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

EU part

Plant protection products

Chapter 6 Ecotoxicology; general introduction and over-arching issues

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Board for the Authorisation of plant protection products and biocides

Chapter 6 Ecotoxicology; general introduction and over-arching issues

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Changes in the Evaluation Manual

Evaluation manual PPP EU part Chapter 6 General introduction and combination toxicology			
Version	**Date**	**Paragraph**	**Changes**
2.1	October 2016		Initial Appendix A combitox
2.2	January 2020		New ecotoxicology chapter created with General introduction and combitox
			Sentence included on the administrative EFSA guidance
2.3	March 2021	3	New subtopic created on the evaluation of ecological models for risk assessment
2.4	February 2022	1.7 And 4	Information 'Mixture risk assessment calculator tool' included (5th CZHW in Ecotoxicology, Brno, November 2019) New topic created on the evaluation of endocrine disruption in the ecotoxicology section of active substance dossiers Name of Chapter adjusted for clarity
2.5	July 2022	2, 2.5	Clarifications about the assessment of walk-in tunnels and other non-permanent structures according to EFSA recurring issues of 2015
2.6	September 2024	1	Updating section 1 on combination toxicology. Adding additional paragraphs
		5	Including a general chapter on co-formulants and bridging
2.7	July 2024	3	Updated section on the Evaluation of ecological models for risk assessment
2.8	May 2026	2	Inclusion of three bullet points from the Central Zone.
2.9	November 2026	General introduction	Addition of a note to align this evaluation manual chapter with the effects of Reg. (EU) 2024/1487.

General introduction

This chapter shortly described some of the general issues in ecotoxicological risk assessment. It concerns approaches or agreements that are relevant for multiple aspect within ecotoxicology, for which a general chapter is more suitable than highlighting the issue in the different chapters.

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.

Note added in the version 2.6 update to align this evaluation manual chapter with the effects of Reg. (EU) 2024/1487 (entry into force on 19 June 2024) defining data requirements for the approval of safeners and synergists and establishing a work programme for the gradual review of safeners and synergists on the market in accordance with Regulation (EC) No 1107/2009:

Data requirements for active substances as described in this chapter likewise apply to safeners and synergists, pursuant to Regulation (EU) 2024/1487 (amended by Regulation (EU) 2025/2274). For the purposes of this evaluation manual, references to active substance shall be understood as referring collectively to active substances, synergists and safeners.

In accordance with (EC) No 1107/2009, Art.81(1), a derogation applies for plant protection products that contain yet non-approved safeners and synergists that have been included in the work programme; until 3 December 2030, such products are subject to the data requirements as they were before the entry into force of (EU) 2024/1487.

1. Combination toxicology

Assessment of the toxicity of combination products for organisms

1.1. Introduction

According to the Uniform principles (Commission Regulation 546/2011), Member states have to take into consideration all relevant information regarding the potentially adverse effects of the plant protection product, its components or its residues when performing a risk assessment for that product. Furthermore, the practical conditions of use and, in particular, the purpose of use, the dose, the manner, frequency and timing of applications, and the nature and composition of the preparation, has to be taken into account. In the specific principles (Commission Regulation 546/2011), and in the data requirements it is pointed out that the potential risk from the product should be considered, and not only the potential risk from the active substance. This means that in many cases it is not sufficient to only look at the risk of the active substance to non-target organisms. Combination toxicology is assessed for formulations containing more than one active substance, and for combinations of products (i.e. tank mixes) that are specified on the label.
In 2019 the European court ruled that also long-term toxicity of plant protection products (i.e. the formulation, and thus the co-formulants) should be considered (C-616/17) .
In several guidance's for ecotoxicological risk assessment, the relevance and the approach of risk assessment for formulations with multiple substances have been included. Further agreements and discussions have been made within expert meetings with EFSA for substance evaluations, and within harmonisation workshops and the central zone steering

committee for product evaluations. In March 2019 an overall guidance on combination toxicology was published:

Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals - - 2019 - EFSA Journal - Wiley Online Library

(Hitherto referred to as the EFSA Guidance on combined exposure (2019).

Combined exposure to multiple chemicals
The combined exposure can be considered in several ways

1) Multiple substances within a formulation
2) Multiple formulations within an application (tank mix)
3) Multiple exposure due to different substances and formulations in space and time (life cycle or landscape approaches)

The main focus for this chapter is on the risk assessment for a formulation with multiple substances (case 1).This does not just consider multiple active substances, but also co-formulants.This issue has already been included in several guidance documents. For tank-mixes which are included on the label of use with a clear name and dose rate, the same approach should be followed as for formulations with multiple substances. For unknown tank-mixes, and life cycle or landscape approaches, the described methods cannot be implemented, as exposure patterns and management decisions are lacking.

Methods for assessing combination toxicology
Several concepts exist for combination toxicology:

1) Similar action or independent action: substances in a mixture act by exerting their effects without diminishing or enhancing each other's toxicity. These concepts are usually incorporated in the risk assessment via dose addition and response addition.
2) Synergism or antagonism: substances in a mixture either enhance or diminish each other's toxicity.

According to the EFSA guidance on combined exposure, true synergistic interactions are rare, although they can, of course, occur. The concept of dose addition is proposed as the default model to assess combination toxicity. In cases where synergism is likely, the dose addition model can be adapted with an extra factor to correct for the possible increased toxicity.
These methods have already be incorporated in the guidance on birds and mammals (EFSA 2009) and the aquatic guidance (EFSA 2013).

From the EFSA guidance on combined exposure (2019):
'EFSA has developed several scientific opinions and guidance documents dealing with pesticide residues and their effects on humans and organisms living in the environment. The combined effects of simultaneous exposures to several pesticide residues were first considered in relation to ecological risk assessments for birds and mammals (EFSA, 2009), and then in the context of risk assessment for pesticides on bees (EFSA PPR Panel, 2012a). Both these pieces of guidance apply dose addition as the concept of choice for combined toxicity and risk assessment, but do not draft details of the specific practical methods that should be applied.

This gap is filled in the Guidance on Tiered Risk Assessment for Plant Protection Products (PPP) for Aquatic Organisms in Edge-of-Field Surface Waters (EFSA PPR Panel, 2013a). A

detailed tiered decision scheme is proposed based on checking data availability for exposure and effect assessments. It filters out situations in which combined exposure risk assessments are not necessary for decision support because a single chemical already dominates the overall effect. The guidance acknowledges the need for considering possible unacceptable effects that may arise due to chemicals already present in the environment, but methods for dealing with this issue are not developed in detail. Dose addition is the recommended default, i.e. Toxic Unit summation based on single chemical chronic toxicity data for the same endpoints within three taxonomic groups, i.e. algae, daphnids and fish. If experimental testing with the formulated product can be conducted, the guidance recommends comparing the results with the dose addition predictions. Comparisons between measured and predicted combined toxicity are recommended to decide on possible synergisms.'

