Evaluation Manual for the Authorisation of plant protection products according to Regulation (EC) No 1107/2009

EU part

Plant protection products

Chapter 6 Ecotoxicology; terrestrial; non target arthropods and plants

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ctgb

Board for the Authorisation of plant protection products and biocides

Chapter 6 Ecotoxicology; terrestrial; non target arthropods and plants

Category: Plant Protection Products

General introduction 5
I Non target Arthropods 5
1. EU framework 5
1.1 Introduction 5
1.2 Data requirements 5
1.2.1 Data requirements for the active substance 6
1.2.2 Data requirements for the product 6
1.2.3 Data requirements for metabolites 6
1.3 Risk assessment 6
1.4 Approval 11
1.4.1 Approval of the active substance 11
1.4.2 Evaluation of plant protection products 11
1.4.3 Decision making for plant protection products 11
1.5 Developments 11
II Non target plants 12
1 EU framework 12
1.1 Introduction 12
1.2 Data requirements 12
1.2.1 Data requirements for the active substance 12
1.2.2 Data requirements for the product 13
1.2.3 Data requirements for metabolites 13
1.3 Risk assessment 13
1.4 Approval 15
1.4.1 Approval of the active substance 15
1.4.2 Evaluation of plant protection products 15
1.4.3 Decision making for plant protection products 15
1.5 Developments 15
2 References 16
3 Appendices 17

Changes in the Evaluation Manual

Evaluation manual PPP EU part Chapter 6 Non targets arthropods and plants			
Version	**Date**	**Paragraph**	**Changes**
2.1	October 2016	Chapter 1.2	Text from data requirements deleted from the Manual, replaced with reference/links to Regulations (EU) No 283/2013 and 284/2013. Short list of data requirements included in the text.
		Chapter 1.3	Further elaboration or clarification on risk assessment issues that are used by Ctgb included in the text of 1.3: Herbicide application in orchards No use of MAF in case of EU (active substance) assessments for non-target terrestrial plants
		Appendix 1, Point 4	Note on correction factor 0.5 from ESCORT 2 for the in field exposure calculation for orchards and vineyards included.
		Appendix 2, Point 5	Criterion included for acceptance of data normality in case of the SSD approach
2.2	January 2020	Chapter 1.3 Non-target arthropods	Conclusions from the Pesticides Peer review Meeting 185 on Recurring Issues on Ecotoxicology (EFSA Supporting publication 2019:EN-1673)
		Chapter 1.3 (non-target plants)	Endpoint based on phytotoxicity
		I.1 and II.1	Sentence included on the administrative EFSA guidance
2.3	July 2021	Chapter 1.3 Non-target arthropods	Note on active substances with a mode of action aimed at suffocation of the target organisms included.
2.4	February 2022	Chapter 1.3 Non-target arthropods	Addition to note on active substances with a mode of action aimed at suffocation of the target organisms (for products with high percentage of oily components).
2.5	July 2022	Appendix 1	- Update of point 7 in the decision tree for NTA in Appendix 1 with regard to the current state of knowledge and expert judgement applied in the higher tier risk assessment using non-target arthropod field studies. In the current framework for the NTA risk assessment (Guidance Document on Terrestrial Ecotoxicology (Sanco/10329/2002 rev 2 final) and ESCORT 2) specific guidance on which endpoints and which trigger values should be applied to

			NTA field studies is lacking, and is therefore based on expert judgement. Inclusion of this expert judgment as a structural approach in the Evaluation Manual creates a dilemma for inclusion in the assessment framework because the methodology has already been applied specific to the case and causes inconsistency when a starting date is introduced. The current update therefore applies to both ongoing and future dossiers. - Copy from Appendix H from the report of the Pesticides Peer review Meeting 185 on Recurring Issues on Ecotoxicology (EFSA Supporting publication 2019:EN-1673) replaced by hyperlink.
2.6	October 2022	Chapter 1.3 Non-target arthropods Chapter 1.3 Non-target plants	Bullet point from the final agreements from the 5th CZHW in Ecotoxicology, Brno, November 2019 on the 'VDF' included. Bullet point from the final agreements from the 5th CZHW in Ecotoxicology, Brno, November 2019 on 'phytotoxicity' included.
2.7	February 2023		- Further clarification added on the use of the VDF. - Update on a.s. with a mode of action targeted against lepidopteran species
2.8	September 2023		Bullet points from the final agreements from the 6th CZHW in Ecotoxicology, Ede (NL), June 2022 regarding non-target arthropods and non-target plants included.
2.9	May 2024		Risk assessment approach regarding the use of aged residue tests in relation to application timing conform GAP included in section 1.3 chapter NTA.
3.0	March 2025		Amendment in section 1.3 chapter NTA 'Risk assessment approach regarding the use of aged residue tests in relation to application timing conform GAP': restrictions based on blocks of half months instead of whole months, and correction of the inconsistent use of 'last application' and 'first application' in the text.
3.1	October 2025		Section 1.2 (both NTA and NTP) is updated with the 2023 versions of the Commission Communications. Hyperlinks are updated when necessary.

GENERAL INTRODUCTION

This chapter describes the data requirements for estimation of the effects on non target arthropods and plants of a plant protection product and its active substance and how reference values are derived in the EU framework (§1 - §1.5) under Regulation (EC) No 1107/2009 .

This chapter consists of two parts: a part about non-target arthropods (I) and a part about non-target plants (II).

I NON TARGET ARTHROPODS

1. EU FRAMEWORK

In this document, the procedures for the evaluation and re-evaluation of active substances as laid down in the EU are described; the NL procedure for evaluation of a substance is reverted to when no EU procedure has been laid down. The NL-procedure for the evaluation of a substance is described in §2 - §2.5 of part 2 of the Evaluation Manual (plant protection products). This document aims to give procedures for the approval of active substances and inclusion in Commission Implementing Regulation (EU) No 540/2011.

Notifiers preparing an assessment report for active substances need to comply with the relevant guidance, instructions and format laid down in the EFSA Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances.

1.1 Introduction

This chapter describes the risk assessment of plant protection products for non-target arthropods.

Non-target arthropods play a vital role in the ecosystem. For this reason plant protection products should cause no unacceptable and prolonged effects on populations of non-target arthropods, not in the treated part and not beyond. An agricultural purpose is served at the same time: the protection of natural enemies in integrated pest control. The risk to non-target arthropods must be assessed in case there is a chance of exposure of these organisms.

Guidelines for the risk assessment for non-target arthropods are given in the Guidance Document on Terrestrial Ecotoxicology (Sanco/10329/2002 rev 2 final) in which the testing procedure is described as elaborated in the report written on the basis of the SETAC/ESCORT 2 workshop [1]

A decision tree with corresponding explanatory notes is presented in Appendix 1. This decision tree summarises the decision scheme for arthropods in non-integrated pest management systems.

Data requirements, evaluation methodologies, criteria and trigger values that deviate from, or further elaborate, the provisions under EU framework (§1), are described under NL framework (§2 - §2.5). The national further provisions can also be used for inclusion of an active substance in Commission Implementing Regulation (EU) No 540/2011.

1.2 Data requirements

In order to qualify for inclusion of an active substance in Commission Implementing Regulation (EU) No 540/2011 [2] a dossier that meets the provisions laid down in Commission Regulation (EU) No 283/2013 and Commission Regulation (EU) No 284/2013 of Regulation (EC) No

1107/2009 must be submitted for the active substance as well as for the product.

Generally, EU and OECD guidelines for the protocol of experiments are mentioned in Commission Communication 2023/C 344/02 and Commission Communication 2023/C 344 01.

When according to the applicant a certain study is not necessary, a relevant scientific justification can be provided for the non-submission of the particular study.

1.2.1 Data requirements for the active substance

The data requirements regarding the risk of the active substance for non-target arthropods are described in Commission Regulation (EU) No 283/2013 , point 8.3.2 (Effects on non-target arthropods other than bees).

Point 8.3.2 consists of the following data requirements:
8.3.2.1 Effects on Aphidius rhopalosiphi
8.3.2.2 Effects on Typhlodromus pyri

1.2.2 Data requirements for the product

The data requirements regarding the risk of the plant protection product for non-target arthropods are described in Commission Regulation (EU) No 284/2013, point 10.3.2 (Effects on non-target arthropods other than bees).

Point 10.3.2 consists of the following data requirements:
10.3.2.1 Standard laboratory testing for non-target arthropods
10.3.2.2 Extended laboratory testing, aged residue studies with non-target arthropods
10.3.2.3 Semi-field studies with non-target arthropods
10.3.2.4 Field studies with non-target arthropods
10.3.2.5 Other routes of exposure for non-target arthropods

1.2.3 Data requirements for metabolites

Except for the active substance and the product, data are also required for metabolites to which non-target arthropods may be exposed. Arthropods may be exposed to metabolites in/on plants and to metabolites in the soil. For metabolites in vegetation, standard laboratory tests are normally not required. Metabolites that are the actually active molecule may be exceptions.

General guidance is given in the general part about metabolites as described under ‘birds and mammals’ (§1.2.3). Where higher tier studies (cage/tent/tunnel or field tests) have been carried out with the pesticide under realistic exposure conditions it can be assumed that the potential risk of metabolites has been taken into account. Soil metabolites: when relevant these are tested with soil meso- and macro-organisms (data point 8.4.2); tests with surface dwelling soil arthropods are therefore not required.

1.3 Risk assessment

The risk assessment methodology for non-target arthropods has in EU context been elaborated in the Guidance Document on Terrestrial Ecotoxicology (Sanco/10329/2002 rev 2 final), which follows the recommendations of the ESCORT 2 workshop [1].

Each study is summarised and analysed separately. The final conclusion and the endpoint per aspect (such as LR_{50}) are presented in a list of endpoints. The risk is assessed against these endpoints.

In **Appendix 1 to this chapter**, a risk assessment scheme for non-target arthropods in non-

integrated pest management systems is included. This decision scheme follows the ESCORT 2 guidance [1], with additions and clarifications such as they have evolved in risk assessment practice over the years. Since these additions and clarifications are in line with what is currently commonly accepted (and required) during EU-reviews, they are included in the EU-part of this chapter. The scheme for integrated pest management systems is included in Appendix 1 to the NL-part of this chapter.

In addition to what is described in Appendix I, there are

1) specific approaches used by Ctgb: see below.
2) agreements from Pesticide peer review meetings on recurring issues on ecotoxicology and from Zonal harmonization workshops: see sections 1.3.1.1 and 1.3.1.2.

Specific approaches used by Ctgb:

- Herbicide application to bare soil strips under trees in orchards:

In the first tier, foliar dwelling arthropods have to be considered for the treated area. When a risk is identified, refinement is possible by taking into account in-field drift to the grass strips, and performing the refined risk assessment for the foliar dwelling arthropods in the grass strips. The exposure in this scenario should be 10% (due to drift from application to the bare soil beneath the trees).

- Active substances with a special mode of action:

It is noted that in the data requirements under Commission Regulation (EU) No 283/2013 and 284/2014, section 8.3.2, it is stated that for active substances with a special mode of action (such as insect growth regulators, insect feeding inhibitors) additional tests involving sensitive life stages, special routes of uptake or other modifications may be required by the national competent authorities, and the rationale for the choice of test species used shall be provided. With regard to this, the following two approaches are used by Ctgb:

Active substances with a mode of action aimed at suffocation of the target organisms:
It is noted that oily active substances generally have a physical mode of action, i.e. insects are killed because an oil film is formed on their body, which prevents them from breathing. The available NTA studies usually are performed with exposure to dried residues. The tested exposure scenarios therefore reflect introduction of species after the product has dried, which is relevant for organisms hiding under leaves or entering from off-field areas. The studies do not cover the direct effect of the application, i.e. when arthropods are oversprayed or come in contact with the wet oil spray, which based on the mode of action are considered the routes of exposure with the highest risk. The standard studies in fact can be considered as ‘aged residue’ studies (i.e. with an ageing time of 1-2 hrs). For the in-field risk assessment, this is acceptable, however for the off-field risk assessment aged residue studies are not acceptable. Therefore, for oily active substances the relevance of the submitted studies may be a point of discussion in the risk assessment for non-target arthropods. The consequence for the risk assessment will be a case by case decision, ranging from an uncertainty analysis to the request for new studies (e.g. lab studies with overspray, or field studies).
It should be noted that the same line of reasoning may apply to:
- other a.s. with a mode of action aimed at suffocation of the target organisms, and
- products with a high percentage of oily components.

Active substances with a mode of action targeted against lepidopteran species
For active substances with a mode of action targeted against lepidopteran species, Ctgb will require a test with larvae of at least one lepidopteran species. It is acknowledged that no

standard test guidelines are available yet. Therefore the following suggestions are provided by Ctgb:

- The applicant could use (adapted) test protocols as used in the efficacy dossier (using non-target lepidopteran species instead of the target species).
- In the public literature two references are available on tests with Bacillus thuringiensis and lepidopteran larvae, which could be used as an example: Broderick, N.A., Raffa, K.F., Handelsman,J. (2006). Midgut bacteria required for Bacillus thuringiensis insecticidal activity. Proc Natl Acad Sci USA, 103, 15196-15199. And: Broderick, N.A., Robinson, C.J., McMahon, M.D., Holt, J., Handelsman, J., Raffa, K.F. (2009). Contributions of gut bacteria to Bacillus thuringiensis-induced mortality across a range of lepidoptera. BMC Biology, 7, 1-9.

