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Fit-for-purpose risk assessment for low-concern active substances and uses

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Abstract

This report describes a harmonised, stepwise methodology for the fit-for-purpose risk assessment of low-concern active substances (LCASs), developed in response to EFSA's call GP/EFSA/PLANTS/2023/04. LCASs include substances such as semiochemicals, botanicals, inorganics, peptides, and double-stranded RNA (dsRNA), which generally have lower risk profiles than conventional active substances. However, the current risk assessment framework – primarily designed for conventional substances – often lacks the flexibility required to appropriately address LCASs. The approach described here is based on problem formulation using generic pathways to harm. It offers a structured methodology aimed at harmonising case-by-case assessments based on the specific properties of individual LCASs. This approach supports both qualitative and quantitative assessments and covers hazards other than conventional toxicity, such as suffocation, desiccation and RNA interference. To apply this approach in practice, a problem formulation toolbox is provided, comprising three main elements:

1. Generic pathways to harm
2. Generic analysis plans, including the Analysis plan tool
3. Guidance on likelihood assessment

Keywords: problem formulation, pathways to breach the protection goals, low concern pesticides, fit-for-purpose risk assessment, waiver criteria, data requirements, qualitative risk assessment

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Summary

The current EU regulatory framework for pesticide risk assessment is mainly conceived for conventional synthetic chemical substances and traditional spraying applications and is not sufficiently flexible to address Low-Concern Active Substances (LCASs), such as botanicals, semiochemicals, microbial metabolites, inorganics, peptides, and dsRNA. These LCASs typically feature alternative, "non-toxic" modes of action, including suffocation, desiccation, hypoxia, RNA interference, mating disruption, and also exhibit distinct environmental behaviour, such as differing potential for leaching.

To close this gap, a fit-for-purpose risk assessment scheme was developed grounded in a structured Problem Formulation (PF) approach using pathways to harm, where *harm* is defined as not meeting the protection goal. This both quantitative and semiqualitative methodology systematically identifies and evaluates critical events necessary for breaching specific relevant environmental protection goals. Detailed, generic pathways to harm and comprehensive analysis plans have been formulated for each relevant hazard (toxicity, suffocation, desiccation, hypoxia, RNA interference, mating disruption and leaching potential), providing clear guidance on assessing the likelihood and significance of these events. The accompanying spreadsheet-based tool organises these analysis plans, facilitating structured assessments, the use of data waivers and integration of New Approach Methodologies (NAMs).

The developed approach and the supporting tool were evaluated through diverse case studies and refined through feedback gathered during dedicated break-out group sessions at an in-person workshop with regulatory stakeholders (EFSA, European Commission, Member States, and Industry representatives).[1]

This approach allows regulators and applicants to conduct tailored risk assessments that match the unique properties and intended uses of LCASs, while also promoting increased harmonisation across the regulatory process. Since the protection goals remain unchanged, the approach maintains a high level of environmental protection while improving efficiency and minimizing redundant testing. This report proposes the establishment of a scheme incorporating the generic pathways to harm framework and a spreadsheet tool and recommends further development to accommodate future emerging LCASs and NAMs.

1 Introduction

1.1 Terms of reference for the mandate as provided by EFSA

The European Food Safety Authority's call GP/EFSA/PLANTS/2023/04 asked for "a stepwise approach for fit-for-purpose risk assessment, in particular for low-concern

[1] https://www.efsa.europa.eu/en/events/ad-hoc-meeting-stakeholders-workshop-development-fit-purpose-approach-assessing-risk-low

active substances and uses" with an emphasis on harmonized PF, science-based waiver criteria and tailored alternative exposure- and hazard-assessment tools.

In response, a consortium of six public organizations led by Aristotle University of Thessaloniki signed an 18-month multi-beneficiary grant agreement. This agreement addresses EFSA's request through seven technical tasks and the associated five formal deliverables (D0-D5). The present document is the final report (D5), due 18 months from the project's kick-off meeting.

Deliverable 2 (D2), an interim report submitted at month 9 effectively tackled tasks 2-6 (criteria for data waivers, NAMs, fit-for-purpose exposure models, establish the risk assessment scheme, and transparent protocol for literature searches) by providing the first comprehensive draft of the PF approach using generic pathways to harm which now serves as the core framework for the final methodology.

Since D2 was delivered, two major milestones have advanced the project:

1. **Stakeholder workshop (Thessaloniki, 15-16 January 2025).** Fifty-three experts from EFSA, European Commission, Member States authorities, academia, and industry reviewed and discussed the draft methodology based on generic pathways to harm. Focused break-out groups on fate and exposure, ecotoxicology, risk assessment and risk management generated targeted recommendations that are captured in deliverable 4 (Vryzas et al., 2025).

2. **Technical refinement of the approach.** The consortium has carefully reviewed and integrated feedback from the workshop in this final methodology and guidelines for application of the methodology presented in this report (D5).

1.2 Background and interpretation of terms of reference

Plant protection products in the EU are regulated by Regulation (EC) No 1107/2009. All active substances other than viable microorganisms are assessed using the same data requirements for chemical active substances laid down in Part A of the Annex of Regulation (EU) No 283/2013 and following similar principles for plant protection products [Regulation (EU) No 284/2013]. However, these requirements mainly address conventional synthetic pesticides and do not fully accommodate active substances considered as of potential Low Concern Active Substances (LCASs), such as semiochemicals, botanicals, inorganics, peptides, antibodies, and dsRNA. In contrast to conventional active substances with toxic modes of action, LCASs may act through non-toxic mechanisms like suffocation. These hazards other than toxicity are currently not addressed in the regulatory risk assessment. Furthermore, LCASs are compounds with a very diverse range of physicochemical properties, multiple mechanisms of actions (e.g. botanicals; peptides), with potential hazards that do not necessarily have a clear dose-response relationship (e.g. suffocation; desiccation; RNA interference).

The current regulatory evaluation process is tailored to conventional synthetic chemical products and specific guidance to applicants on how to prepare a dossier for a LCAS is not available. Therefore, under the current regulation, dossiers for LCASs end up with many data gaps, which discourage their progress from discovery to the market. On the other hand, there is a lack of guidance on how to perform the risk assessment for these types of active substances. In the past years, applicants and regulators have used a case-by-case approach to solve the mismatch of assessing the risk of a LCAS within the framework for conventional substances. However, these case-by-case approaches lead to uncertainty due to lack of harmonisation.

This bottleneck for LCASs has been acknowledged and progress has been made in the past years by the European Commission, EFSA, OECD and Member States and several documents relevant for non-conventional substances have been recently endorsed. These include the 'Guidance to provide justifications as referred in point 1.5 of the Introduction of the Annexes of Regulations (EU) No 283/2013 and No 284/2013: Problem formulation for environmental risk assessment in the context of Regulation (EC) No 1107/2009' (EC, 2024a). Building on this PF approach, the risk assessment approach for LCASs should furthermore be:

- ✓ tailored specifically to the properties of LCASs and include hazards other than toxicity (e.g. suffocation; desiccation; hypoxia; RNA interference; mating disruption and particularities in leaching potential)
- ✓ accommodating both quantitative and qualitative information
- ✓ flexible enough to include upcoming new types of substances
- ✓ facilitating integration of all information relevant for the assessment of a protection goal (birds and mammals, aquatic organisms, bees and pollinators, non-target arthropods, soil macro-organisms, soil microorganisms, non-target terrestrial plants, and leaching potential to groundwater)
- ✓ transparent for better communication
- ✓ harmonized and easy to use

The objective is not to reduce protection standards but rather to develop a more appropriate, efficient and harmonized methodology.

1.3 Reading guide

This report provides a structured overview of the methodology developed in this project and its practical application. Chapter 1 outlines the context, including the terms of reference and the development of the methodology. Chapter 2 forms the core of the report: Section 2.1 provides all background information on the PF approach using pathways to harm, including its scope, regulatory context, and underlying principles. Section 2.2 explains how to apply the approach in practice.

The appendices offer detailed resources to support the use of the approach, including generic pathways to harm (Appendix A), generic analysis plans (Appendix B), guidance on performing literature searches (Appendix C), and a template for presenting the outcome of the approach (Appendix D). A concise case study is also included to illustrate the application of the methodology (Appendix E). Furthermore, Appendix F contains an inventory of previously used waiver criteria and Appendix G summarising the current knowledge on NAMs and their potential use in LCASs risk assessment. The table of contents can be used to navigate directly to specific sections of interest.