1.2. Risk assessment for formulated products using formulation toxicity data

When formulation data is available, a risk assessment can be performed based on the same principles as for active substances, as described in the various ecotoxicology chapters of this evaluation manual. In most cases, formulation data is required and available. However, estimation of exposure to the formulation is difficult for multiple applications and long-term scenarios, as information on dissipation is usually only available for the active substances. Therefore, it is often assumed that the toxicity of the formulation is caused by the active substances. The endpoint for the formulation should then be recalculated to be expressed in total active substance, and the predicted exposure will also be expressed in total active substance.
Alternatively, the exposure concentrations could be recalculated to an exposure concentration of the formulation. However, it should be noted that this is not always a worst-case assumption. Please note that multiple applications should always be considered in the risk assessment, as well as worst-case exposure parameters such as persistency, relevant routes of exposure and the correct expression of toxicity endpoints (according to e.g. EFSA Recurring Issues 2019, Appendix J (aquatic organisms)). Please note that the expression of endpoints intend to correct for realistic (or in some cases conservative) exposure in the study itself and not for mixture toxicity.

1.3. Risk assessment based on combination of active substances, or products (in case of tank mixes)

For using a dose addition default model several general approaches can be followed: calculation of the combined result (CombiTER or Summation) of the risk assessment (see 3.1) or calculation of a mixture endpoint (see 3.2). These calculations are based on the same scientific principles.

Using a mixture endpoint in risk assessment will obtain the same results as when calculating the risk using the combined result method (combiTER or summation). In cases of substance specific refinements, the approach described in 3.1 is more useful, while in cases where it is more important to compare endpoints (because of possible formulation effects), the approach described in 3.2 is more useful.

For the aspects for which the risk assessment is based on product data anyway, combination toxicity calculations are less relevant and are considered to be less certain than data based on formulations. This applies to the risk assessment for non-target arthropods and non-target plants. For soil micro-organisms, formulation data is also considered to be more relevant, as the risk assessment is not suitable for combination addition calculations.

1.3.1. Combined result approach

1.3.1.1. Combi-TER

For plant protection products the TER (Toxicity-Exposure Ratio) is used as a standard in several areas of the ecotoxicological risk assessment. The TER must be higher than a trigger value to comply with the standards.

For the risk assessment of products containing more than one active substance and for tank mixtures the following formula is used:

$trigger_{substance\ 1}/TER_{substance\ 1} + trigger_{substance\ 2}/TER_{substance\ 2} + trigger_{substance\ i}/TER_{substance\ i}$.

When for each substance the trigger values are equal, the combined TER value can be calculated according to:

- $TER_{combi} = 1/((1/TER_{substance\ 1})+(1/TER_{substance\ 2})+(1/TER_{substance\ 3}))$

An acceptable risk is expected when TER_{combi} > trigger.

In case of unequal triggers, the combined TER value can be calculated using the following formula:

- $Trigger_{combi} = trigger_{substance\ 1}/trigger_{substance\ 2}/trigger_{substance\ i}$
- $TER_{combi} = trigger_{combi}/((trigger_{substance\ 1}/TER_{substance\ 1})+(trigger_{substance\ 2}/TER_{substance\ 2})+(trigger_{substance\ i}/TER_{substance\ i}))$

An acceptable risk is expected when $TER_{combi} > trigger_{combi}$.
In this formula, 'triggers' are the trigger values as mentioned in the corresponding chapter of the Evaluation Manual.

Note: in the Northern Zone guidance, a similar formula is included, which uses the same principles and will obtain the same conclusions:

$$\frac{Trigger_A\ value}{TER_A} + \frac{Trigger_B\ value}{TER_B} + \cdots = SUM$$

If SUM < 1 the risk assessment is acceptable

Where:
- "Trigger-value" represents the uncertainty factor of chemical A, B etc.
- TER is the Toxicity Exposure Ratio calculated from the substance specific effect concentration (e.g. EC50, EC10 or NOEC) divided by the expected environmental exposure.

1.3.1.2. Summation

For bees and non-target arthropods HQ-values are calculated in the assessment. These values may be summed up for the different active substances and related to the trigger (for bees the trigger is 50 and for non-target arthropods the trigger is 2 in the first tier assessment and 1 in the case of extended laboratory tests). If the summed HQ-value is lower than the trigger value, the risk is acceptable. If this is not the case the product is not permissible, unless an adequate risk assessment shows that there are no unacceptable effects under field conditions after application of the product according to the proposed GAP.
For aquatic organisms, the risk assessment prior to the EFSA (2013) guidance used TERs to express the risk assessment. In the EFSA (2013) guidance, the acceptability of the risk is expressed in PEC/RAC ratios. As with the HQ approach, PEC-RACs can be added to each other. The sum of the PEC/RAC ratios should not exceed 1.

1.3.2. Mixture endpoint

In the most recent guidance documents for ecotoxicological risk assessment (birds and mammals, aquatic organisms), the concentration-addition approach is used to take mixture toxicology into account. Although the scientific knowledge behind this approach is the same as given above, the aim of the calculation is to come to a combination endpoint, rather than a combination TER. The first step is to calculate the fraction of each active substance in the mixture. This will give the ratio between the different actives in the mixture and to the sum of these ratios should be 1.
The LD50 mixture can be calculated as:

endpoint mixture = $(1/((\text{fraction}_1/\text{endpoint}_1)+ (\text{fraction}_2/\text{endpoint}_2) +(\text{fraction }_i/\text{endpoint}_i))$

The endpoint obtained above is expressed based on total active substances, however, it is also possible to convert the calculation to an endpoint based on formulation.

This endpoint should be used in risk assessment, in combination with the appropriate exposure concentration. In general, this exposure concentration should be based on the same assumptions as the active substance risk assessment. When the endpoint is based on total active substance, the exposure concentrations should be the sum of the exposure concentrations of the separate active substances in tier 1 (see also aquatic guidance (EFSA 2013). More precise exposure concentrations can be used in a higher tier.

Since the mixture endpoint could also be expressed in formulation units, the total exposure of the active substances should equally be converted to formulation units (usually proportion and density corrections).

Note that the ratio between the concentrations of the active substances in a product may change after application, because the active substances will behave differently in the environment after application, dependent on the characteristics of the substances themselves, and the environment (half-life and sorption will differ for each active). In order to perform a correct risk assessment with the mixture endpoint, the mixture endpoint might require a recalculation based on the proportion of active substances during exposure. In the aquatic guidance recalculation of the endpoint is considered necessary if there is 20% difference in the concentrations of active substances in the formulation and the concentration of the active substances at maximum exposure (See aquatic guidance, EFSA 2013; and EFSA guidance on mixture toxicity, EFSA 2019).

When using the Combi-TER or summation approach, this issue is automatically corrected.

