010). Aquatic*
 1031 *Macrophyte Risk Assessment for pesticides (AMRAP). SETAC Press & CRC*
 1032 *Press, Taylor & Francis Group, Boca Raton, London, New York., p. 46-56*

1033 All of the above studies can be carried out with plant protection products containing more
 1034 than one active substance. However, there is uncertainty regarding what should be
 1035 analysed and hence how the results should be presented.

In the OECD test guidelines, there are references to “test substance” and that this should be maintained within $\pm 20\%$ of the nominal concentration throughout the test. When dealing with a study carried out with an active substance, it is clear what should be measured, i.e. the “test substance” is the active substance. However, when dealing with a plant protection product, especially where it contains more than one active substance, the meaning of “test substance” is less obvious and it is less clear what should be measured.

One reason there is a lack of clarity regarding what to measure is that it is unclear why these studies are carried out.

Presented below are HSE’s views on the above points.

Why are studies with the plant protection product carried out?

In trying to determine what should be measured, it is necessary to determine why these studies are done. It is appreciated that there is a lack of clarity as to why studies with plant protection products are carried out. It is the opinion of HSE that these studies are done to provide an indication of the toxicity of the plant protection product as a whole, i.e. the entire plant protection product, with all of its components. This information can be used as follows:

- To determine if the plant protection product is more or less toxic compared to the active substance(s) on its/their own
- Where the plant protection product has more than one active substance it should enable an assessment as to whether there may be synergism or additive toxicity due to one or more co-formulants or additional active substances adding to the toxicity of an active substance. If there is either additive toxicity or synergism then this could indicate that the risk assessments carried out for the individual active substances may not be sufficiently protective of the risk posed by the plant protection product
- To assess the risk to non-target organisms posed by other chemicals in the plant protection product which is not covered by the assessment for the active substance(s) alone.
- The studies are used for classification and labelling of the plant protection product.

In order for a study to be used to carry out any of the above, it has to be reliable. Whilst each study will have to meet the respective validity criteria, it is also key that there is sufficient information to determine what the exposure levels were. Section 3.1 of EFSA (2015) provides guidance on how to present the endpoints from aquatic studies and hence it is important that studies – including those conducted with plant protection products – comply with this guidance. The primary focus of EFSA (2015) is the assessment of the

active substance and not specifically with approval of plant protection products, therefore, what is presented below aims to deal with this latter issue.

Which active substance(s) should be measured when there is more than one in the plant protection product?

Assuming that reliable studies as outlined in EFSA (2015) are required, then HSE proposes the following should be considered when deciding which substance(s) to measure to ensure that the endpoint⁴ from the study is reliable:

- a) At least one active substance needs to be measured to demonstrate correct dosing (i.e. to determine if nominal concentrations were achieved) and to characterise exposure of test organisms over the study duration (i.e. to see if test concentrations were maintained).⁵
- b) Ideally the least stable active substance should be measured. However, there should also be a consideration of the proportions of different substances in the plant protection product, the toxicity compared to the other active substance(s) and a decision taken as to which one should be measured. In addition, the following should be noted:
 - i. If the plant protection product study indicates that toxicity is not driven by the measured active substance, then there could be uncertainty in the evaluation and use of this study.
 - ii. If the toxicity of the plant protection product can be predicted by one active substance, then this active substance should be the focus of analysis.
 - iii. If the least stable compound has been measured, then the following can be applied:
 - a. If this substance is maintained within 80-120% of nominal throughout the study, then the nominal concentration can be used for the study endpoint. (Note that if initial concentrations are not within 20% of nominal but mean measured are within 20% of initial, then initial measured values can be used.)

⁴ It is assumed that most studies carried out with the plant protection product will be acute or short-term studies and hence the endpoint will be either an LC50 or EC50.

