Ecotoxicology Guidance

FORMULATION STUDIES AND COMBINED RISK ASSESSMENT IN ECOTOXICOLOGY: Guidance on the need for studies and their use in risk assessment

1. Introduction

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

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

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

This guidance covers formulation toxicity studies (sections 2 and 3) and risk assessment (sections 4 and 5).

2.1 Terrestrial vertebrates (Annex points 10.1.1 (birds) & 10.1.2 (terrestrial vertebrates other than birds))

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

10.1.1.1(birds):

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

10.1.2.1 (terrestrial vertebrates other than birds):

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

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

In Appendix B it is stated that '*The basic concept of the risk assessment for birds and mammals is that animals are exposed to residues of active substances in the environment, e.g. via their food. Thus, the following steps do not refer to an assessment of formulation toxicity as such, but of the expected effects from exposure to a mixture of active substances (and possibly also toxic co-formulants) in the environment resulting from use of that formulation*.'

2.1.3 CRD guidance:

In relation to effects on terrestrial vertebrates (birds and mammals), the toxicity of pesticide residues in food and drinking water from spray applications is considered unlikely to be affected by the formulated product and because of this, the risk assessment can currently be based on toxicity studies conducted with the technical active substance(s), formulation studies are not usually required.

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

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

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

2.2 Aquatic organisms (Annex point 10.2)

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

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

"*Testing shall be performed where:*

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

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

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

Tests shall be carried out on one species from each of the three/four groups of aquatic organisms, that is to say fish, aquatic invertebrates, algae and, where relevant, macrophytes

as referred to in point 8.2 of Part A of the Annex to Regulation (EU) No 283/2013, if the plant protection product itself may contaminate 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*."

2.2.2 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 PECsw 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 PECsw integrating all routes of exposure (i.e. the normal 'PECsw or PECmax). 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."

2.2.3 CRD 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 spray drift acute TER for the active substance is more than 10 times greater than the relevant Annex VI trigger testing of such groups with the formulation may not be necessary, providing a well reasoned case can be submitted to demonstrate the low toxicity of the co-formulants.

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. Such a reasoned case would need to take account of the potential toxicity to aquatic life of any co-formulants present.

Where acute studies are presented for hazard classification purposes and these studies indicate a higher level of toxicity than predicted based on active substance content, then an acute spray drift risk assessment should be provided by comparing the formulation toxicity

endpoints with the initial PECsw for the formulation (this only applies to formulations applied as sprays)[1].

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 3.1) do not require new formulation studies.

Major formulation changes (see Section 3.2), 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 (see Section 5).

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).

For UK national registrations CRD would not normally require the assessment of chronic toxicity formulation studies - since formulations would not be expected to remain intact over chronic timescales.

2.3 Bees (Annex point 10.3)

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

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

(*a) food storage in enclosed spaces;*
(b) non-systemic plant protection products for application to soil, except granules;
(c) non-systemic dipping treatments for transplanted crops and bulbs;
(d) wound sealing and healing treatments;
(e) non-systemic rodenticidal baits;
(f) use in greenhouses without bees as pollinators.

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

[1] CRD does not consider that intact formulations are likely to be prone to transport via drainflow or runoff (including runoff via HARDSpec). For these routes of exposure the risk assessment would normally be based on active substance toxicity endpoints/PEC values Applicants should note that at present the use of the FOCUSsw tools for National Authorisations in the UK has not yet been agreed and as such the formulation exposure assessment for a UK national approval should be based on the standard Rautmann spray drift data (see Appendix 1, SANCO 3268/2001, 1st October 2001). This assessment is required for professional products only; the risk from Home Garden products can usually be mitigated by the use of the phrase "Direct away from ponds and other surface water bodies".

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

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

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

10.3.1.1. Acute toxicity to bees

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

10.3.1.2. Chronic toxicity to bees

Circumstances in which required

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

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

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

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

10.3.1.4. Sub-lethal effects

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*".

2.3.2 Relevant SANCO guidance (SANCO 10329/2002, October 2002):

No specific additional guidance on the need for formulation studies is provided. In relation to assessing acute oral and contact toxicity in standard laboratory studies it is stated that "*if there are problems with the solubility of the active substance, then the test should be conducted with a representative formulation*."

2.3.3 CRD guidance:

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, 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.