1.4. Combination toxicology for long-term/ reproductive effects

Formulation data on long-term or reproductive effects for birds, mammals, fish and aquatic invertebrates are usually not available, nor required according to the data requirements. In the current aquatic guidance document, **Aquatic guidance (EFSA 2013)**, chronic data with the formulation is only required when the acute toxicity endpoint of the is a factor of ten or more toxic than would be expected based on the active substances, in order to prevent unnecessary testing. However, it should be taken into account that exposure to the formulation/combination of the actives could also trigger reproductive effects. Therefore, a combination toxicity risk assessment must also be performed for the reproductive risk assessment, using combination toxicology calculations as described above. For birds and mammals this is in line with the zonal agreements (see below), and this is also included in the update of the birds and mammal guidance birds and mammals EFSA (2023) . For

aquatic organisms, Chapter 10 described the steps to be taken for mixture toxicity. Although not very explicitly mentioned, it is hinted that this also concerns chronic toxicity:
‘ *In view of (i) the data typically available for the RA of PPP and their a.s., (ii) recent scientific opinions on the implementation of mixture RA in chemicals regulation (SCHER, SCCS, SCENHIR, 2012) and (iii) elements already applied and/or proposals currently brought forward by regulatory authorities of several European Member States (Altenburger et al., 2012; German Federal Environment Agency, 2013), two options are considered most adequate for the assessment of hazards and risks of pesticide mixtures under Regulation (EC) No 1107/2009 that involve measured and calculated mixture toxicity. As the intention is to improve mixture RAs without increasing testing requirements, the use of mixture toxicity calculations should be considered whenever justified (a priori, no synergistic effects) and possible (e.g. mixture composition of a.s. is different in the formulation than expected in the environment or experimental testing is technically not feasible).*’
‘ The CA model is based on the following equation, for deriving a predicted ECx or NOEC value for a mixture of (active) substances with known toxicity (ECxmix-CA or NOECmix-CA), assuming concentration additivity.´

The interpretation that the aquatic guidance also includes chronic mixture toxicity is confirmed by the EFSA guidance on mixture toxicity (2019), which specifically refers to the inclusion of the chronic data in the mixture assessment for aquatic organisms. Also the Working Group of the member states DE, DK, AT, NO and NL, that developed the Aquatic MixTox tool to facilitate implementation of the aquatic mixture toxicity approach, came to the conclusion that chronic aquatic combination toxicity needs to be assessed (see FAQ document v2 and Section 1.8 - refer to zonal agreement from January 2022). For soil organisms, chronic studies are now included in the data requirements, meaning that also for soil organisms reproductive effects should be considered in formulation and mixture toxicity.

A consistent line of reasoning can be extracted based on the ongoing discussions and decisions: The risk assessment for mixtures should also consider long-term / reproductive effects.

Only when it can be excluded that combined effects may occur, because the effects seen in the organisms are clearly not related, combination toxicology may be disregarded for reproductive effects.

1.5. Possible antagonistic or synergistic mixture.

The aquatic guidance (EFSA 2019) was the first guidance that included a specific approach for formulations with a diminished or enhanced toxicity compared with the active substance data.

The approach of dose addition will be a suitable approach for substances that are similar or have an independent mode of action, and will be a worst-case assumption in case of possible antagonistic effects. As a diminished effect of a formulation can also be masking effects rather than actual antagonism, the dose addition approach is preferred in the various guidances.

In case of enhanced toxicity, the dose addition method underestimates the risk. In those cases, formulation data should be used. However as discussed above, in some cases the ratio of the active substances at the time of exposure in the environment does not fit the ratio of the active substances in the formulation at the start, and in some cases no (mainly chronic) data is available.

The Aquatic guidance (2013) addressed these issues in several ways:

In general, active substances in a formulation are considered to be possibly synergistic, if the formulation endpoint is at least 5 times more toxic than would be expected based on active substance addition methods. In that case, additional steps need to be taken in risk assessment.

An important step is to determine if it is indeed synergism, or that the toxic effect could be explained due to co-formulants or study artefacts (i.e, trapping effects). In case a co-formulant could explain the toxicity, there is no synergism. However as the co-formulant clearly nevertheless is toxic enough to alter the overall formulation toxicity, the co-formulant should then be included in risk assessment for any steps where formulation data is not available.

In case the enhanced toxicity cannot be explained, formulation endpoints should be used in risk assessment, as long as the ratio of active substances in the formulation is similar to the ratio of active substances at maximum exposure.

In cases where these ratios are not similar, a calculated endpoint based on the active substances in the ratio of maximum exposure should be used, but corrected for the factor of enhanced toxicity. The same should be done in case there is no (chronic) formulation study. Note that for aquatic organisms chronic formulation studies are required if the acute enhanced toxicity is more than a factor of 10 and could not be explained, as mentioned above, by other factors.

The general decision scheme in the aquatic guidance considering enhanced toxicity might also be relevant for terrestrial species, as well, and similar methods have been incorporated in updated guidances for birds and mammals (EFSA 2023) and for bees EFSA (2023)[1]. However, following the exact same steps for all other organisms might deviate from the existing guidances. For birds and mammals, usually only an acute formulation study for mammals is available. If this study shows a clear enhanced toxicity, this should not be ignored. In these cases it should also be discussed whether there is likely synergism, or if the enhancement could be explained by another factor, before requiring additional studies. Correcting CombiTERs or combination endpoints with the enhanced toxicity is preferred if there is a real enhanced effect expected.
For bees and soil organisms usually both active substance data and formulation data should be available and should be used in risk assessment. When using both formulation assessment and Combi endpoint assessment, enhanced toxicity will be covered, but the endpoint used in risk assessment might not completely fit the ratio of the active substances at exposure (i.e. in cases with multiple applications and very dissimilar dissipation patterns of the active substances). On the other hand, using summation/ CombiTER approaches, the relevant ratios of active substances are included in the risk assessment by default, but any enhanced toxicity might be missed.
For those organisms, it should be carefully considered which methods are most appropriate for the risk assessment and a weight of evidence decision should be made on a case-by-case basis.

For non-target arthropods, non-target plants and soil micro-organisms, in most cases only formulation data is available. Therefore the issues of enhanced effects and/or dissimilar exposures cannot considered for these organisms.

[1] At the moment of this update, those guidances are published, but not yet into force. As long as these guidances are not implemented, they are considered as indicative for the general appraoch for assessing combination toxicity.

1.6. Consideration of metabolites for combination toxicity

According to the aquatic guidance document (EFSA 2013) metabolites should be considered for risk assessment, if they are relevant (in terms of toxicity and exposure). Also the updated EFSA Guidance document for birds and mammals (2023) consider the combined assessment of relevant metabolites and (parent) active substances appropriate in case of simultaneous exposure. The Working Group of the member states DE, DK, AT, NO and NL, that developed the Aquatic MixTox tool to facilitate implementation of the aquatic mixture toxicity approach, developed an approach on how and when to consider metabolites in the combination toxicity assessment (see FAQ document v2 and 1.8 - refer to zonal agreement from January 2022).
Generally, it is considered appropriate to include known and relevant metabolites in the combination toxicity risk assessment for all organism groups, if simultaneous exposure is expected.

