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Problem formulation and conceptual framework for landscape-based environmental risk assessment of pesticides☆

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ABSTRACT

The use of plant protection products (PPPs) remains a major concern for biodiversity, ecosystem integrity, and human health, even under robust regulatory oversight. Current regulatory assessments are often fragmented: they typically examine single substances and single crops in isolation at local or simplified scales. As a result, they struggle to capture the cumulative and combined effects of multiple PPPs and the way exposure propagates and interacts across space and time (fields, crops, and seasons). Our previously proposed landscape-based Environmental Risk Assessment (ERA) framework offered an integrative solution. By jointly representing agricultural practices, environmental characteristics, species movement among habitats, and the combined impacts of multiple PPPs, the current framework delivers predictions that are more adapted to the field reality. These insights are valuable both for regulatory decision-making and for understanding how PPP risks contribute to the

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overall environmental stress. In this manuscript, we explore the needs, challenges, opportunities, and modelling tools for implementing a landscape-based ERA in both prospective (ex-ante) and retrospective (ex-post) contexts. Drawing on expert discussions and collaborative initiatives, we propose a conceptual framework with four pillars: (1) flexibility to meet diverse user and stakeholder needs, different decision contexts, and varying data availability; (2) ecological realism, the capacity to represent multiple stressors, cumulative effects, exposure pathways driven by species movement, and recovery dynamics; (3) data integration and transparency, combining monitoring and regulatory datasets for calibration, validation, uncertainty analysis, and reproducibility; and (4) regulatory uptake and interoperability, ensuring compatibility with existing ERA methodologies and producing outputs that can be interpreted and used at the landscape level across jurisdictions and tools. Beyond regulatory compliance, landscape-based ERA is a dynamic and adaptative system that provides a robust scientific basis for setting protection goals, designing targeted risk mitigation measures, shaping sustainable agricultural strategies, and communicating realistic, multi-stressor risk trade-offs to stakeholders and the public.

1. Introduction

Agricultural landscapes are spatially and temporally dynamic systems shaped by crop distribution, management practices, and seasonal cycles. These dynamics strongly influence how pesticides are applied, transported, transformed, and encountered by non-target organisms (Fahrig et al., 2010; Vasseur et al., 2013).

Environmental risk assessment (ERA) is a mandatory component of the authorization process for plant protection products (PPP). It relies on problem formulation to translate policy objectives into operational protection goals, define assessment endpoints, and establish plausible pathways to harm linking pesticide use to ecological effects (Devos et al., 2019; USEPA, 1998). In earlier work, we proposed a conceptual framework for assessing pesticide risks at the landscape level (Tarazona et al., 2024). The present manuscript builds on this foundation by advancing the next step: a problem formulation framework to support the regulatory implementation of landscape-based ERA.

In the European Union (EU), overarching policy goals such as biodiversity protection must be operationalized into implementable protection goals (Devos et al., 2019). Current ERA, as codified in the Uniform Principles Regulation, largely assumes that acceptable environmental protection can be achieved through substance-by-substance regulation. However, this assumption is increasingly challenged (Duquesne et al., 2026; Schäfer et al., 2019; Topping et al., 2020), as a growing body of evidence links biodiversity decline in agricultural landscapes to pesticide pressures (Li et al., 2020; Mineau and Kern, 2023; Fritsch et al., 2025). A key limitation of current approaches is the misalignment between ecotoxicological endpoints (often derived from sub-organismal or individual level tests), and biodiversity indicators such as taxonomic richness and population abundance. This disconnect complicates causal interference between chemical stressors and observed biodiversity outcomes (Baccaro et al., 2025).

There is increasing recognition that new conceptual approaches are needed to reflect real-world exposure complexity and cumulative pressures (Tissier et al., 2025). Addressing this challenge requires accounting for cumulative exposures to single or multiple pesticides resulting from successive applications across crops, seasons, and neighboring fields within a landscape. Landscapes mediate exposure through spatial configuration, temporal overlap, and organism movement, thereby shaping cumulative risk pathways that remain largely invisible to assessments focused on individual substances or single fields.

Although landscape-level ERA has often been criticised due to the limited availability of spatially explicit population models, recent advances in monitoring data, geographic information systems and exposure modelling now enable large-scale assessments of combined pesticide use (Porta et al., 2025) and spatially explicit exposure patterns (Rigal and Perrot, 2025). These advances support the development of risk indicators relevant for both ecosystems and human populations exposed via the environment (Galimberti et al., 2025; Urionabarrenetxea et al., 2023; Bullock et al., 2024).

Within regulatory frameworks, pre-market authorizations serve as a critical safeguard to minimize potential adverse effects of chemical exposure on human health and the environment. While substance-by-substance assessments remain a cornerstone of regulatory ERA, they are insufficient on their own. For PPPs containing multiple active substances, authorization already requires product-specific risk assessments that consider the combined properties of active substances and the co-formulated product. Extending this logic to incorporate spatiotemporal application patterns, cumulative exposures across multiple fields, and interactions with ecological networks would provide a more realistic and ecologically relevant characterization of risk (Streissl et al., 2018).

Landscape ERA integrates spatial and temporal variability in exposure and effects along with broader agronomic and ecological context, constituting an essential step towards systems-based ERA approaches (Axelman et al., 2024). The framework proposed here is forward-looking and exploratory, outlining how landscape-based ERA could be structured and progressively implemented within a regulatory context. It does not yet represent a fully operational methodology for immediate regulatory adoption and will require validation through ongoing aquatic and terrestrial case studies. Rather, it identifies key components, integration pathways, and current limitations that must be addressed in future work. By providing a holistic, context-driven framework for assessing cumulative risks and supporting verification through retrospective monitoring, this proposal advances a flexible and adaptive problem formulation approach for integrating landscape-level considerations into practical regulatory decision-making.