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

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.

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

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

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

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

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

2.4 Arthropods other than bees (Annex point 10.3.2)

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

10.3.2 Effects on non-target arthropods other than bees:

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

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

(b) wound sealing and healing treatments;

(c) enclosed spaces with rodenticidal baits.

Testing shall be required if:

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

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

For plant protection products, two indicator species, the cereal aphid parasitoid 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 50 ([2]), ER 50 ([3]) 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

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[2] LR_{50}, abbreviation for '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] ER_{50}, abbreviation for '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.

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 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".

2.4.2 Relevant SANCO guidance (SANCO 10329/2001, October 2002):

Section 5 of the SANCO Terrestrial Ecotoxicology guidance document recommends that the requirements and risk assessment for 'other terrestrial arthropods' be as agreed under the 'ESCORT 2' workshop. Under this methodology, a standard first tier risk assessment is initially conducted based on the results of glass plate residual toxicity studies conducted with two standard indicator species - *Aphidius rhopalosiphi* and *Typhlodromus pyri*. In-field and off-field exposure is compared against the residue LR50s for each species, with further testing (such as extended lab, semi-field or field studies) being required if the derived 'hazard quotient' is equal to or greater than 2.

2.4.3 CRD guidance:

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 penetration/uptake of the active substance. Also, occasionally co-formulants may

be directly toxic to non-target arthropods, although such effects are considered to be infrequent.

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

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

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

Where changes in formulation are 'minor' (as defined in Section 3.1), no further consideration is required.

Where formulation changes from that originally evaluated are 'major' (as defined in Section 4.2), an assessment of the 'acceptability' of the risk to non-target arthropod from the 'new' formulation is required. For major changes in formulation (Section 3.2) the following advice is given:

Where the formulation type of the 'new' formulation is the same as that previously tested in higher tier studies, it may be possible to make a case for the extrapolation of the "higher tier" data, with this including a comparison of the previously tested and proposed formulation.

Where the formulation type of the 'new' formulation is different from that previously tested in higher tier studies, some additional studies conducted with the new formulation may be required, unless a well reasoned and convincing case can be provided as to why the change will not pose a greater risk to non-target arthropods. Major formulation changes, particularly those involving significant increases in organic solvent and/or surfactant concentrations are amongst those considered most likely to increase the toxicity to non-target arthropods. It is suggested that new higher tier formulation toxicity studies are initially conducted with the previously identified most sensitive indicator test species. Further toxicity testing with other species would usually only be required where the results of this initial testing indicated a potential for increased toxic effects (see also Section 6).

2.5 Earthworms (Annex point 10.4.1)

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

10.4.1: Earthworms

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

10.4.1.1: Sub-lethal effects:

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

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

10.4.1.2: Field studies:

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

Circumstances in which required
Where the relevant risk quotient analysis indicates a chronic risk to earthworms a field study to determine effects under practical field conditions shall be conducted and reported as an option for refined risk assessment".

2.5.2 CRD guidance:

According to Regulation 284/2013, a formulation study with the plant protection product is, as stated above, required when the toxicity of the product cannot be predicted from the data on the active substance. Extrapolation is usually possible for minor formulation changes. CRD considers that it may also be possible to extrapolate from certain formulation types and hence reduce the need for a study with every formulation.

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

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

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

If there are data on the toxicity of the formulations containing the separate active substances, then it may be possible to make a case on the basis of additive toxicity and similarity of the co-formulants. For example:

- A proposed product is a combination of active substance A and B and the product is a WP

- Data are available on the toxicity of active substance A on its' own in a WP formulation
- Data are also available on the toxicity of active substance B on its' own in a WP formulation

Then it may be possible to use this information to address the formulation data requirement for a study on a WP with A and B, e.g. by comparing co-formulants assuming additive toxicity.

Similarly, if we have a study on an WP formulation with a.s. A and a water-dispersible granule (WDG) formulation with a.s. B, then it may be possible to use the information from these two studies to address the formulation data requirement for a study on a WP (or WDG) with A and B, e.g. by comparing co-formulants, toxicity of a.s., proportions of a.s. in the formulation AB etc.

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

Circumstances in which required

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

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

(b) wound sealing and healing treatments;

(c) enclosed spaces with rodenticidal baits.

Testing shall be required if:

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

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

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

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

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".