It is noted that in the Scientific Opinion addressing the state of the science on risk assessment of plant protection products for non-target arthropods (EFSA Journal 2015;13(2):3996), which will be used for updating the current guidance for NTA, the panel recommends as standard requirement to carry out a Tier 1 oral toxicity test with lepidopteran larvae. Thus, the Ctgb-approach is in line with the data requirements and with expected developments in the future.

- <u>The use of aged residue tests in risk assessment: recovery time and intended GAP</u>

According to SANCO/10329/2002 there is acceptable risk to non-target arthropod populations if the data shows that in-field recovery/recolonisation can occur within one year after the first application, but preferably in a shorter period depending on the biology (seasonal pattern) of the species. The in-field risk assessment is further based on ESCORT 2 and is based on the *possibility* for recovery, however, as noted in ESCORT 3, does not guarantee that actual recovery will occur. Considering the fact that many NTA species go into diapause during winter, the latest application timing in the year should be taken into account when using the recovery time determined in aged residue tests for the risk assessment. Based on the latest intended application timing, the time point at which the product residues should reach acceptable levels for recolonisation may be reached only during the cold period in late autumn and winter. However, the presence of adult non-target arthropod species or their reproductive activity in- and off-field at this point in time are expected to be low due to unfavourable environmental conditions. In general, (parasitized) eggs will enter diapause, while emergence occurs in spring. In spring, when recolonisation from off-field areas might commence, the next application of the product may already take place, which will cause unacceptable effects on the non-target arthropods.

For The Netherlands, it is assumed that the earliest date at which the first species go into diapause, is October 1st (based on expert judgement, until better data comes available). Therefore the time point at which effects should be at an acceptable level (<50%) is set at October 1st.

This means that, taking into account the biology and ecology of the non-target arthropod species, the results of the aged residue studies and the intended application pattern, the date at which establishing new in-field populations is considered possible within one year after the first application is determined by counting back the recovery period determined in the aged residue tests from the 1st of October. (For example: acceptable recovery time in the aged residue tests was 42 days, this means that the in-field residues will have to reach acceptable levels no later than the 21st of August.)

It is noted that actual recovery may be hampered for several reasons, i.e. effects are still at the 50% level at the determined ageing time, recolonisation is limited due to the characteristics of

the intensively managed agricultural landscape, the limited number of tested species may not cover interspecies differences in recovery time. It is also noted that this approach does not cover species that go into diapause earlier.

The above will be implemented by Ctgb via a restriction sentence on the Dutch label. Restrictions for timing are communicated based on blocks of half months (rounded off downwards). (E.g.: for the example above, this means that the following restriction should be included in the label: To protect non-target arthropods, application in (name specific crop) is not authorized after the 15th of August.)

For zonal dossiers, a final decision on this restriction sentence is to be taken at MS level.

1.3.1 Agreements from 'Pesticide peer review meetings on recurring issues on ecotoxicology' and from 'Zonal harmonization workshops'.

1.3.1.1 Pesticides Peer review Meetings on Recurring Issues on Ecotoxicology

In the Pesticides Peer review Meeting 185 on Recurring Issues on Ecotoxicology (EFSA Supporting publication 2019:EN-1673; Outcome of the Pesticides Peer Review Meeting on general recurring issues in ecotoxicology (wiley.com)), the agreements that were reached are presented below. These agreements apply to EU active substance dossiers submitted from 7 July 2019 and zonal product assessments submitted from 1 January 2020:

- Vegetation distribution factor (VDF):
  The experts agreed that the VDF value should be changed as better data are now available. Overall, the majority of the experts agreed on the recommendation of using a VDF of 5 for all the tiers of the assessment. It was highlighted that this recommendation should be considered as an interim solution until the revision of the current risk assessment scheme. Such an interim solution should be reflected in the (European Commission, 2002) document and its implementation should be further considered.

  Based on these minutes, according to EFSA a VDF of 10 has to be applied in EU active substance dossiers until the current guidance document for NTA risk assessment is updated.

  With regard to the VDF in product dossiers, in the Central Zone Harmonisation Workshop in Brno, 12-14 November 2019, the following was agreed (bullet point): The majority of MSs agreed to be in line with the EFSA Technical Report (2019) and use a VDF of 5 for all the tiers of the assessment for non-target arthropods. However, in the EFSA Technical Report, it was highlighted that 'this recommendation should be considered as an interim solution until the revision of the current risk assessment scheme. Such an interim solution should be reflected in the (European Commission, 2002) document and its implementation should be further considered.' Based on this highlight, the CZSC has made an urgent request to the Commission to adjust this issue in the guidance document as soon as possible, and decided that as long as this adjustment to the guidance document has not been made, a VDF of 10 should be applied in core assessments.

  Based on the above, in core assessments a VDF of 10 will be applied. See Chapter 7 'Ecotoxicology; terrestrial; non-target arthropods and plants - NL part' for an explanation on the VDF that will be used in the NL-addendum.

- Substrate in aged residue studies:
  It was agreed that until further guidance is developed, the substrate used in the aged residue studies does not need to be relevant for the crop under assessment.

- Risk assessment for non-target arthropods when oral exposure is relevant:
  It was agreed that, until guidance is developed and adopted, data for herbivorous species should not be requested. In cases where a concern is raised (e.g. based on the mode of action of the active substance), then this should be highlighted in the risk assessment and acknowledged in the EFSA conclusion.

- Minimum detectable difference in higher tier field studies:
  It was overall considered premature to recommend calculating the MDD for higher tier studies with NTA, as criteria to help interpret these MDD values are currently lacking (e.g. classes of MDD, minimum number of taxa with an acceptable MDD). According to Ctgb, this agreement does not exclude the possibility that an MDD analysis could provide useful information on a case-by-case basis.

- Evaluation of NTA field studies*:
  The experts at the meeting acknowledged that using the guidance by de Jong et al. (2010) is useful and that some aspects of the guidance should be used for EU-level assessments until further guidance for the evaluation of NTA field studies is available. The elements agreed upon have been in included in a template in Appendix H from the report of the meeting (EFSA Supporting publication 2019:EN-1673; Outcome of the Pesticides Peer Review Meeting on general recurring issues in ecotoxicology (wiley.com)). It was recommended by the meeting that this template is followed when reporting the studies in the RARs/DARs. It should be noted that the template contains some modifications as compared to the report from de Jong et al. (2010).

Note Ctgb: For further details on the current state of knowledge and expert judgement applied in the higher tier risk assessment using non-target arthropod field studies, see point 7 in the decision tree in Appendix 1 from this chapter of the Evaluation Manual.

1.3.1.2 Zonal harmonisation workshops

Bullet points from the final agreements from the 6th CZHW in Ecotoxicology, Ede, June 8-10 2022

The agreements of this 6th CZHW in Ecotoxicology apply for product dossiers submitted from 1 September 2023.

Bullet point 6: NTAs – The use of ER50 in the Tier 1 of the risk assessment of NTA

The MS agreed to use the ER50 from *T. pyri* and *A. rhopalosiphi* in Tier 1 when these are lower than the LR50. Furthermore, it was noted that sublethal effects should always be assessed and reported in the Tier 1 tests.
It was noted that in the meantime (prior to the decisions of this meeting going into force), MS will still potentially receive tests without sublethal/reproduction endpoints reported. It was agreed that this will be addressed in a qualitative way (zRMS to note this in the study evaluation indicating that reproductive effects are more sensitive).

1.4 Approval

This section describes the approval criteria for active substances (section 1.4.1) and plant protection products (section 1.4.2 and 1.4.3). For the EU approval procedure of active substances a representative formulation has to be included in the dossier. Therefore section 1.4.1 to 1.4.3 apply. For the zonal applications of plant protection products only section 1.4.2 and 1.4.3 apply.

Approval of the active substance

Annex II of Regulation (EC) No 1107/2009 provides the procedure and criteria for the approval of an active substances, safeners and synergists.

Point 3 of Annex II of Regulation (EC) No 1107/2009 gives the criteria for the approval of an active substance.

Evaluation of plant protection products

The principles for the evaluation regarding the effects on the environment are presented in Commission Regulation (EU) No 546/2011 (i.e. the Uniform Principles). The specific principles for evaluation for non-target arthropods are included in Part B Evaluation, point 2.5.2 Impact on non-target species, point 2.5.2.4.

Decision making for plant protection products

The principles for the decision-making regarding the effects on the environment are presented in Commission Regulation (EU) No 546/2011 (i.e. the Uniform Principles). The specific principles for decision making for non-target arthropods are included in Part C Decision making, point 2.5.2 Impact on non-target species, point 2.5.2.4.

1.5 Developments

In March 2010 a follow-up of ESCORT II was organised, the ESCORT III workshop. It is expected that the risk assessment will change on certain points. The report from this workshop is expected to be input for the revision of the Guidance Document on Terrestrial Ecotoxicology (Sanco/10329/2002). This revision will be undertaken by EFSA, and the following EFSA opinion was published on the science behind the upcoming revision with regard to the risk assessment for non-target arthropods: Scientific opinion addressing the state of the science on risk assessment of plant protection products for non-target arthropods (EFSA Journal 2015; 13(2):3996) .

II NON TARGET PLANTS

1 EU FRAMEWORK

In this document, the procedures for the evaluation and re-evaluation of active substances as laid down in the EU are described; the NL procedure for evaluation of a substance is reverted to when no EU procedure has been laid down. The NL-procedure for the evaluation of a substance is described in §2 - §2.5 of part 2 of the Evaluation Manual (plant protection products). This document aims to give procedures for the approval of active substances and inclusion in Commission Implementing Regulation (EU) No 540/2011 .

Notifiers preparing an assessment report for active substances need to comply with the relevant guidance, instructions and format laid down in the EFSA Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances.

1.1 Introduction

This chapter describes the risk assessment of plant protection products for terrestrial non-target plants. Terrestrial non-target plants are plants positioned outside the treated field without being a crop.

Terrestrial non-target plants play an important role in the ecosystem. This is why plant protection products should cause no unacceptable and prolonged effects on terrestrial non-target plants. The risk to terrestrial non-target plants must be evaluated if there is a chance of exposure of such plants.

Guidelines for the evaluation of the risk to terrestrial non-target plants are given in the Guidance Document on Terrestrial Ecotoxicology (Sanco/10329/2002 rev 2 final) .

The decision tree with corresponding explanatory notes is presented in Appendix 2. These decision trees summarise the decision scheme for terrestrial non-target plants.

Data requirements, evaluation methodologies, criteria and trigger values that deviate from, or further elaborate, the provisions under EU framework (§1), are described under NL framework (§2 - §2.5). The national further provisions can also be used for inclusion of an active substance in Commission Implementing Regulation (EU) No 540/2011.

1.2 Data requirements

In order to qualify for inclusion in Commission Implementing Regulation (EU) No 540/2011 [2] a dossier that meets the provisions laid down in Commission Regulation (EU) No 283/2013 and Commission Regulation (EU) No 284/2013 of Regulation (EC) No 1107/2009 must be submitted for the active substance as well as for the product.

Generally, EU and OECD guidelines for the protocol of experiments are mentioned in Commission Communication 2023/C 344/02 and Commission Communication 2023/C 344 01.

When according to the applicant a certain study is not necessary, a relevant scientific justification can be provided for the non-submission of the particular study.

1.2.1 Data requirements for the active substance

The data requirements regarding the risk of the active substance for non-target plants are described in Commission Regulation (EU) No 283/2013, point 8.6 (effects on terrestrial non-target higher plants).

Point 8.6 consists of the following data requirements:
8.6.1: Summary of screening data
8.6.2: Testing on non-target plants

1.2.2 Data requirements for the product

The data requirements regarding the risk of the plant protection product for non-target plants are described in Commission Regulation (EU) No 284/2013, point 10.6 (available data from biological primary screening in summary form).

Point 10.6 consists of the following data requirements:
10.6.1: Summary of screening data
10.6.2: Testing on non-target plants
10.6.3: Extended laboratory studies on non-target plants
10.6.4: Semi-field and field studies on non-target plants

1.2.3 Data requirements for metabolites

Standard laboratory tests are normally not required for metabolites. Exceptions may be formed by metabolites that are the actually active molecule. See the general part about metabolites as described in §1.2.3 of Chapter 7 Ecotoxicology; Terrestrial; Birds and mammals for general guidance. Where higher tier studies have been carried out with the pesticide under realistic exposure conditions, it may be assumed that the potential risk of metabolites has been taken into account.

1.3 Risk assessment

The risk assessment methodology for non-target plants has in EU context been elaborated in the Guidance Document on Terrestrial Ecotoxicology (Sanco/10329/2002 rev 2 final) .

