APPENDIX A – Meeting minutes

"Workshop on the development of a fit-for-purpose approach for assessing the risk of low-concern active substances.

15th and 16th January, 2025, Mediterranean Palace Hotel, Thessaloniki, Greece

In attendance:

Last name	First name	Break-out Group
ALONSO PRADOS	Elena	3
ARTS	Gertie	2
AUTERI	Domenica	1
BERTRAND	Cedric	1
BREMMER	Ingrid	2
DALAKOURAS	Athanasios	4
DEVENIENE	Vaida	3
DROVTAR	Krista	1
DUCHARD-YAMADA	Sophie	4
DUQUENE	Lise	2
FERILLI	Franco	3
FRAGKOULIS	Georgios	1
GLANDORF	Debora	4
GRAUBE	Laura	2
GUIJARRO	Belén	3
HATJINA	Fani	2
HINGER	Isabella	1
KARANASIOS	Evangelos	2
KARAZAFEIRIS	Emmanouil	3

KARPOUZAS	Dimitrios	3
KIENZLER	Aude	2
KOCH	Claudia	4
KOUTSOUMANIS	Kostas	1
KRÄMER	Wolfgang	4
KRUSKOPS	Krists	3
KUBÁTOVÁ-HIRŠOVÁ	Hana	2
LAVA	Roberto	3
LIEGEOIS	ERIC	4
LINC	Gabriella	3
LYNCH	Donal	1
LYTHGO	Christopher	1
MALTBY	Lorraine	3
MATHIEU	Laura	4
MENKISSOGLU-SPIROUDI	Urania	3
MIRICESCU	Alexandra	2
MRNJAVCIC VOJVODA	Ana	3
NOGUEIRA DE DIEGO	Natalia	4
OCVIRK	Miha	4
OLIVEIRA	Ana Bárbara	3
PAPADAKIS	Emmanouil Nikolaos	1
PAPADOPOULOU	Kalliope	4
PATINO-ROPERO	María José	4
PILLING	Edward	2
POLST	Bastian	2
SHARP	Rachel	4

STEENBERGH	Anne	4
STORSET	Audun	3
TSALOUMI	Sofia	2
TSAMPOULA	Aggeliki	1
TZVETKOV	Nikolay Kirilov	2
VEGIENE	Egle	1
VERNILLET	Anaïs	1
VRYZAS	Zisis	1

- **Welcome**

Professor Kostas Koutsoumanis welcomed everyone in Thessaloniki and addressed the participants, stating that he has been very happy with his participation in EFSA programs all these years. Working with EFSA differs from the academic approach to work and it is an excellent prospect to collaborate with EFSA recommending this to all scientists.

- **Introduction to the project and the workshop**

Professor Vryzas welcomed everyone in Thessaloniki and presented the goals of the workshop. The workshop focuses on the development of a risk assessment approach for Low Concern Active Substances (LCASs), in the framework of the PERA project. The aim is to develop a harmonised stepwise approach for a fit-for-purpose risk assessment of active substances that are falling under Part A of the Data Requirements (Regulation 283/2013) and that are potentially of low concern. An introduction to the PERA project and the purpose of the Workshop was presented by Domenica Auteri from EFSA, including an overview of the Multiannual Plan (funding, partnerships, objectives), a definition and categories of LCASs and Key Sub-Objectives of the Project. The main goals are:

- ✓ To define criteria for the identification and classification of LCASs.
- ✓ To define criteria for not submitting established studies (e.g. toxicity, exposure).
- ✓ To investigate alternative methods for risk assessment.
- ✓ To develop an adapted exposure assessment approach.
- ✓ To create a progressive risk assessment methodology.
- ✓ To identify criteria for literature review.
- ✓ To identify knowledge gaps.

Details concerning the duration & collaborations were presented by Prof. Vryzas. As mentioned, the workshop is designed to engage Member States (MS) and stakeholders in refining the draft proposal. It will provide a platform for:

- ✓ Gathering feedback on the current risk assessment practices for LCASs.
- ✓ Introducing the problem formulation and the Pathway to Breach the Protection Goals (PBPG) methodology.
- ✓ Facilitating group discussions on the application of these methodologies.

This workshop represents a crucial step toward developing more streamlined, efficient, and scientifically sound methods for evaluating Low Concern Active Substances.