2 The problem formulation approach using pathways to harm

2.1 Introduction to the approach and background information

2.1.1 Scope of this document

The method described in this document applies to the environmental risk assessment of LCASs. In lieu of a legal definition within the EU for biopesticides, the term LCAS is used for substances for which it might be expected *a priori* that their use will have a lower adverse effect when comparing with conventional chemical products. They comprise a heterogeneous group of substances with various modes of action. Examples of LCASs include certain plant extracts, semiochemicals and inorganic substances. Natural substances with a high toxicity, such as certain purified microbial metabolites, might not be of low-concern; a conventional approach might be more relevant for these substances. It is expected that most LCAS will fall within the new category of biocontrol active substances once a definition for this latter category is available (EC, 2025).

The approach of PF using generic pathways to harm is in principle applicable to any type of substance for which the conventional risk assessment approach is not fully fitting. As it is the aim of the approach to make the assessment fitting to the properties of the substance, it is not needed to first assess if the substance is fitting for the approach. However, as the current data requirements and uniform principles have been developed to assess risks of synthetic substances due to toxicity, the approach is especially relevant for natural or nature-identical substances which do not have a broad-spectrum, toxic mode of action. The approach described in this document does not aim for a 'lighter' assessment, but a more fit-for-purpose and thereby more efficient assessment. In the case of LCASs this will lead to streamlined and more efficient assessments, but not to lowering the level of protection. If the approach is used for natural or nature-identical substances with a broad-spectrum toxic mode of action (e.g., certain microbial metabolites or plant extracts), it will lead to an overall approach which is equivalent to the current risk assessment approach for conventional substances in which effects resulting from the components of complex mixtures need to be addressed. In such cases, the approach can also help identify the most appropriate testing methods when existing data requirements are insufficient or not fully adequate.

For those types of LCASs for which specific guidance documents are applicable, it may not be relevant to apply the approach described in the present document. For example, for semiochemicals of which the exposure resulting from their use is comparable to natural exposure to these compounds, no further information may be needed for the risk assessment based on specific guidance (EC, 2024b). In this case, while the PF approach using generic pathways to harm is appropriate and can be applied, it would not make the assessment more fit for purpose or efficient. For semiochemicals, the approach using generic pathways to harm is therefore most relevant in cases where exposure is not similar to natural exposure, which may for example be relevant for application methods other than dispensers when these result in exposure routes other than by the vapour phase.

The approach described here is based on generic pathways to harm. These pathways link individual hazards to each of the specific protection goals for the environmental risk assessment. The generic pathways to harm included in this document aim to cover the hazards (modes of effect) which may apply to current LCAS: toxicity, desiccation, suffocation, hypoxia, mating disruption/mass trapping, RNA interference (RNAi), and leaching to groundwater. The pathways to harm for each of these hazards are generic for all types of substances for which this hazard is relevant. For example, the pathway for the hazard of desiccation is the same whether it is applied to an inorganic substance or a fatty acid. In this way, the approach in this document covers all substances for which one or more of these hazards are relevant. To assess future LCASs to which other hazards apply, additional generic pathways may need to be developed.

Active substances which are microorganisms are outside the scope of this project. Also, while they may be an important element in the assessment of PPP based on LCAS, co-formulants are outside the scope.

The method described in this document covers the environmental risk assessment. The human risk assessment and the assessment of efficacy are outside the scope of this document.

2.1.2 Regulatory context of the method described in this document

Under Regulation (EC) No 1107/2009, a PPP may only be authorised if it is sufficiently effective and if its use meets the protection goals – namely, that it does not cause immediate or delayed harmful effects on human or animal health, and does not have unacceptable effects on the environment. These conditions apply to all PPPs, regardless of the type of active substance they contain (e.g., of natural origin, low-risk, chemical or microbial).

The criteria used to determine whether these conditions are met are defined by specific evaluation criteria and data requirements. These include Article 4(3) and Annex II of Regulation (EC) No 1107/2009, as well as several implementing regulations: Regulation (EU) No 283/2013 (data requirements for active substances), Regulation (EU) No 284/2013 (data requirements for plant protection products), and Regulation (EU) No 546/2011 (uniform principles).

As active substances which are microorganisms are not in the scope of this document, the relevant criteria and requirements are given in Part A of the Annexes of the data requirements and uniform principles. These criteria and requirements have been developed to address risks which are relevant for conventional chemical PPP. As such, they are not always appropriate for substances which are not synthetic and which have a mode of action other than toxicity. This is acknowledged in Point 1.5 of the introduction of the Annexes of the data requirements which states that "*information is not required where a justification is provided showing that the information is not* *necessary owing to the nature of the PPP or its proposed use, or the information is not scientifically necessary"*. In these cases, the data may be 'waived' by providing this substantiated justification.

To harmonise the application of this Point 1.5, the European Commission has provided a guidance document which was endorsed in January 2024 (EC, 2024a). In this 2024 guidance document, a PF method is described to determine which experimental data would not be necessary for the environmental risk assessment for a particular substance and representative use. The current document builds on this method and expands its applicability in risk assessment, as the proposed method is not only used to determine if data waiving is appropriate, but also as framework to determine the approach for fit-for-purpose, case-by-case risk assessments of LCASs and to assess the likelihood of breaching the protection goal.

Firstly, the approach using generic pathways to harm provides a practical step-by-step method of PF to justify waiving of data as provided by Point 1.5. It does so by providing generic pathways to harm which provide guidance on which information can be used to justify waiving of data. These generic pathways to harm described in this document aim to improve the harmonisation and thereby predictability of the approach.

Secondly, making the risk assessment more fitting to the properties of substances requires more than waiving of data. It may for example be needed to adapt the testing or modelling strategy. Also, a qualitative risk assessment approach may be more fitting, while the current risk assessment schemes are only suitable for quantitative data. The PF method using generic pathways to harm as described in this document addresses all these issues. The aims of this document are therefore broader than those of the 2024 guidance on PF (see also Section 1.2).

2.1.3 Introduction to the general concept and principles of problem formulation using generic pathways to harm

The generic pathways to harm described in this document are an adaptation of the PF approach using pathways to harm (Raybould, 2006). In general, a pathway to harm is a sequence of events through which a hazard can lead to adverse effects. For the generic pathways to harm, 'harm' is defined as adverse effects which are sufficiently severe to breach the protection goal (i.e., not meeting the protection goal; risk managers may consider the effects unacceptable). As a result, adverse effects which are less severe are in the context of the current approach not considered to constitute a 'harm'.

The aim of the generic pathways to harm is to assess the likelihood of breaching the protection goal. Each generic pathway consists of a number of events which must all take place in order for effects to be severe enough to breach the protection goal (see Figure 1). This means that if any of the events in the pathway can be demonstrated not to take place, the likelihood of breaching the protection goal is *negligible* and the consortium proposes a low risk can be concluded. In general, this situation will occur if there is an absence of hazard or of exposure.

The generic pathways to harm are equally – or perhaps even more – relevant for those cases where neither hazard nor exposure are absent. In these cases, the PF approach using generic pathways applied at the start of the risk assessment will provide guidance on which data is most relevant for the assessment. To do so, each of the generic pathways is accompanied by a generic analysis plan which lists the types of information that are needed for the assessment. The generic pathways will subsequently help to assess the likelihood of breaching the protection goal based on the available information. For the latter, the assessment of the likelihood of each event in the pathway is combined to assess the likelihood of the full pathway and thereby perform a qualitative risk assessment. The generic pathways are in this way used as a method to combine all lines of evidence for an overall weight-of-evidence assessment. In this respect, generic pathways are fundamentally different to decision trees for the risk assessment (Hauschild et al., 2025).

Figure 1: Example of a generic pathway to harm (in this case for the specific protection goal for terrestrial non-target higher plants due to the hazard of toxicity). All generic pathways for the different hazards have been developed in a similar way: the first event is the use of the PPP; the last event is the breaching of the specific protection goal. The intermediate steps include events which are based on hazard characterisation (in this case toxicity) or the exposure assessment, or on the combination of the two (risk characterisation). In the same way, some events address

effects at the level of individuals of a non-target species, while others may address effects at population level or recovery of populations, depending on the protection goal.

2.1.3.1 Introduction to the generic pathways to harm

This document includes generic pathways to harm that link potential hazards to the relevant protection goals which can, in principle, be used to any type of LCASs (see Appendix A). The reason for drafting these generic pathways is twofold:

- They prevent the need to draft pathways to harm from scratch for each assessment;
- They contribute to the harmonisation of the risk assessment approach of LCAS.

In this way, generic pathways combine the advantages of case-by-case and harmonised approaches for the risk assessment of LCAS.

Each of the generic pathways addresses the risk arising from one specific hazard for one protection goal. The hazards which are covered by the generic pathways include not only toxicity, but also suffocation (mostly relevant for oily substances), desiccation (for example for inorganic substances), mating disruption (for sex pheromones) and RNA interference (for ds-RNA compounds). In this way, examples of generic pathways are toxicity to non-target plants (see Figure 1) or desiccation of pollinators.