1.7. Recurring issues ecotoxicology for combination toxicology

In the Pesticide Peer review meeting on general recurring issues in ecotoxicology in October 2018, the following issue related to combitox or formulation toxicity was included : Outcome of the Pesticides Peer Review Meeting on general recurring ((June 2019)):

How to consider the formulation within the evaluation of the active substance:
The purpose of this discussion point was to achieve a better understanding and enhance the harmonization between Member States on how to consider the toxicity of the formulation relative to the toxicity of the active substance and how to deal with the risk assessment of the PPP within the peer review of the active substances. The discussion concerned those situations in which some data on both the active substance and formulation are available in the EU dossier (usually only for acute toxicity). In particular, EFSA proposed for discussion two main points for the different groups of non-target organisms:

- *In which situations should a formulation be considered as being more toxic than the substance under assessment?*
- *What is the best approach to take when a formulation is more toxic and a comprehensive risk assessment has not been performed?*

In relation to 'when a formulation should be considered more toxic than the active substance', the proposal was to account for a difference of a factor of three, as recommended in the guidance from the Directorate-General for Health and Food Safety (SANCO/10597/2003 rev. 10.1) (European Commission, 2012) on the equivalence of batches and in the aquatic guidance (EFSA PPR Panel, 2013). This means that when the endpoint of the PPP (expressed in terms of the active substance) is at least three times lower than the equivalent endpoint for the active substance, it should be considered to be more toxic. This factor was agreed by the majority of the experts, to be applied consistently to Tier 1 studies for all groups of non-target organisms.

For birds and mammals, the data on mammals from the mammalian toxicology section should be considered first. If, based on the comparison of data on mammals, it is clear that the formulation is more toxic, it was agreed that the risk assessment should be performed based on the formulation endpoint, expressed in terms of the active substance, as reported in Regulation (EU) 284/2013. However, before asking for further vertebrate studies (e.g. on birds), other elements should be considered, such as the margin of safety in the risk assessment for mammals or factors which may have an impact on the overall toxicity of the formulation (e.g. carriers, dose spacing, method of dosing).

In the case that multiple studies are available that give contradictory information in terms of the comparison of toxicity between active substance and formulation, it was recommended that all the available data should be considered and a decision made on a case-by-case basis; for example, by considering the sensitivity of the tested species.

For aquatic organisms, if the formulation is more toxic than the active substance, the majority of the experts considered that separate risk assessments for the active substance and for the formulation with their respective endpoints could be provided. In the absence of a comprehensive exposure characterization for the formulation, the predicted environmental concentrations in surface water (PECSW) values generated for the active substance accounting for all the routes of exposure should be used in combination with the formulation endpoint expressed as active substance.

For bees and soil organisms, if the formulation is more toxic than the active substance, the majority of the experts agreed to follow the same approach as described above for the aquatics, i.e. to perform separate risk assessments: one with the active substance and the other with the endpoint for the formulation expressed as active substance.

Some experts expressed the concern that when more than one substance is included in the formulation, the approach of assuming that the toxicity is entirely due to the substance under evaluation may result in a too conservative risk assessment. This is because the entire toxicity of the formulation will be attributed to the substance under evaluation. However, the approach agreed at the meeting is in line with Regulation (EU) 284/2013 and will only be used when an applicant does not provide a comprehensive formulation risk assessment.
There was no discussion on this point for NTAs and non-target terrestrial plants, since only data on formulation are usually available for these organisms. Where data on the active substance and on the formulation are available, a separate risk assessment should be performed as for the other organism groups.

Overall, it can be concluded that when a PPP appears to be more toxic, i.e. its toxicity endpoint is three times lower than the equivalent endpoint of the active substance, according to the data requirement the lower endpoint should be used for the risk assessment or risk assessments for both the active substance and PPP could be provided.

Note that the discussion above is mainly based for substance assessment, and that the factor of three is used for determining when formulation studies should be taken into account in substance risk assessment.

1.8. Zonal agreements on combination toxicology

The following points related to combination or formulation toxicity have been discussed in harmonisation workshops and agreed upon by the Central Zone Steering Committee. Note that some of the issues are not just ecotoxicology related, while others are specific for a certain area of the risk assessment. Below, the entire list of the decisions is reproduced, this list can also be found at CircaBC:

<u>March 2014:</u> National addendum - safeners
-The assessment of safeners is by most MS addressed in the national addendum until data-requirements are set; after that moment the assessment should be included in the core dossier. For work sharing purposes, DE will always include data on safeners in the core dossier.

<u>January and April 2016:</u>
- Long-term combitox for birds and mammals should be assessed for applications submitted from 1st of June 2016:
– In the (draft) Registration Report, a calculation of the long-term combitox risk

according to the concentration addition (CA) model should be presented for tier 1.
– Refinement options and possible consequences are not clear yet, however:
– when the CA combitox assessment indicates no acceptable risk, applicants may present information to demonstrate that adverse effects of the actives are not similar.
- Industry will be asked to cover combitox assessment (birds and mammals, aquatic) in DRR for Article 43 applications.

May 2016: combitox and art. 43 applications: for PPP containing 2 or more active substances: where the renewal of the second active substance is more than 12 month apart from the renewal of the first one, the applications are to be dealt with separately.
The full combitox for all active substances in PPP should be addressed by the applicant in the core dRR (OPEX, chronic birds and mammals, aquatic). There was no full agreement among member states and there will be differences between member states in the approach to combitox. Therefore, when combitox was not assessed by the zRMS, combitox will be assessed by the individual MS in the corresponding national addenda. Applicants are advised to go to particular MS to be informed about their individual national approaches. Please note, the combitox assessment for birds and mammals (chronic) is nevertheless to be considered for applications by 1st of June 2016.

November 2017: Regarding the assessment of ecotoxicology in connection with Article 43, agreement has thus far been reached on the following points (please also refer to "2016-07 Bullet points CZSC May 2016"):
– As agreed in May 2016, the full combitox for all active substances in PPP should be addressed by the applicant in the core dRR.
– If the assessment is performed at renewal of the first a.s., new endpoints for the first a.s. and old endpoints for the others are applied.
– For the Tier 1 combitox assessment, MS rely on the respective guidance documents (and where applicable also on already existing agreements at zonal level).
– For higher Tier refinements, there are various approaches by the MS, most of whom would rely on a WoE approach if no agreed methods/ guidance are available; some MS would exhaust single a.s. refinements as a first step for the refined combitox assessment.

Long-term combitox for birds and mammals should also be assessed for Article 29/33 applications (please refer to "2016-05 Bullet points CZSC January-April 2016").

January 2022:
Mixture risk assessment calculation tool (from CZHW 2019, Brno)
An Excel based tool for the mixture risk assessment calculations (called "Aquatic Mixture Toxicity Tool and additional information")was developed by a group of Member States from the central and northern zone. The first version v1.15 was published on the 21st of January 2021 in the CIRCABC Expert exchange forum. It can now be downloaded at the EFSA Knowledge Junction (https://zenodo.org/record/7788826#.ZGtARNpByHs)) under a stable link, which always displays the most recent version of the tool (at the time of installing a stable link version v1.22 was published).
The tool is intended to be an extension and implementation of the assessment given in the aquatic guidance document (EFSA Journal 2013;11(7):3290) and to facilitate the associated mixture calculations. Alongside the tool itself an FAQ document was developed as separate file, in which proposals are given for the assessment of complex mixture risk assessment topics (e.g. how to handle metabolites, chronic combination toxicity, combining different FOCUS Steps and elaborations on the driver assessment). It is also accompanied by a proposal for a dRR template (to be added to section 9.5.2) to report the results of the aquatic mixture toxicity assessment according to the EFSA Aquatic Guidance Document 2013.
This tool will be further developed in the future and follow-up versions are available via the above stable link.