2. An integrated problem formulation framework for PPP ERA

The current ERA paradigm is based on frameworks developed in the 1980 s and 1990 s, where problem formulation defines the assessment plan and is followed by parallel evaluations of exposure and effects (Norton et al., 1992; USEPA, 1998). Within this structure, the problem formulation stage plays a pivotal role by translating broad protection goals into scientifically verifiable elements. The identified assessment endpoints have been defined as "an explicit expression of the environmental value that is to be protected, operationally defined by an ecological entity and its attributes" (USEPA, 1998). These endpoints specify both the ecological entity and attributes to protect such as survival, growth, reproduction, community structure, and ecosystem functions.

In pesticide ERA, a distinction is made between target organisms (e.g., the pests intended for control) and non-target organisms that form the basis of the assessment of ecological effects. While regulatory ERA frameworks across jurisdictions share similar principles, they differ in terminology and procedural specifics. In the US, the Risk Quotient (RQ) approach is used by the USEPA (USEPA Office of Pesticide Programs, 2004) to compare estimated environmental concentrations with toxicity benchmarks. In the EU, the "Uniform Principles Implementing Regulation" (Regulation (EU) No 546/2011) specifies the use of Toxicity Exposure Ratios (TERs) and Hazard Quotients (HQs) to evaluate risks to non-target organisms. In both regulatory systems, initial ERAs are based on a tiered approach. Screening-level assessments typically compare conservative endpoints derived from laboratory toxicity studies with predicted environmental exposure levels. However, according to current EFSA principles, different tiers of effect and exposure estimation can be integrated to derive risk. For instance, a refined Tier 3 exposure estimate may be compared with a Tier 1 effect endpoint, or conversely, to ensure the assessment is both protective and scientifically proportionate. If the resulting RQ falls below the acceptable threshold, the risk is considered acceptable and manageable. This is equivalent to the TER (Toxicity Exposure Ratio) exceeding the threshold, as RQs and TERs work inversely. However, if the RQ exceeds the threshold further refinement is required. This refinement may include higher-tier studies such as mesocosms or (semi-)field studies which provide more ecologically realistic data. Additionally, risk mitigation measures – such as application restrictions or buffer zones – may be proposed to reduce exposure and support product authorization (Candolfi et al., 2001).

2.1. Integrating landscape contexts into regulatory problem formulation for ERA

Assessing the combined effects of multiple chemicals, including PPPs, within regulatory frameworks remains a major challenge (Bopp et al., 2019). In ERA, framing involves identifying and integrating key elements – such as sources, stressors, exposures, and receptors – into structured pathways like Agent-Pathway-Receptor-Intervention-Output (Paoli et al., 2022), which help translate scientific understanding into regulatory assessment questions (USEPA, 1998). The output of this framing process must be directly relevant to regulatory decision-making, necessitating effective communication between risk assessors and risk managers.

In the EU, a dual-level process applies: active substances are assessed and approved at EU level, while formulated PPPs are assessed at the zonal level – where zones group countries with similar agri-environmental conditions – and authorized by individual Member States (MSs). These authorizations are time-limited, subject to periodic renewal, and may be withdrawn if critical concerns arise. Despite this regulatory complexity, integrating landscape-based ERA is warranted, as it provides more realistic insights into cumulative risks, strengthens causal links between PPP use and ecological outcomes, and supports the achievement of high-level policy goals such as biodiversity conservation and sustainable agriculture. Implementing landscape-based ERA approaches would require a clear mapping of procedural steps, stakeholder roles, and regulatory requirements across the assessment process (Fig. 1).

Hazard-based assessments evaluate the intrinsic potential of a chemical to cause harm, while risk-based assessments integrate both hazard and exposure to estimate the likelihood of adverse effects. EU legislation incorporates both approaches: hazard-based criteria are used to identify substances that cannot be approved regardless of exposure, while comprehensive risk assessments and risk-based uniform principles guide the approval of active substances and the authorization of formulated products. The EU-level assessment of each active substance serves multiple purposes: confirming compliance with hazard-based criteria, ensuring that at least one proposed use meets the risk-based uniform principles, and establishing a standardized "list of endpoints" for use by MSs in subsequent PPP evaluations. MSs then determines the specific GAPs to be authorized for each PPP. These two regulatory processes – substance approval at the EU level and PPP authorization at the MS level – rely on individual, pesticide-specific and scenario-specific assessments, which remain essential for decision-making. However, these assessments alone are not sufficient to capture the full complexity of pesticide use.

The proposed scheme for this integrative framework is summarized in Fig. 2.