By explicitly including the hazards in the generic pathways it becomes immediately more clear which data would be required to assess the effects resulting from this hazard - and in which cases conventional testing guidelines or e-fate models may not be appropriate or alternative methods are available.

Because the generic pathways are applicable to any type of LCAS to which one of the above-mentioned hazards applies, the approach is also suitable for new types of substances for which these hazards apply. The approach is therefore flexible; the same generic pathways can be used for different types of LCASs (e.g., substances of plant or animal origin, or inorganic substances).

In Figure 3 several categories of LCASs are depicted together with their potentially relevant combinations of hazards and protection goals. Note that while the hazard of toxicity is potentially relevant for all categories of LCASs, other hazards are only relevant for a single category of LCASs (e.g., RNA interference for dsRNA).

To develop these generic pathways to harm, two inventories were made:

- Inventory of the agreed specific protection goals;
- Inventory of hazards.

While the specific protection goals are provided in relevant implementing regulations and guidance documents, there is no agreed set of hazards which are considered relevant for the risk assessment other than the hazard of toxicity. The inventory of hazards provided here includes other hazards which may be more relevant for LCAS than toxicity. Also, in theory, additional hazards beyond those included in this inventory may be relevant for LCAS.

In principle, all hazards which may result in foreseeable risks (see point 1.1 of the Annex of the data requirements) should be included in a risk assessment. Which hazards are relevant for a specific LCAS depends on its properties, in particular on the mode of action. Obviously, if the substance has a toxic mode of action, an assessment of risks due to toxicity is needed. Similarly, if the substance kills the target organisms through suffocation, this hazard should be addressed in the risk assessment.

Whether or not other hazards in addition to the one responsible for the mode of action should be assessed is less straightforward. Current practice is to assess the hazard of toxicity for all substances, irrespective of their mode of action. The reverse is not current practice: for example, effects due to suffocation or desiccation are not assessed for conventional (toxic) substances, while they may in principle apply to these substances. Also for the assessment of LCASs as described in this document, effects resulting from toxicity should be addressed for all LCAS. Whether effects resulting from other hazards need to be addressed depends on the properties of the substance (see Section 2.2.2.1).

The rationale for always having to address toxicity in the PF step, while the need to address other hazards depends on the properties of the substance, is that the assessment of effects resulting from one hazard can be covered by the assessment of effects caused by another hazard. For conventional, toxic substances, the risk assessment for effects caused by hazards other than toxicity will be covered by the risk assessment for toxic effects. For LCASs which have a non-toxic mode of action the effects of this non-toxic hazard may only partially cover the potential effects resulting from toxicity. This is because in contrast to the hazard of toxicity, hazards such as suffocation and mating disruption are not relevant to all groups of non-target organisms. While non-target arthropods can be affected by oily substances due to the hazard of suffocation, this will not apply to birds and mammals. Similarly, mating disruption by sex pheromones is not relevant for non-target organisms other than arthropods. Also, as hazards such as suffocation and desiccation cause acute effects; these effects will dissipate quickly. This is in contrast to effects caused by toxicity. Therefore, the assessment of chronic effects caused by toxicity will as a rule of thumb not be covered by the assessment of effects due to these other hazards.

For the approach of PF using generic pathways to harm the above means two things: 1) The hazard of toxicity is considered potentially relevant for all types of LCAS. While this does not mean that guideline studies are always required for the assessment of toxicity, an adequate justification is needed for all groups of non-target organisms in case of data waiving. 2) For certain hazards, generic pathways to harm are only relevant for those groups of non-target organisms which can potentially be affected by this hazard; only these generic pathways have been included in this document.

2.1.3.2 Introduction to the generic analysis plans

For each of the events in the generic pathways to harm a generic analysis plan was drafted. These analysis plans are included in the generic pathways to harm which are given in Appendix A. Furthermore, in Appendix B the Analysis plan tool is given, which can be used as a reference when applying the approach (see also Section 2.2.2.2).

The generic analysis plans were drafted by using information on previously proposed waiver criteria (see Appendix F), NAMs and possible adaptations to the current exposure assessment methodology (see Appendix G). In addition, the potential of using data on the efficacy of LCASs was examined and corresponding suggestions were included in the generic analysis plans.

2.1.4 Qualitative versus quantitative risk assessments

The objective of a risk assessment for PPPs is to evaluate the risks associated with their use. To understand the distinction between qualitative and quantitative assessments, it is helpful to first consider the concept of risk itself. According to the EFSA Scientific Opinion on risk assessment terminology (EFSA, 2012), risk is commonly defined as the probability of an adverse outcome. As stated in the document:

"Although they differ in detail, most definitions of risk have a common core – that risk is the probability of an adverse outcome. It follows that expressions of risk should comprise a specification of the outcome of interest, and an expression of its probability. Both should be expressed as clearly and unambiguously as possible, to facilitate clear understanding by risk managers and stakeholders."

This definition underscores the importance of clearly articulating both the potential adverse outcomes (e.g., breaching the protection goal) and their likelihood to ensure effective communication and informed decision-making by risk managers (also see EFSA, 2014).

The current risk assessment framework for PPP is mostly quantitative: risk characterisation is generally performed by combining quantitative data on exposure with quantitative data on effects. These values can be compared to threshold values to determine if the effects may be considered as acceptable by risk managers. To be able to use this quantitative approach, risk assessment schemes are in place including exposure models, defined effect endpoints (including test guidelines to derive these endpoints) and thresholds for when effects can be considered as acceptable by risk managers (see for example EFSA, 2023; EFSA 2013). These models, guidelines and thresholds have been developed for the assessment of conventional active substances and for the hazard of toxicity. As a result, they may not be appropriate or fitting for the assessment of LCAS.

In some cases, it is obvious that the conventional approach is not fitting. This is for example the case for the aquatic assessment of substances which are not miscible with water (e.g., oily substances) because the exposure models may not be appropriate due to the physical-chemical properties of the substance. In other cases, it is not as obvious that the conventional risk assessment schemes may not be appropriate. This may be the case where effects are caused by other hazards than toxicity. While predicted environmental concentrations may be calculated with the conventional exposure models, and effect testing can in principle be performed using the standard test guidelines, the outcome of these tests and calculations, and also the thresholds to compare these outcomes to, may not be appropriate for hazards other than toxicity – especially for the lower tiers of the assessment.

In order to apply the tiered, quantitative approach, which was developed for conventional active substances to LCAS, it may be needed to adapt the current risk assessment schemes or even develop new risk assessment schemes which are appropriate for the different types of LCAS. Information on how the approaches for effect testing and predicting exposure may be adapted to the properties of specific types of LCAS is included in Appendix B. Alternatively, quantitative data could be generated using higher tier (field) studies. However, as a first step it should be determined if a fully quantitative risk assessment is in fact needed in order to provide risk managers with the information they need. Performing a fully quantitative risk assessment should not be an end in itself, but a tool to be used when needed. This is already reflected in the approach for the risk assessment of active substances which are microorganisms. For example, the assessment of metabolites of potential concern is based on a qualitative or semi-quantitative assessment (EC, 2023; EC, 2024c) and quantitative data on exposure to the microorganisms or metabolites is only required when qualitative information is insufficient to conclude on an acceptable risk (Section 7 of Regulation (EU) No 283/2013).

The same approach can be applied to LCASs by using the PF approach to assess the likelihood of breaching the protection goal. In this approach, the generation of quantitative data is only triggered when insufficient information is available to conclude that the likelihood of breaching the protection goal is *very unlikely* or *negligible*. In these cases, the generic pathways to harm and the associated analysis plans will provide guidance on which information may be generated as a next step. In those cases where sufficient information is available to conclude that the likelihood of breaching the protection goal is *very unlikely* or *negligible*, the assessment of the likelihood is used to justify waiving the requirement for quantitative data (see Section 2.1.2).

A frequently identified drawback of qualitative risk assessments is their subjectivity. The availability of harmonised likelihood descriptors (see Section 2.1.5), generic pathways to harm and analysis plans, and information on how to apply the approach all aim to reduce subjectivity and increase harmonisation. However, a certain level of subjectivity will remain in any risk assessment. This is for example acknowledged in the FAO/WHO guidelines on Risk characterization of microbiological hazards in food (FAO/WHO, 2009), which note:

> ‘Assessing the probability of any step in the risk pathway, or the overall risk, in terms of high, medium, low, negligible, etc., is subjective, as the risk assessor(s) will apply

their own concepts of the meanings of these terms. These meanings may (and probably will) differ from person to person. This is one of the major criticisms levelled at qualitative risk assessments. However, these final risk assessors' estimates should never be viewed in isolation, just as numerical outputs from quantitative risk assessments should not, and reinforces the need for transparent documentation of the data and logic that lead to the assessor's estimate of the risk.'