1.9. Combination/formulation/mixture toxicity per organism group

Below a table is constructed how to approach combitox/formulation tox. Pease note that for aspects that are not necessarily Dutch specific, this should in principle be addressed in the core assessment.

	Zonal (PPP)		**Interzonal (PPP)***		**DAR/RAR (a.s.)**
	Core	**NL addendum**	**Core**	**NL addendum**	**M-CP**
Terrestrial vertebrates (incl secondary poisoning)	(calculated) formulation endpoint or TERcombi (acute and chronic) approach#		-	-	(calculated) formulation endpoint or TERcombi (acute and chronic) approach#
Aquatic organisms	-MDR -AGD MixTox Tool en FAQ (Section 9.5.2) (acute & chronic)	MDR see core assessment -Sum up PEC/RACs	-MDR -Mixture Toxicity AGD en FAQ combined with GEM exposure (Section 9.5.2)	MDR see core assessment -Sum up PEC/RACs (if not already done in the core)	AGD MixTox Tool / FAQ
Bees* **	Formulation assessment and/or sum up HQ values**, untill update of bee guidance ***		Formulation assessment and/or add up HQ values**, untill update of bee guidance ***		Formulation assessment and/or add up HQ values**, untill update of bee guidance ***
Non-target arthropods	Formulation assessment	Formulation assessment	-	Formulation assessment for IPM only	Formulation assessment
Soil organisms (except soil microorganisms)	Formulation assessment and/or TERcombi (chronic)**				Formulation assessment and or TERcombi (chronic)**
Non-target terrestrial plants	Formulation assessment	Formulation assessment (including MAF)	-	-	Formulation assessment

Note that a formulation assessment is more informative than a combination toxicity assessment unless there are indications for synergism. Thus TERcombi assessment is not always needed (i.e. if formulation data are available).

Incase of substance specific refinement such as DT50 refinement, the ratio between the active substances changes and the calculated formulation endpoint might change. In these cases preference is given to the combiTER approach.

*uses in permanent (closed) greenhouses

**both or most critical approach

*** currently noted SANCO bee guidance does not address combination toxicity. Draft revised EFSA bee guidance 2023 will be in analogy to the approach AGD 2013 and a tool will be developed.

2. General ecotoxicology agreements at EU and zonal level

In the Pesticide Peer review meeting on general recurring issues in ecotoxicology in October 2018, the following general issues were discussed (Outcome of the Pesticides Peer Review Meeting on general recurring issues in ecotoxicology (June 2019)): see 2.1-2.5, below. Furthermore, agreements 2.6-2.9 were made at the Central Zone level.

2.1. How to consider studies when the analytical methods are not validated

In line with Commission Regulation (EU) No 283/20132, methods for the determination of non-isotope-labelled residues used in support of ecotoxicology studies should be generated and reported in the dossier. This information should be provided both for old studies (of the original peer review) and new studies (for the renewal). This is applicable to all areas of the risk assessment (i.e. for the purposes of testing toxicological, ecotoxicological, environmental, residue and physico-chemical properties). The usual matrices of interest in the case of the ecotoxicity testing are soil, water, sediment and feedstuffs (European Commission, 2000).
Currently, the validation of the analytical methods is performed in the physico-chemical properties area and the related assessment is reported in Volume 3, Chapter B.5. When methods are not fully validated, the experts responsible for the other sections should be informed (see EFSA (2017a) for further details).

It is noted that, mostly in the case of approval for the renewal of active substances, often the methods in the 'old studies' (e.g. those performed before the publication of Regulation 283/2013), cannot be validated in accordance with the current guidance (European Commission, 2000). In those cases, depending on the available information and on the basis of the expert judgement, it could be concluded that a method is not validated but nevertheless is fit for purpose and, therefore, supports the ecotoxicity studies.

To enhance the harmonisation of the evaluation of this issue in the assessment reports, it was considered and discussed that the validation status of the analytical methods should be considered in the appraisal of the quality of each ecotoxicity study. The validity of the studies for which the analytical methods are not validated or considered fit for purpose should be questioned. However, for the sake of reducing the vertebrate testing, the repetition of a study on vertebrates should be carefully considered. This approach is also followed for mammalian toxicology studies (EFSA, 2016).

The experts at the meeting agreed that where the method is not validated or not fit for purpose, a case-by-case evaluation should be conducted. All the available information, including the toxicological profile of the substance and the margin of safety of the risk assessment, should be considered before rejecting studies. The applicants should be requested to provide justifications to support endpoints from studies where the analytical method was not fit for purpose. In the event that a study supported by a method not fit for purpose is used in the risk assessment this should be flagged in the list of endpoints.
Additionally, it was recommended that in Volume 3 Chapter B.9 of the renewal assessment reports (RARs) the conclusion of the assessment on the validation the analytical method should always be reflected as part of the evaluation of each ecotoxicological study. In line with previous agreements (EFSA, 2017a), the related assessment should be reported in Volume 3 Chapter B.5.

2.2. Risk assessment for PPPs: How to consider the formulation within the evaluation of the active substance

Regulations (EU) 283/2013 and 284/20133 set out the data requirements for active substances and plant protection products (PPP), respectively, (including requirements for ecotoxicological data for both the active substances and the PPP).

According to Regulation (EU) 283/2013, Section 8, for the approval of the active substance, data not only on the active substance but also on the PPP might be submitted, depending on which information is more appropriate to address the toxicity. This is reported as follows:
'In the case of certain study types, the use of a representative plant protection product instead of the active substance as manufactured may be more appropriate, for example testing of non-target arthropods, bees, earthworm reproduction, soil micro-flora and non-target terrestrial plants. In the case of certain plant protection product types (for example encapsulated suspension) testing with the plant protection product is more appropriate to testing with active substance when these organisms will be exposed to the plant protection product itself. For plant protection products where the active substance is always intended to be used together with a safener and/or synergist and/or in conjunction with other active substances, plant protection products containing these additional substances shall be used.'
According to Regulation (EU) 284/2013, when the toxicity cannot be predicted from the active substance or when the results of the acute toxicity study indicate higher toxicity of the formulation, studies performed with the PPP are required. This means that the standard assessment presented for the active substance will not be sufficient to conclude on the risk from both active substance and formulation and specific studies would be performed on the PPP. This is mentioned in several places and in the specific sections in the Regulation.
The purpose of this discussion point was to achieve a better understanding and enhance the harmonisation between Member States on how to consider the toxicity of the formulation relative to the toxicity of the active substance and how to deal with the risk assessment of the PPP within the peer review of the active substances. The discussion concerned those situations in which some data on both the active substance and formulation are available in the EU dossier (usually only for acute toxicity). In particular, EFSA proposed for discussion two main points for the different groups of non-target organisms:

- In which situations should a formulation be considered as being more toxic than the substance under assessment?
- What is the best approach to take when a formulation is more toxic and a comprehensive risk assessment has not been performed?