Levels 1 and 2 focus on traditional substance-by-substance assessments, supporting PPP authorization decisions through defined endpoints and tiered risk evaluations. Levels 3–4 introduce spatially explicit exposure modelling across aquatic and terrestrial ecosystems, enabling aggregate risk estimation based on landscape characteristics and crop distribution. Level 5 advances prioritization by evaluating combined effects of multiple active substances at the crop level, incorporating

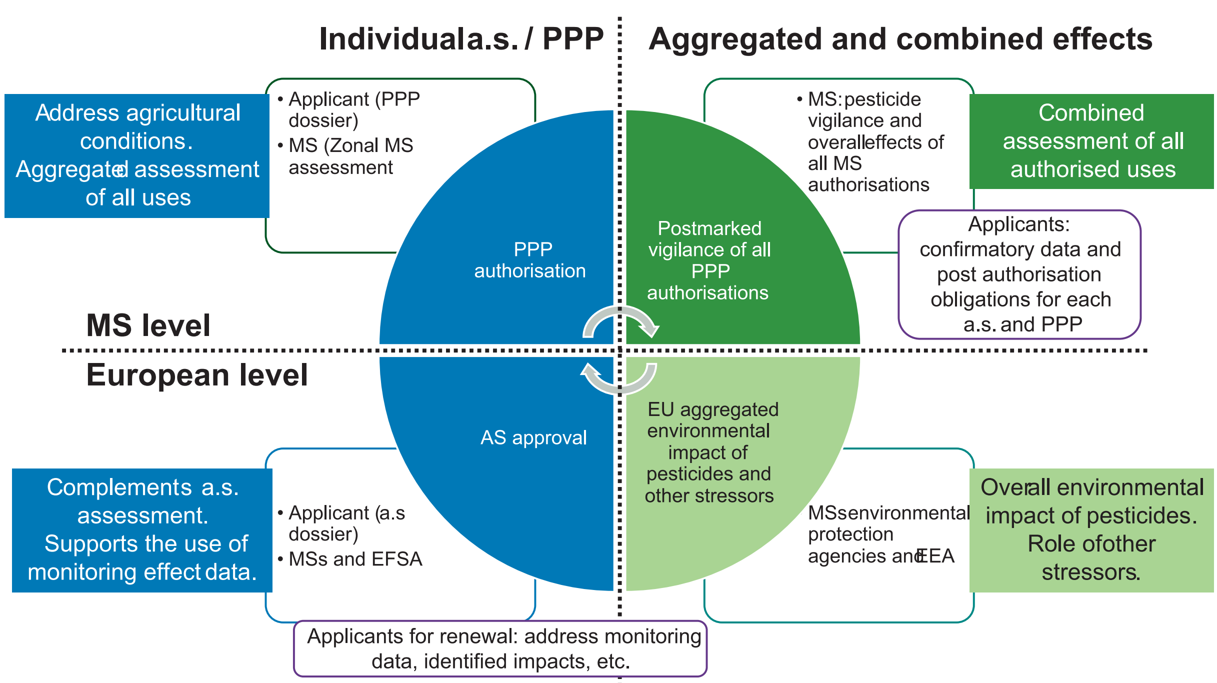

Fig. 1. Roles, users, and stakeholders involved in landscape-based Environmental Risk Assessment (ERA) across different regulatory processes and levels of Plant Protection Product (PPP) assessment in the European Union. (Abbreviations: a.s.: active substance, EEA: European Environment Agency, EFSA: European Food Safety Authority, ERA: environmental risk assessment, EU: European Union, MS: Member States, PPP: plant protection product). Color codes follow the PERA framework for systems-based ERA (see Graphical Abstract and Fig. 4).