⁵ It is often argued that for studies on plant protection products, it is only necessary to measure one active substance at the start of the study to indicate that dosing is correct. If this is done, then there is uncertainty as to what the test organisms were exposed to – see EFSA (2015) for further explanation.

b. If this substance deviates by more than $\pm 20\%$ from nominal values, then the plant protection product endpoint should be corrected based on mean measured concentrations of this active substance alone. This is considered worst case.

c. When determining the concentration there is a need to ensure that a suitable limit of detection (LOD) and limit of quantification (LOQ) is used. If the concentrations drop below either the LOQ or LOD at the end of the study, note should be taken of EFSA (2015).

c) If one active substance (that is not the least stable) is expected to drive the toxicity of the plant protection product (either through toxicity or amount in the plant protection product or a combination) the Applicant should consider measuring this active substance as well. This will allow consideration of the actual exposure in the study to the most critical substance. In this situation if measured concentrations are not maintained, it is suggested to base mean measured values on the active with the worst recovery (unless it can be shown that it isn't significantly contributing to the toxicity).

d) The applicant is free to measure all active substances in a plant protection product (which may be useful where several active substances have similar stability and toxicity) - the above is the minimum requirement.

It is acknowledged that the above approaches are worst case since the concentration of the plant protection product is adjusted based on the recovery of a single component, but they are considered necessary in order to demonstrate correct dosing, to characterise exposure throughout the study and to avoid the need for repeat studies.

If the above is agreed, then the next question is how should these endpoints be used in a risk assessment?

How to use these endpoints in a risk assessment

It should be noted that EFSA (2013) should be followed along with the following additional advice:

Assuming the most unstable active substance has been measured (and the endpoint corrected as necessary) the toxicity of the plant protection product can be compared to the predicted toxicity of the active substances to determine if toxicity is additive or not (see EFSA (2013)).

If there is a large difference in the stability of the active substances it might be possible to use the measured concentrations of each active as part of this consideration rather than assuming the same proportions as were present at the start of the test.

The endpoint from the plant protection product study should be used in a standard spray drift assessment.

What to do with plant protection products where the least stable active substance has not been measured and the study is required

It is appreciated that many studies exist where the analysis has not been carried out as outlined above. This means that they are “non-ideal” and that there will be uncertainty in using these for risk assessment and hazard classification purposes.

Outlined below is a proposal as to how these data could be used.

1. Has at least one substance been measured to confirm dosing? If not, a new study will generally be required (noting Appendix I).
2. Are there studies with the active substance of the same design (i.e. static, flow-through etc) as the plant protection product study? If not, the approach below is not appropriate and a new study will be required (noting Appendix I).
3. If 1 and 2 both apply, identify all the following endpoints:
 - a. Plant protection product endpoint – either nominal or corrected for initial measured
 - b. Agreed Annex I active substance endpoints as used for the risk assessment for the active substance (nominal or measured as appropriate).
 - c. Active substance endpoints for all active substances not confirmed as stable in the plant protection product study / measured in the plant protection product study expressed as initial or nominal concentrations.
4. Calculate the toxicity of the plant protection product based on nominal or initial concentrations (NB this is referred to as PseudoTox) of the active substance assuming additivity and compare to the plant protection product endpoint, also expressed in terms of nominal/initial measured concentrations (this means we are

comparing “like with like”⁶. If the PseudoTox and nominal/initial measured endpoints are within a factor of 5⁷ then this indicates additive toxicity has been demonstrated (This also accounts for anything else in the plant protection product). If toxicity exceeds that predicted assuming additivity, then further consideration is required.