- **Introduction on the use of problem formulation in risk assessment.**

Dr. Glandorf had a presentation about the application of problem formulation in the Environmental Risk Assessment (ERA) of Genetically Modified Organisms (GMOs). The presentation covered the involvement of various EFSA working groups and panels in assessing GMOs, synthetic biology, and other related topics. Key aspects included:

- ✓ Different approaches for the risk assessment of GMOs, such as one-size-fits-all and case-by-case approaches.
- ✓ The steps in ERA, including problem formulation, hazard characterization, exposure characterization, risk characterization, and risk management strategies.
- ✓ The importance of identifying protection goals and developing plausible pathways to harm.
- ✓ Examples of how to formulate risk hypotheses and acquire information for hypothesis testing.
- ✓ Using the pathway to harm (PTH) to assess the potential risks associated with GMOs.

- ✓ The advantages of problem formulation in providing flexible, focused, and transparent analysis plans.

The presentation emphasizes the importance of having clear operational protection goals and considering multiple pathways to harm to ensure a comprehensive risk assessment.

- **Introduction to PBPGs (pathways to breach the protection goal) for a stepwise approach of a fit-for purpose risk assessment**

The presentation by Dr. Anne Steenbergh (Ctgb, NL) outlined a new methodology for assessing low concern active substances (LCAS) using pathways to breach the protection goal (PBPGs) as developed within the project. The contents included:

- ✓ The need for a new approach as existing methods for conventional pesticides are deemed inadequate for LCAS risk assessment due to their complexity. A new approach is needed to better fit the properties of these substances.
- ✓ The need for a harmonized and transparent approach that integrates both qualitative and quantitative information.
- ✓ Details about the PBPG method: The PBPG method assesses the likelihood of breaching protection goals through a series of steps, each evaluating different aspects such as exposure and toxicity. It emphasizes flexibility and the integration of all relevant information.
- ✓ Application of the method: This method is repeatable and adaptable to new data. It is designed to assess both the likelihood and severity of potential breaches.

The presentations concluded that the case-by-case approach remains essential for many LCAS and that a harmonized PBPG approach supports this by offering an appropriate and transparent method for risk assessment, combining all available information and fitting both qualitative and quantitative data. Moreover, a PBPG-based approach provides a structured and transparent way to assess risks, which is more fitting for the properties of LCAS and ensures better communication and harmonization in the assessment process.

- **Experience from EC & MS on the assessment of LCAs**

The presentation shared experiences of the European Commission as a risk manager for low-concern active substances in plant protection products. Key points included:

- ✓ **Trends in Applications**: The number of applications for new active substances, including biopesticides, has increased significantly since 2001, reflecting a growing interest in low-hazard active substances.

- ✓ **Definitions and Clarifications**: The presentation provided definitions for various terms such as low-risk active substances, biopesticides, and bio-control agents. These definitions are crucial for developing fit-for-purpose risk assessments.

- ✓ **European Green Deal**: The presentation aligned with the objectives of the European Green Deal, which aims to reduce the use and risk of chemical pesticides by 50% and achieve 25% organic farming by 2030.

- ✓ **Problem Formulation in Risk Assessment**: The presentation emphasized the need for a problem formulation approach in environmental risk assessment, focusing on potential effects, hazards, and exposure.

- ✓ **Case Studies**: Several real case studies illustrated the application of fit-for-purpose risk assessments for various types of active substances, including natural oils, minerals, and plant compounds.

- ✓ **Challenges and Reflections**: The presentation highlighted the challenges in current risk assessments, including the need for flexibility and ongoing research to complement existing guidance.

Overall, it advocated for a harmonized, transparent, and flexible approach to assessing the risks of low-concern active substances.

Ireland's Experience in Assessing Low Concern Active Substances (LCAS)

The next presentation was by Dr. Alexandra Miricescu, a Regulatory Environmental Toxicologist from the Department of Agriculture, Food and the Marine in Ireland. This presentation highlighted the current challenges and suggested improvements in evaluating LCAS, emphasizing a need for standardized approaches and better study designs. Key points included:

- ✓ Experience concerning an overview of LCAS evaluated by Ireland, issues with available data and data requirements and use of expert judgement to decide on the robustness of waivers and bridging principles/read-across.

- ✓ Issues with studies concerning quality of aquatic studies and issues with analytical verification and inadequate study designs that do not consider the Mode of Action (MOA) of the active substances.

- ✓ Issues with high application rates and frequency of application, challenges in determining background levels and the presence of co-formulants that could lead to data gaps, Endocrine Disruptor (ED) assessment relies on waivers due to no applicable ED scenario.