How to transparently report on the outcome of the risk assessment when using generic pathways to harm is described in Section 2.2.

2.1.5 Definitions used in this document

A comprehensive list of definitions is included in the Glossary section. Below, proposed descriptors and definitions are presented that can be used to express the likelihood of events.

Likelihood descriptors

Likelihood descriptors are used to qualitatively (i.e., in words) express the probability of an event occurring. The likelihood of an event occurring refers to the probability that the event will occur given the use of the PPP. In turn, the estimate of this probability reflects both variability and uncertainty. Variability refers to the inherent randomness of the system; it cannot be reduced by generating more information. In contrast, uncertainty is caused by imperfect information and can therefore be reduced by generating more data. As an example: the likelihood of an event that occurs only under exceptional circumstances (i.e., *very unlikely*) may be assessed as *unlikely* (might occur or should occur at some time) or even *unknown* due to the magnitude of uncertainty in this assessment caused by limited availability of data.

The likelihood descriptors can be used to describe the likelihood of individual events within the generic pathways as well as to describe the likelihood of breaching the protection goal (i.e., the likelihood of the last event in a generic pathway to harm occurring).

The likelihood descriptors proposed in this document and their accompanying subjective probability ranges (see below) are a condensed form of the approximate probability scale recommended for harmonised use to describe uncertainty in EFSA (EFSA, 2018). The definitions of these descriptors proposed in this document are inspired by the likelihood descriptors given in the WHO/FAO guidelines on risk characterization of microbiological hazards in food (FAO/WHO, 2009). The resulting descriptors, definitions and subjective probability ranges as proposed by the consortium are given in Table 1.

Note that while the probability range is given in quantitative terms (as percentages), these probability ranges are subjective values: they are an interpretation based on expert judgement and not purely based on quantitative estimates. The subjective probability ranges aim to harmonise likelihood assessments by ensuring comparability between assessments performed by different individuals (EFSA, 2018).

Note that a description of the probability is implicitly included in quantitative risk assessments performed for conventional substances. For these substances, tiered risk assessment schemes have been developed to assess if the exposure (mostly expressed as Predicted Environmental Concentrations which reflect a percentile of the calculated concentrations or percentile concentrations estimated from measure data) resulting from the proposed use in combination with the hazard properties of the substance are expected to meet the specific protection goals. The quantitative thresholds which are used in these risk assessment schemes (e.g., toxicity-exposure ratios) are thresholds which have been agreed upon by risk managers to determine if effects can be considered as acceptable; meeting these thresholds does not mean that harm will not occur under any circumstance (see Steenbergh et al., 2025).

Table 1: Descriptors, definitions and subjective probability ranges to express the likelihood of events taking place as proposed by the consortium

Descriptor	Definition	Subjective probability range
Certain	Is certain to occur.	100%
Extremely likely	Is expected to occur in almost all circumstances; almost certain.	95 – 100%
Likely	A reasonable to high probability of occurring; covering a wide range of probabilities from events that might occur or should occur at some time to those that will probably occur in most circumstances.	33 – 95%
Unlikely	May occur, but less probable than not.	10 – 33%
Very unlikely	Not expected to occur; may occur only in exceptional circumstances.	0 – 10%
Negligible	Likelihood not distinguishable from zero.	0%
Unknown	Not sufficient information available to assess the likelihood with sufficient certainty.	0 – 100%

2.2 Using the approach

In this document, a method is described which aims to make the risk assessment of LCASs more fit-for-purpose and more efficient. This method may be used as a tool in those cases where it is considered relevant and useful. Depending on the assessment at hand, the approach may be used for the assessment related to any number of the specific protection goals (ranging from none to all). The approach is explicitly not intended to serve as an end in itself, nor to increase the requirements or workload involved in the assessment.

The applicability of the approach is described in Section 2.2.1. Section 2.2.2 provides guidance on how to apply the approach.

2.2.1 Applicability of approach

2.2.1.1 To which substances can the approach be applied?

The method of PF using generic pathways to harm can be applied to 'Part A'[2] substances for which the conventional risk assessment approach is not fully fitting and in particular for those substances which do not have a broad-spectrum, toxic mode of action (see also Section 2.1.2). These substances include certain plant extracts, peptides, fermentation products and dsRNA.

The generic pathways have been drafted to address the hazards of currently known LCAS. In case a hazard is known to apply to the active substance which is not addressed by the generic pathways included in this document, the principles of the approach apply,

[2] Substances which are assessed according to the Parts A of the Annexes of the data requirement and uniform principles, i.e., all active substances excluding those which are a microorganism.

but new pathways may need to be developed. Information on whether this applies to a specific substance may come from the information on the mode of action (see Section 2.2.2.1).

2.2.1.2 When can the approach be applied?

While the PF method using generic pathways can be used at any stage of the risk assessment, ideally, the approach could be already used by the applicant during the pre-submission stage. In this way, the method could help to determine the overall approach for the risk assessment, and the identification of the type of data needed (e.g., literature data, guideline testing, NAMs, modified effect studies considering the mode of action/effect). At this pre-submission stage, upon generating this data, the PF step can be repeated/elaborated to include the new information and in this way determine the most appropriate next step (whether it is needed to generate further data or not). An additional advantage of this approach is that information from all sections is combined at an early stage, which prevents contradictory information in different sections of the application dossier.

The outcome of applying the approach can be used to support discussions at pre-submission meetings. By using generic pathways in combination with the available information on the active substance, a preliminary agreement can be sought between the applicant and RMS on the overall approach for the dossier and risk assessment. Please note that the outcome of these discussions has no legal status in the EU.

For those elements of the risk assessment where the PF approach is relevant, information on this approach should be included in the dossier. The template provided in Annex D can be used to this end. The completed template can be included in IUCLID Section 13 (Summary and evaluation) and referred to throughout the dossier.

At the evaluation stage, the approach can be applied to the assessment regardless of whether the approach was used at the pre-submission stage. By using this approach, information which is included in different sections of the dossier is combined in a structured way. Using the resulting overview, the appropriateness of justifications for not providing data can be better assessed. Furthermore, the approach not only helps to structure the risk assessment, but also to interpret the results and communicate on the outcome (i.e., the likelihood of breaching the protection goal) and thereby enable informed risk management decisions.

2.2.2 How to apply: using the problem formulation toolbox

The PF toolbox consists of three main elements:

- The generic pathways to harm;
- The generic analysis plans;
- Guidance on the likelihood assessment.

The aim of the generic pathways is to assess the likelihood of breaching the protection goal (see Section 2.2.2.1). The generic pathways consist of a number of events which all must take place in order to breach the protection goal. The generic analysis plans provide information on which analyses may be used to assess the likelihood of the individual events in the generic pathways (see Section 2.2.2.2). How to assess the likelihood of individual events and how to combine the information within and across the generic pathways is described in the guidance on the likelihood assessment (see Section 2.2.2.3).

2.2.2.1 Generic pathways to harm

Which hazards, and thereby which generic pathways, are relevant for the assessment of an active substance depends on the properties of this substance. The mode of action of a substance can be used as an initial indicator of these hazards. Note that the hazards which are relevant for a substance do not automatically follow from the type of LCAS (being e.g., plant extract, microbial metabolite, inorganic substance): there is no one-to-one link between the different categories of LCASs and their potential hazards. For example, plant extracts may have a toxic mode of action, but can also act through suffocation, as a repellent or induce resistance.

For all types of LCAS, generic pathways from toxicity (potential hazard) for each protection goal should be considered (see Section 2.1.3.1). The same holds for the assessment of leaching to groundwater. In addition to these two hazards, other hazards may apply. To guide the process of determining which hazards, and thereby which generic pathways are relevant for a specific active substance, the flow scheme in Figure 2 can be used.