5. The plant protection product endpoint may underestimate toxicity since the defined exposure may not have been maintained over the study duration, so it is necessary to use the active substance endpoints to conduct an additive assessment to cover the combined risk. If the PseudoTox endpoint (derived in step 4) is higher than the plant protection product endpoint, then the factor between them should be applied to the additive toxicity endpoint (PredictedTox endpoint) used in the risk assessment. For example, if the plant protection product endpoint is 1.5 times lower than the PseudoTox endpoint assuming additive toxicity, the additive toxicity endpoint used in the risk assessment should be divided by a factor of 1.5. The reason for including this additional factor is that in normal circumstances if a larger buffer zone is triggered based on the plant protection product than for the active substance(s), we would set the overall buffer zone at the greater distance, i.e. we would not check to determine whether the plant protection product study indicated additive toxicity and if it did, set the buffer zone on the basis of the active assessment (unless higher tier data was available).
6. It is important to note that the additive toxicity endpoint used to compare against the plant protection product endpoint (PseudoTox), which is based on nominal or initial measured concentrations, may not be the appropriate endpoint to use in the risk assessment. The appropriate additive toxicity endpoint to use in the risk assessment will be determined using the active substance endpoints that are used in the risk assessments for the individual active substances, i.e. it may be based on mean measured concentrations.
7. For classification purposes, it is proposed to stick to the agreed approach outlined in Guidance on the Application of the CLP Criteria Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures Version 4.1 June 2015.

See **Decision Tree** (Appendix 2) and **Worked Example** (Appendix 3) for further information

⁶ Only studies conducted to the same approach, e.g. semi-static and with endpoints presented in the same way, can be used for this approach.

⁷ Please note that a spread sheet is available. The factor of 5 has been chosen to be the same as in EFSA (2013) aquatic guidance.

1196 Further HSE Guidance on Extrapolating 1197 between formulations

1198 This section assumes that the proposed use of the new product does not represent an
1199 increase in exposure above that currently considered acceptable. When extrapolating
1200 toxicity data on one formulation to another, a comparison of the formulation details should
1201 be provided, together with a detailed and well supported explanation as to why any
1202 differences are unlikely to increase the toxicity to those groups highlighted above. For
1203 minor formulation changes as defined in Section 3.1 new formulation data would not
1204 normally be required. In addition, minor formulation changes would not normally require
1205 new risk assessments. If the GAP is also being changed such that the potential for
1206 exposure is increased or new guidance has been noted and implemented new risk
1207 assessments will be required.

1208 For formulation changes that are not 'minor', new formulation studies should be provided
1209 to cover the areas outlined in Section 3 unless robust scientific cases can be provided to
1210 justify why they are not necessary.

1211 A degree of extrapolation from other formulation types may be possible, particularly in
1212 situations where the level of environmental exposure is not increased and where the
1213 previously conducted risk assessment indicated an 'acceptable' risk. Given that
1214 emulsifiable concentrations are often more toxic to non-target species than other
1215 formulation types (due to the inclusion of high levels of surfactants, solvents and
1216 emulsifiers), it may be possible to use data on an emulsifiable concentrate (EC)
1217 formulation to support a wettable powder (WP), suspension concentrate (SC), soluble
1218 concentrate (SL), suspo-emulsion (SE) or emulsion in water (EW) formulation provided the
1219 amount of active substance contained within that formulation is the same or less than
1220 previously considered. The applicant should, however, provide a detailed case to justify
1221 why such extrapolations are appropriate. Particular attention should also be paid to the
1222 total amount of surfactants, solvents and emulsifiers present. Where such co-formulants
1223 are present in significantly greater proportions in the new formulation, then at least a
1224 detailed case to support the extrapolation should be provided. This applies even if the
1225 formulation types are the same. Cases are also known where increased levels of such co-
1226 formulants (and lower levels of active substance) have resulted in an increase in
1227 formulation toxicity.

1228 Certain product types, such as controlled release formulations, may significantly affect the
1229 exposure profile compared with other formulations or the technical active substance. New
1230 formulation toxicity tests may be required. However, it is envisaged that a bridging data
1231 package, focussing on the most sensitive species present in the key environmental

1232 compartment(s) affected may be sufficient. Applicants are advised to consult HSE prior to
1233 conducting extensive toxicity testing.