Each study is summarised and analysed separately. The final conclusion and the endpoint per aspect (such as ER_{50}) are presented in a list of endpoints. Risk is assessed against these endpoints.

In Appendix 2 to this chapter, a risk assessment scheme for non-target terrestrial plants is included.

There are a few issues which need some more explanation, because it is not described clearly in the Guidance Document on Terrestrial Ecotoxicology:

- *Use of MAF*
  In the EFSA technical report: Outcome of the pesticides peer review meeting on general recurring issues in ecotoxicology, December 2015, the following is agreed regarding the use of a MAF in the risk assessment for Non-target Terrestrial Plants. Note that this is only valid for EU assessments (DAR/RAR):

  It was agreed that, from a scientific point of view, there is a logical reason to account for multiple applications in the risk assessment for NTTP. There were various approaches as to how this could be considered (i.e. foliar or soil default values of ESCORT II or EFSA PPR Panel (2014)). However, the experts could not agree which approach should be applied to the risk assessment and it was noted that currently different MAF values were being used by different RMS's (i.e. no harmonised approach). Therefore, it was agreed that for the risk assessment of active substances, no MAF values should be used by default, until a guidance document is developed.

For product assessments the following was agreed in the Central Zone Harmonisation Workshop in Ede (NL) of June 2022 (bullet point):
'The majority of MS agreed to use the same MAF as the Northern Zone. It will be clarified in the Central Zone Evaluation Manual that no refinement based upon DT50 is accepted for vegetative vigor, as this is in line with the NZ policies.'

- *Species Sensitivity Distribution: Acceptability criteria HC5*
  If an SSD is run, the data normality must be accepted at no less than 0.05 significance level to be acceptable for use in RA (look under "goodness-of-fit"). Modelling which does not pass at least this level (i.e. only passes at 0.025 or 0.01) indicates a poor fit for the data and a less reliable outcome[1]. This also in line with the current agreement in the draft NTP guidance.

- *Phytotoxicity*
  In the Pesticides Peer review Meeting 185 on Recurring Issues on Ecotoxicology (EFSA Supporting publication 2019:EN-1673; Outcome of the Pesticides Peer Review Meeting on general recurring issues in ecotoxicology (wiley.com)), the issue of phytotoxicity was raised. In addition to seedling emergence, OECD T 208 (OECD 2006a) and vegetation vigour, OECD TG 227 (OECD 2006b), other variables, such as visual phytotoxicity, and sometimes shoot length, are evaluated according to these respective guidelines. ERX values for visual observations (also referred to as 'visible detrimental effects' or 'visual injury', such as chlorosis, necrosis, wilting, leaf and stem deformation) could be determined, where a dose–response relationship is available, but this is not often the case. The experts at the meeting discussed the relevance of using this endpoint in the Tier 1 risk assessment. The experts considered that effects on growth may also cover the phytotoxicity endpoint, which may be subjective being based on visual assessment. However, it was noted that the EFSA PPR Panel (2014) reported that for a significant number of cases this endpoint was reported as being lower than the others. Therefore, considering that the endpoint is part of the test guidelines and that the data requirements do not specify the parameters to define the endpoint for risk assessment, the experts concluded that the ECX based on phytotoxicity should be reported in the study summary and in the list of endpoints. Where the derived endpoint is the lowest of those available, it should be considered for the Tier 1 risk assessment. Such an interim solution should be reflected in the (European Commission, 2002) document and its implementation should be further considered.

  In the Central Zone Harmonisation Workshop in Brno, 12-14 November 2019, the following was agreed which matches with the point above (bullet point):
  'The majority of MSs agreed that phytotoxicity endpoint should be considered in the risk assessment, in line with EFSA Technical Report (2019), i.e. all effects and endpoints will be reported in the study summary and the lowest endpoint should be used by the zRMS ensuring a harmonized risk assessment at zonal level.'

- *Deviation from test conditions (but not from validity criteria) in NTTP testing*
  In the Central Zone Harmonisation Workshop in Ede (NL), June 2022, the following was agreed:
  'The MS agreed that the CZMS will carefully evaluate NTTP tests for major deviations from recommended conditions (e.g., temperature, humidity, plant density). Furthermore,

[1] As the significance level decreases (and the critical value increases), it becomes less and less probable that the sample derives from a normal distribution.

if unexpectedly low toxicity is observed for herbicides, a comparison will be made with efficacy screening data to check, e.g., whether appropriate sensitive species have been tested. On a case-by-case basis it may be necessary to have new tests, or to decline from using tests with major deviations in SSDs.

- *Aquatics and NTTPs – SSD*
  A proposal was presented for the harmonized evaluation and interpretation of SSD data. The MS agreed to use the approach when evaluating SSDs (aquatic and NTTP) in future dossiers and to bring the paper forward to the EFSA to be considered in the next general issues meeting. The proposal is presented in Appendix 3.

Further elaborations of the EU evaluation methodology:
Combination toxicity
Combination toxicity must be determined when plant protection products contain several active substances. The issue of combined toxicity is further described in G 7. general introduction.

1.4 Approval

This section describes the approval criteria for active substances (section 1.4.1) and plant protection products (section 1.4.2 and 1.4.3). For the EU approval procedure of active substances a representative formulation has to be included in the dossier. Therefore section 1.4.1 to 1.4.3 apply. For the zonal applications of plant protection products only section 1.4.2 and 1.4.3 apply.

1.4.1 Approval of the active substance

Annex II of Regulation (EC) No 1107/2009 provides the procedure and criteria for the approval of an active substances, safeners and synergists.Point 3 of Annex II of Regulation (EC) No 1107/2009 gives the criteria for the approval of an active substance.

1.4.2 Evaluation of plant protection products

The evaluation, as applied for the risk assessment for non-target plants, has been elaborated in the Guidance Document on Terrestrial Ecotoxicology (Sanco/10329/2002 rev 2 final).

1.4.3 Decision making for plant protection products

Decision making, as applied in the risk assessment for non-target plants, has been elaborated in the Guidance Document on Terrestrial Ecotoxicology (Sanco/10329/2002 rev 2 final).

1.5 Developments

Revision of the Guidance Document on Terrestrial Ecotoxicology (Sanco/10329/2002 rev 2 final) is taking place at this moment (by EFSA), and the following EFSA opinion was published on the science behind the upcoming revision: Scientific Opinion addressing the state of the science on risk assessment of plant protection products for non-target terrestrial plants (EFSA Journal 2014; 12(7): 3800).

2 REFERENCES

1. Candolfi MP, Barrett KL, Campbell PJ, Forster R, Grandy N, Huet MC, Lewis G, Oomen PA, Schmuck R and Vogt H (eds) (2001): Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods. From the ESCORT 2 workshop. SETAC, Pensacola, 46 p

2. De Jong et al. (2010). Guidance for summarising and evaluating field studies with non-target arthropods. RIVM report 601712006.

3 APPENDICES

Appendix 1 Explanatory notes decision tree risk to non-target arthropods..... 18
Appendix 2 Explanatory notes decision tree risk to terrestrial non-target plants 25
Appendix 3 Proposal for the 6th Central zone harmonization workshop, June 2022. SSD and its exemplary use for aquatic organisms and non-target terrestrial plants- data selection and statistical procedure -.....28

Appendix 1 Explanatory notes decision tree risk to non-target arthropods

1) A distinction is made between integrated and non-integrated pest management systems because the evaluation for non-target arthropods for these two types of systems is essentially different. In the case of integrated pest management systems natural enemies are deliberately brought into the cropping system to control pests. In the case of non-integrated pest management systems the risk is estimated for non-target arthropods that are present by nature. The scheme for non-integrated systems is dealt with in this chapter. The scheme for integrated pest management systems is included in Appendix 1 to the NL-part of this chapter.

   NB: See section 1.3 (Chapter I Non-target arthropods) for additional agreements and approaches that apply for the risk assessment of non-target arthropods.

2) The applicant should always submit data about the risk to non-target arthropods if there is a chance of exposure of these organisms (question 283/2013 8.3.2 and 284/2013 10.3.2). In case of applications on the soil and on crops there is practically always chance of exposure. It should be noted that some species have overwintering larvae in the soil, which, if relevant, must be taken into account in the risk assessment as well.
   The chance of exposure is low in case of application of products for sealing and healing of pruning wounds.

3) The first step consists of the performance of glass plate tests with the standard test organisms *Aphidius rhopalosiphi* and *Typhlodromus pyri*, preferably dose-response tests so that an LR50 value can be established. When, however, a low toxicity is expected, limit tests can also be carried out with a dose that is equal to the maximum use dose multiplied by the Multiple Application Factor (MAF). These tests should normally be carried out with the formulation. For determination of the MAF reference is made to the ESCORT 2 report [1].

4) The standard species mentioned above are not suitable for formulations such as granules, seed dressings, baits and IGRs (Insect Growth Regulators) in view of:
   - technical reasons: laboratory glass plate tests with the two standard species cannot be carried out with granular formulations, seed dressings and baits;
   - the fact that effects cannot be detected in a standard laboratory test with the standard species as result of a different mode of action (e.g. an acute laboratory test with an Insect Growth regulator (IGR) on *A. rhopalosiphi* will probably not show any effect).

   The approach described in the Guidance Document on Terrestrial Ecotoxicology (Sanco/10329/2002 rev 2 final) is followed for these types of products:
   - For products which are applied into the soil (e.g. granules, seed dressings, baits) studies should be carried out with *Hypoaspis aculeifer* or *Folsomia candida*. When considered suitable, studies can be carried out with *Aleochara sp.* (N.B. test compound should be mixed into the soil).
   - For products which are applied on (bare) soil, tests with several soil (surface) dwelling species are acceptable (e.g. *Hypoaspis aculeifer*, *Folsomia candida, Aleochara bliineata, Poecilus cupreus, Pardosa sp.).*
   - For IGRs the tests should be concentrated on those stages of non-target arthropods that are sensitive to the plant protection product in question (e.g. juvenile stages) while taking relevant absorption routes into account. Tests

must be carried out with *Typhlodromus pyri* and one other species (e.g. *Coccinella septempunctata*, *Orius laevigatus* or *Chrysoperla carnea*).
- See section 1.3 for further explanation on a.s. with a special mode of action (active substances with a mode of action aimed at suffocation of the target organisms or targeted against lepidopteran species).

There are several examples of special applications such as drenching treatments, application via drip irrigation, etc. Such cases should be dealt with pragmatically, which means that it should be considered case by case which types of organisms are exposed and in which way the test can be conducted.

Except for the active substance and the product, data are also required for metabolites to which non-target arthropods may be exposed. Arthropods may be exposed to metabolites in/on plants and to metabolites in the soil. For metabolites in vegetation standard laboratory tests are normally not required. Metabolites that are the actually active molecule may be exceptions. General guidance is given in the general part about metabolites as described under 'birds and mammals'.
Where higher tier studies (cage/tent/tunnel or field tests) have been carried out with the pesticide under realistic exposure conditions it can be assumed that the potential risk of metabolites has been taken into account.
Soil metabolites are tested with soil organisms; tests with surface dwelling soil arthropods are therefore not required.

5) A Hazard Quotient (HQ) must be calculated for both standard species and both the 'in-field' risk as well as the 'off-field' risk are taken into account. For the method according to which the 'in-field' and 'off-field' exposure must be calculated we refer to the Guidance Document on Terrestrial Ecotoxicology, on the understanding that for national risk assessments NL-specific drift figures are used for calculating the 'off-field' exposure, for which we refer to §2.3 (NL-part).

Note on correction factor 0.5 from ESCORT 2 for the in field exposure calculation for orchards and vineyards:
- This correction factor can be used in the exposure calculation for the HQ when the effect endpoint is based on a 2D-test (i.e. glass plate or leaf disc). If the test is in a '3D-system', i.e. spraying of whole plants, the correction factor is not applicable.
- This factor can only be used for orchards and vineyards (but not other '3D crops' such as e.g. tomatoes).

VDF (vegetation distribution factor) for the off-field exposure calculation:
In core assessments and EU-dossiers, a VDF of 10 will be applied. (See section 1.3 Chapter I Non-target arthropods for details.)

The criterion for both HQ values is that these should be lower than 2 (or effects in limit tests <50%). This criterion is based on available (semi-) field data where lethal, sublethal and reproduction endpoints have been measured for a considerable number of types of substances and species. This means that this first step in the evaluation (in which the criterion HQ < 2 is applied) also covers sublethal and reproduction effects and it is not necessary to separately consider sublethal and reproduction endpoints in the first step of the evaluation.

Where also other species than *Aphidius rhopalosiphi* and *Typhlodromus pyri* have been tested in first tier laboratory tests, these cannot be tested against the HQ trigger of

2 because this trigger has only been validated for Aphidius and Typhlodromus.
The results of these tests will be assessed against the criterion of 50% effect (or HQ of 1, if LR50 and ER50 values are available).