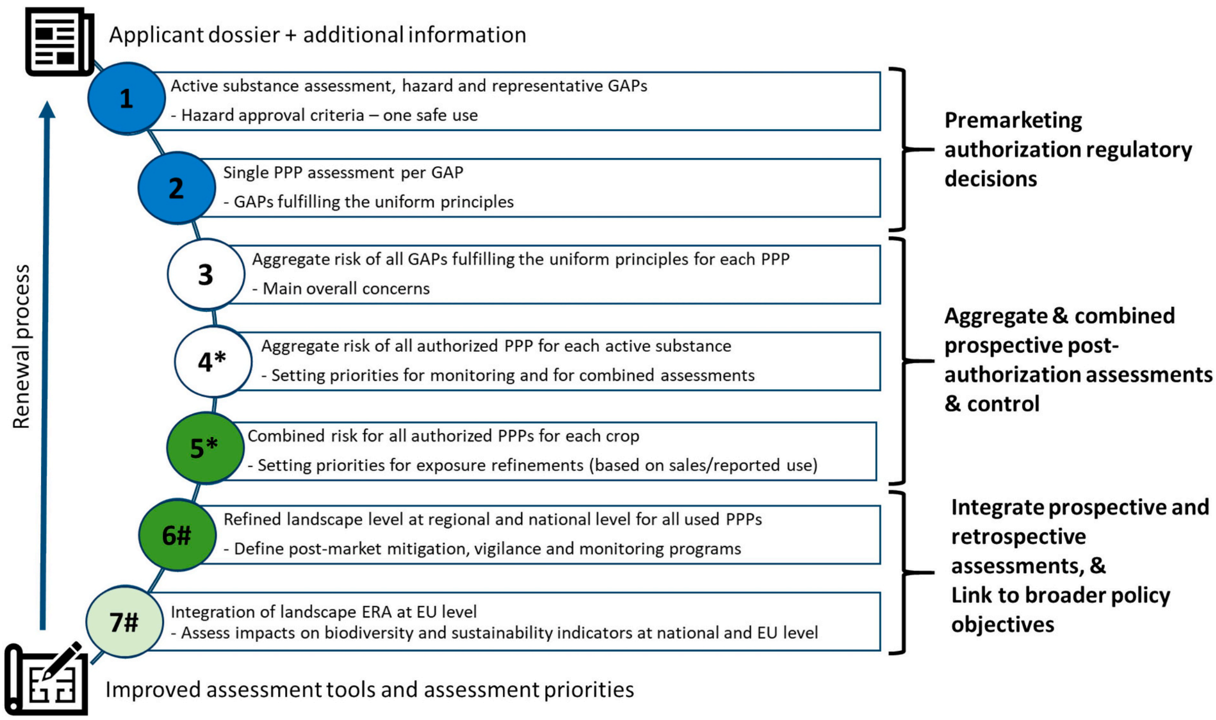

Fig. 2. Proposed scheme for an informative landscape-based problem formulation for pesticide ERA. The term "level" is used here to describe the progressive stages of integration, to maintain consistency with terminology applied elsewhere in this text. Color codes follow the PERA framework for systems-based ERA (see Graphical Abstract and Fig. 4): Levels 1–2 (blue) AS and product-level assessments. Levels 3–4 (white) integrate product- and landscape-level ERAs. Levels 5–6 (dark green) landscape-level ERA. Level 7 (light green) connects landscape ERA to systems-based approaches, linking environmental outcomes with biodiversity, sustainability, and policy objectives. Levels marked with * indicate integration with other regulatory uses of the substance under the One Substance – One Assessment approach. Levels marked with # should consider additional stressors such as agricultural practices and climate change.

agronomic knowledge and probabilistic use patterns. Level 6 integrates these insights into regional or national landscape scenarios, supporting retrospective ERA, including post-market environmental monitoring and adaptive risk management. Finally, Level 7 expands the scope to include broader stakeholder engagement and policy integration, embedding pesticide risk within sustainability assessments and agricultural strategy development.

The operationalization of the proposal is facilitated by its design. The initial levels (1–2) draw on current information requirements and regulatory assessments. Subsequent levels focus on integrating those results with additional evidence to identify main risk drivers for prioritization and, where feasible, assessment. The extended framework (Levels 6–7) allows for the integration of biodiversity and sustainability indicators, thereby linking PPP risk characterization to broader environmental and policy goals.

This expanded regulatory perspective provides a link between premarketing assessments and post-market ecovigilance options, including:

- Prospective post-authorization assessments and controls: follow-up activities conducted after a product has been authorized but before any potential adverse outcomes are observed. They include targeted monitoring, adaptive management measures, and verification of model predictions under real-use conditions, acting as a regulatory safety net to ensure that authorized uses continue to comply with acceptable risk levels over time.
- Retrospective assessments: backward-looking evaluations that analyze monitoring data, field observations, and long-term ecological indicators to determine whether previous authorizations have led to unanticipated environmental effects.

The knowledge generated can be used to update Levels 1–2, strengthening their predictive power through a continuous, iterative feedback loop so that early problem formulation evolves continuously based on empirical insights; this is promoting adaptive management and continuous improvement in ERA practice.

The proposed framework can be adapted to other legislative frameworks, such as Biocidal Products (non-agricultural pesticides) and ERA for industrial chemicals under the REACH Regulation. Levels 1–3 are sector specific, level 4 covers the aggregated risk under the One Substance One Assessment (OSOA) approach, an EU initiative to harmonize chemical assessments across legislations, under the EU Chemical Strategy on Sustainability, and levels 5–7 covers overall environmental impact. Progress can be accelerated through ongoing initiatives under the EU Green Deal, the EU's policy framework for achieving sustainable and climate-neutral growth, including the common data platform established by Regulation (EU) 2025/2455 enhancing data sharing across regulations and monitoring programs.

To meet environmental protection goals, PPP risks need to be assessed under realistic environmental conditions, accounting for the influence of multiple co-occurring stressors such as habitat degradation, agricultural intensification, and climate change. The key challenge is therefore to evaluate and manage pesticide risks within a realistic ecological context while preserving regulatory usability.

The proposal is explicitly designed to integrate the PERA framework (Axelman et al., 2024; Sousa et al., 2022), balancing realism, complexity, and uncertainty. While added realism yields more informative evaluations, it can introduce new uncertainties. These uncertainties should be explicitly identified, and decisions about whether the information/knowledge is sufficient to progress to the next level should be consciously taken. Where information is insufficient, the framework pinpoints gaps, supporting an informed appraisal of the needs, costs, and benefits of generating the missing data and tools.

Contemporary PPP ERA is already perceived as complex. Much of this stems from fragmentation: experts must consult numerous guidance documents, scenarios, tools, and models – often hosted on different platforms. Efforts are therefore needed to integrate tools and models within a single platform. In our proposal, Levels 1–4 could be incorporated into a spatially explicit platform that delivers more informative assessments without adding system–level complexity, as demonstrated for the PERSAM model. The main and unavoidable additional complexity lies in the assessment of combined exposure, yet this is precisely where the greatest need exists, as discussed in the following sections. Clear limitations remain. Current information requirements address only part of the potential environmental risks of pesticides. Ongoing activities under PARC, including benchmarking exercises and terrestrial/aquatic case studies, are evaluating the pros and cons of the proposed conceptual model (Tarazona et al., 2024) and will inform specific recommendations. This manuscript does not allocate institutional responsibilities across the levels in Fig. 2; determining who does what, when, and with which decision rights lie outside our scope and will require inter–agency discussions and agreements (to be developed in a separate roadmap). In addition, landscape–level assessments must be underpinned by well–defined, representative scenarios that capture EU's diverse agricultural and environmental conditions, ensuring assessments are both realistic and comparable across Member States.

The framework provides a practical pathway to progressively build and apply integrated assessments using both generic and real–world scenarios. The approach is therefore designed to evolve with available data and tools, rather than relying on idealised modelling capacities that do not yet exist.