2.5.3 CRD guidance:

This data requirement relates to an assessment of long-term effects on soil meso- and macro-fauna.

Please refer to the CRD guidance in the NTA section for the recommended approach.

2.6: Soil non-target micro-organisms (Annex point 10.5)

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

10.5 Effects on soil nitrogen transformation

"*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 basis of data for the active substance, unless the applicant shows that no exposure occurs".

2.6.2 CRD guidance:

Given that formulations are unlikely to remain 'intact' in soil over chronic timescales, long-term effects from the formulation on soil micro-organism activity are considered unlikely. Therefore specific formulation testing is not usually required. In most cases it should be possible to extrapolate effects data from studies conducted in support of the active substance data requirements.

2.7 Effects on terrestrial non-target higher plants

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

Summary of screening data

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

Circumstances in which required
Screening data shall be required for plant protection products other than those exhibiting herbicidal or plant growth regulator activity, and if the toxicity cannot be established from

data on the active substance (point 8.6.1 of Part A of the Annex to Regulation (EU) No 283/2013). The data shall include testing from at least six plant species from six different families including both mono- and dicotyledons. The tested concentrations/rates shall be equal or higher than the maximum recommended application rate. If screening studies do not cover the specified range of species or the concentrations/rates necessary, then tests in accordance with point 10.6.2 shall be carried out.

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

10.6.2. *Testing on non-target plants*

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

Circumstances in which required

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

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

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

10.6.3 Extended laboratory studies on non-target plants

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

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

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

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

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

2.7.2 Relevant SANCO guidance (SANCO 10329/2001, October 2002):

Section 7 of the SANCO Terrestrial Ecotoxicology guidance document provides guidance on risk assessment methodology for non-target plants. This guidance makes it clear that it is necessary to assess potential adverse effects from spray drift exposure to non crop plants

located outside the treatment areas – with it being necessary to consider both pre and post-emergence effects. In relation to the use of formulated product Section 7.1 of SANCO/10329/2002 provides the following advice: *"For foliar applications, the bioassays should be conducted by spraying the product on the plants, reproduce as far as possible the realistic exposure conditions and, in particular, spray drift. Soil application should be chosen if that is more appropriate with regard to the mode of action. The test substance should be the lead formulation (or another formulation) because formulations contain, besides the active substance, all those components and co-adjuvants required for maximising biological activity. For systemic products applied on the ground/soil, the tests should produce this application pattern."*

2.7.3 CRD guidance:

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

2.9 Additional advice for Terrestrial organisms

Section 2.4 of SANCO/10329/2002 (Terrestrial Guidance Document), offers the following general advice on the need for formulation studies for those groups of organisms covered by the document: *"Each Annex point has to be addressed; however, it is not always necessary to generate experimental data with the formulation; instead the data on the active substance could be sufficient. The decision should be based on the following considerations:*

If the risk indicators (TER, HQ) based on the active substance are well above the TER trigger or below the HQ trigger (e.g. 100-fold) then studies with the formulation could be considered dispensable. However, a decision should be made on a case-by-case analysis in agreement with the RMS and be reported.

It might be sufficient to test the formulation with that species of a group that was most sensitive with the active substance.

In cases where further information is considered necessary it should be examined, whether a direct step to higher-tiered-tests would be more appropriate than repeating the basic test with the formulation.

If a notifier is of the opinion that tests with a formulation are not needed, an explanation must be given."

2.9.1 CRD guidance:
The SANCO guidance represents a reasonable and pragmatic approach for terrestrial organisms. As a point of clarification, and based on data held by CRD, the term '100-fold' should be interpreted as referring to the extent to which for the active substance the respective Annex VI TER triggers should be exceeded, or the extent to which the respective HQ values needs to be below the respective Annex VI triggers.

3 Changes in formulations

3.1 Minor Changes

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

- no more than a 10% change (±) in the concentration of the active substance(s)
- no more than a 20% change (±) in the concentration of the surfactants, solvents and emulsifiers

3.2 Major Changes

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

- change in the formulation type (e.g. SC to WP, SL to EC) – (see Section 5),
- changes in the concentration of active substance(s) of more than 10% (±) or in the concentration of surfactant/solvents of more than 20% (±) of previously approved content
- replacement or addition of a surfactant/solvent
- changes to the base for baits/pellets/granules (see Section 2.1),
- addition of another active substance (see Section 4)

4 Risk assessment for formulations that contain more than one active substance

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 formulants.