When it concerns tests with the soil organisms *Hypoaspis aculeifer* and *Folsomia candida*, the NOEC (mg/kg soil) is the relevant endpoint. For risk assessment a safety factor of 5 is applied. In the case that artificial soil is used in the test, correction for the percentage of organic matter is necessary (if log Kow > 2).

Off-crop interception:
In cases that only exposure of soil dwelling species is relevant (for example when a reasoned case is made that soil surface spiders are the most sensitive species), interception by the off-crop vegetation may be taken into account in the off-field risk assessment.
For the time being the following interception percentages are applied - till better underpinned percentages come available - which are considered realistic worst-case:
- December – February: 20%
- March: 30%
- April: 40%
- May – September: 50%
- October: 40%

It should be noted that when these percentages are taken into account, the vegetation distribution factor cannot be used in the HQ-calculation (off-field).

6) Where the HQ values are $\geq$ 2 and suitable or desirable risk reduction measures 'in-field' and/or 'off-field' are not possible, higher tier tests must be carried out. First, the sensitive species for which the HQ value is $\geq$ 2 should be studied in such a higher tier test where extra species are tested: in case that only the HQ for the 'in-field' risk estimate is exceeded, one extra species must be tested; in case the HQ for 'in-field' as well as 'off-field' is exceeded, two extra species. The preferred species are: *Orius laevigatus*, *Chrysoperla carnea*, *Coccinella septempunctata* and *Aleochara bilineata* in view of the fact that the available data indicate that these organisms are relatively sensitive and that good test methods are available. The species *Aleochara bilineata* should in any case be used for products that are applied early in the season and where products are applied on the soil.

Higher tier tests concern extended laboratory tests (with natural substrate) and (semi) field tests. 'Aged-residue' tests also come under the higher tier tests. These tests can be used for establishing the duration of the effect in view of the possible recovery of populations by recolonisation. See also note 7) below.

If the only available data are extended laboratory tests with *A. rhopalosiphi* and *T. pyri*, tests with two additional species will be required, irrespective of the acceptability of the risk for *A. rhopalosiphi* and *T. pyri.* The reason for this is that in this case no first tier risk assessment can be performed to establish the requirements for additional species.

It should be noted that generally, in-crop field studies are considered not acceptable to address off-crop risks. When a field study is chosen as approach to address the off-crop risk to non-target arthropods, it should be demonstrated in this study that no unacceptable effects on a non-target arthropod community that is representative for fauna of off-crop habitats in The Netherlands (e.g. meadow, hay field or (agricultural) verge) will occur as a result from drift exposure. Studies conducted in e.g. Northern France and Germany are

also considered representative for The Netherlands. Preferably a multi-dose rate (NOEC) design is used. Before such a study is undertaken, the study protocol may be discussed with the Ctgb.

If an in-crop field test is performed to address an in-crop risk, and *A. rhopalosiphi* and *T. pyri* do not occur in the crop of concern, it is acceptable that these species are not present in the study, as long as a representative fauna for this crop is present.

Further guidance on the evaluation of arthropod field studies can be found in De Jong et al. (2010) (Guidance for summarising and evaluating field studies with non-target arthropods. RIVM report 601712006/2010).

For 'in-field' and 'off-field' the following risk reducing measures are among the options:

'in-field':
- reduction of the dose level;
- changes in application frequency and application interval;
- changes in timing of the application.

'off-field':
- measures that reduce the amount of drift to the area outside the crop such as:
. buffer zones;
. wind hedges:
. drift-reducing application techniques.

7) The risk is unacceptable if the effects found in the extended laboratory tests are equal to or higher than the trigger value (trigger value is 50%) and there is no potential (rapid) recovery or recolonisation. When risk-mitigating measures neither lead to an acceptable risk to non-target arthropods, the product cannot be authorised.

   The criterion for (potential) recovery or recolonisation for 'in-field' is that this must be the case before the following application season. The period for 'off-field' is shorter, for the time being without a specific definition. The Guidance Document on Terrestrial Ecotoxicology (Sanco/10329/2002 rev 2 final) mentions an ecologically relevant period. It should be noted however, that under the new data requirements, aged residue tests can no longer be used for the off-field risk assessment. This means that for the off-field risk assessment, off-field field studies demonstrating no effects or actual recovery should be provided. Ctgb is of the opinion that the 'ecologically relevant period' should be very short, because the off-crop area is important for recolonisation of species into the in-field area. Hence, a relatively undisturbed off-crop area is necessary to make recolonisation possible (recolonisation of the in-field area from the off-crop area can cause source-sink effects, which is an additional stress-factor to the off-crop area). Further, when aged residue tests are used in the risk assessment, the recovery time should be related to the latest application timing according to the intended GAP. See chapter 1, section 1.3 for more details.

   For field tests, ESCORT 2 does not provide fixed trigger values for acceptability of effects. For risk assessment in the light of current knowledge, reference is made to the EFSA scientific opinion on the state of science on risk assessment of plant protection products for non-target arthropods (EFSA Journal 2015; 13(2):3996) (having reviewed ESCORT 3 and other recommendations). This scientific opinion concludes that small plot studies might possibly be used to determine threshold level

effects but are (unlike e.g. aquatic mesocosms) an unreliable basis for determining any recovery. Due to small test plots within a larger untreated field, which are often used in the off-field studies (i.e. with a 'checkerboard design'), the conditions for recovery by immigration are more favourable than in typical field margins (linear structures, separated by large field areas). Hence, the actual level of protection for off-field NTA resulting from a risk assessment using a NOEAER based on class-2 effects can be expected to be lower than observed in the experimental off-field studies. Therefore, for off-field risk assessment no class 2 NOAERs should be used, but instead class 1 effects should be used (NOER). Furthermore, based on the taxonomic resolution provided, it is often not possible to judge whether actual recovery occurred or whether other species of the studied group took over the ecological niche. Consequently, off-field RACs should be determined based on NOERs at the population level.

An additional reason to use the NOER instead of the NOAER is the fact that in the small-plot off-field field studies ('checkerboard design') test doses may have been applied only once (i.e. in a dose response design), while the intended use of the product is often multiple times. When this is the case, accumulation of effects is not addressed which is another reason for using the NOER instead of the NOAER.

For studies with larger scale plots (≥ 1 ha*)* and in which the test substance is applied conform the intended use, the choice between the NOER or a NOAER will be a case by case decision until further guidance becomes available.

Currently there is no guidance on assessment factors to be used for field studies with arthropods. For the time being, a safety factor of 2 and a safety factor of 3 is applied on the population NOER and the population NOAER respectively, in line with the aquatic GD on tiered RA for edge-of-field surface water (EFSA Journal 2013; 11(7): 3290).

For the NOAER, only class 2 effects will be accepted, i.e. effects of limited magnitude and duration, for reasons as stated above (a relatively undisturbed off-crop area is necessary to make recolonisation possible and recolonisation of the in-field area from the off-crop area can cause source-sink effects, which is an additional stress-factor tot the off-crop area). To further specify 'effects of limited magnitude and duration', Ctgb considers this to be 'slight and transient effects' cf. Effect Class 2 in the Guidance for summarising and evaluating field studies with non-target arthropods (De Jong et al. , 2010). In De Jong et al. (2010), Class 2 effects are defined as: Quantitatively restricted response of one or a few taxa and only observed on one sampling occasion.

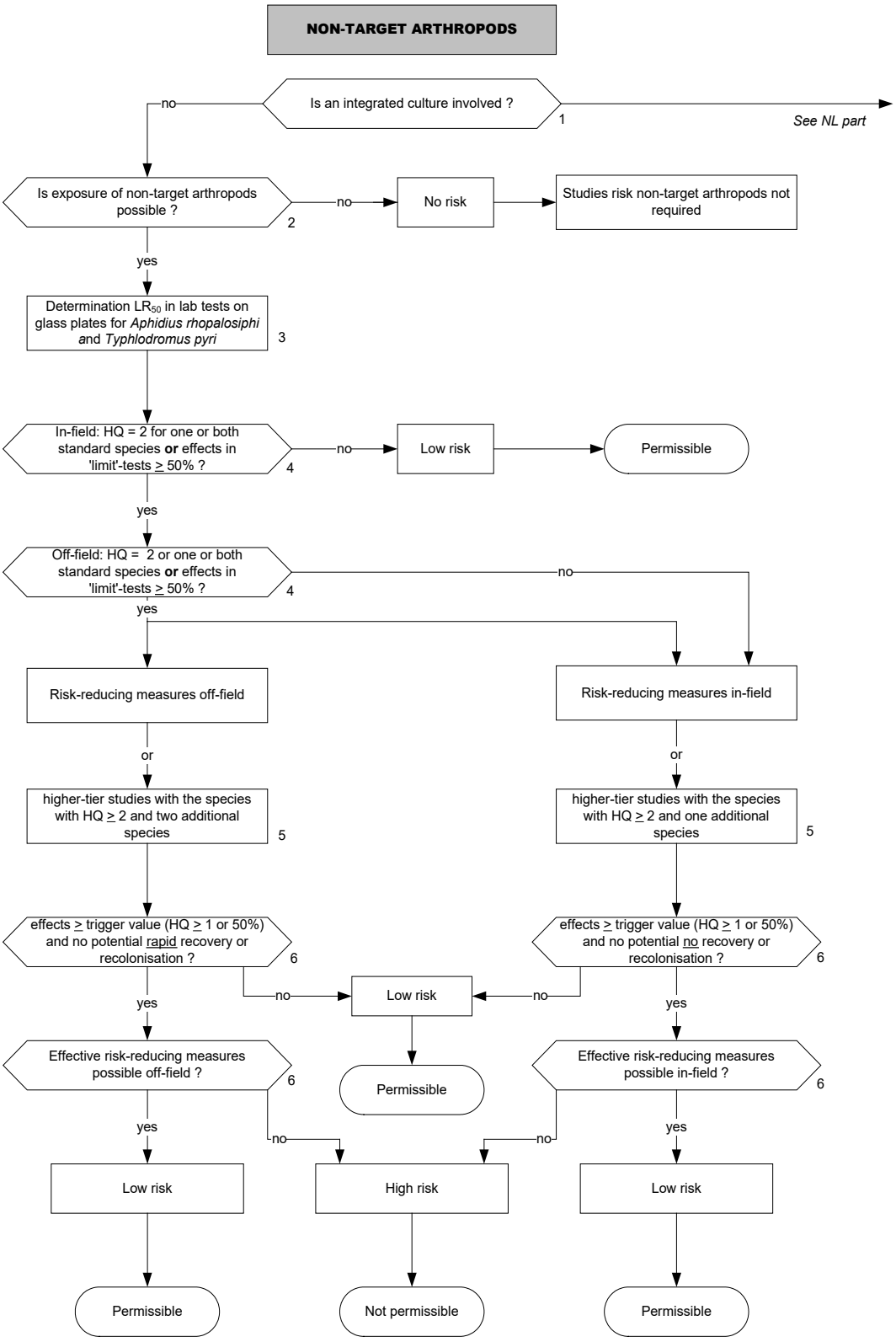
The RAC (population NOER or NOAER together with the assessment factor) will be compared with the PERoff-field, which is calculated as follows: Application rate x MAF x drift rate. Note that no VDF-value is used, because the field study is a 3D-test system.

For the in-field risk assessment, if in-field field studies are available, recovery before the start of the next application season should be demonstrated. This applies to Effect Class 6 or lower from de Jong et al. (2010) (depending on timing of first and last application conform GAP).

Usually in-field field studies are not using small plots as discussed above for the off-field field studies, and are performed conform GAP. But if an in-field study is using the checkerboard design, the same concerns apply as described above and a NOER-value

would be used as endpoint.

It is noted that in the Pesticides Peer review Meeting on Recurring Issues on Ecotoxicology held in 2019 (EFSA Supporting publication 2019:EN-1673), the experts concluded that the effect classes from De Jong et al. (2010) are not considered for the time being. It is optional to report them but if they are missing from the report it would not lead to a lowering of the reliability score. The proposal of using effect classes can be further considered in future development activities. (e.g. EFSA PPR Panel, 2015).


NON-TARGET ARTHROPODS
Is an integrated culture involved ?
1
no
See NL part
Is exposure of non-target arthropods possible ?
2
no
No risk
Studies risk non-target arthropods not required
yes
Determination LR50 in lab tests on glass plates for Aphidius rhopalosiphi and Typhlodromus pyri
3
In-field: HQ = 2 for one or both standard species or effects in 'limit'-tests ≥ 50% ?
4
no
Low risk
Permissible
yes
Off-field: HQ = 2 or one or both standard species or effects in 'limit'-tests ≥ 50% ?
4
no
yes
Risk-reducing measures off-field
Risk-reducing measures in-field
or
or
higher-tier studies with the species with HQ ≥ 2 and two additional species
5
higher-tier studies with the species with HQ ≥ 2 and one additional species
5
effects ≥ trigger value (HQ ≥ 1 or 50%) and no potential rapid recovery or recolonisation ?
6
effects ≥ trigger value (HQ ≥ 1 or 50%) and no potential no recovery or recolonisation ?
6
no
Low risk
no
yes
yes
Effective risk-reducing measures possible off-field ?
6
Permissible
Effective risk-reducing measures possible in-field ?
6
yes
no
no
yes
Low risk
High risk
Low risk
Permissible
Not permissible
Permissible

Appendix 2 Explanatory notes decision tree risk to terrestrial non-target plants

1) Definition: terrestrial non-target plants are plants positioned outside the field to be treated without being a crop.