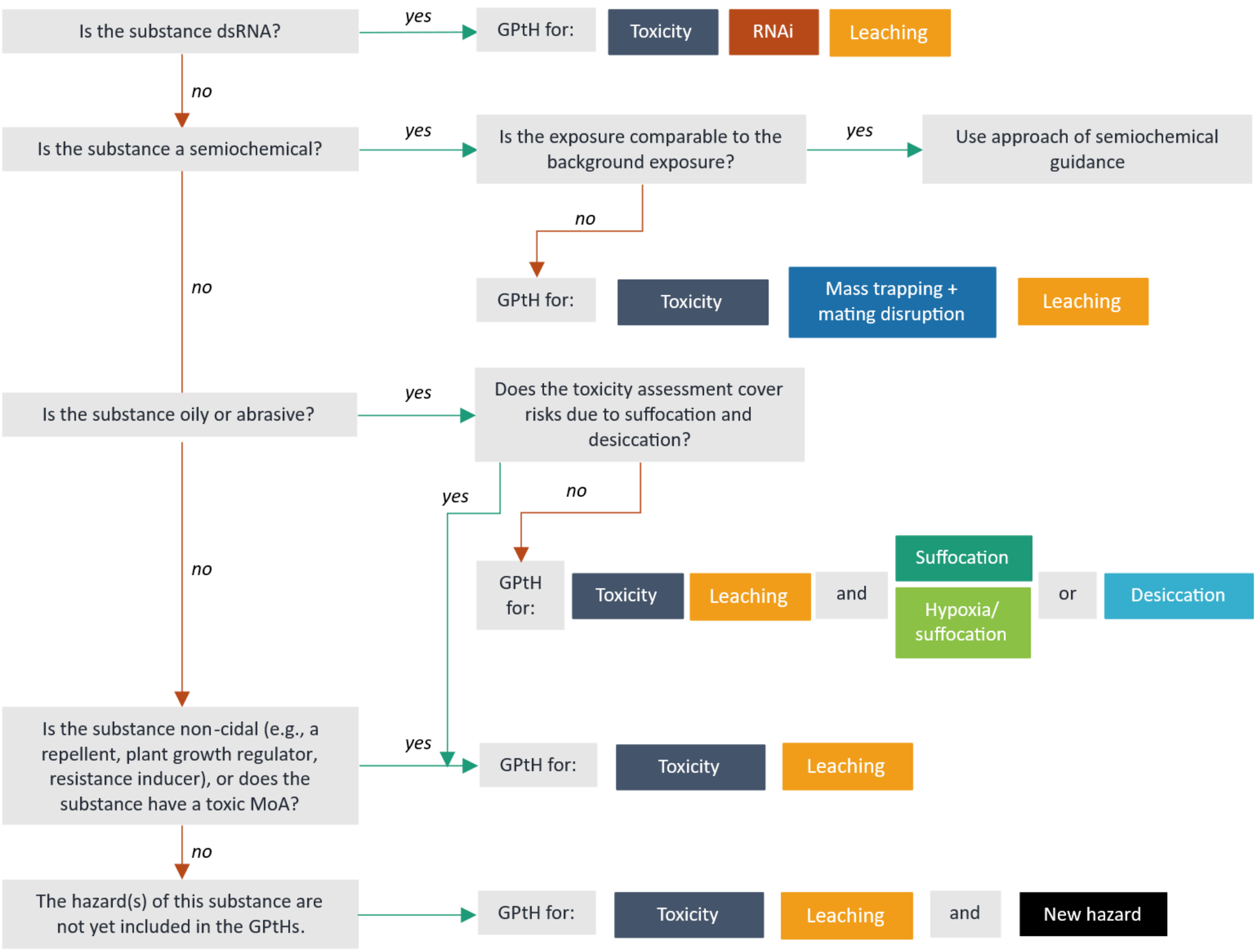

Figure 2: Flow scheme to determine which generic pathways to harm are relevant for an active substance. MoA = mode of action; GPtH = generic pathway to harm.

An overview of the generic pathways for the risk assessment of LCASs is given in Figure 3, where each line depicts a single generic pathway. The complete generic pathways are included in Appendix A.

Each generic pathway is a combination of a hazard (e.g., toxicity) and a specific protection goal (e.g., the specific protection goal for terrestrial non-target plants). As not all hazards are relevant to all specific protection goals, the number of generic pathways differs per hazard.

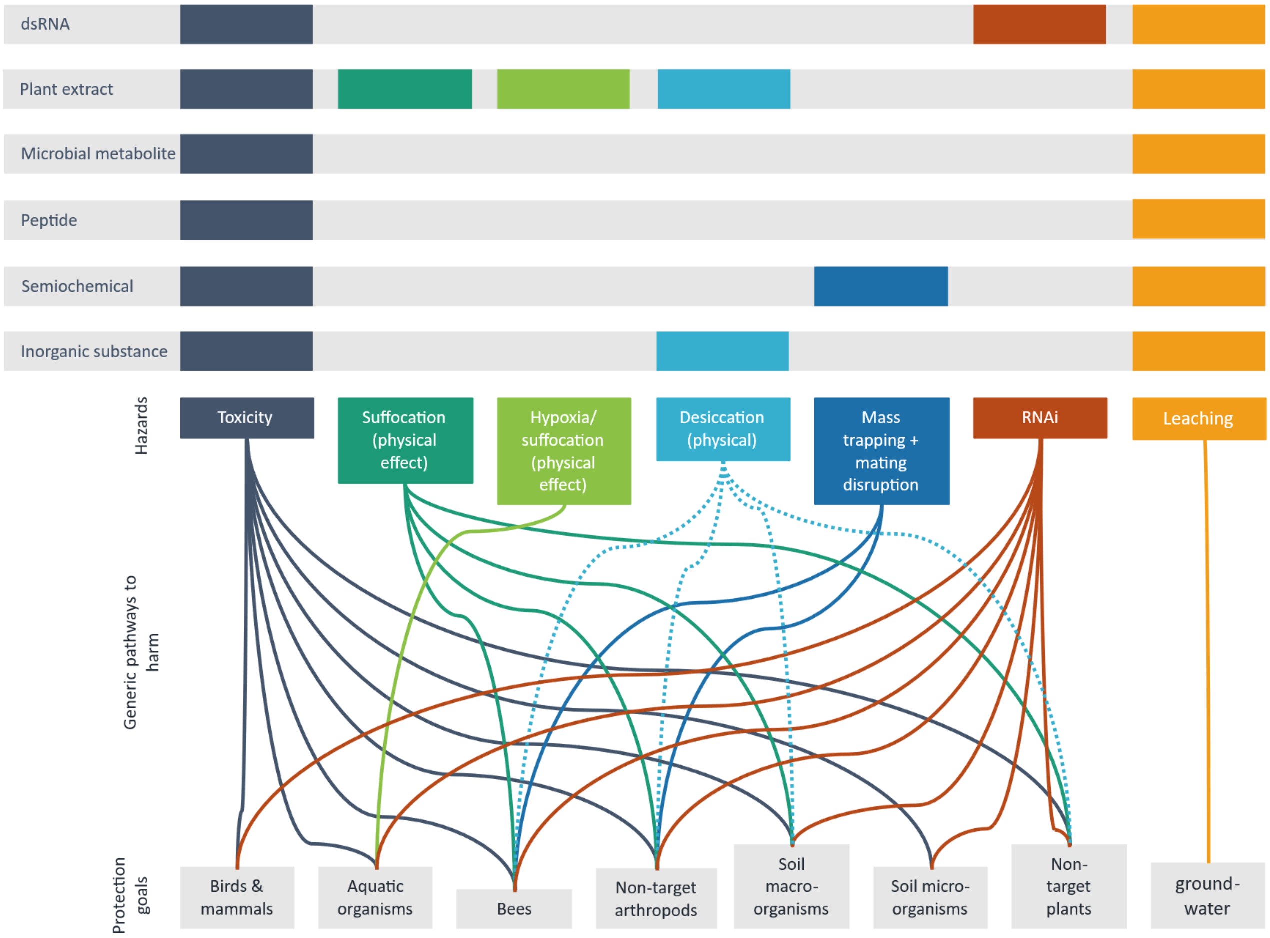

Figure 3: Overview of LCAS categories and their potentially relevant combinations of hazards and protection goals. Which generic pathways to harm are relevant for a particular substance within a category can be determined using the scheme shown in Figure 2. Each of the lines depicts an individual generic pathway (see Figure 1 in Section 2.1.3 for an example of a single generic pathway). The colours and line types are intended to help distinguish the individual lines and have no further meaning.

2.2.2.2 Generic analysis plans

The generic analysis plans can be used as a basis to determine which approach is most appropriate for the case at hand – they are not intended as guidelines to prescribe a specific approach. An overview of the generic analysis plans is presented in Appendix A, alongside the generic pathways to harm. In Appendix B (the Analysis plan tool; see text below) more detailed information on the generic analysis plans is provided.

The generic analysis plan for a single event contains at least one analysis option. In many cases, the analysis plan contains several options for a single event. In these cases, information is given on whether the separate options are most relevant for a particular type of substance or situation. The analysis options in the analysis plans cover different types of analyses such as literature studies, in silico methods, NAMs, and guideline studies. More information on the methodological approach for data collection and collation when performing literature searches is provided in Appendix C.

Please note that the fact that an analysis option is included for an event does not automatically mean that the analysis option is the most appropriate choice for the substance at hand; rather, it reflects the best option available based on current knowledge and understanding. Vice versa, in case an analysis option is not included in the analysis plan this does not mean that it is not suitable for the substance at hand.