- ✓ Suggestions for improvement concerning harmonization and clarification of data requirements with a standardized approach, minimum data requirements based on the MOA of the active substance, study design reflecting the MOA and application scenarios, discussion of risk mitigation proposed by applicants, focusing on co-formulants and increased applicant awareness of requirements for LCAS authorization.

Example of application to LCAs: Case studies presentations

Members of the consortium presented some of the case studies developed within the project by the consortium (inorganic substance used as an insecticide, an oily substance (plant extract; edible oil) acting as an insecticide and a microbial metabolite acting as an insecticide).

- **Example of application to LCAs: Case studies presentations-Inorganic substance with insecticidal activity**

The next presentation was by Dr. Menkissoglou-Spyroudi Urania concerning a hypothetical case study of the use of an inorganic substance with insecticidal activity. Here are the key points:

- ✓ **General Information**: LCAS include botanicals, semiochemicals, microbial metabolites, inorganics, peptides, and dsRNA. Their data requirements and risk assessment approaches do not always align with their use patterns or modes of action so a new risk assessment scheme based on problem formulation (PF) and pathways to breach the protection goals (PBPGs) was proposed.

- ✓ **Case Studies**: The workshop presented hypothetical case studies to illustrate the proposed approach for environmental risk assessment. In this case, an inorganic substance with insecticidal activity is being investigated.

- ✓ **Inorganic Substances**: Various inorganic substances have insecticidal properties not based on toxicity. Potential hazards include toxicity, desiccation, and leaching. The PBPGs

relevant for these substances included toxicity to non-target organisms, desiccation effects, and leaching to groundwater.

- ✓ **Specific PBPGs for Inorganic Substances**: In the presentation toxicity to in-field non-target arthropods, desiccation to in-field non-target arthropods: and leaching to groundwater were investigated.

In conclusion, the PBPG approach highlights that hazards for inorganic substances differ from those for conventional chemicals. A risk assessment scheme for desiccation hazards is proposed to improve evaluation methods. Continued research and development of new risk assessment schemes for LCAS are necessary for better regulatory processes.

- **Example of application to LCAs: Case studies presentations-Oily substance (plant extract) with insecticidal activity**

The next presentation by Dr. Polst concerning a hypothetical case study of the use of a botanical oily insecticide. Key points included:

- ✓ **Background Information**: Botanical substances cover a range of modes of action, including toxic and physical effects, while these substances fall under the same regulatory frameworks as chemical plant protection products.

- ✓ **Physical Mode of Action**: Loss of functionality of protective layers leads to pest demise and penetration to the respiratory system of insects, releasing the active ingredient internally and inhibiting oxygen entrance.

- ✓ **Application and Efficacy**: Plant oily substances are used as a foliar spray on soft-bodied insects and insect eggs, demonstrating low mobility, rapid degradation, low water solubility, low toxicity for birds, mammals, bees, and non-target arthropods. In any case, data gaps exist.

- ✓ **Protection Goals (PBPGs)**: Presentation focused on toxicity to aquatic organisms, hypoxia/suffocation of aquatic organisms, and leaching to groundwater proposing different pathways to harm and analysis plans for assessing risks.

- ✓ **Conclusions and Future Prospects**: Need for guidelines and testing protocols for physical effects. PBPGs can limit data required and structure assessments of botanical substances based on their properties.

In conclusion, the workshop aimed to improve the risk assessment process for botanical oily insecticides by addressing unique challenges and proposing structured approaches.

- **Example of application to LCAs: Case studies presentations-Microbial metabolite with insecticidal activity**

The next case study was a presentation by Dr. Guijarro concerning a hypothetical case of a microbial metabolite with insecticidal activity. Key points include:

- ✓ **Introduction and Background**: The workshop aimed to address the regulatory challenges associated with LCAS, including microbial metabolites with insecticidal activity. These substances are regulated under the same EU frameworks as chemical plant protection products.

- ✓ **Properties of the Active Substance**: The active ingredient is a hypothetical BAM produced through fermentation. It has a 95% purity and affects the nervous system of insects. Proposed scenarios for use include soil application, foliar applications, and bait concentrate in orchards.

- ✓ **Protection Goals (PBPGs)**: The presentation identified generic PBPGs for microbial metabolites, focusing on toxicity to birds, mammals, non-target arthropods, and leaching to groundwater. Each PBPG outlines potential hazards and pathways to harm.