2) Data on the risk to terrestrial non-target plants are not always required. Where exposure is negligible, no data need to be submitted, e.g., in the case of:
   - Rodenticides
   - Seed treatments
   - Granules
   - Bulb dipping
   - Drenching treatment
   - Substances used to cover and cure pruning wounds
   - Substance that are used in stored products

3) This step is based on the already available data, with a preference for screening data. Data on at least 6 species of different taxa tested with the highest nominal dose (1x) should be available. These species should cover monocotyledonous as well as dicotyledonous species. Besides these data, further information available in the biological dossier or obtained from various field experiments such as efficacy studies, residue studies, environmental-behavioural and ecotoxicological studies about efficacy, selectivity, phytotoxicity etc. can be provided.
   This first step can be skipped for herbicides and plant growth regulators because these substances will as result of their envisaged effect on plants always reach the second step.

   The criterion is that the risk can be considered as acceptable where no data indicate that one or more species experience more than 50% phytotoxic effects at the maximum dose level. If the results show that there is more than 50% effect for one species or that there are clear indications of effects on more than one species, additional research needs to be carried out.

4) Where a potential risk is identified (more than 50% effect for one or more species at the maximum dose), specific information must be submitted about the toxicity of the substance for terrestrial plants. These are laboratory experiments on a selection of plants. It is strongly recommended to conduct dose-response tests with 6 –10 plant species representing families for which significant herbicidal effect is claimed.
   These tests should resemble realistic exposure conditions as much as possible. For applications on leaves, e.g., the tests must be carried out by spraying the pesticide on the plant. Application on soil should be carried out where this is more suitable in view of the mode of action.

   Tests must be carried out with the formulations.
   Suitable test protocols are available: OECD guideline 208 (Seedling emergence and seedling growth test) and OECD guideline 227 (Vegetative vigour test).

5) This step consists of a quantitative risk assessment according to the exposure/effect approach. Exposure as well as effect are expressed in application dose (g/ha).
ER50 values (ER50 = the dose at which 50% effect is observed) are available from the plant tests as mentioned under step 2 of the data requirements. There are two possible approaches for the risk assessment: the deterministic approach and the probabilistic approach. The most suitable approach depends on the dataset.

Deterministic approach
In the deterministic approach the toxicity of the most sensitive species is taken as starting point for the effect. Where the ratio toxicity/exposure is higher than 5, the risk is considered acceptable. This trigger value of 5 is valid where data on at least 6 plant species are available. In case data on significantly more than 6 plant species are available, this trigger value may –where appropriate – be adjusted slightly upward (expert judgement).

Probabilistic approach
Probabilistic methods in which the 'species sensitivity distribution' (SSD) is used may in principle be applied because data on 6 – 10 species are available. This approach requires a log-normal or a differently defined type of distribution of the data. If a SSD is run, the data normality must be accepted at no less than 0.05 significance level to be acceptable for use in RA (look under "goodness-of-fit"). Modelling which does not pass at least this level (i.e. only passes at 0.025 or 0.01) indicates a poor fit for the data and a less reliable outcome[2]. This also in line with the current agreement in the draft NTP guidance. In case the ER50 for at least 95% of the species (HR5) is above the highest estimated exposure level, the risk to terrestrial non-target plants is considered acceptable. If not, the risk is high.

In cases that only exposure by the soil is relevant (e.g. when an active substance has only adverse effects on pre-emergence stadia of non-target plants), some interception by the off-crop vegetation may be taken into account. For the time being the following interception percentages are applied - till better underpinned percentages come available - which are considered realistic worst-case:
- December – February: 20%
- March: 30%
- April: 40%
- May – September: 50%
- October: 40%

If a plant protection product contains several active substances, the combination toxicity must be determined as well as for combinations of plant protection products of which the combination (tank mix) is recommended in the directions for use.

For the acute risk assessment, the combination toxicity on the basis of the tests with the product are compared with the combination toxicity on the basis of toxicity research with the separate active substances. The risk of combination products is determined on the basis of the lowest TER as calculated based on the toxicity of the separate active substances or the toxicity of the product.

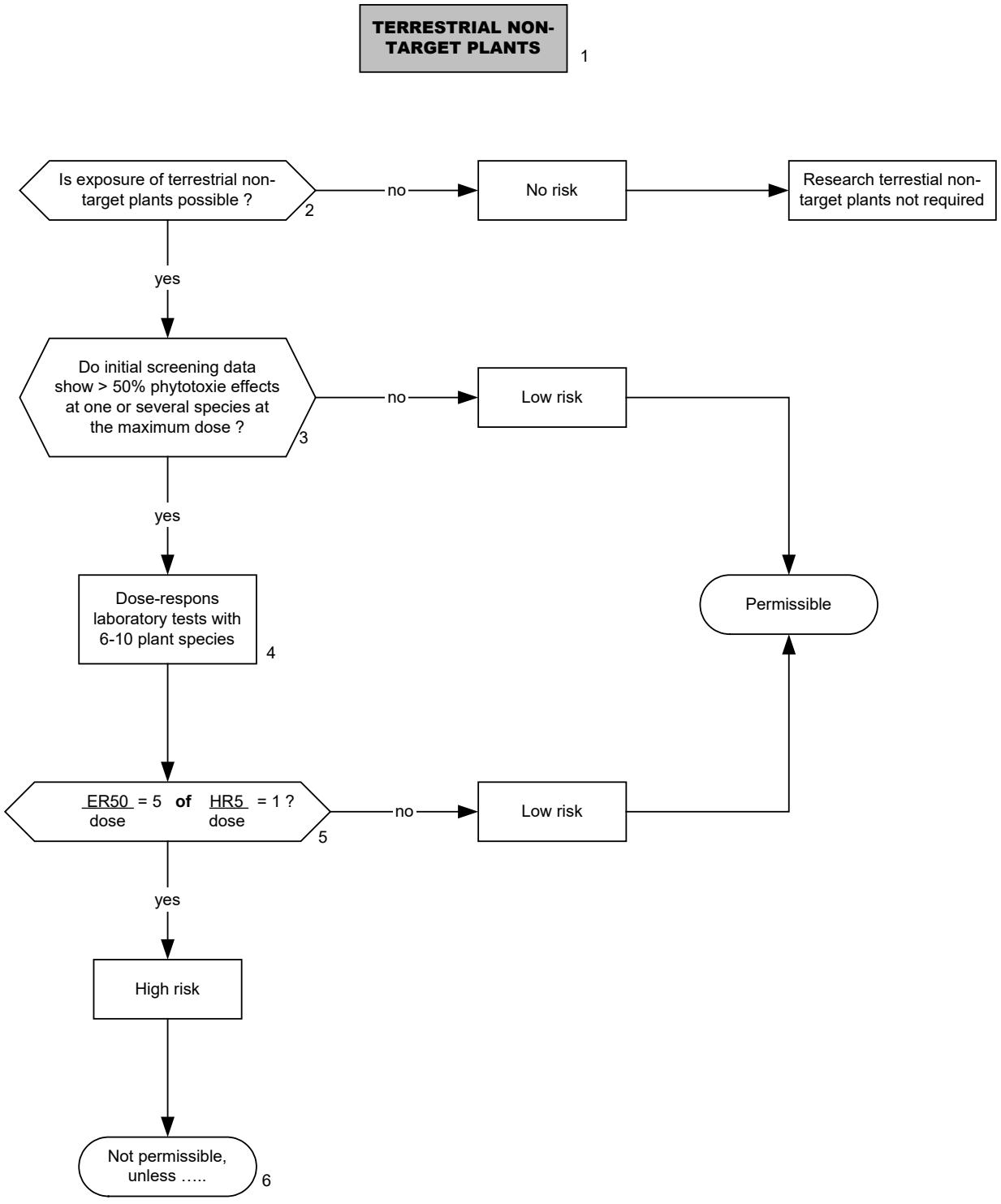
[2] As the significance level decreases (and the critical value increases), it becomes less and less probable that the sample derives from a normal distribution.

The combination toxicity is determined on the basis of concentration addition. For the calculation method see G 7. general introduction.

6) Where on the basis of the previous step a high risk is concluded to exist, the use is not permissible unless it can be demonstrated by means of adequate risk evaluation that there are no unacceptable direct or indirect effects for terrestrial non-target plants.

An adequate risk evaluation may consist of the performance of a (semi) field study to investigate the effects on non-target plants under realistic application conditions. Because such studies take a long time and are expensive, it is recommended to investigate whether options exist for refinement of the exposure and/or effects. In addition, (semi) field studies are not required if the risk identified in step 2 can sufficiently be reduced by means of risk-mitigating measures.
Field and semi-field studies with non-target plants have not been standardised.
It is therefore recommended to contact the Ctgb beforehand to discuss the protocol.
Generally, it can be stated that in such tests effects on plant abundance and biomass production at different distances from the crop or at exposure levels representing exposure at different distances from the crop, need to be analysed.

Because the exposure of terrestrial non-target plants is mainly caused by drift of pesticides, possible measures to reduce the risk to these plants are based on reduction of the amount of drift. In principle, all already existing drift-mitigating measures can be applied. The drift reduction of drift reducing measures, which are easy to realise in practice are mentioned in paragraph 2.3 of the NL part, together with the standard drift percentages without drift reducing measures.


TERRESTRIAL NON-TARGET PLANTS
1
Is exposure of terrestrial non-target plants possible ?
2
no
No risk
Research terrestial non-target plants not required
yes
Do initial screening data show > 50% phytotoxie effects at one or several species at the maximum dose ?
3
no
Low risk
yes
Dose-respons laboratory tests with 6-10 plant species
4
Permissible
ER50 / dose = 5 of HR5 / dose = 1 ?
5
no
Low risk
yes
High risk
Not permissible, unless …..
6

Appendix 3: Proposal for the 6th Central zone harmonization workshop, June 2022. SSD and its exemplary use for aquatic organisms and non-target terrestrial plants- data selection and statistical procedure -

List of abbreviations

AGD	Aquatic Guidance Document
a.s.	Active substance
CI	Confidence Interval
cZone	Central Zone
d.w.	Dry weight
EC	Effect Concentration
ED	Effective Dose
EP	Endpoint
ER	Effect Rate
HC_5	5th percentile of the Hazard Concentration
HR_5	5th percentile of the Hazard Rate
ini	Initial concentration
LC	Lethal Concentration
$LLHC_5$	Lower limit of the confidence interval of the hazardous concentration for 5 % of the species of an SSD
m.m.	mean measured concentration
MoA	Mode of Action
Nom	Nominal concentration
NOEC	No Observed Effect Concentration
NTTP	Non-Target Terrestrial Plants
OECD	Organisation for Economic Co-operation and Development
RA	Risk Assessment
RAR	Regulatory Acceptable Rate
SANCO	Health and Consumer Protection of the European Commission
SE	Seedling Emergence
SSD	Species Sensitivity Distribution
VV	Vegetative Vigour
zRMS	Zonal Rapporteur Member State

Background

This document aims to give detailed guidance for calculating an SSD in ecological risk assessment. Beside some general aspects on the SSD approach, this document deals with the application of the SSD for aquatic organisms and for NTTP. Therefore, it also points out some specific aspects to consider for each of these groups

Recommendations presented in the current document follow those reported in chapter 8. of the Aquatic Guidance Document (AGD) (EFSA Journal 2013;11(7):3290). When judged necessary, further explanations were added based on concrete experiences gained from the

regulatory practice.
The focus is on the selection of data and the statistical procedure.

The application of the SSD approach for NTTP is described in the Guidance Document on Terrestrial Ecotoxicology (TGD, SANCO/10329/2002 rev 2 final). But this document needs to be urgently revised including the section related to SSD that do not provide much recommendations. Therefore, in this document the recommendations provided for aquatic organisms (EFSA 2013) are analysed in order to assess if they could be applied to NTTP.

To facilitate the reading, specific approaches concerning aquatic organisms and NTTP are presented in separate columns.

Crucial aspects for each section
Data selection:

- For aquatic organisms, follow recommendations of EFSA (2013). Special emphasis regarding insecticides, herbicides and fungicides are given in chapters 8.4.3.1, 8.4.3.2 and 8.4.3.3 of the AGD, respectively.
- For NTTP follow recommendations of SANCO/10329/2002 rev 2 final given in chapter 7.1.
- Be aware of the representativeness of the taxa tested regarding the specific MoA of the a.s.
- Select the same estimates (e.g. EC_{10}; ER_{50}) and preferentially identical variables to calculate an SSD. Note that similar variables as dry weight and fresh weight might be mixed to assess the variable biomass for primary producers (aquatic and NTTP) or for invertebrates.
- EPs should also be expressed with same concentration or rate units.
- Verify that the EPs used are reliable (e.g., calculate the normalised CI around the EP)
- Different test designs – i.e. Tier 1 and tier 2C data (aquatic organisms) and VV and SE data or laboratory and field or semi-field studies (NTTP) cannot be mixed.