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 actives 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:

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

This is equivalent to the endpoint for A, so it is considered that the formulation toxicity is driven by active A,

The following example shows where the toxicity is not driven by one of the active substances:
Formulation 'Test2' contains two active substances, C (20 %w/w) and D (30 %w/w). Studies on *Daphnia magna* are available for both actives 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
C	6.2	mg a.s./L
D	9.7	mg a.s./L
'Test2'	14.9	mg formulation/L

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

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

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

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

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

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

The approach for aquatic organisms and birds/mammals is discussed further below:

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

The guidance recommends counter-checking calculated and measured mixture toxicity using the Concentration Addition (CA) method.

- The observed and calculated mixture toxicities are considered in agreement if the MDR (Model Deviation Ratio) is between 0.2 and 5.0.

- More-than additive (i.e. synergistic) mixture toxicity is indicated if the MDR is > 5. If synergistic effects cannot be excluded, the assessment should preferably be based on measured values.

- Less-than additive toxicity mixture toxicity is indicated if the MDR is < 0.2. If less-than additive toxicity (i.e. antagonistic) mixture toxicity is indicated and no plausible toxicological explanation for this apparent antagonism can be provided (e.g. special feature of the formulation type), the RA should be based on the calculated mixture toxicity.

<u>CRD guidance for acute exposure via spraydrift:</u>

Please note that CRD will undertake different approaches in the Core Registration Report and UK Addenda.

Core Registration Report

In the Core Registration Report where CRD is the zRMS, CRD will compare the measured (from a study) and calculated mixture toxicity using the Finney equation (total load formulation with Finney DF, 1942). This will be undertaken to establish whether less-than or more-than additive toxicity is indicated. Further consideration of the combined risk will be best addressed at Member State level.

UK Addenda

In the UK addenda CRD will present a formulation risk assessment for exposure via spray drift using the measured formulation endpoints, even if less-than additive toxicity is indicated. If reliable formulation data has been provided it is not considered appropriate to disregard these data.

Options for refining the acute risk via spray-drift include use of drift reduction technology(http://www.hse.gov.uk/pesticides/topics/pesticide-approvals/pesticides-registration/data-requirements-handbook/fate/active-substance-uk.htm), more acute data (excluding the generation of further vertebrate data) to enable geomean/SSD approach, higher tier data.

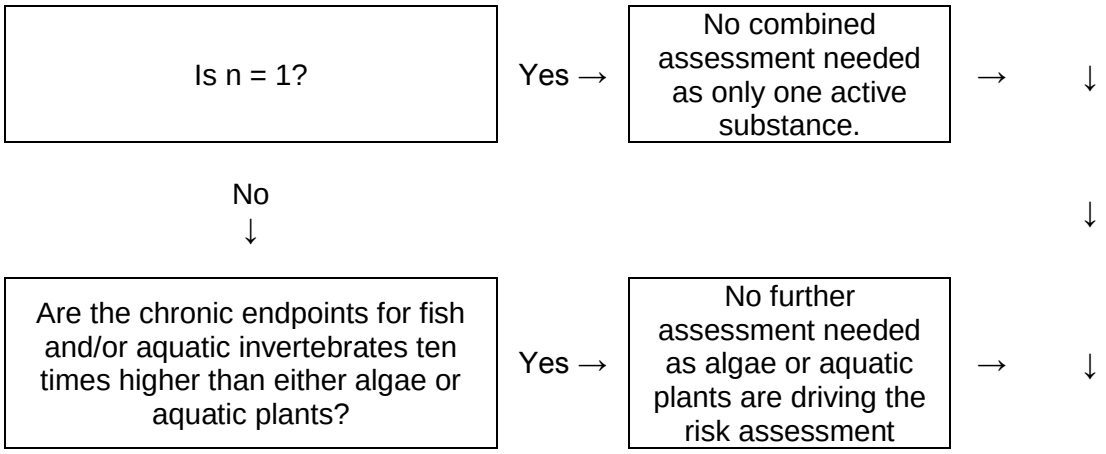
The acute assessment guidance covers the acute risk to fish and aquatic invertebrates and the risk to algae and aquatic plants.