In relation to 'when a formulation should be considered more toxic than the active substance', the proposal was to account for a difference of a factor of three, as recommended in the guidance from the Directorate-General for Health and Food Safety (SANCO/10597/2003 rev. 10.1) (European Commission, 2012) on the equivalence of batches and in the aquatic guidance (EFSA PPR Panel, 2013). This means that when the endpoint of the PPP (expressed in terms of the active substance) is at least three times lower than the equivalent endpoint for the active substance, it should be considered to be more toxic. This factor was agreed by the majority of the experts, to be applied consistently to Tier 1 studies for all groups of non-target organisms.

For birds and mammals, the data on mammals from the mammalian toxicology section should be considered first. If, based on the comparison of data on mammals, it is clear that the formulation is more toxic, it was agreed that the risk assessment should be performed based on the formulation endpoint, expressed in terms of the active substance, as reported in Regulation (EU) 284/2013. However, before asking for further vertebrate studies (e.g. on birds), other elements should be considered, such as the margin of safety in the risk

assessment for mammals or factors which may have an impact on the overall toxicity of the formulation (e.g. carriers, dose spacing, method of dosing).

In the case that multiple studies are available that give contradictory information in terms of the comparison of toxicity between active substance and formulation, it was recommended that all the available data should be considered and a decision made on a case-by-case basis; for example, by considering the sensitivity of the tested species.

For aquatic organisms, if the formulation is more toxic than the active substance, the majority of the experts considered that separate risk assessments for the active substance and for the formulation with their respective endpoints could be provided. In the absence of a comprehensive exposure characterisation for the formulation, the predicted environmental concentrations in surface water (PECSW) values generated for the active substance accounting for all the routes of exposure should be used in combination with the formulation endpoint expressed as active substance.

For bees and soil organisms, if the formulation is more toxic than the active substance, the majority of the experts agreed to follow the same approach as described above for the aquatics, i.e. to perform separate risk assessments: one with the active substance and the other with the endpoint for the formulation expressed as active substance.
Some experts expressed the concern that when more than one substance is included in the formulation, the approach of assuming that the toxicity is entirely due to the substance under evaluation may result in a too conservative risk assessment. This is because the entire toxicity of the formulation will be attributed to the substance under evaluation. However, the approach agreed at the meeting is in line with Regulation (EU) 284/2013 and will only be used when an applicant does not provide a comprehensive formulation risk assessment.
There was no discussion on this point for NTAs and non-target terrestrial plants, since only data on formulation are usually available for these organisms. Where data on the active substance and on the formulation are available, a separate risk assessment should be performed as for the other organism groups.

Overall, it can be concluded that when a PPP appears to be more toxic, i.e. its toxicity endpoint is three times lower than the equivalent endpoint of the active substance, according to the data requirement the lower endpoint should be used for the risk assessment or risk assessments for both the active substance and PPP could be provided.

2.3. Equivalence of batches

The issues proposed for discussion were:
1) Whether the concentrations and subsequent endpoints should be corrected for the purity of the test item. This is primarily relevant for studies where chemical analysis is not routinely performed or when the endpoint is expressed in terms of nominal concentration.

2) To agree on the best way to present and conclude on the equivalence of the batches used in the ecotoxicity studies.

In relation to point 1, the experts at the meeting agreed that for substances with less than 90 % purity, when the endpoints are expressed in terms of nominal concentrations, these should be corrected for the purity of the technical material. It must be noted that in such situations the tested item is to be considered a mixture. Expressing the endpoint in terms of pure active ingredient content may overestimate the toxicity of the active substance, but it would ensure consistency when the toxicological endpoint is compared with the exposure estimates in the risk assessment.

In relation to point 2, the experts agreed to report in Vol.3 B.9 of the assessment reports studies for which the compliance of batches was not demonstrated. As agreed at the

meeting, a template for how the assessment of the compliance of the batches with the technical specification (new and old, if any) should be reported in Volume 4 has been developed and included in Appendix D. It was agreed that an overview of the batches used in all the available ecotoxicological studies should be presented in line with the Commission guidance (European Commission, 2012): a Tier 1 assessment should be presented for all the batches used in the ecotoxicological studies while a Tier 2 assessment should only be performed for those batches used in key studies (i.e. studies used for risk assessment).
Studies using batches which have not been demonstrated to be equivalent to the technical material should also be flagged in Volume 3. There was a consensus that, in general, the issue is not of such significance to identify a critical area of concern and only a data gap should be identified in the EFSA conclusions in situations where it has not been demonstrated that the material in the ecotoxicity studies complies with the technical specifications. However, where the available information indicates a potential concern (e.g. impurity considerably more toxic than the active substance), then a critical area of concern may be identified in the EFSA conclusion.

2.4. Use of EC10 values in environmental risk assessments

In the first general ecotoxicology meeting (Pesticides Peer Review Meeting 133) the evaluation of the reliability of EC10 calculations were discussed and some guidance was developed, as reported in the technical report of the meeting (EFSA, 2015). A follow-up discussion was proposed for the second general meeting, in order to consolidate the previous agreement.

The experts at the meeting concluded that an update of the guidance given in Appendix F of the technical report (EFSA, 2015) was needed. The update is included as Appendix E of the second general meeting (EFSA, 2019). Reference is made to this report.

2.5. Risk assessment for uses in protected structures

The EFSA Guidance Document on Protected Crops[2] (EFSA, 2014) provided definitions for different types of protected crops and as well guidance on deriving the exposure for different types of compartments. Following the publication of this guidance, it was considered necessary to address the ecotoxicological risk assessment for the organisms for which the exposure is not covered by the Guidance on protected crops. Therefore, this topic was discussed in the general ecotoxicology meeting, Pesticide Peer Review Meeting 133 in September 2015[3].
Included below is the summary on risk assessment for non-target organisms for various types of structures, as published in the EFSA Supporting publication 2015:EN-924.

Table 2: Summary of the need for a risk assessment for non-target organisms for various types of protected structures

	Terrestrial vertebrates	Aquatic organisms	Bees	Non-target arthropods	Soil organisms	Non-target plants	Biological methods of sewage treatment	Introduced pollinators

[2] EFSA Journal 2014;12(3):3615 EFSA Guidance Document on clustering and ranking of emissions of active substances of plant protection products and transformation products of these active substances from protected crops (greenhouses and crops grown under cover) to relevant environmental compartments
[3] EFSA Supporting publication 2015:EN-924, Outcome of pesticides peer review meeting on recurring issues in ecotoxicology

Low mini tunnel	✓	EF	✓	✓	EF	✓	X[2]	✓
Plastic shelter	✓	EF	✓	✓	EF	✓	X[2]	✓
Net shelter and shade house	✓	EF	✓	✓	EF	✓	X[2]	✓
Walk-in tunnel	✓	EF	✓	✓	EF	✓	X[2]	✓
Permanent greenhouse	X[1]	EF	X	X	EF	X	✓	✓
Indoor seedling treatments	Case-by-case							

✓ Assessment required
X No assessment required
EF Depends on the environmental fate assessment

[1] No assessment necessary except via secondary poisoning if the substance has a log P_{ow} >3 and exposure to surface water and/or soil is expected.

[2] No quantitative risk assessment is needed given that exposure from uses in fields (including protected structures in fields) are unlikely to lead to direct contamination of drains hence sewage treatment plants.