2.2. Building fit-for-purpose platforms for implementing landscape-based environmental risk assessment of pesticides

The proposed landscape-based ERA framework is structured into seven progressive Levels, each representing a distinct layer of complexity, integration, and regulatory relevance. The formal regulatory decision to authorize a PPP occurs at Level 2. The subsequent Levels 3–6 establish a prospective validation process considering the risk of approved PPPs, based on adaptive risk management and offering timely updates to authorization conditions if necessary. This framework supports both prospective and retrospective evaluations, enabling more informed decision-making across spatial and temporal scales.

Problem formulation for *Levels 1–2* should rely on the endpoints defined in regulatory assessments that support authorization decisions. In the EU, this problem formulation involves distinct evaluations of the active substance (*Level 1*) and the formulated PPP (*Level 2*). For PPPs in other jurisdictions and Biocidal Products in the EU the focus is primarily on Level 2 with no formal approval process for the active substance. Nevertheless, informal Level 1 assessments are often carried out to facilitate PPP evaluations and support decisions regarding product equivalence. Within our framework, *Levels 1–2* should be expanded to generate robust foundational information that informs subsequent Levels. A key challenge in integrating *Levels 1–2* lies in the tiered structure of regulatory ERA. Typically, assessments begin with conservative risk screening based on standardized information requirements. If thresholds are exceeded, refinement proceeds through additional hazard studies, ranging from laboratory tests with alternative species to mesocosms or field studies, depending on the results of the previous tier. Consequently, the availability and quality of data across active substances, PPPs, and endpoints is variable. More extensive datasets are often generated for substances with higher ecotoxicological concern, which requires additional studies to support refinement. This variability must be carefully considered when linking *Levels 1 and 2* to broader landscape-level assessments.

Levels 3–4 extend the assessment framework to landscape-based approaches that estimate aggregate exposure from all approved PPPs containing the same active substance. This extension requires spatially explicit data on crop distribution and realistic application schedules to model active substance behavior across environmental compartments such as soil, air, and water. Our conceptual model proposes complementary exposure assessments for both aquatic ecosystems and terrestrial agroecosystems. While worst-case scenario selection remains a valid approach (Wang et al., 2022), current technologies and information availability, particularly in developed countries, support full-scale exposure assessments at national or continental levels (Porta et al., 2025). For example, the EU soil exposure model PERSAM generates continental-scale concentration maps (Joris et al., 2023), although only percentile values are currently used in regulatory decision-making. Aquatic emissions (e.g., spray drift) can be modelled with scenario-based approaches, while more complex processes like runoff require well-calibrated hydrological models (e.g., Métayer et al., 2024 for runoff). Terrestrial exposure estimates must include not only in–field areas but also edge–of–field zones, where non–target organisms are frequently exposed (Schad et al., 2023), which are critical for assessing risks to non-target organisms. Repeated observations indicate that current models often underestimate pesticide concentrations and fluxes in environmental compartments (e.g. Riedo et al., 2021; Weisner et al., 2022; Froger et al., 2023; Knuth et al., 2024) suggesting that mechanisms of dissipation and dispersion and their parameterization should also be reviewed. For mobile terrestrial organisms, additional considerations are necessary, as these species may be exposed to multiple PPP applications across different crops and seasons. Their potential for recovery and recolonization, and thus population-level impacts, depends heavily on landscape structure and connectivity (Hisamoto et al., 2024).

Advancements in analytical methods are allowing large scale monitoring studies that measure pesticide residue levels across environmental compartments (Mauser et al., 2025) and support non-target chemical analysis (Tkalec et al., 2024). The development of georeferenced databases, enhanced through automated curation, combined with knowledge of actual use patterns, is key for validating and calibrating prospective exposure models.

At this level, hazard assessment continues to focus on single substances, but requires the incorporation of novel, non-conventional (non-standardized) endpoints, such as behavioral alterations, ecosystem functions and processes, or measurements at lower levels of biological organization that reveal specific modes of action such as endocrine disruption, or genotoxicity, may provide greater sensitivity and enhance ecological relevance. Unlike regulatory approval assessments, which aim to demonstrate "safe use", the objectives at Levels 3–4 are to identify key ecological adverse effects and define exposure-time-response relationships that inform higher-tier assessments. These objectives include evaluating species beyond standard model organisms (Carlson et al., 2025) and considering population-relevant effects that are difficult to capture in laboratory settings such as increased susceptibility to disease or neurobehavioral impairments, endocrine disruption, and the ecological consequences of genetic adaptation (Siddique et al., 2024).

The conceptual framework proposed by Tarazona et al., (2024), Carlson et al., (2025) and Siddique et al., (2024), encompasses a three-dimensional approach for implementing landscape-level ERA. This framework is designed to capture the spatial, temporal, and biological complexity of pesticide exposure and effects across agricultural landscapes. The XY axis represents geographic location and temporal dynamics, enabling the linkage of exposure routes and levels across space and time. The Z axis reflects biological complexity, with positive values assigned to terrestrial organisms and negative values for aquatic organisms (as further detailed in Tarazona et al., 2024).