Statistical procedure:
- Check detailed procedure regarding censored EP and make sure that the minimum data requirement to conduct an SSD for this organism group is fulfilled.
- Check if the data is unimodal and fits adequately the assumed distribution (e.g. log-normal or log-logistic)
- Check the reliability of the results, with a particular emphasis on the fit and thus choice of the model (log-normal, log-logit, Weibull…)

Special case of primary Producer in aquatic
- If the minimum data requirement is not met because of too many censored E_rC_{50}, instead of going back to lower Tier, we propose the possibility to calculate the SSD with E_yC_{50} values.

Application examples:
- Example on how to report the results as zRMS (approaches 1 and 2)

Selection of Toxicity Data

Effect Side
Selecting toxicity data on the basis of toxic mode of action of the substance

Be aware of the representativeness of the taxa tested regarding the specific MoA of the substance.

Aquatic organisms	NTTP
No deviation to AGD. Follow chapters 8.4.2 and 8.4.3 (p. 92): "*If, for example, the First tier toxicity value for Chironomus is an order of magnitude lower than that of Daphnia and/or Americamysis bahia, it is recommended to construct, in the first instance, a SSD with toxicity data for insects, or to explore which insects and crustaceans (e.g. macro-crustaceans) can be combined in a single SSD on the basis of all relevant information available*." (AGD 2013) As another example for primary producers, in case of auxin herbicides, dicotyledonous species are usually more sensitive. Thus, check that this group is sufficiently represented in the data set and consider constructing an SSD with only dicotyledonous species. In addition, check if rooted macrophytes are sufficiently represented as well.	No deviation to SANCO/10329/2002 rev 2 final (chapter 7.1, Tier2): "*In order to generate data that are useful for probabilistic approaches there should not be a focus exclusively on species assumed to be the most sensitive. If, from the screening data, a specific mode of action is evident, or strong differences in the species sensitivities are identified, this evidence should be used in the selection of the appropriate test species*." E.g., if the First-tier toxicity values are lower for dicotyledonous (which might be the case for auxin herbicides), it might be recommended to construct, in the first instance, an SSD with toxicity data for this group if possible.

Further information regarding the sensitivity of the non-target organisms against the a.s. under evaluation can be found in the respective EU-LoEP(s)/D(R)AR(s) and in addition for NTTP in the efficacy data (c.f., CA B3 or D(R)AR Vol.3 CA/CP -B.3 for zonal and EU applications, respectively). Note that screening data submitted for the evaluation of herbicidal activity of metabolites might also be informative.

Estimates and variables

Terminology:

Endpoint: is the combination of an estimate and a measured variable.
Estimates: is referring to the magnitude of effect described (e.g., ECx, NOEC …)
Variables: is the response variable measured

Aquatic organisms	NTTP
Estimates	
E_rC_{50}: EC_{50} calculated with growth rate EyC_{50}: EC_{50} calculated with yield EbC_{50}: EC_{50} calculated with area under the curve EC_{10}: e.g. reproduction, body weight EC_{50}/LC_{50}	ER_{50}

Variables	
Algae: cell counts (surrogate for biomass and thus most frequently called “biomass”) Macrophytes: frond number, frond area, biomass wet weight, biomass dry weight etc...	Seedling emergence: emergence, mortality, biomass (fresh weight/ dry weight), plant height, visual injury Vegetative vigour: biomass (fresh weight/ dry weight), plant height, mortality, visual injury
Selection of estimates and variables in SSD calculation	
Select identical estimates and preferentially identical measured variables However, for aquatic and terrestrial primary producers, wet weight and dry weight might be pooled to assess the variable biomass (see section 7.1).	
Specific recommendations available for aquatic organisms: **Acute risk assessment:** The AGD sees the possibility to construct an SSD based on NOEC/EC_{10} values. However, no further recommendations are provided regarding the decision making for regulation (*i.e.*, which approach should be then preferred?). In general, LC/EC_{50} values are most robust and reliable and should be used for constructing an SSD. An SSD based on NOEC/EC_{10} values might be suitable in cases when LC/EC_{50} are less reliable (e.g. in case of very steep dose-response curves).	No further specific recommendations available. The SSD is simulated with ER_{50} values as recommended in SANCO (2002)
Chronic risk assessment: Classically, NOEC or EC_{10} values are available for multiple biological variables (e.g., reproduction, body weight, body length...). Select same estimates (e.g. only EC_{10} values) and preferentially identical biological variables as underlying data for an SSD. EC_{10} is the preferred estimate.	

Exposure Side
Test design

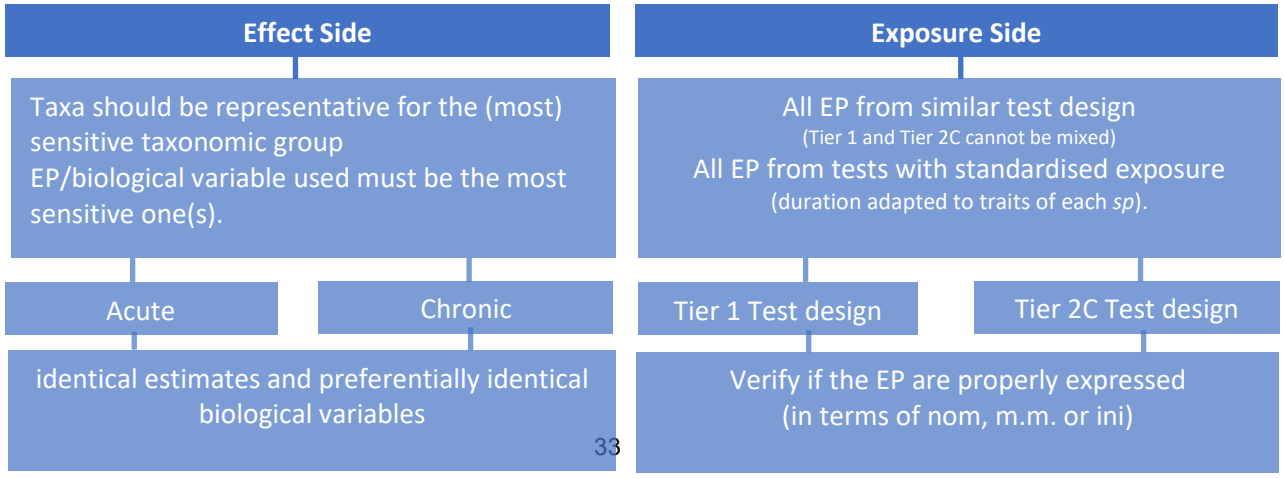
Aquatic organisms	NTTP
Different test designs cannot be mixed	
Note that Tier 1 and Tier 2C data cannot be mixed within an SSD. **SSD based on Tier 1 data:** All endpoints used for the SSD are derived	ER_{50} cannot be mixed within an SSD if they are from - (i) SE and VV tests or - (ii) from tests having different application methods (sprayed *versus* mixed to the

from standard (i.e. OECD) tests; however please note that the duration of the test might differ according to the traits of the tested species (e.g. 48 h for *D. magna* but 96 h for *A. bahia*), as mentioned in the AGD under 8.4.2. Note that for certain insect growth regulators, the standard duration (48–96 hours) of the acute toxicity test may not be sufficient, since latency of effects may occur (refer to AGD 2013, p. 94). **SSD based on Tier 2C data**: In theory, it is possible to calculate an SSD with EPs derived from refined exposure tests (e.g. pulses and/or water-sediments lab tests, i.e. Tier 2 C). In practice, this is problematic since there are a number of critical issues for refined exposure test. In such case, it has to be carefully verified that each single refined exposure test is acceptable for risk assessment.	soil) or - (iii) from tests having different duration or - (iv) from tests with different settings (e.g. from laboratory and semi- or field conditions)

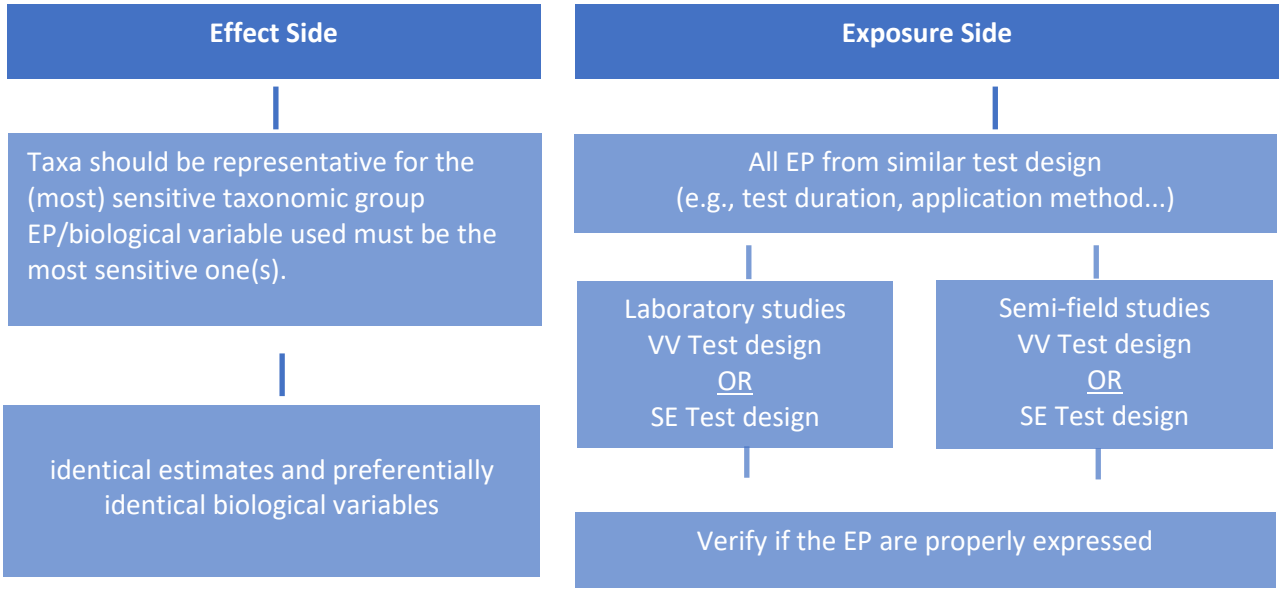
Expression of endpoints

Aquatic organisms	NTTP
For both Tier 1 and Tier 2C tests, carefully verify that the EP is properly expressed in terms of e.g., nom, m.m., or ini. concentrations. . Please refer to section 3.1 in EFSA Supporting publication 2015:EN-924 as well as to Appendix J in EFSA Supporting publication 2019:EN-1673.	All EP should be expressed in the same unit (e.g. in g product / ha).

Summary schemes for data selection
Scheme for data selection for aquatic



Scheme for data selection for NTTP



Statistical procedure

Pooling different types of endpoints

For terminology, please refer to section 5.3.2.

Estimates: Cannot be mixed within an SSD.

Variables: Should in general not be mixed. In case the more sensitive biological variable differs between species (e.g. reproduction for *D. magna versus* body weight for *A. bahia* or plant height *versus* plant biomass for NTTP), different SSD have to be calculated for each variable.
There is an exception for identical variables, such as wet weight and dry weight for aquatic and terrestrial plants (see section 9.1). If available variables differ only slightly, they might be mixed to construct an SSD (e.g. fresh weight and dry weight for primary producers or invertebrates.

For the special case of aquatic primary producers, please refer to section 7.

Censored endpoints

Some endpoints might be expressed as censored values, i.e. less than (<) or greater than (>) values.
Censored EPs are also referred as “unbound values” in AGD.

In principle, censored EP can be dealt as recommended in EFSA (2013),” *i*.e. to include censored EP as “= value” in the SSD data set, only when those EP are out of the range of sensitivity of the species tested. Censored EP within the range of sensitivity of the species tested should be excluded from calculation”. Additionally, EFSA 2013 recommends to conduct an SSD with this potentially restricted data set, only if the minimum number of EP needed for

calculation is still required (*i.e.*, n ≥ 8 and n ≥ 5 for fish). See also section 6.3.1 and 2. below for more details. In case this minimum requirement is not fulfilled, the SSD refinement option should be rejected.

We suggest to enlarge these recommendations to NTTP. This means that in case censored ER_{50} are part of the data set, they should be treated as recommended in EFSA (2013), i.e. > or < ER_{50} should be further considered only when they are out of the range of sensitivity of the species tested. The minimum number of EP available for SSD calculation should be n ≥ 6 as reported in SANCO/10329/2002 rev 2 final.