Although the recommendations are in place to ensure a harmonised risk assessment of the active substances, the Ctgb decided to apply these recommendations as well at the product level.

2.6 General aspects on the ecotoxicological assessment in the core dRR and national addenda (CZSC, June 2020)

- All MS agree that the full ecotoxicological assessment, including all parts that may be relevant for the concerned Member States (cMS) must be done in the core dRR.
- More specifically, the summary of all submitted studies (also when aimed at national circumstances), the evaluation of higher tier refinements and of risk mitigation measures must be included in the core.
- National specific elements such as national exposure models or considerations about relevance of species in the specific Member State may be included in the national addenda.
- Any national addenda evaluated by the zonal rapporteur (zRMS) should be made available to the cMS.

2.7 Decision-making in the Central Zone for ecotoxicology (CZHW Brno, November 2019; CZSC, April 2022)

To further facilitate the harmonisation of approaches for the aspect ecotoxicology in the Core assessment, a „majority decision“ (or “majority of MS”) is considered if not more than 1/3 of MSs disagree. The CZSC agreed that the harmonised approach of majority decisions must be used in the core assessment.

2.8 Deviation to the LoEP (CZHW, Warsaw (PL), December 2023; CZSC October 2025)

Scenario: Endpoints in the LoEP are not expressed in line with the current requirements
All MSs agreed not to re-evaluate the EU-agreed Tier 1 endpoints listed in the current LoEP, even when the new not yet noted LoEP is available.

Scenario: New endpoints are available (DAR/RAR) but not yet peer-reviewed (no new EFSA Conclusion published) and/or not yet noted by the SCoPAFF.
If the Applicant submits a.s. data which is not yet included in the current LoEP/EFSA Conclusion and this new a.s. data is necessary to demonstrate an acceptable risk, the ZRMS could make use of unpublished/not peer-reviewed LoEP/study evaluation. With regard to the new studies submitted to support the zonal process, all experts agreed that these studies should be evaluated in line with the current standards.

Scenario: Factual errors are included in published LoEP
In case the zRMS finds out that there is an error in the LoEP, the correct endpoint should be used and a respective comment should be made in the Core Assessment to inform cMS why there is a difference between the endpoint used and this reported in the LoEP. EFSA and RMS should be notified.

2.9 Exposure reduction due to specific application method (CZHW, Warsaw (PL), December 2023; CZSC October 2025)

GAP for the zonal Core Assessment should include a full application rate per hectare without reduction. In case there is a risk, it should be indicated that at the national level the spot application or any other specific application method may be considered for refinement, however due to various approaches in MSs this will not be dealt with at the zonal but at the national level.

3. Evaluation of ecological models for risk assessment

In EFSA guidance documents such as the EFSA aquatic guidance document, the EFSA guidance document for birds & mammals, and the EFSA Bee guidance, the possibility of using ecological modelling as an option for risk refinement is discussed. Applicants can take advantage of this option and submit ecological modelling approaches (usually developed by industry or consultancies) for risk refinement. It is recommended to submit refinements based on ecological modelling approaches as part of risk assessment dossiers and with a relevant GAP. In some exceptional cases, applicants might wish to submit and have the ecological model evaluated before the submission of the rest of the risk assessment dossier (for such cases please see point **3.4** below). When such models are submitted to the Ctgb within a dossier, the Ctgb conducts a screening of the submitted information, which includes the conceptual model, model documentation as well other relevant documents, to determine whether a detailed evaluation could be conducted. If serious flaws are already identified at this preliminary stage then the Ctgb will not proceed with a detailed evaluation. If a decision is made to proceed with the detailed evaluation then an intake is conducted. Once all underlying documents and files are provided, the model evaluation can be planned in the system. Please also consult the priority list for the intake.

3.1 Evaluation of model submission

3.1.1 Underlying information

The following underlying information and files are required to be submitted with an ecological modelling submission:

- **Model documentation**
  Model documentation should be as described in the EFSA Scientific Opinion on good modelling practice (e.g. TRACE documentation).

- **Model files**
  All executable model software with user manual and full source code, input and output files, sensitivity analyses and related software, etc.

- **Underlying studies**
  Reports of all underlying field, laboratory and literature studies should be provided, preferably in Dutch or English (or a translated version if applicable).

- **Any other information**
  This list is not exhaustive and more information can be requested on a case-by-case basis. Applicants can contact the Ctgb for more information about their dossier or request a pre-submission meeting (see point **3.3** below).

3.1.2 Ctgb model evaluation report

Upon receipt of all underlying information, ecological model submissions will be evaluated by the Ctgb and this evaluation will be presented in an evaluation report. The Ctgb evaluation report will follow the recommendations from the EFSA Scientific Opinion on Good Modelling Practice (2014) and will typically consist of the following components:

1. Evaluation of all literature data used in the model (ecological and toxicity data): This step checks which model parameters and assumptions are derived from the literature, field or laboratory studies, how they were derived, and how they are used in the model.
2. Specification of the questions to be answered by the model and evaluation of the conceptual model.
3. Evaluation of the conservativeness of the environmental scenario, i.e., whether the landscape and exposure scenarios are representative and sufficiently conservative for the requested use in the GAP.
4. Model implementation and verification: evaluating the model code (functions, routines, logic of sequence, and debugging if necessary) and whether the output of the model makes sense.
5. Sensitivity analyses: analysis of which parameters are sensitive to model output (globally and/or locally).
6. Model validation: comparison of model simulations with independent data sets and/or analysis of the output by means of model simulation patterns (pattern-oriented modelling).
7. Uncertainty analyses: Sources and description of model uncertainties propagated to the model output.

3.2 Ctgb procedural decisions regarding model evaluations

The evaluation of ecological modelling submissions is a time and resource-intensive exercise. From July 1, 2020 onwards, the Ctgb has decided to accept ecological modelling submissions only for zonal applications for which the Ctgb is the zRMS.

At the request of an applicant, it can be examined whether an ecological model evaluation is possible, wherein the Ctgb determines on a case-by-case basis whether sufficient capacity and room in the planning can be made available for the evaluation. Within other national-

specific application types, such as NLWERG, NLKUG, and cMS, there is no possibility to evaluate ecological models because of procedural reasons.

For cMS applications for which the zRMS **has** conducted an evaluation, the Ctgb will provide comments. If the zRMS sufficiently addresses the concerns raised by the Ctgb then the model submission need not be reevaluated in the NL addendum.

For cMS and WERG applications for which the zRMS **has not** conducted an evaluation or has conducted an insufficient evaluation or has deferred the evaluation to the member state level, the Ctgb will make a decision without including the refinement based on ecological modeling.

3.3 Pre/post-submission meetings for ecological modelling submissions

For questions or discussions regarding ecological modelling submissions, applicants can request a pre-submission meeting. Once the model is submitted and the evaluation process begins, there is a possibility to also request a limited number of post-submission meeting(s), where Ctgb questions or doubts related to the submitted information could be discussed and clarifications could be provided. The aim of these meetings is to avoid rejection of ecological modelling submissions based on misunderstandings or misinterpretation of the submitted information. This provision can only be availed on a case-by-case basis and is heavily dependent on capacity within the Ctgb.