The Analysis plan tool (Appendix B)

The Analysis plan tool consists of seven excel sheets: one sheet per hazard (i.e., toxicity, hypoxia of aquatic organisms, suffocation, desiccation, mating disruption, RNA interference and leaching). Each sheet is horizontally divided in three sections:

- The columns which include the events of all generic pathways to harm for the specific hazard. The filter buttons in row 4 can be used to select the event of interest. Please note that for the last event in each pathway ('harm', meaning not meeting the protection goal) no separate event has been included in the Analysis plan tool. This is because the likelihood of this event, and thereby harm, occurring is assessed based on the assessment of the likelihood of the preceding events in the pathway (see Section 2.2.2.3 – combining the likelihoods of events within a pathway).
- The columns indicating for which type of substance(s) the analysis plan is applicable (green section in the excel sheets).
- The columns with the generic analysis plans (text in italics refers to the column headers):
    - *Type of information for likelihood assessment*: this first column describes the type of information which can be used to assess the likelihood of an event.
    - *How information can be obtained or generated*: this second column is the core element of the analysis plan tool, as it describes how the required information can be gathered or generated.
    - *Guidance on assessing the likelihood*: this column provides guidance on how to assess the likelihood of the event based on the information generated or obtained according to the analysis plan. Where relevant, information on how the outcome of the likelihood assessment of the individual event affects the assessment of the full pathway occurring is also provided in this column.
    - *Examples from non-EU assessments:* Where available, examples are given of non- EU assessments in which the proposed analysis plan was used.

2.2.2.3 Guidance on the likelihood assessment

Upon determining which generic pathways to harm are relevant for the environmental risk assessment of a specific LCAS (see Section 2.2.2.1), the likelihood of breaching the protection goal due to the identified hazards can be assessed. This process entails several steps, which are described in the sections below. In brief, the outcome of the assessment of the likelihood of individual events in the pathway are combined to assess the likelihood of a full pathway. Where multiple hazards are relevant for an individual specific protection goal, the likelihood of breaching the protection goal due to the combined hazards is assessed in a subsequent step.

Body of knowledge

Before starting any risk assessment, a good overview is needed of general information on the active substance and the way the substance is proposed to be used. This information should at least include general information on the production process (including information on the organism from/by which the substance was produced, where relevant), the natural occurrence of the substance and its other uses, physical-chemical properties, the mode of action, the target organism(s) and the application method.

Uncertainty analysis

As for any risk assessment, the uncertainty of the likelihood assessment should be indicated (EFSA, 2018). This holds both for the assessments of the likelihood of individual events and generic pathways. Uncertainty in the assessment can be described in a qualitative manner to indicate both the magnitude of the uncertainty and in which direction the uncertainty is going, ranging from -- to ++, where - means a potential to make the true risk lower (or put differently: the data may result in a worst-case estimate of the likelihood) and + means a potential to make the true risk higher (the data may result in a best-case estimate of the likelihood). Uncertainty which can go either way can be indicated as +/-.

As an example, in case a toxicological reference value is known which is given as > 2000 mg/kg body weight, the actual reference value may be (much) higher than this value. When using the value of 2000 mg/kg body weight in the risk assessment, the uncertainty in the reference value is in the direction of a conservative estimation (and can therefore be indicated as -). In case a small number of samples were used to derive an endpoint, the uncertainty might be bidirectional (+/-).

The assessment of the likelihood combines the information on the variability (the inherent randomness of the system) and the uncertainty (caused by imperfect information; see also Section 2.1.5).

Assessing the likelihood for a single generic pathway to harm

When using generic pathways, it is important to be aware of three principles:

1. The events in the pathway do not need to be assessed in a fixed order. Which order of events is most appropriate depends on the properties of the substance and its use and on the information which is already available.

2. It is not compulsory to assess the likelihood of all the events in the pathway. Once sufficient information is available to assess the likelihood of breaching the protection goal as *negligible* or *very unlikely*, no further information is needed. This means that for some cases only a single event needs to be assessed, while for other cases an assessment of all events within the pathway is needed.

3. The process of using generic pathways is adaptive and iterative. In this way, it is more similar to playing chess (where each move depends on how the board looks at that time) than to following a fixed recipe where each step is pre-written and must be followed in order. The assessment starts with a provisional evaluation in which the information available on a substance is compared against the generic pathway. This provisional evaluation is used to determine at which event to start the likelihood assessment. Depending on the information which is generated during this assessment, it may be necessary to revisit events which have already been assessed to reduce the uncertainty of this assessment for a more accurate assessment of the likelihood.

<u>Determining at which event to start</u>

The best starting point for the assessment is determined based on a provisional evaluation of what is already known for the substance and its use. Using this information, the likelihood of the events in the pathway can be provisionally estimated, while the likelihood of events for which information is lacking is provisionally marked as 'unknown'. In this way, the event can be selected which is easiest to assess and is critical for the outcome of the assessment. 'Critical' means that the result of the likelihood assessment will have a big impact on the assessment of the full pathway – that is, knowing whether or not the event is likely to occur will substantially change the overall risk estimate. Therefore, the most critical events are those where the assessment is expected to have the lowest likelihood. Which event this is will depend on the properties of the substance, on the availability of data and on the effort required to generate data. When the PF methodology is used during the dossier preparation phase, also the need to generate data for harmonised classification and labelling (CLH) can be taken into account. Applicants can consider whether the data required for CLH can also be used in the risk assessment to ensure efficiency and avoid duplication.

<u>Assessing the likelihood of a single event</u>

To assess the likelihood of a particular event occurring, the suggestions in the generic analysis plan can be used (see Section 2.2.2.2). More information on the types of analyses is given in the Analysis plan tool (Appendix B). Which type of analysis is most appropriate for the assessment of the likelihood of an event, will depend on the properties of the substance and its use, as well as on the information which is already available.

At this stage (following the preliminary evaluation), the assessment of the likelihood should consistently be substantiated with appropriate data or information. The result of this assessment of a single event is a combination of a likelihood descriptor and a description of the associated uncertainty and includes a list of the data and information on which this assessment is based. A template in which the likelihood, uncertainty and underlying data and information can be presented is included in Appendix D. The full set of likelihood descriptors, their definitions and the associated subjective probability ranges are given in Table 1 in Section 2.1.5. Information on how to describe uncertainty is given above in the current section.

Assessing the likelihood of the full generic pathway

After the assessment of the likelihood and uncertainty of a single event, this information is combined with information on other events in the pathway. In this way, all available information for the full generic pathway is combined to assess the likelihood of breaching the protection goal (being the last event in the pathway) and the uncertainty in this assessment. This process is repeated every time new data or information is included in the assessment which results in changes of the assessment of the likelihood or uncertainty of individual events.

There are no fixed calculation rules on how to combine the likelihood of the events in a pathway. As a rule of thumb, the event with the lowest likelihood sets the upper limit for the likelihood of the full pathway. The uncertainty in this event plays a key role in the overall uncertainty of the pathway.

Whether or not the likelihoods of several events in a pathway can be combined (e.g., *very unlikely* + *very unlikely* = *negligible likelihood*) depends on whether the events are independent. For instance, if the events concern different aspects such as exposure and effects, it may be appropriate to combine their likelihoods in this way. In contrast, if the events are related – for example, effects at the individual level and effects at population level – then their likelihoods cannot be added, as they are not independent.

In those cases where an event in the generic pathway is assessed as having a *negligible likelihood*, it can be concluded with sufficient certainty that the likelihood of breaching the protection goal is *negligible*. This holds for those cases where a hazard is not relevant for a substance (e.g., toxicity to mammals for a substance used and having the quality needed for it to be food), or when exposure does not occur.

In all other cases, an assessment of the likelihood of several events is needed to assess the likelihood of breaching the protection goal. In these cases, the full pathway provides a framework for a systematic approach to scientific argumentation. Upon completing the assessment of the likelihood of a single event, the likelihood of breaching the protection goal is determined. In case the information is not sufficient to assess this likelihood as *very unlikely* or *negligible*, more data should be generated and assessed. The most relevant event for which next to generate and assess additional data can be identified using the same approach used to select the initial event in the assessment.

The result of the assessment of the likelihood of a full pathway is again a likelihood descriptor and a description of the associated uncertainty. The same likelihood and uncertainty descriptors can be used for the full pathway as for the individual events. A template to include this information for the full pathway is also included in Appendix D.

Assessing the likelihood of breaching the protection goal for multiple generic pathways to harm

In those cases where more than one generic pathway to harm is relevant for a single protection goal, the likelihood of all these pathways should be considered collectively when assessing the likelihood of breaching that goal. In such cases, the resulting likelihood cannot be lower than the highest of the individual pathways. Whether the resulting likelihood is higher than the highest of the individual pathways depends on whether the effects caused by the two hazards are additive. For instance, this may be the case if larval stages of a non-target organism population are vulnerable to suffocation, whereas adult stages are affected by toxicity. In many cases, the risk from one hazard is effectively covered by the risk from another, especially when both depend on the same exposure conditions. If exposure is high enough to cause significant effects through one pathway (e.g. toxicity), it may also trigger effects through the other (e.g. suffocation), but often to a lesser extent. Individuals affected by the more sensitive hazard are already removed from the population, so the second hazard adds little to the overall outcome. In such cases, the likelihood of the dominant pathway determines the overall risk of breaching the protection goal.