Calculation

Following calculation methods for SSD simulations are possible:

- ETX program: It is the usual approach considering lognormal models and non-censored endpoints.
- R-package fitdistrplus: it is developed by Sandrine Charles from the University of Lyon and implemented in the platform MOSAIC (https://mosaic.univ-lyon1.fr/ssd)[3]. This program has many advantages since:
    - (i) it considers censored values,
    - (ii) it takes confidence interval into account, which is particularly relevant when uncertainties around the EP exist (i.e., large CIs, which often occur in case of NTTP); with this approach, relevant available information regarding the robustness and reliability of the single estimates is included in the SSD, and
    - (iii) it is possible to apply different models (log-normal, log-logistic, Weibull…), whereas in ETX only the log-normal model is used.

UBA developed an Excel Tool connected with R to implement the R-package fitdistrplus. It has been published by UBA on the EFSA Knowledge Junction platform Zenodo on 26 October 2022: https://zenodo.org/record/7249239

Pre-requisite for SSD calculation	
Aquatic organisms	**NTTP**
Sufficient representative toxicity data according to the AGD must be available (see AGD p. 92-93; i.e. n ≥ 5 (only for fish) or n ≥ 8) after that censored EP in the range of species sensitivity have been excluded from data set.	Sufficient representative toxicity data according to SANCO/10329/2002 rev 2 final must be available, the minimum requirement is n ≥ 6 for NTTP. Thus, we suggest a minimum of 6 available ER_{50} after that censored EP in the range of species sensitivity have been excluded from data set.

For calculation, we propose:

- Approach 1: to follow EFSA (2013) that recommends to simulate an SSD only with censored EP that are out of the range of species sensitivity of non-censored EPs (see below)
- Approach 2: additionally, to simulate an SSD with the whole data set (*i.e.*, using all censored and non-censored EP) by using the R-package fitdistrplus (see below). Indeed, in case censored endpoints and/or confidence intervals are available in the SSD data set, approach 2 (R-package fitdistrplus) might be more appropriate more

[3] Kon Kam King G. Veber P., Charles S., Delignette-Muller M. L. (2014) MOSAIC_SSD: A new web tool for species sensitivity distribution to include censored data by maximum likelihood. Environmental Toxicology and Chemistry 33(9) 2133-2139

reliable, as the results of the simulations consider more information than only the EP. See also Green, 2016 and 2018[4,5].However, results of the R-package fitdistrplus simulations might be more complex to evaluate.

Decision on which approach (i.e., 1 or 2) as well as which simulation models is the most appropriate (*i.e.*, log-normal, log-logistic, Weibull…) should be done on a case-by-case basis considering the recommendations provided in section 5.4. In case of the inclusion of "bigger than" censored values (e.g., LC_{50} > 10 mg a.s./L), the approach with *fitdistrplus* provides in our view more reliable results as it considers intervals as such (e.g., LC_{50} > 10 mg/L a.s. belongs to the interval 10; +∞; see below)

Approach 1: Data selection according to EFSA (AGD 2013)

Data are selected excluding censored EPs in the range of species sensitivity and the SSD is performed according to AGD (p. 92-93). Censored EPs out of the range of species sensitivity are considered as non-censored EPs in the SSD (e.g. > 42 mg/L is considered as 42 mg/L).

Although no specific program for SSD calculation is recommended in the AGD and in SANCO (2002), the program ETX is commonly used by MS.

However, we also recommend to use the R-package fitdistrplus as it can consider more than only the lognormal model. Moreover, this approach also takes confidence intervals of single estimates into account, which might be particularly relevant for NTTP (see 5.3 above).

Take decision on which model is the most appropriate according to section 5.4.1.

[4] Green (2016) Species Sensitivity Distribution with censored values. SETAC (Nantes) 2016.

[5] Green, Springer & Holbech (2018) Statistical Analysis of Ecotoxicity Studies ISBN: 978-1-119-48881-1| July 2018| 416 Pages|

Approach 2: Including all censored EP

First, data are selected excluding censored EPs in the range of species sensitivity as in approach 1 (see 5.2). Then, Approach 2 is applied only if sufficient toxicity data according to EFSA (2013) and SANCO (2002) are still available.

In approach 2, data used for the SSD include all censored EP (i.e., within and outside the range of species sensitivity of non-censored EPs) and censored EP are considered as such in the SSD (e.g., LC_{50} > 10 mg a.s. is used as interval : 10; +∞). The SSD is modelled with the R-package fitdistrplus (e.g., available in the platform MOSAIC).

The particularity of the R-package fitdistrplus is that the program can treat "interval values". This means that the package can treat Confidence Intervals (CI) as well as Censored Endpoints.
Indeed, censored values belong to an interval. E.g., LC_{50} > 10 mg a.s./L belongs to the interval [10; +∞[; LC_{50} < 10 mg/L belong to the interval]-∞; 10].

(i) Uncertainty: Perform the SSD analysis with the Confidence Intervals (CI) of EP.
(ii) Censored values: Enter all censored endpoints as an interval as described just above.

When reporting the results with R-package fitdistrplus add the following:
"*SSD calculation is conducted with the R-package fitdistrplus, which allows including censored data and consideration of confidence intervals (for details see https://doi.org/10.1002/etc.2644*)

Note that a detailed example of Approach 2 is given in section 8.

Reliability check
Model selection and model fit

If a calculation method is chosen that enables the application of different models (such as the R-package fitdistrplus), it is advised to fit several models (log-normal, log-logistic, Weibull…) and to compare different criteria to select the model (e.g. Akaike Information Criterion (AIC)). The best fitting model should be selected. Also test statistics from the goodness of fit estimations can be considered for model comparison.

The quality of the model, especially the fit of the underlying distribution, should be checked (i) by visual inspection of the output graph and (ii) if possible the qq-plot (*e.g.* does the model reflect the assumed distribution of the EPs?). If available goodness of fit estimations such as the Cramér–von Mises test can be considered to check if the underlying distribution is significantly deviating from the data set. Note that the check of the model fit and selection might result in the rejection of the SSD simulation.

Furthermore, we highly recommended to check the width of the confidence interval around the median HC_5. Indeed, the model underlying an SSD is always linked with uncertainties expressed in an interval – the confidence interval. Thus, the confidence interval provides the uncertainty of the model and is dependent on the model structure, data structure, and fitting method. Given the uncertainty of the model, the median HC5 (or just HC5) is estimated to be

correct with a probability of 50%, whereas the lower and upper limit HC5 simulate the HC5 with a probability of 95%. It is important to notice that the confidence interval does not provide the confidence existing around the median HC5 but rather provide confidence in the model fit, given that the underlying assumptions of the model are met.
E.g., we advise to compare the position of the $LLHC_5$ to the median HC_5. In case the $LLHC_5$ is less than 1/3 of the median HC_5, reliability and/or protectiveness of the simulated median HC_5 might be questioned (i.*e*., consider rejecting the SSD or eventually select a higher AF or regulate on another Effective Dose proposed below in 6.4.2 below). This is also addressed in the AGD 2013, since it is suggested under section 2.1.4.2 to consider that for "*The lower limit value of the HC5*. If the lower limit HC5 derived from the curve is less than 1/3 of the median HC5, a higher AF in the proposed range may be warranted."

Note also that:

(i) Violation of goodness of fit might be acceptable if the distribution of the data in the lower tail of the SSD is considered as relatively conservative (see AGD 8.4.1).
(ii) In some cases, a split of dataset and conduction of specific SSD might be required (see section 5.3.1 of this position paper or 8.4.1 and 8.4.3 of the AGD).

Choice of the AF (aquatic organisms) or relevant Effective Dose (NTTP)

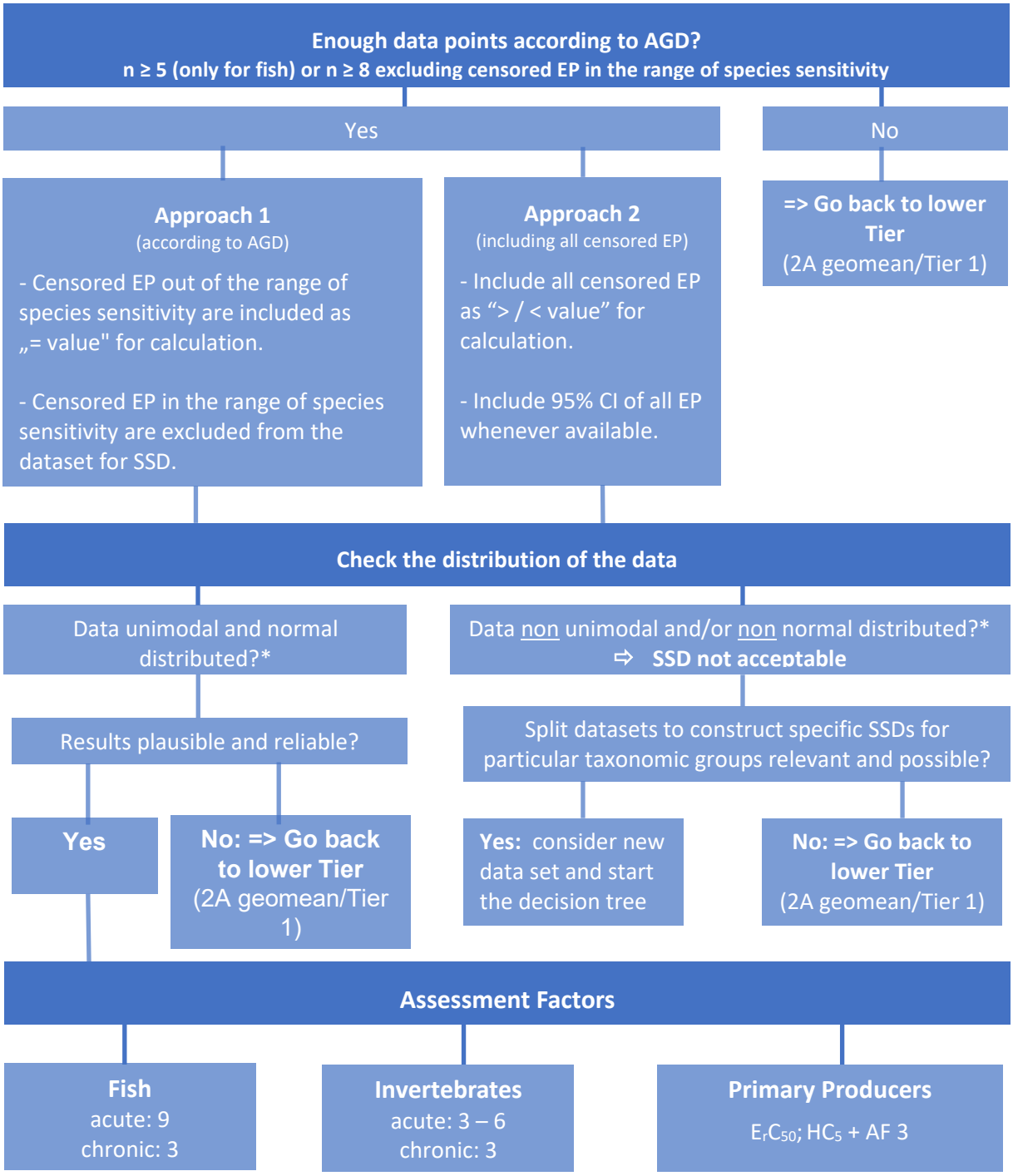
For aquatic organisms, we follow the recommendations provided in EFSA (2013).

For NTTP, SANCO (2002) reports that: "if *the ED50 (Effective dose 50 %) for less than 5 % of the species is below the highest predicted exposure level, the risk for terrestrial plants is assumed to be acceptable*", which corresponds to an AF =1. However, SANCO 2002 does not precise whether the Effective Dose should rely on the median or LLHR5. Thus, we suggest to carefully check which ED (median or $LLHR_5$) is the most appropriate according to some recommendations provided in the check list reported in the table below. Note that these recommendations are adapted from those provided in EFSA (2013).

Aquatic organisms	NTTP
Follow recommendations as provided in EFSA (2013) section 2.1.4.2 (p. 20)	We propose to adapt the recommendations provided in EFSA (2013) in section 2.1.4.2, as follow: - If the $LLHR_5$ is less than 1/3 of the median HR_5, then the protectiveness of the median HR_5 should be questioned; the $LLHR_5$ might me better appropriate. - If the median HR_5 is lower than the RAR derived at the lower Tier (i.e., lowest ER_{50}/5), then the relevance of the SSD approach should be questioned. Indeed, in principle following the tiered approach, a RAR higher Tier should be higher than a RAR lower Tier. - Consider the position of the toxicity data in the lower part of the tail of the SSD (around the HR_5). Indeed overall, if they are positioned on the right side of the SSD curve, the derived HR_5 estimate may be considered relatively “conservative” for the most sensitive species. This may indicate that the median HR5 is appropriate. In contrast, if in the lower tail the toxicity data are, overall, positioned on the left side of the SSD curve, this may be a reason to question the protectiveness of the median HR_5. $LLHR_5$ might me better appropriate. - *The steepness of the SSD curve*. In the case of a relatively steep SSD curve (e.g. less than a factor of 100 between lowest and highest ER_{50} value used to construct the SSD curve), the $LLHR_5$ might me better appropriate since exposure concentrations that exceed the RAR may have ecotoxicological consequences for a larger number of taxa. - *Read-across information for compounds with a similar toxic mode of action*. For a PPP with a well-known mode of action, sufficient information on related compounds may be available that allows the evaluation of the predictive value of the median HR_5 and/or lower limit of the HR_5 (e.g. known strong sensitivity of some species but not tested with the PPP under evaluation). This information may be used to decide on the protectiveness of median HR_5 vs $LLHR_5$ or of the whole SSD approach.