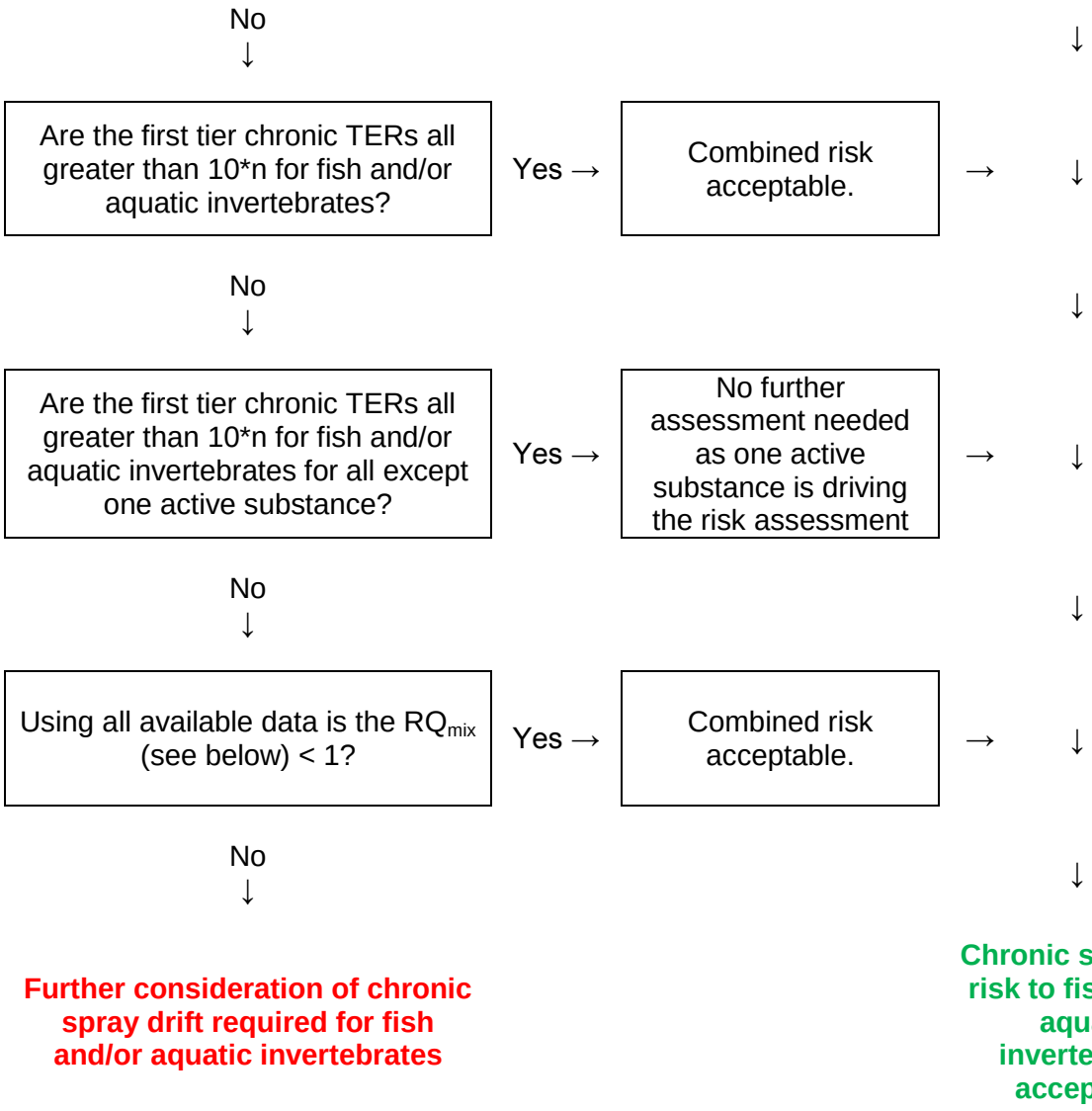
Therefore, chronic schemes (for spray drift and drainflow exposure) **ONLY** need to cover the chronic risk to fish and aquatic invertebrates. The chronic decision scheme for spray drift is shown in figure 1 and for drainflow in figure 2.