- ✓ **Specific Case Study**: The case study examined three generic PBPGs: toxicity to birds and mammals, toxicity to in-field non-target arthropods, and leaching to groundwater. The likelihood of breaching these protection goals is assessed as unknown due to various uncertainties.

- ✓ **Conclusions and Future Prospects**: The PBPG approach provides a structured way to assess risks associated with microbial metabolites. The workshop emphasized the need for a case-by-case approach and highlighted that the natural origin of a substance is not sufficient to waive data requirements. Continued development of the PBPG approach is recommended to improve risk assessments for LCAS.

In conclusion, the presentation underscored the importance of a harmonized and transparent risk assessment process for LCAS, considering their unique properties and use patterns.

- **Introduction to the break-out groups**

The presentation by Dr. Rachel Sharp from EFSA outlines the objectives and structure of the Break-out session, focusing on environmental risk assessment of low-concern active substances (LCAS). Here are the key points:

- ✓ **Objectives**: To collect stakeholder feedback on the current situation and the proposed approach for pathways to breach protection goals and to share and discuss knowledge, experience, and ideas related to LCAS.

- ✓ **Breakout Groups**: The workshop is divided into four breakout groups, each chaired by a facilitator and supported by co-chairs and note takers. The four different group topics include fate and behavior aspects, ecotoxicology aspects for substances with a physical mode of action/effect, fit-for-purpose risk assessment methodology and risk assessment and communication to risk managers.

- ✓ **Process**: Breakout discussions involve three sessions; in the first session the same questions were asked to the four groups, whereas in session 2 and 3 questions were different. Note takers collect ideas and knowledge shared during the sessions. Facilitators provide feedback to the plenary session at the end of each day.

In conclusion, the scope of workshop is to gather insights, share experiences, and develop fit-for-purpose risk assessment methodologies for LCAS.

- **Sum-up in plenary - session 1**

Dr Karpouzas summarised the key points from the workshop break-out rooms discussing the current regulatory framework and proposed approach for assessing low-concern active substances (LCASs) in plant protection products. Here are the main points:

1. **Current regulatory framework**:

- General consensus that the current framework is inefficient for LCAs due to various reasons.
- Lack of clear guidance and standardized processes adapted to LCAs particularities.
- Inadequate data requirements and difficulties in understanding modes of action (MOA) of LCAs.

2. **Proposed approach**:
   - The proposed approach aims to be more fit-for-purpose and efficient by harmonizing communications and providing a clear framework for peer review.
   - Potential benefits include quicker, cheaper, and more transparent risk assessments tailored to specific MOAs.
3. **Feedback on proposed approach**:
   - Pros: Harmonization, transparency and focus on key issues.
   - Cons: Need for better-defined likelihood terms and criteria, as well as additional waiving criteria and testing methods.
   - Suggestions for improvement include simplifying terminology, developing specific scenarios for assessment, and clarifying qualitative scoring of likelihood.
4. **Summary**:
   - Need for clear guidance documents to support the proposed scheme.
   - Importance of both qualitative and quantitative approaches, depending on the substance.
   - Advantages include a more transparent and harmonized approach that addresses MoAs other than toxicity.
   - Disadvantages include the need for clearer definitions of likelihood and handling of "unknown" outcomes.

In conclusion, the presentation highlighted the need for a more tailored, harmonized, and transparent approach to assessing the risk of LCAs in plant protection products.

- **Summary of day 1 – Introduction to day 2**

Day 2 of the workshop started with Gertie Arts summarizing the major outcomes of the previous day. It was pointed out that the current risk assessment procedures are both inefficient and not satisfying in the case of Low Concern Active Substances whereas the Pathway to Breach the Protection Goal was received positively as being transparent and helpful. However, improvements were suggested in terminology, in the possibility of using a quantitative approach, in the identification of additional waiver criteria and in detailed guidelines. An explanatory table for the likelihood descriptors accompanied by proposed associated percentages was presented. An outline of the program for Day 2 was also presented.

- **Experience from Stakeholders**

Ed Pilling on behalf of Corteva and CLE pointed out that the risk assessment approach should adapt to relevant species and exposure pathways. Several challenges were acknowledged such as the difficulty of implementing standard test methods, the acceptance of non-standard test methods as well as the use of alternative approaches to address concern. Moreover, a tiered approach to fate data and the application of worse-case assumptions for exposure were suggested.