1234 For ready-for-use formulations based on simple dilutions in water of an approved
1235 concentrate formulation, the toxicity can be estimated by calculation from the concentrate
1236 toxicity, with no additional studies being required. It would also be expected that provided
1237 the proposed use is similar with no increase in environmental exposure, reasoned cases
1238 would be sufficient to address the risk assessment.

1239 Where extrapolation is possible but not clear-cut bridging studies on key organisms can
1240 provide useful support.

1241 In all cases where new formulation studies have been presented and these indicate higher
1242 levels of toxicity compared with existing studies from which extrapolation has been
1243 claimed, or a higher level of toxicity than predicted based on the active substance content,
1244 then the new studies should be fully evaluated and revised risk assessments in the
1245 appropriate areas provided. For any given active substance, or mixture of active
1246 substances, it would be expected that a new formulation type, particularly those containing
1247 high levels of surfactants, solvents and emulsifiers, would be supported by a
1248 comprehensive body of acute formulation studies. For active substances where data for a
1249 range of approved formulation types already exists, it should be much easier to present
1250 well-argued scientific cases for extrapolation.

1251 Regarding multiple applications, it is currently not possible to accurately predict the
1252 potential build-up of a formulation hence it is considered sufficient to base the formulation
1253 risk assessment on a comparison of the acute formulation toxicity endpoint with the initial
1254 formulation PEC. Where the formulation contains an active substance, which has the
1255 potential to accumulate, this should be addressed in the risk assessment for the active
1256 substance.

1257 **Data protection**

1258 Where extrapolations are being considered, it is necessary to ensure that appropriate data
1259 access is available/provided, or that the data are no longer protected. Studies which in
1260 HSE's opinion are non-essential will not be afforded any level of protection.

1261

1262 **Research requirements**

1263 It is clear that an assessment of the toxicity and associated risk of the formulation is
1264 required; this can be done via the generation of a complete data package as outlined in
1265 284/2013 (full ref?), however HSE is of the view that it should be possible to extrapolate
1266 from existing formulations and hence build on some of the 'rules of thumb' noted above. In
1267 light of this HSE would welcome further research into this area and would be keen to
1268 participate?

1269

1270 References

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1294 Appendix 1 (relates to section 6)

1295 Which groups should be tested?

1296 Section 10.2.1 of Regulation 284-2013 provides limited information regarding what group
 1297 (i.e. fish, aquatic invertebrate, algae or higher aquatic plant) should be tested. The EFSA
 1298 Aquatic Guidance Document provides further information on this point (see Section 7.5.1
 1299 of EFSA (2013)); presented below are some additional criteria that could be considered
 1300 prior to carrying out studies with plant protection products where the product contains
 1301 more than one active substance.

- 1302 a) If all active substances are a factor of 10 less toxic to one or more groups than the
 1303 critical group a study with the plant protection product is not needed with the less
 1304 sensitive group(s).
- 1305 b) It may be possible to make a case for not testing a specific group (especially if it is
 1306 fish) when the exact criteria is not met for all active substances, but overall it is clear
 1307 that the risk assessment will not be driven by this group (for example, 3 herbicides,
 1308 A is 20 times as toxic to algae as fish, B is 50 times as toxic to algae as fish, but C
 1309 is only 8 times as toxic to algae as fish – it is not expected that an additional
 1310 vertebrate study will aid the risk assessment and a replacement study should not be
 1311 requested if the analytical measurements are not on the most appropriate active).
- 1312 c) Consideration is required before commissioning studies using fish and full use
 1313 should be made of the existing data as well as approaches such as “the threshold
 1314 approach” (see Creton *et al* (2014)). However, prior to carrying out any studies it is
 1315 proposed that the additive toxicity of the plant protection product is determined
 1316 using the Finney equation; if the resulting endpoint and associated
 1317 “toxicity:exposure ratio” or TER is greater than 300⁸, then no further testing is
 1318 required, however if it is less than 300, then in the first instance the threshold
 1319 approach should be used.
- 1320 d) Plant protection product studies will generally be required for any groups that are
 1321 sensitive to any one of the active substances in the plant protection product.