<u>Outcome of the risk assessment and risk management</u>

Which level of probability of breaching the protection goal may be considered as acceptable is a risk management decision. In general, when the likelihood of breaching the protection goal is assessed as *very unlikely* or having a *negligible likelihood*, the consortium proposes that a low risk may be concluded. In this case, the effects may be considered as acceptable by risk managers.

To support informed decision-making, it is essential to clearly specify the level of uncertainty associated with the likelihood assessment as not doing so may lead to misinterpretation and a higher perceived level of risk. When the likelihood of breaching the protection goal is assessed as *unlikely* or higher (i.e., more likely), this may reflect either the true level of risk or a lack of sufficient data to justify a classification of *very unlikely* or lower (i.e., more unlikely). The risk assessment should therefore explicitly state which of these applies, with reference to the uncertainty associated with the pathway. Similarly, if the likelihood is assessed as *unknown*, the actual risk may still be low, but the necessary data to demonstrate this are lacking. In this case, the PF approach can be used to determine which data would be needed to resolve the unknown likelihood.

3 Conclusions and future developments

The proposed PF approach using generic pathways to harm can serve as the basis for a more fit for purpose risk assessment for LCAS. Using this-approach at the start of the risk assessment process guides the risk assessment and makes clear which data requirements need to be fulfilled. It also helps the discussion between the applicant and the risk assessor to agree on the data waivers and on the use of alternative method to address data requirements. Also, if applied during the evaluation of the dossier it can help to assess the justification of data waivers and alternative approaches as suggested by the applicant and to interpret and communicate on the results of the assessment.

Furthermore, the PF approach can be applied to bring to light and assess concerns which are currently not addressed by the risk assessment, for example those arising from hazards other than toxicity (e.g., suffocation or desiccation). For these hazards other than toxicity, the current risk assessment schemes (effect testing, exposure assessment and quantitative thresholds) may not be appropriate. This holds for example for substances with a physical mode of action that require direct exposure during application (e.g., oily substances). A key benefit of the approach using generic pathways to harm is it can guide the applicant at an early stage to perform effect studies which are fit-for-purpose rather than just following the ecotoxicity testing developed for standard chemicals, and to increase the acceptance of these fit-for-purpose studies across Member States.

Based on the above, we propose the following next steps could be considered for a more appropriate and efficient risk assessment of LCAS:

- Development of a guidance document on PF using pathways to harm.
- For clearly defined categories of LCAS, the approach described in this document can be used to draft/improve guidance documents (e.g., for RNAi, antibodies).
- For categories of substances whose hazards (e.g., suffocation, desiccation) or other intrinsic properties (e.g., not miscible with water) render the current risk assessment scheme not appropriate, and for which quantitative data are needed to demonstrate a level of probability of breaching the protection goals which may be considered as acceptable by risk managers, it may be necessary to develop or adapt test guidelines, exposure models and quantitative thresholds to support such assessments (see Table 2). As a first step, it could be determined for which hazards or categories of substances such quantitative data are needed.
- During the application of the methodology (case studies), as well as during the compilation of the toolbox, specific data or knowledge gaps were identified that could not be addressed by the existing waivers (Appendix F) or by current knowledge on NAMs (Appendix G). Indicative (non-exhaustive) examples of data or knowledge gaps, and respective recommendations (adaptation of existing methods, new guidelines, establishment of threshold values), are listed in Table 2.

- While out of scope for the current project, this approach can be applied to microbial PPP (see Steenbergh et al., 2025).
- Lastly, while not only out of scope of the current project, but also out of scope of Regulation (EC) No 1107/2009, the assessment of LCAS could benefit from including information on overall environmental impact comparisons compared to current practice with conventional pesticides.

Table 2: Indicative (non-exhaustive) examples of data or knowledge gaps, and respective recommendations (adaptation of existing methods, new guidelines, establishment of threshold values) for the risk assessment of LCAS

Type of information for likelihood assessment	**Knowledge or data gap**		
	Effect-Testing guidelines (modification/generating data)	**Exposure Assessment (model adaptation)**	**Quantitative assessment (establish threshold values)**
Hazard: toxicity			
Assess likelihood of NTOs being exposed to the substance in toxicologically relevant concentrations for substances with high volatility	Development of inhalation toxicity test on terrestrial NTOs for highly volatile substances. Acute avian inhalation test is available for microbial pesticides (Office of Prevention, Pesticides and Toxic Substances [OPPTS] 885.4100 Avian inhalation Test; USEPA, 1996b]. Respiratory exposure to volatile organics in burrowing mammals (Gallegos et al., 2007) (Ref.: Appendix B, sheet: toxicity cell: AU18)	Development of Inhalation exposure model for highly volatile substances (Ref.: Appendix B, sheet: toxicity cell: AU18)	Development of trigger values based on the magnitude of effects caused by the substance combined with predicted exposure (environmental concentrations – based on proposed use) (Ref.: Appendix B, sheet: toxicity cell: AU18)
Hazard: Suffocation			
Assess likelihood of direct exposure of susceptible life stages of NTAs, soil macro-organisms and plants directly to the oily substance during application	Suffocation tests on different life stages (egg, larvae, adult) of NTAs (slide-dipping technique (Campbell and Miller 2017; Abd-Elnabi et.al., 2023) according to the FAO's suggested procedure (Stribley et al., 1983)) or topical exposure methods (over-sprayed) (Mohamad et al., 2013). (Ref.: Appendix B, sheet: suffocation, cell: AA8)	Assessment of the drift of oily substances to assess the off-field exposure, the surface of off-field areas that are exposed to oily spray upon application. Assessment of the exposure time window before substance dries (Ref.: Appendix B, sheet: suffocation, cell: AA9). Assessment of crop interception of oily substances (Ref.: Appendix B, sheet: suffocation, cell: AA10)	
Assess likelihood of effects on individuals and populations of NTAs, soil macro-organisms, plants, and recovery			Development of trigger values based on the magnitude of effects (suffocation) caused by the substance combined with predicted direct exposure (estimated in concentration (ug/L) or deposition area (ug/area) (Ref.: Appendix B, sheet: suffocation, cell: AB13) Population model for assessing population-level effects and recovery (Ref.: Appendix B, sheet: suffocation, cells: AA14-19)

Type of information for likelihood assessment	Knowledge or data gap		
	Effect-Testing guidelines (modification/generating data)	**Exposure Assessment (model adaptation)**	**Quantitative assessment (establish threshold values)**
Hazard: hypoxia			
Assess the likelihood of a layer of the active substance forming on top of the water column		Spreading rate regression model capable of predicting rate of spread of oil spills on water and stability (weathering, evaporation, oxidation, biodegradation, and emulsification) (Ref.: Appendix B, sheet: hypoxia, cell: I7) (already exists for crude oils).	FOCUS models may be adapted to be able to describe the behaviour of oils in aquatic systems (e.g., predicting the amount of substance per unit area of aquatic systems). When using this approach, it is crucial to align the approach for the exposure and the effect assessment, including dose expression for effect testing. (Ref.: Appendix B, sheet: hypoxia, cell: I7)
Assess likelihood of effects on individual aquatic organisms	Hypoxia testing to demonstrate the susceptible aquatic organism (Ref.: Appendix B, sheet: hypoxia, cell: I9)		Development of trigger values based on expected magnitude of oxygen depletion based on the predicted exposure (calculate the environmental exposure as DEPOSITION AREA IN mg of substance per m2 of water surface area, 2D approach, or AS CONCENTRATION IN ug of substance per L of water, 3D approach) (Ref.: Appendix B, sheet: hypoxia, cell: I10)
Assess likelihood of effects on populations of aquatic organisms (other than vertebrates)			Population model for assessing population-level effects and recovery (Ref.: Appendix B, sheet: hypoxia, cell: I11)
Hazard: desiccation			
Assess likelihood of effects on individual NTOs and populations			Development of trigger values based on the magnitude of effects (desiccation) caused by the substance combined with predicted exposure (environmental concentrations – based on proposed use) to the active substance in its effective form (i.e., dry and sufficiently undiluted) (Ref.: Appendix B, sheet: desiccation, cells: V9-11, 13)