Cédric Bertrand from Akinao and IBMA stated that IBMA supports a robust and efficient safety evaluation for all biocontrol products and that a case-by case analysis is needed for the assessment of LCAS. The data decision tree approach, already published, is thus suggested to be used. As far as the problem formulation using the pathway to beach the protection goal is concerned, Mr Bertrand pointed out that the proposal needs to be improved in terms of clarity, definitions and precision on key elements.

Professor Dimitrios Karpouzas from the University of Thessaly presented the main tasks and goals of the RATION project whose objective is the development of a novel risk assessment scheme for Low-Risk Pesticides of biological origin (microbials and microbiome solutions; plant extracts, semiochemicals, pheromones; ds-RNA). Stakeholders include members from 18 countries involved in industry, regulatory bodies and academia. The presentation gave a short description of WPs 1-5 and highlighted the major outcomes in each one so far.

- **Break-out group session 3**

Discussion in the breakout groups resumed for this final session. The objective was to follow up from the break-out session 2 and gather any additional ideas from the participants on possible solutions for the fit-for purpose exposure assessment for LCASs to be further investigated.

- **Sum-up in plenary - session 2 and 3**

Zisis Vryzas presented the key points from sessions 2 and 3, breakout-group 1

- It is best to use representative values and realistic scenarios. Worst case scenarios can also be used when applicable
- Imperfect data can be used
- Evidence should be collected in an unbiased systematic way
- Examples of good exposure assessment practices created by experts should be collected
- Focus models can be used or adapted for specific types of LCASs
- Precision applications and different environmental compartments should be taken into account
- Likelihood descriptors should be linked with the outcome of breach/or not the pathway

Gertie Arts presented the key points from sessions 2 and 3, breakout-group 2

- LCAs acting via a physical MOA (oil-type (for aquatic &NTAs); inorganics); desiccation and suffocation and when the predominant route of exposure is inhalation & volatiles substances would require non-standard testing
- Unless supported by fate properties of the substances, both 2- and 3-D approaches would be required for aquatic invertebrates if toxicity and exposure in the water column cannot be excluded
- Appropriate tier I test guidelines are needed
- Waivers are acceptable provided they are based on experimental data and their use is on a case-by-case basis (general waivers might not be appropriate).

Dimitrios Karpouzas presented the key points from sessions 2 and 3, breakout-group 3

- A comprehensive, targeted approach seems to be more appropriate for data collection

- There is sufficient EFSA guidance for data collection
- Data can be collected from other sources (e.g. national monitoring programs)
- Information from other sections of the assessment can be taken and tabulated as to be used in a WoE approach
- The proposed scheme should be discussed between the applicant and RMS in pre-submission meetings. RMS could intervene at the earlier stages to ensure the correct application of the PBPGs
- Information from studies not designed to be used in the risk assessment can be supportive and should not be discarded by default
- Uncertainty should always be checked and an uncertainty analysis should always be included
- Likelihood descriptors should be clarified

Anne Steenbergh presented the key points from sessions 2 and 3, breakout-group 4

- More detailed EFSA conclusions would be useful for Risk Managers and risk assessors at product level
- Uncertainty assessment should be meaningful, contextualized and more relevant
- The uncertainty should be balanced and taken into account in the WoE and explained in the final conclusion
- The PBPG assessment will force the assessment to be more contextualized
- Reasons for reiteration should be explained
- Some risk managers have a desire for clear conclusions with indications of uncertainty.
- WoE should also consider unquantified risk mitigation
- Development of a way to identify which LCAs are of concern and need a detailed risk assessment would be helpful
- Likelihood descriptors and scales need polishing and reasoning

- **Conclusions and next steps – Closing of the meeting**

On the question asked by EFSA whether the consortium thinks that the workshop achieved its goals, Dimitrios Karpouzas responded that in his mind the goal was achieved. Some areas where further work needs to be done were identified. Other areas that could not be addressed within the time frame of the project were also identified. He concluded that many ideas and suggestions heard during the workshop will be included in the report. Zisis Vryzas added that many ideas were heard, and opinions exchanged during the break-out group sessions. Gertie Arts agreed and remarked on the very fruitful discussions in the Ecotox group. Anne Steenbergh commented on the difficult problem versus easy solution way of thinking and stated that no-one size fits all approach might be the way. Finally, EFSA remarked on the efforts made by the authorities to bring together the stakeholders in the workshop.

Zisis Vryzas presented the next steps of the project:

- The interim report 3-D4 which will include the Workshop minutes and outcomes
- The Final report D5 which will be based on all previous deliverables
- Work from the project will be presented in the 35th annual SETAC Europe meeting in Vienna

- **End of the Workshop**