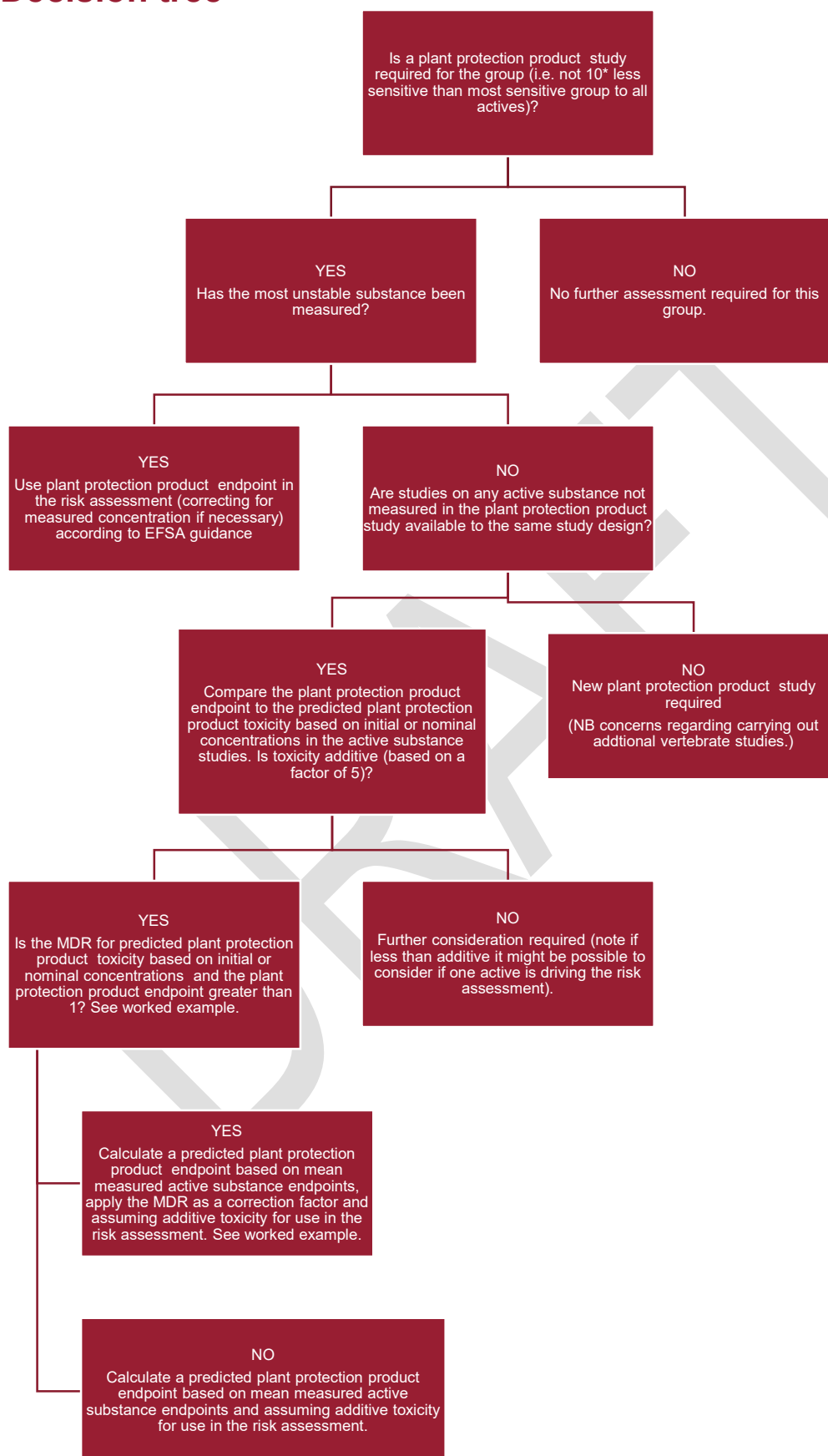
1322

⁸ A trigger value of 300 is proposed to give a degree of conservatism and ensure that the approach is protective. The factor of 3 is based loosely on the information in SANCO/10597/2003 –rev. 10.1

13 July 2012 Guidance Document on the Assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009

1323

Decision tree



1324

1325 Worked example

1326 Presented below is a worked example of how existing data can be used. The example is
 1327 based on a plant protection product that contains two active substances, i.e. 20% w/w
 1328 Active 1 and 20% w/w Active 2.