3.4 Pre-submission applications for ecological modelling submissions

Considering that the evaluation of ecological modelling approaches is a time-consuming process, the Ctgb agrees with the need to have a longer period for a model evaluation than the time frame of a product application procedure allows. In some exceptional cases, applicants might wish to submit and have the ecological model evaluated before the submission of the rest of the risk assessment dossier. In such cases, to accommodate the evaluation of ecological models and to avoid unnecessary delay of a product application, the Ctgb also allows for pre-submission applications for the evaluation of these models via a service desk (SD) request. Such an SD request has to be connected to a zonal application with NL as the zRMS that will be submitted following the SD request.

It is important to note that the model evaluation performed during the pre-submission phase of the dossier will only contain a preliminary evaluation by the Ctgb. For a complete evaluation, the model submission should always be connected to a risk assessment dossier with a definitive GAP. During the commenting round of the zonal application (connected to the SD request), the evaluation will be shared with the other cMS offering them a chance to comment. After the zonal application is finalized, the Ctgb will issue a final decision document including the dRR which includes the conclusion on the acceptance of the ecological model.

4. Evaluation of Endocrine Disruption (active substances only)

An evaluation of the potential for endocrine disruption is required for all active substance dossiers as outlined in Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties.

The evaluation of the potential for endocrine disruption will carried out according to ECHA/EFSA Guidance of 2018, including all updates an annexes (e.g., Annex A of 2021) at the time of submission of the active substance dossier to the NL as RMS.

In the case of the ecotoxicology assessment, this means that appropriate tests in fish and amphibians will be required to address the estrogen, androgen, and steroidogenesis (EAS) and thyroid axis (T) modalities, respectively.

4.1 Testing for EAS modalities

For EAS modalities, this generally means a test according to OECD 229 or OECD 230, including gonad histopathology (which is "optional" in the Guidelines, but required for an adequate evaluation). However, under some circumstances it may be appropriate to perform a test under OECD 234. This test is considered more appropriate when there are indications of anti-androgenicity observed in the *in vitro* or mammalian toxicology dataset and may also be considered for new actives for which no ELS study (OECD 210) has yet been performed. Since a study according to OECD 210 is required for most active substance assessments, and since OECD 234 is in fact an extension of OECD 210 to cover endocrine endpoints, depending upon the in vitro and mammalian toxicology dataset it could be considered whether a test according to OECD 234 might be performed to cover both data requirements. Should a fish full-life cycle study be required according to the data requirements for fish testing for the dossier in question, applicants are encouraged to include endocrine endpoints (as, for example, in OECD 240). These may then also be considered adequate to cover the requirements for fish testing for the EAS axis. Applicants are encouraged to consult with the Ctgb for further consideration of the fish testing options.

A test according to OECD 250 (EASZY) may be considered appropriate under specific circumstances, particularly as a screening assay or in a weight-of-evidence consideration. Several other *in vitro* assays for the EAS axis are in the pipeline for OECD test guideline status (e.g., RADAR). The Ctgb may also accept these under specific circumstances. Applicants are encouraged to consult with the Ctgb as to when/whether these tests may be appropriate for their dossier.

4.2 Testing for T modalities

For thyroid-axis modalities, this means either a test according to OECD 231, or a test according to OECD 248. Annex A (2021) of the ECHA/EFSA Guidance provides information on deciding which thyroid axis test should be performed, and applicants are encouraged to consult with the Ctgb when in doubt on this subject.

4.3 Public literature

In addition, a separate literature search according to ECHA/EFSA 2018 is required, including endocrine-specific keywords and organisms (e.g., amphibian). This search may be incorporated into the literature search requirements according to Regulation (EU) 283/2013, and EFSA Journal 2011; 9(2): 2092, however, this should be clearly stated and highlighted when discussing the literature search. In addition, the exclusion criteria used for the general literature search may not be appropriate for the literature search for endocrine disrupting properties, as the assessment of endocrine disruption is a hazard assessment (e.g.,

mechanistic data with non-standard exposure/dosing and data in non-standard species are considered potentially relevant).

4.4 Format and placement in the dossier

Summaries according to OECD format for fish and aquatic-phase amphibians should be placed in Vol 3, B9, CA, under the heading “endocrine disruption” in the aquatic organisms toxicity section of the CA. Additional tests found in the public literature, for example, may be placed under the heading “Endocrine disruption” in the section on other terrestrial vertebrates, should they have been performed in terrestrial vertebrates. Otherwise, a reference can be made to Vol. 3, B6 CA under this heading.

In addition, applicants should include all relevant ecotoxicology tests and endpoints in an excel file according to Appendix E of the ECHA/EFSA Guidance and present an assessment of the potential for endocrine disruption, including a summary table outlining lines of evidence according to Table 3 of the ECHA/EFSA Guidance.

5. Co-formulants and bridging

In 2019, due to a judgement of the European court (C-616/17) the issue for formulation toxicity and co-formulant toxicity has become an important factor for the authorization of formulations. This also means that any formulation changes or bridging to other formulations should be considered carefully, as the contribution of the co-formulants to the toxicity of the product should be considered. Although there is a guidance document for formulation changes, SANCO 12638/2011 (20 Nov 2012 rev. 2) this guidance lacks an approach for the environment : “*Guidance on appropriate assessment procedures and/or criteria for the similarity assessment regarding environmental risk is not given in this guidance document and should be dealt with in separate way*. “
Nevertheless, both regulation 1107 and the guidance for formulation changes indicate that (changes in) formulation composition should be considered for ecotoxicology as well. As long as formulation data is available the risk assessment can be performed based on those endpoints. However in case composition changes or other cases that desire bridging between formulations, potential effects on non-target organisms and the ecotoxicological risk assessment should be carefully considered: A case must be presented showing that the difference in the formulation will not affect the conclusion of the risk assessment. This can be done by submitting bridging studies as well as using co-formulant toxicity data from other databases or discussing the types of changes or and overall weight of evidence. This information can be presented as a qualified bridging statement in Part C, together with a comparison of the compositions of all formulations used in the risk assessment.

5.1 Zonal agreements

September 2023
Bridging between formulations- (also relevant for Data-Matching)*
If applicants wish to use data generated with a different product, the question to be answered is whether the products are similar or not. Thus the zRMS should check if the applicant has shown that formulations are sufficiently similar for the data from the lead formulation to be considered relevant for the proposed product under assessment.
This should be done by submitting a qualified bridging statement that compares the compositions of the proposed and the surrogate formulation(s) in terms of the nature (hazard) and quantity of the active substances, formulation type and co-formulants (to be placed in Part C or Volume 4 for confidential information). If applicants provide alternative studies with similar tests/same species the “rule of 3” (i.e., endpoints which differ by >3x indicate significantly different (more critical) toxicity and the studies should therefore be considered more critical) should be applied unless a test shows another species to be more sensitive.

* The zonal agreement was discussed as ‘data-matching; however this does not concern data matching, but bridging between formulations. To avoid confusion with the bullet points from the CZSC the title has not been changed. For actual data matching, please check the relevant guidance on data matching SANTE/2016/11449, 2021