Figure 1: Chronic spray drift assessment for fish and aquatic invertebrates

NOTE where this scheme is triggered from the drainflow scheme substitute “drainflow” for “spray drift”!

n= number of actives in formulation





$$RQ_{mix} = \sum_{i=1}^{n} \frac{PEC_i}{RAC_i}$$

If following the scheme results in "**Further consideration of chronic spray drift required for fish and/or aquatic invertebrates"** – then further consideration of the risk is required.

Steps that can be considered include:

- Consideration of the fate and behaviour of the active substances (properties including the DT_{50}) and hence the likelihood of co-occurrence

- Consider the effects seen in the study (e.g. growth, reproduction) – is this the same for both / all active substances? If different life stages are affected further combined assessment might not be necessary
- Microcosm / mesocosm studies for aquatic invertebrates
- Use the Finney formula to calculate a toxicity endpoint to use in a risk assessment determining the risk mitigation required

Potential additive effects should also be considered if the route of entry is via drainflow (see below).

CRD guidance for exposure via drainflow:

Exposure via drainflow for mixed active substances is based on consideration of additive toxicity of the individual active substances – as exposure will not be in the form of the intact formulation.

For formulated products containing more than one active substance, consideration of the combined risk via drainflow is required. Similarly if the active substance and metabolite(s) are likely to co-occur then this risk should also be considered.

Screening step – acute risk

For the acute risk to fish and aquatic invertebrates and the risk to algae and aquatic plants and acceptable combined risk from a product containing *n* active substances can be determined if:

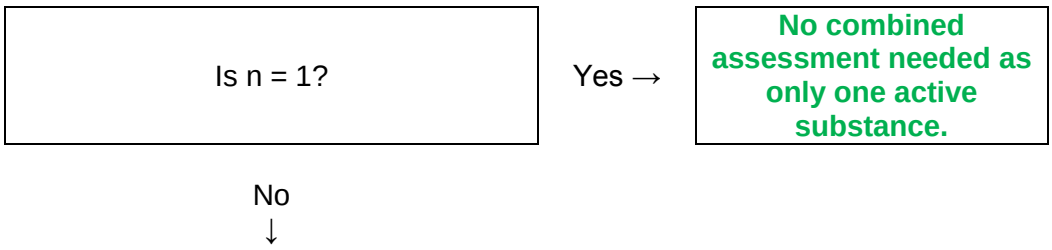
a) The TERs for all active substances are more than *n* times the trigger value for the group being considered (because the combined TER would also be above the trigger)
b) The TERs for all active substances except 1 are more than *n* times the trigger value for the group being considered (because one active substance is driving the risk assessment.

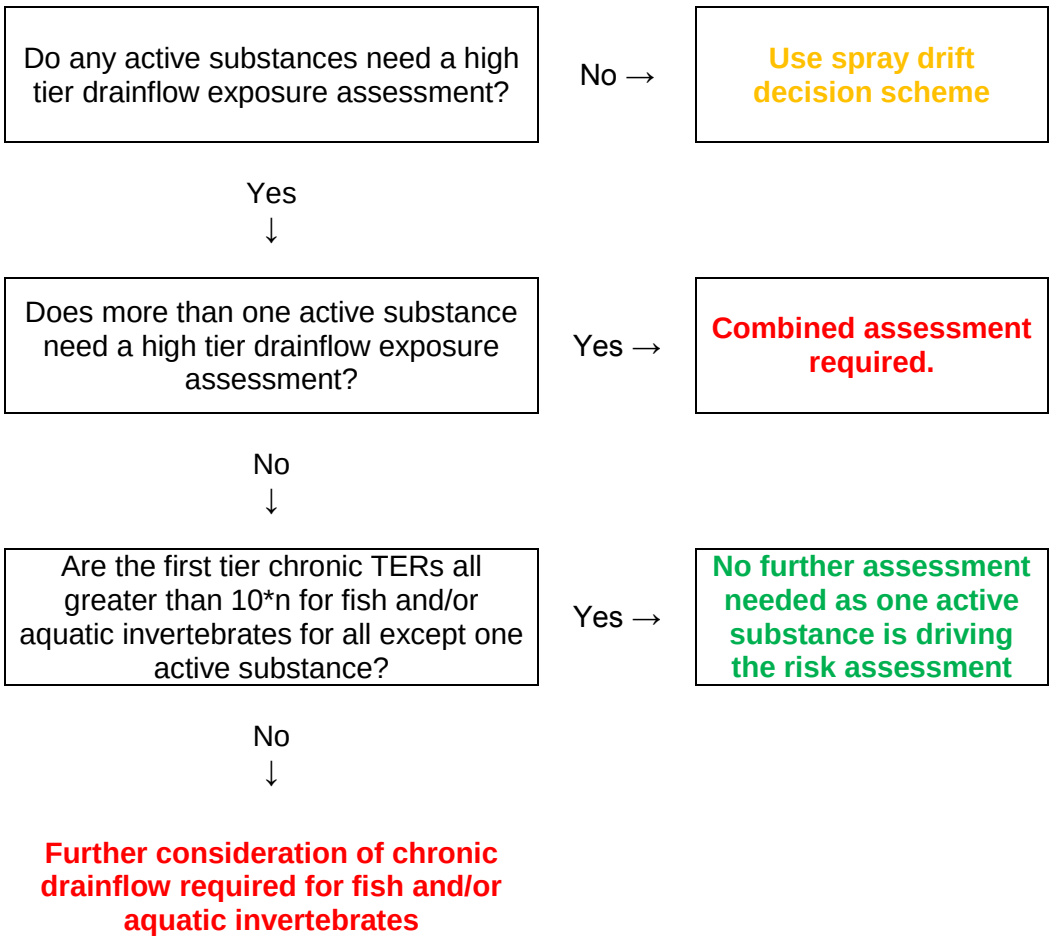
Screening Step – chronic risk assessment