Experimental studies typically provide data at the organism level ($Z = |3|$), while mesocosm and field studies inform effects at the population ($Z = |2|$) or community level ($Z = |1|$). To bridge these scales, effect modeling tools (e.g., Larras et al., 2022) are employed to extrapolate individual-level impacts to higher levels of biological organization, including population dynamics, community structure, and ecosystem functions. Ideally, the information gathered for each active substance at these lower levels should serve as the foundation for higher-tier assessments. To support this process, each active substance and endpoint can be classified into predefined concern levels, as illustrated in Fig. 3. This figure maps Level 1–3 inputs (e.g., substance-specific data) to Level 4 outputs, prioritizing the most relevant taxonomic groups for inclusion in combined assessments at higher levels. Level 4 outcomes are grouped by the grade of concern for each non-target organism group. The highest concern corresponds to scenarios where a single active substance may cause direct environmental impacts under some landscape conditions. The lowest concern confirms a very low likelihood of even indirect environmental impacts. Intermediate concern levels differentiate between direct toxic effects arising from the combined use of multiple active substances, and indirect effects connected to impacts on other organisms and their ecological functions. These intermediate concern levels are relevant for assessing combined effects at Level 5 and beyond, where multiple stressors and landscape-level interactions are considered.

Level 5 introduces a complementary prioritization step focused on assessing the combined effects of multiple active substances at the crop level. Implementation at this level requires agronomic knowledge to define the crop protection needs and the plausibility of actual use of different PPP combinations during the seasons. This knowledge needs to focus not just on treatments for different weeds, diseases and pests, but also consideration for each, as several PPPs may target the same pest, weed or disease, they are often alternated to mitigate resistance evolution. Additionally, Level 5 must account for uses of active substances in surrounding crops, which may contribute to exposure through runoff, air-drift, or subsurface water fluxes. A comprehensive inventory of PPP use by crops at the landscape scale can be a highly valuable tool for agronomists working with the main crop types in a given system. Such an overview helps identify patterns of use and potential hotspots, and its practical value becomes particularly evident when selecting the most sustainable PPP options that align with local protection goals and when designing integrated crop–protection strategies.

Once plausible PPP combinations are identified, probabilistic screening approaches can be applied. These may rely on surrogate data (e.g., sales figures, market penetration, recommended or reported uses, agronomic farm management system inventories) and spatial crop distributions to estimate exposure scenarios of PPP usage within the landscape. A critical component of this process is the integration of cumulative risk from multiple active substances for each selected taxon or ecological trait. The simplest method involves calculating and aggregating RQs or margins of exposure, though this provides only a coarse estimate of combined risk. More refined approaches are needed to accurately capture the temporal dynamics and ecological relevance of cumulative exposures in landscape-level ERA. Traditional mixture toxicity models, such as dose addition, response additivity, or independent action (De Zwart & Posthuma, 2005), are typically designed for simultaneous exposures, whereas pesticide applications often result in sequential exposure over time. The modelling of sequential effects is an emerging area of research, with toxicokinetic-toxicodynamic models emerging as key tools that could help in this area (Ashauer et al., 2017; Schunck & Liess, 2022).

A more robust approach involves modelling the relationship between exposure levels and key population-level parameters, such as survival and reproduction rates. These quantitative relationships can then be aggregated across multiple active substances and used to simulate population dynamics, offering a more ecologically relevant assessment of cumulative impacts (Tarazona et al., 2021). The development of such approaches at Levels 3 to 5 provides the datasets and mechanistic understanding needed to support decision-making at level 6, where assessments move from individual fields to landscape, regional, and national scales. The selection of landscape scenarios at regional or national scales, combined with a dedicated landscape ERA tool, enables the screening of cumulative risks associated with all authorized PPPs. This approach provides a robust foundation for regulatory decision-making (EFSA, 2018). For permanent crops and other stable land uses or structures, georeferencing can rely on actual spatial distributions. However, arable land presents additional challenges due to crop rotation, which complicates prospective ERAs. In such cases, estimations may be based on historical use patterns or generic landscape scenarios that reflect the predominant agricultural conditions of each region. Alternatively, there are increasingly satellite and airborne remote sensing data products that can be used to build a picture of the spatial distribution of crops within a given landscape (Bullock et al., 2024; Melissande et al., 2024).

This integration process involves three key steps:

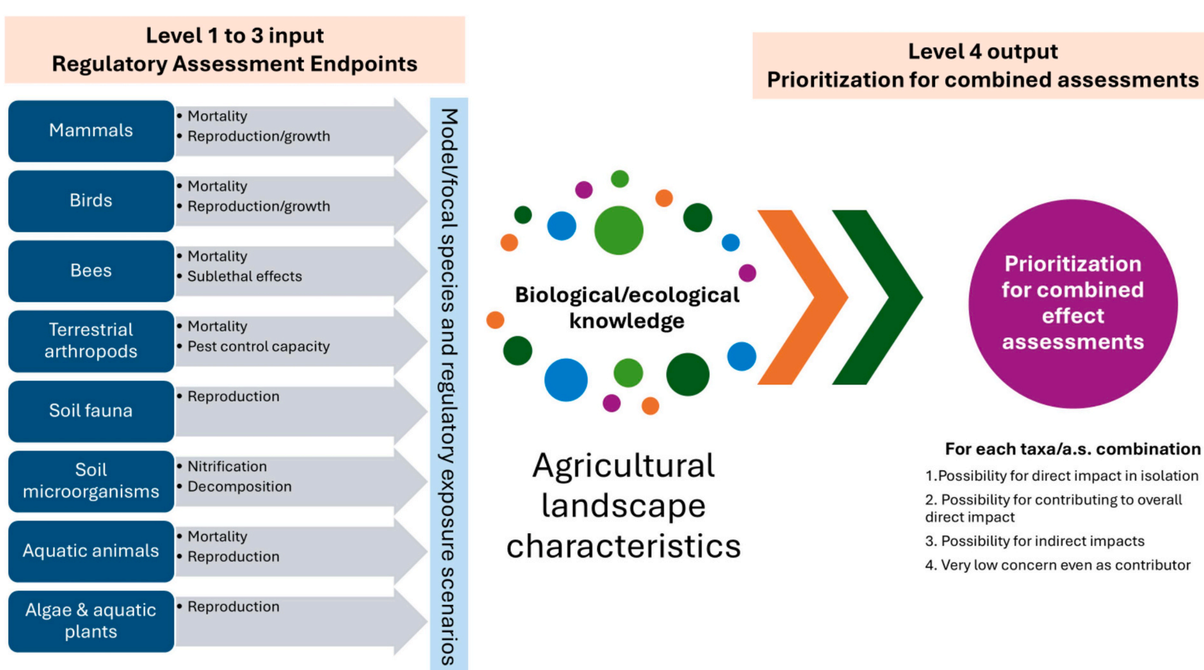

Fig. 3. Schematic representation of Level 4 process: integration of regulatory assessment data with landscape characteristics to identify taxonomic groups of highest concern for each active substance.

- Assessment of potential effects at the individual level (Z = |3|). Evaluating direct impacts on individual organisms, such as physiological or behavioral changes.
- Evaluation of population-level impacts (Z = |2|). Incorporating biological traits and agricultural context to understand how individual effects scale to population dynamics, including survival, reproduction, and dispersal.
- Assessment of community-level effects (Z = |1|). Analyzing ecological interactions – such as competition, predation, and mutualism – to determine broader consequences for community structure and ecosystem function.

Each taxon or ecological trait requires tailored considerations. This complexity makes it unlikely that a single assessment tool will be sufficient to conduct the desired range of modelling applications. Instead, the proposed approach advocates for the integration of multiple tools and models within the landscape level conceptual framework (Tarazona et al., 2024), ensuring a more comprehensive and ecologically relevant evaluation of environmental risks.

The implementation of Level 6 should provide regulatory authorities with a comprehensive overview of the combined environmental risks posed by all authorized PPPs in relevant agricultural landscapes. It should also support forecasting the potential consequences of new authorizations, restrictions, or withdrawals, and inform the design of post-market monitoring and vigilance programs tailored to local and regional conditions.

There is increasing pressure in some jurisdictions to expand organic agriculture, which restricts pesticide use to natural substances. In parallel, an emerging trend is the broader adoption of microbial pesticides with unique biological properties and modes of action (Steenbergh et al., 2025) and RNAi pesticides (Fletcher et al., 2020). The policy driver is that natural products and biopesticides are expected to present lower (although not negligible) risk to non-target organisms. Landscape-level ERA frameworks are needed for confirming the expectation, considering also the precise choice of products used (Martínez-Megías et al., 2025); and informing the selection of pest management strategies based on their short- and long-term consequences for biodiversity and ecosystem function across multiple spatial scales.

3. From pesticide risk assessment to measurable environmental protection indicators

Environmental risk assessment (ERA) aims to protect biodiversity, yet it remains difficult to link ERA outcomes to measurable environmental effects. Existing indicators (e.g., monitoring data, ecological status metrics under the Water Framework Directive) are not systematically connected to pesticide use, limiting the ability to attribute observed biodiversity changes to chemical pressures. Transitioning toward spatially explicit and integrated exposure assessments through landscape-based ERA represents a critical advancement in addressing this gap (Streissl et al., 2018; Tarazona et al., 2024).

While mixture toxicity, particularly synergistic interactions, is often highlighted as a key uncertainty in ERA, most empirical evidence derives from laboratory studies, typically at elevated exposure levels. Field evidence remains limited, largely due to the small number of studies explicitly designed to detect such effects under realistic conditions. Available field and semi-field studies show mixed outcomes. Bjergager et al. 2011 reported synergistic effects of a pyrethroid–azole mixture on aquatic invertebrates, exceeding additive predictions. In contrast, Schmuck et al. 2003 found no synergistic effects on honeybee foraging or colony vitality. More recently, Woodcock et al. 2025 showed that co-exposure altered community structure more than single-compound exposure, even when the second compound alone had no detectable effect. Overall, synergistic effects appear context-dependent rather than ubiquitous but remain insufficiently characterized. These findings support the need for targeted studies and monitoring strategies to identify conditions under which such interactions become ecologically relevant.

Pesticides are applied within modified agricultural environments, where distinct areas such as in crop zones, edge of field, and off-crop areas each require tailored protection goals (EFSA Scientific Committee, 2016). The spatial dimension of landscape-level ERA should be adapted to reflect the ecological traits and habitat use of different taxa, ensuring that ERAs are both context-specific and biologically relevant. (Bertrand et al., 2025; Fritsch et al., 2025). Implementing broader ecological impacts (including indirect effects, e.g. food-web interactions) into the approval and authorization of individual active substances and PPPs (*Levels 1–2*) is key and considered in the proposed concept. A pioneering example is the Commission Implementing Regulation (EU) 2023/2660 for glyphosate, which explicitly addresses indirect effects and prescribes adapted risk management measures to account for them. More broadly, addressing indirect and cascading effects on ecosystem functioning demands the inclusion of trophic interactions and network-level dynamics (Faburé et al., 2025). While this inclusion substantially increases assessment complexity, it is indispensable for ensuring ecologically meaningful protection across agricultural landscapes.