1329 The “agreed” endpoints for Active 1 and Active 2 are presented below:

1330 Active 1

Organism	Endpoint (mg a.s./L)
Fish	19
<i>Daphnia magna</i>	12
Algae	5
<i>Lemna</i>	>100

1331

1332 Active 2

Organism	Endpoint (mg a.s./L)
Fish	100
<i>Daphnia magna</i>	10
Algae	0.8
<i>Lemna</i>	13

1333

1334 On the basis of the available data, algae are the most sensitive and we have two studies
 1335 with the active substances.

1336 Active 1 (20% w/w) ErC50 = 5 mg a.s./L (nominal, concentration maintained >80%)

1337 Active 2 (20% w/w) ErC50 = 0.8 mg a.s./L (mean measured as the concentrations
 1338 were not maintained (measured 35% of nominal)). The nominal ErC50 was 2.29 mg
 1339 a.s./L.

1340 One plant protection product study is available in which only Active 1 was measured and
 1341 this was maintained >80% of nominal⁹ and gave an endpoint, based on nominal
 1342 concentrations, of ErC50 = 7 mg a.s./L. Following the guidance in EFSA (2013) and in

⁹ NB: The least stable active substance is Active 2, therefore if this study was to be repeated then the least stable active substance should be analysed.

particular Section 2.5, it is necessary to determine whether the combined toxicity Active 1 and Active 2 is equivalent to additive toxicity. This is assessed via the use of Model Deviation Ratio (MDR). Presented below are the results using the “agreed” Annex I endpoints.

Using EU agreed endpoints (i.e. measured) you get:

Plant protection product toxicity: calculated ¹⁰	3.448
Plant protection product toxicity: measured	7
MDR	0.493

MDR¹¹ results:

Key	< 0.2	Less-than additive
	0.2 - 5	Additive
	> 5	More-than additive (synergistic)

The above assessment indicates that the combination of active substance A and B is additive, however there is uncertainty in this prediction as the data are not equivalent, i.e. the Plant Protection Product study is not based on measured concentrations.

If endpoints based on nominal concentrations are used for the “unstable” active you get the following MDR.

Plant protection product toxicity: calculated ¹²	7.853
Plant protection product toxicity: measured	7
MDR	1.12

Additive toxicity is shown to be a reasonable estimation of toxicity when “like for like” endpoints are used (based on a factor of <5 difference (see above table)¹³).

It is further proposed to use the comparison to the plant protection product data with nominal concentrations to demonstrate additive toxicity, however, the calculated endpoint based on mean measured concentrations (i.e. **3.448 mg/L**) rather than the plant protection product endpoint (**7 mg/L**) should be used for the risk assessment. However, in this case as the MDR is greater than one, then it is proposed that an additional factor of 1.12 is also

¹⁰ Calculated via Finney’s formula, i.e. $1/((0.2/5)+(0.2/0.8))$

¹¹ Model Deviation Ratio – see Section 10.3.4 of EFSA (2013)

¹² Calculated via Finney’s formulae, i.e. $1/((0.2/5)+(0.2/2.29))$

¹³ See EFSA (2013)

1364 applied to the calculated endpoint based on mean measured concentrations (i.e.
1365 $3.448/1.12 = \mathbf{3.08 \text{ mg/L}}$) and that this endpoint is used in the risk assessment.

1366 Using this approach should address the combined toxicity of the two active substances
1367 based on mean measured concentrations.

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Further information

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