Type of information for likelihood assessment	Knowledge or data gap		
	Effect-Testing guidelines (modification/generating data)	**Exposure Assessment (model adaptation)**	**Quantitative assessment (establish threshold values)**
			Population model for assessing population-level effects and recovery (Ref.: Appendix B, sheet: desiccation, cell: V12)
Hazard: mating disruption			
Assess likelihood of effects on individual NTAs and populations			Development of trigger values based on non-toxic effects (behavior and physiology) in combination with predicted exposure (environmental concentrations – based on proposed use) (Ref.: Appendix B, sheet: mating disruption, cells: P9-11, 13) Population model for assessing population-level effects and recovery (Ref.: Appendix B, sheet: mating disruption, cell: P12)
Hazard: RNAi			
Assess likelihood of effects on individual NTOs and populations			Development of trigger values based on the magnitude of effects caused by the substance combined with predicted exposure (environmental concentrations – based on proposed use) (Ref.: Appendix B, sheet: RNAi, cells: AX17-19, 21-22) Population model for assessing population-level effects and recovery (Ref.: Appendix B, sheet: RNAi, cells: AX20, 23)
Hazard: leaching			
Determine PECgroundwater		Development of appropriate models for inorganic substances (Ref.: Appendix B, sheet: leaching, cell: G10)	Laboratory tests whose results feed into the FOCUS groundwater models should quantify volatilisation and degradation separately to accurately simulate leaching for volatile compounds. (Ref.: Appendix B, sheet: leaching, cell: G8)

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Glossary and Abbreviations

Glossary

Where available, and unless stated otherwise, the definitions included below were taken from EFSA's multilingual glossary (https://www.efsa.europa.eu/en/glossary-taxonomy-terms; accessed 7/17/2025).

Term	Definition
Abrasive	A property of active substances which causes mechanical damage to the outer surface of organisms, such as the exoskeletons of arthropods. This damage can lead to desiccation of the organisms.
Active Substance	A substance that acts against harmful organisms, such as pests or diseases, which affect plants.
Biopesticides	Plant protection products (PPPs) that contain micro-organisms (including viruses), botanicals, or semiochemicals as active substance. (Ctgb Evaluation Manual Biopesticides Part 2: Botanicals version 2.0, 2022)
Botanical active substance	Active substance consisting of one or more components found in plants and obtained by subjecting plants or parts of plants of the same species to a process such as pressing, milling, crushing, distillation and/or extractions. The process may include further concentration, purification and/or blending, provided that the chemical nature of the components is not intentionally modified/altered by chemical and/or microbial processes. (SANCO/11470/2012– rev. 8)
Desiccation	A physical hazard associated with substances that cause excessive water loss in non-target organisms, particularly arthropods, by compromising the protective functions of their cuticle.
Ecotoxicology	The study of the adverse impacts of substances, particularly chemicals, in relation to the environment and public health.
Endpoint	A physical or chemical outcome that can be assessed by a test; for example, blood pressure or levels of a potential toxin in the body.
Environmental Risk Assessment (ERA)	The process of assessing potential harm to the environment caused by a stressor. This may include the introduction of GM plants, the use of pesticides, or the spread of plant pests. In the context of this report, it relates to the use of Low-Concern Active Substances.
European Food Safety Authority (EFSA)	An agency of the European Union set up in 2002 to serve as an impartial source of scientific advice to risk managers and to communicate on risks associated with the food chain.

Term	Definition
Exposure	Concentration or amount of a particular substance that is taken in by an individual, population or ecosystem in a specific frequency over a certain amount of time.
Exposure Assessment	One of the key steps in risk assessment, this relates to a thorough evaluation of where, who, or what, will be exposed to a hazard and a quantification of the amounts involved.
Exposure Model	A tool used to estimate the place and level of exposure of organisms or humans to a substance.
Fit-for-Purpose Risk Assessment	A regulatory evaluation designed to match the unique properties and intended uses of LCAS.
Generic pathway to harm	A conceptual model to assess the likelihood of breaching the protection goal that sets out the events that must occur if the use of the LCAS is to cause harm, i.e., breaches the protection goal.
Harmonised Classification and Labelling (CLH)	A system to categorize and communicate hazards of substances. Harmonised classifications are listed in Annex VI to CLP Regulation.
Hazard	A substance or activity which has the potential to cause adverse effects to living organisms or environments.
Hazard characterisation	The second step in risk assessment, this involves defining the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food or other relevant matrices. The process should, if possible, involve an understanding of the doses involved and related responses.
Inorganic substance	Chemical that does not generally contain carbon-hydrogen bonds; for example, water, oxygen, sodium chloride. When carbon has a chemical bond to hydrogen, these substances are classified as organic.
Low Concern Active Substances (LCASs)	In the context of this report, LCASs refers to active substances with expected lower adverse effects compared to conventional chemical active substances (see https://www.efsa.europa.eu/sites/default/files/documents/art36/gpefsaplants202304/call-for-proposals-stepwise.pdf).
Mode of Action	A sequence of biological (physiological, biochemical or physical) events by which a pesticide exerts its effect in a target organism.
New Approach Methodologies (NAMs)	Innovative risk assessment methods beyond traditional toxicity testing.
Organism	A living thing such as humans, animals, plants and microbes (e.g. bacteria, viruses).

Term	Definition
Pesticide	Substance used to kill or control pests, including disease-carrying organisms and undesirable insects, animals and plants.
Plant Protection Product (PPP)	Products used to protect, preserve or influence the growth of desirable plants or to destroy or control the growth of unwanted plants or parts of plants.
Population	Community of humans, animals or plants from the same species.
Problem Formulation (PF)	The process of defining the specific problem being addressed in, for example, an environmental risk assessment. It involves articulating a question and defining how it may be answered (e.g. by identifying the endpoints to be measured)
Protection Goal	The environmental or health standard that must not be compromised by the use of a plant protection product.
Qualitative Risk Assessment	A risk evaluation method using descriptive terms rather than numerical data.
Quantitative Risk Assessment	A risk evaluation method using numerical data to estimate risk levels.
Risk characterisation	The final stage of risk assessment, in which the likelihood that a particular substance will cause harm is calculated in the light of the nature of the hazard and the extent to which people, animals, plants and/or the environment are exposed to it.
Risk management	The management of risks which have been identified by risk assessment. It includes the planning, implementation and evaluation of any resulting actions taken to protect consumers, animals and the environment.
RNA	A type of nucleic acid found in the body, similar to DNA but single stranded. The best-known function of RNA (ribonucleic acid) is transmitting instructions from DNA to the cellular machinery responsible for making proteins.
RNA Interference (RNAi)	A biological process where RNA molecules inhibit gene expression.
Suffocation	A physical hazard associated with certain oily substances that can impair or obstruct the normal respiratory function of non-target organisms.
Threshold	A dose or exposure below which adverse effects are not detected.
Toxicity	The potential of a substance to cause harm to a living organism. In the context of this report, '**toxicity**' refers to chemical toxicity and thereby to the degree of a substance being poisonous (i.e., to damage susceptible sites or cells in living organisms).

Term	**Definition**
Uncertainty	Scientific concept used in risk assessment to describe all types of limitations in available knowledge at the time an assessment is conducted, with the agreed resources, that affect the probability of possible outcomes to the assessment.
Waiving of data	in the context of this document, data waiving refers to not submitting specific data normally required under the data requirements by providing an adequate and substantiated justification as outlined in point 1.5 of the Annexes of Regulation (EU) No 283/2013, demonstrating that the data are not necessary due to the nature of the PPP or its proposed uses, or that their submission is not scientifically necessary.

Abbreviations

AUTH	Aristotle University of Thessaloniki
CLH	Harmonised Classification and Labelling
CSIC	Consejo Superior de Investigaciones Científicas
Ctgb	Dutch Board for the Authorization of Plant Protection Products and Biocides
dsRNA	Double-stranded Ribonucleic Acid
EC	European Commission
EFSA	European Food Safety Authority
HAO	Hellenic Agricultural Organization - DIMITRA
ERA	Environmental Risk Assessment
EU	European Union
FAO/WHO	Food and Agriculture Organization/World Health Organization
INIA	Spanish National Institute for Agricultural and Food Research and Technology
LCAS	Low Concern Active Substances
MoA	Mode of Action
NAMs	New Approach Methodologies
OECD	Organisation for Economic Co-operation and Development
PEC	Predicted Environmental Concentrations
PF	Problem Formulation
PPP	Plant Protection Products
RNA	Ribonucleic Acid
UTH	University of Thessaly
WENR	Wageningen Environmental Research

Appendix A – Generic pathways to harm

Appendix B – Analysis plan tool

Appendix C – Key considerations for conducting literature searches and data collection

Appendix D – Template for output of using the generic pathway to harm approach

Appendix E – Case study

Appendix F – Waiver criteria - Summary and grouping

Appendix G – Current knowledge on NAMs and their potential use in LCASs risk assessment