The decision scheme in figure 2 can be used to determine if a chronic drainflow assessment is required:

Figure 2: Chronic drainflow assessment for fish and aquatic invertebrates

n= number of actives in formulation





Combined drainflow assessment

The consideration of combined drainflow does not necessarily require a numerical combined drainflow assessment. This requirement will depend on a number of factors including the fate and behaviour of the individual active substances and therefore is best considered in conjunction with the fate and behaviour specialist. Factors which require consideration include – whether the product will be applied during the UK drainflow period (October – April). Consideration of the soil types used to grow the produce is required, also the relevant DT_{50s} in soil for the active substances (i.e. will any of the active substances persist in soil and therefore still be present during the drainflow period even if applications are made earlier in the year). If the product is applied outside of the drainflow period and the active substances have short DT_{50s} then no further assessment may be required.

If the product is to be applied during the drainflow period and/or the active substances have longer DT_{50s} from which significant levels will persist in to the drainflow period then further consideration will be required.

With higher tier drainflow, due to the different properties of the individual pesticides, it is likely that the maxima of the PECsw would not occur on the same day therefore it will be necessary to identify the individual day on which the maximum PEC occurs and combine these. From the individual properties of each pesticide it may also be possible to argue that if

the Koc is very high (for example 15000 mL/g) and therefore very immobile, or the DT_{50} is very short, (less than 1 day) that that substance is unlikely to enter drainflow.

From an ecotoxicology perspective it will require consideration of whether all groups of aquatic organisms pass at first tier for both active substances. If so and the TERs indicate a wide margin of safety, then no further consideration of the risk is required (see screening steps above). If any group of aquatic organisms fail for more than one active substance then further consideration will be required. However, whether a full combined higher tier modelling is required will depend on whether one active substance can be clearly shown to be driving the risk assessment. If for example the chronic risk to aquatic invertebrates fails for one active substance but all other groups pass at first tier and for the other active substance all groups apart from algae pass at first tier – then a case could be made that a combined risk assessment is not required (depending on the size of the TERs i.e. margin of safety at first tier). If more than one active substance fails for the same group at first tier then some form of combined assessment will be required.

If required, a combined assessment can be carried out considering annual maximum PEC_{SW} values and using the Finney equation to produce a combined toxicity value. The number of exceedences can then be compared between the individual active substances and the combined value. If this does not pass – then a full higher tier modelling assessment will be required. Higher tier drainflow modelling using either the preferential flow model, MACRO, or Webfram (http://www.webfram.com) will be accepted.

The ecotoxicology evaluator will need to confirm that appropriate Regulatory Acceptable Concentrations (RACs) have been used in the fate and behaviour assessment. The overall assessment will need ecotoxicology and fate and behaviour specialist collaboration (if they are assessed by different individuals).