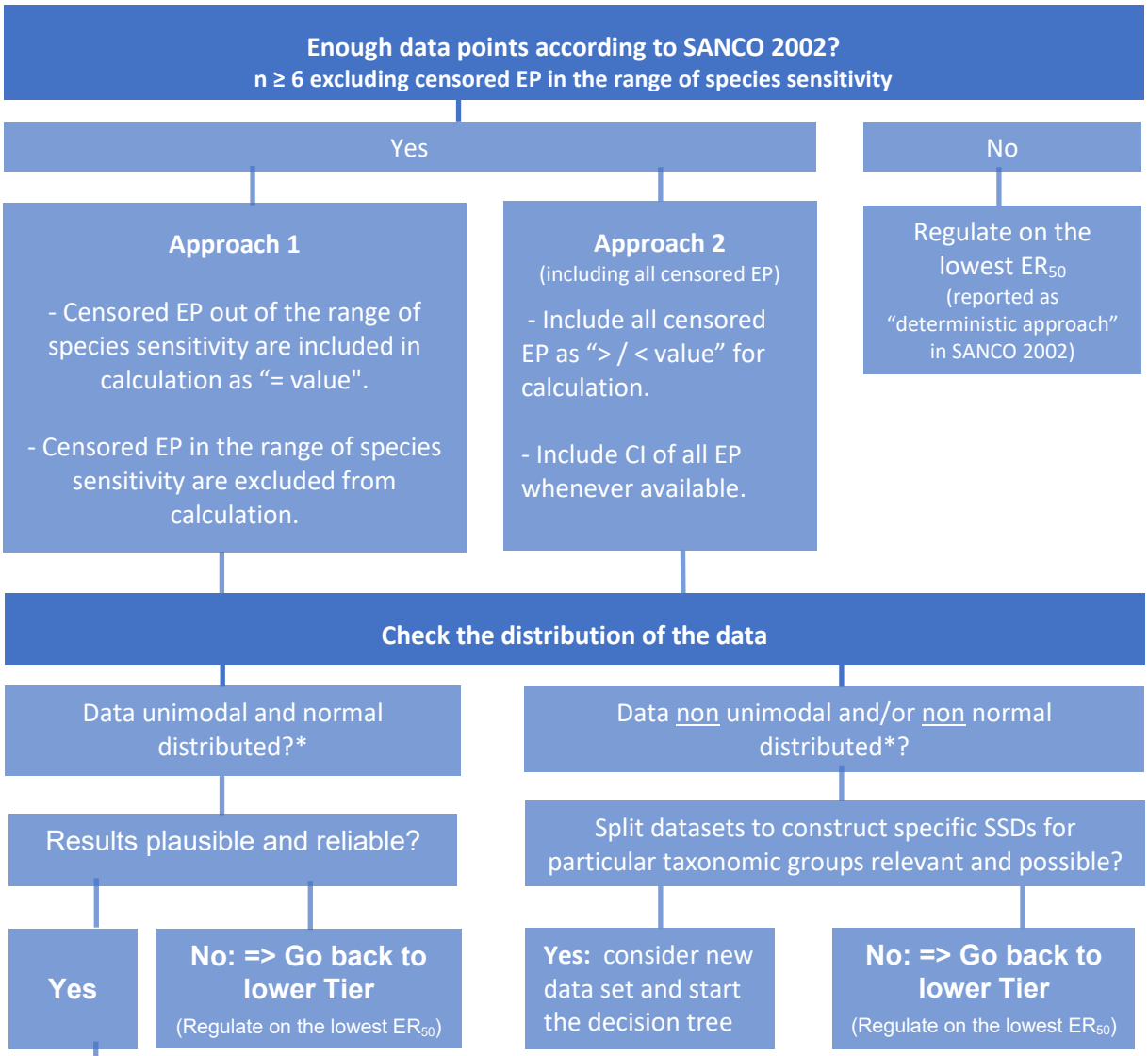
Summary schemes of the SSD procedure

Aquatic organisms: scheme for statistical procedure



* Please note that this is a simplification. SSDs should follow the modelled underlying distribution (usually log-logistic or log-normal, which are similar to the normal distribution).

NTTP: scheme for statistical procedure



* Please note that this is a simplification. SSDs should follow the modelled underlying

Effective Dose used for regulation

In principle, SANCO (2002) reports that "*if the ED_{50} (Effective dose 50 %) for less than 5 % of the species is below the highest predicted exposure level, the risk for terrestrial plants is assumed to be acceptable*", which corresponds to an AF =1.

However, SANCO 2002 does not precise whether the ED should rely on the median or $LLHR_5$. Thus, we suggest to carefully check which ED (median or $LLHR_5$) is the most appropriate according (c.f. section 5.4.2).

Special case of primary producers in aquatic

Pooling endpoints for algae and macrophytes

Variables for aquatic plants do often differ and the AGD is not specific regarding the pooling of such variables. In case several variables are measured, preferably calculate the SSD for each variable independently and regulate on the lowest HC_5. In case only different variables are measured, a pragmatic approach is used to separate the variables for primary producers in two categories:

i) "weight related" (dry weight, wet weight, biomass)
ii) "growth related" (frond number, shoot length, shoot number…)

SSDs can only be conducted for variables from one category (*i.e.*, i or ii).

The AGD recommends to pool algae and macrophytes in a single SSD for primary producers only under the following conditions:

i) In Tier 1 tests, data (EP) on macrophytes and algae differ less than a factor of 10.
ii) No difference in mode of action leading to a sensitivity difference is described or observed (i.e. algae and macrophytes should be randomly distributed along the SSD curve).

Censored endpoints

The occurrence of censored endpoints is usually more common for the E_rC_{50} estimate than for the E_yC_{50} (or E_bC_{50}) estimates. EFSA (2013) is preferably using the E_rC_{50} estimates but at the same time, EFSA is excluding censored EP from the SSD analysis when they are in the range of sensitivity of uncensored endpoints. Therefore, this might lead in some cases to a restricted data set (n <8) and no possibility to apply the SSD

In case the dataset is too small for an E_rC_{50}-SSD analysis (if for E_rC_{50} EP, n < 8 once censored EP in the range of sensitivity have been excluded), alternatively an E_yC_{50}-SSD might be calculated (if for E_yC50 EP, n ≥ 8, as E_yC50 EP are usually not (or less) frequently censored).

Application examples

Higher tier refinement – SSD aquatic invertebrates

The applicant proposed to refine the short-term risk to aquatic invertebrates by conducting an SSD (Tier 2b). Acute data on aquatic invertebrates (either 48 or 96 hours) are shown in the Table below.

Table: Short-term toxicity data to aquatic invertebrates.

Species	**EC_{50} in mg/L**	**95% confidence intervals**
Daphnia magna	0.48	0.34 – 0.69
Asellus aquaticus	3.43	2.75 – 4.26
Gammarus pulex	0.23	0.20–0.25
Neocaridina denticulata	>5	Not available
Procambarus sp.	1.2	0.75–1.93
Chironomus riparius	0.44	0.32–0.59

Anax imperator	1.63	Not available
Cloeon dipterum	0.31	0.26–0.38
Notonecta maculata	2.78	Not available
Paraponyx stratiotata	>4	Not available
Plea minutissima	1.29	0.92–1.80
Ranatra linearis	3.33	2.95–3.76
Sialis lutaria	0.96	Not available

Two approaches are used to model the HC_5:

- The inclusion of censored values outside the range of species sensitivity as non-censored values, using software ETX fitting a log-normal distribution to the toxicity data (i.e., equivalent to Approach 1 in 5.3.1) and
- The inclusion of all censored data and the consideration of confidence intervals, using the R-package *fitdistrplus* (for details see Kon Kam King et al. 2014 Environmental Toxicity and Chemistry)

The available confidence intervals and censored endpoints shown in the Table are taken into account when fitting the SSD model with the R-package *fitdistrplus* (version 1.0.14).

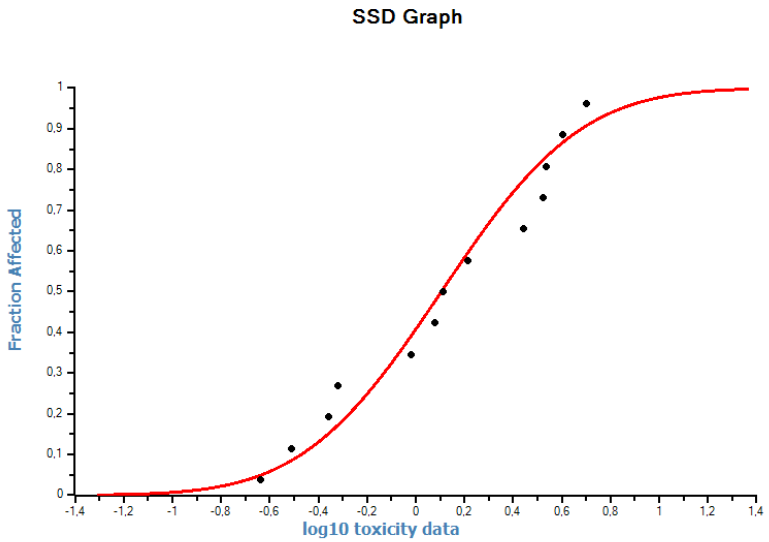
Results ETX:

Test for normality:

Test	**Significance level α = 0.05**
Anderson-Darling	accepted

HC5: 0.223 mg/L (CI: 0.08035 – 0.416)

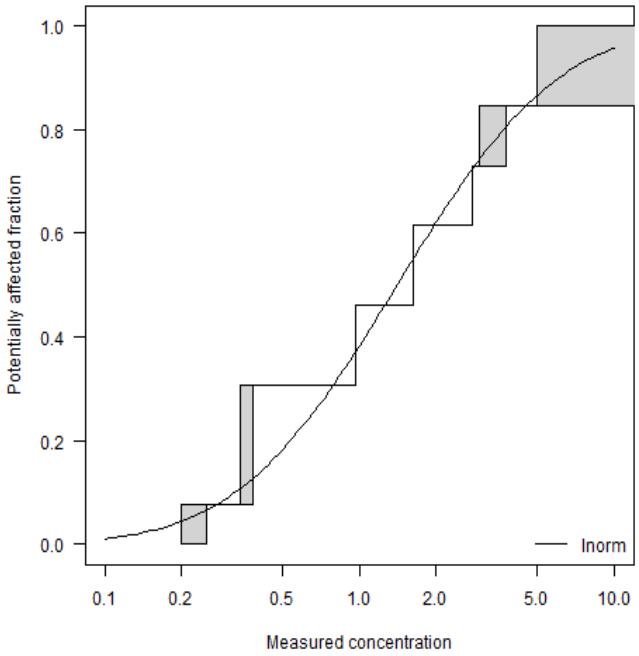
The fitted model by ETX is shown in the following plot.



Results R-package *fitdistrplus* (log-logistic model)*:*
Q-Q plot (not displayed here) indicates that a log-normal distribution of the data can be assumed.

HC5: 0.21345 mg/L (CI: 0.11 – 0.56).

The fitted model derived from the R-package *fitdistrplus* including confidence intervals for single endpoints and censored endpoints is shown in the following plot.



Conclusions on the SSD-HC_5:
The derived HC_5 is in general highly dependent on the fitted model and calculation method. To overcome uncertainties, two statistically sound approaches are used and the more reliable approach is selected. The underlying data in the models can be assumed to follow a log-normal distribution. The calculation with *fitdistrplus* allows to take intervals into account, which in this case due to right censored values and available confidence intervals is relevant. Therefore, the calculations with the R-package *fitdistrplus* is more robust and preferred compared to the calculation with ETX. The HC_5 is 0.21 mg/L.

Notes:
- For determination of the precise AF, WoE shown on page 98 and 99 of the AGD should be taken into account.
- Note that in the plot with *fitdistrplus* displays not all data points, as this would result in an unclear graphic illustration. However, all data points are taken into account for fitting the model and calculation of the HC_5.
-

References:

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.

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EFSA (European Food Safety Authority), 2015. Technical report on the outcome of the pesticides peer review meeting on general recurring issues in ecotoxicology. EFSA supporting publication 2015:EN-924. 62 pp.

EFSA (European Food Safety Authority), 2019. Technical report on the outcome of the Pesticides Peer Review Meeting on general recurring issues in ecotoxicology. EFSA supporting publication 2019:EN-1673. 117 pp. doi:10.2903/sp.efsa.2019.EN-1673 ISSN: 2397-8325.