Guidance on the presentation of higher tier drainflow modelling results for use in aquatic risk assessments can be found on the following link:
http://www.hse.gov.uk/pesticides/topics/pesticide-approvals/pesticides-registration/data-requirements-handbook/fate/macro.htm

As regards a suitable precedent in terms of the numbers of combined scenario years failing the relevant TER trigger, CRD proposes that a pass rate of 90% should be set as a guide to an appropriate value (i.e. the total scenario years failing plus any land area that remains unquantified by the modelling should be no greater than 10%). Such a trigger is likely to be appropriate for use against effects endpoints derived from tests on species with the potential for rapid recovery (e.g. algae and aquatic plants). Such a trigger may not be appropriate when the critical risk is identified to be against other species e.g. fish and aquatic invertebrates. Currently our experience is mainly limited to situations where effects against algae, aquatic plants or invertebrates are driving the risk assessment and if your risk assessment is being driven by either an acute or chronic effect endpoint against fish you should consult CRD.

Guidance for the use of Webfram is in the process of being finalised and will be published on the CRD website when it becomes available.

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 long-term effects** on birds and mammals. Applicants should note that this is **relevant for all formulation types** i.e. seed treatments, granuels and foliar sprays.

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.

Guidance on how to carry out a combined risk assessment

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

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

1/T overall = P1/T1 + P2/T2 + P3/T3 etc

Where P1/P2 etc are the proportions of the component active substances and T1/T2 etc represent their respective toxicities.

An alternative risk assessment approach to the use of an “overall toxicity” estimate, is to estimate exposure in terms of “toxicological equivalent” amounts of the more toxic component active. For example, if active A is twice as toxic as active B, the toxicological equivalent level of exposure for a 50:50 mixture would be 1.5 times that of active A. This method is particularly suitable for estimating the risk to terrestrial vertebrates from exposure to a mixed active formulation containing actives of equivalent or similar modes of action. {It could also be used to take account of the effect of combined exposure to an active substance and its structurally similar toxicologically relevant metabolite.}

For the long-term risk assessment, CRD will apply the recommendations of Appendix B of EFSA (2009) which uses a toxic unit approach for the Tier I formulation assessment. If the Tier I risk assessment fails then further refinements will be required. Refinements may involve the standard ecological refinements outlined in EFSA (2009) or may be based on a toxicological argument. In the case of granules, seed treatments, pellets and baits, to which terrestrial vertebrates may be directly exposed, this could include a more detailed consideration of other aspects e.g. nutritive value, attractiveness and availability.
N.B. CRD do not consider it necessary to conduct additional toxicity studies when making these refinements and applicants are strongly advised to consult with CRD Ecotoxicology experts before commissioning any such studies.

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

5 Extrapolations and risk assessments

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

For formulation changes that are not 'minor', new formulation studies should be provided to cover the areas outlined in Section 2 unless robust scientific cases can be provided to justify why they are not necessary.

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

Certain product types, such as controlled release formulations, may significantly effect the exposure profile compared with other formulations or the technical active substance. New formulation toxicity tests may be required. However, it is envisaged that a bridging data package, focussing on the most sensitive species present in the key environmental compartment(s) affected may be sufficient. Applicants are advised to consult CRD prior to conducting extensive toxicity testing.

For ready-for-use formulations based on simple dilutions in water of an approved concentrate formulation, the toxicity can be estimated by calculation from the concentrate toxicity, with no additional studies being required. It would also be expected that provided the

proposed use is similar with no increase in environmental exposure, reasoned cases would be sufficient to address the risk assessment.

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

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

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

6 Data protection

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

7 References

Creton S, Clook M and Wheeler JR (2014) Application of the threshold approach for acute fish toxicity testing to plant protection products: a proposed framework. Chemosphere 96 (2014) 195–20.

Finney DF 1942 The analysis of toxicity tests on mixtures of poisons, Ann. Appl. Biol. 29, pp82-94

EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2013. Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters; EFSA Journal 2013;11(7):3290, 268 pp. doi:10.2903/j.efsa.2013.3290.

EFSA Guidance Document on risk assessment for birds and mammals; EFSA Journal 2009; 7 (12): 1438.

EFSA Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera*, *Bombus* spp. and solitary bees); EFSA Journal 2013; 11 (7): 3295.