At this stage, the problem formulation requires the involvement of a broader group of risk managers and stakeholders. The impacts identified at *Level 6* should be contextualized and linked to implementable actions that go beyond the binary approval or withdrawal of PPPs from authorization. At higher levels, landscape ERA outputs can inform broader policy decisions by linking pesticide risk to biodiversity and sustainability indicators. In the near term, this linkage could support alignment with existing frameworks (e.g. CAP, Water Framework Directive) through improved use of monitoring and spatial exposure data. At *level 7*, the risk of pesticides should be integrated as part of the overall impact assessment of proposed alternatives for food production and crop protection. In the EU there is a parallel legislation requiring the sustainability assessment of pesticides, Directive 2009/128/EC, of which the effectiveness should be further improved (Helepciuc & Todor, 2021). Although not yet done, an opportunity exists to align regulatory PPP assessments with the development of sustainability indicators (Kosnik et al., 2022). The proposed framework, especially *Levels 4, 5, and 6*, offers a structured pathway to bridge existing gaps in PPP ERA by supporting the development and refinement of risk-based sustainability indicators; aligning ERA with broader sustainability and biodiversity goals.

The proposed framework builds on the PERA concept (Axelman et al., 2024; Sousa et al., 2022) by linking product-level and landscape-level assessments within a systems perspective (Fig. 4).

An important advantage of implementing landscape-based ERA is its ability to connect large-scale prospective studies (Porta et al., 2025) with retrospective evaluations (Rigal & Perrot, 2025). Conducting sensitivity analyses and benchmarking predictive models of varying complexity ensures that regulatory ERA procedures focus on the parameters most critical for risk characterization.

While landscape-based ERA is increasingly recognized as a priority (EFSA, 2025), its implementation requires further development of tools, data access, and validation approaches. Ongoing case studies under PARC are designed to advance this effort and address these gaps by testing spatially explicit methods and supporting their future regulatory use. Consistent with recent evaluations (Bertrand et al., 2025; Faburé et al., 2025; Fritsch et al., 2025), to fully implement the proposed framework, it is essential to expand representation to include a broader range of taxa and functional groups, ensuring that ecological diversity and key ecosystem processes are adequately captured in ERAs.

4. Exploring the mechanistic foundation for implementing landscape-level next generation ERA (NGERA)

Policy initiatives push toward reduced reliance on animal testing, aiming for a transition toward *in silico*, *in vitro*, and other non-animal

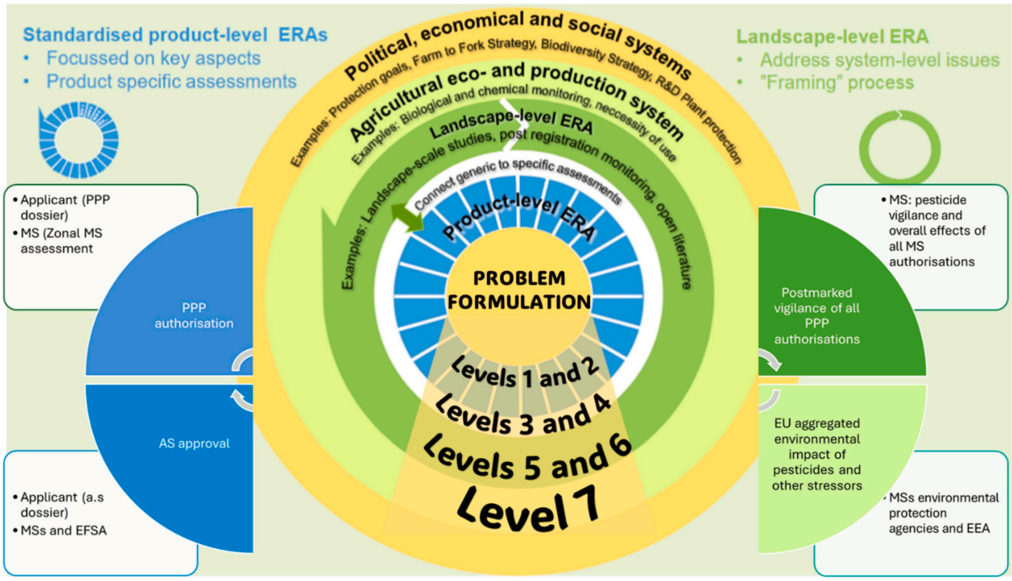

Fig. 4. The proposed problem formulation for landscape ERA operationalizes the PERA conceptual framework (Sousa et al., 2022). The central circular structure, adapted from PERA, illustrates the systems-based view of ERA, where the product-level ERA (blue) and landscape-level ERA (dark green) are embedded within the broader agricultural eco-production system (light green) and the overarching political, economic, and social context (yellow). The landscape-level components are linked to the seven regulatory Levels (Fig. 2), showing how ERA outputs inform successive stages of assessment, authorization, and post-authorization monitoring. On the left- and right-hand side, connections to the institutional and stakeholder roles (Fig. 1) depict the distribution of responsibilities among applicants, MSs, EFSA, and EU policy actors.

models (EC, 2024). This shift creates opportunities for future problem formulations to be increasingly mechanistic, providing knowledge that can be linked into the landscape-based ERA framework to increase the reliability of the decisions made. The potential use of such mechanistic information within a more integrated ERA approach is explored in the following section. Here, we focus on integrating mechanistic toxicology, supported by New Approach Methodologies (NAMs), into this framework to enhance biological relevance, predictive capacity, and population-level extrapolation.

4.1. Exposure dynamics and multi-stressor contexts

Exposure remains a key consideration at the landscape axis of ERA, particularly due to its spatial and temporal variability. Short term concentration peaks drive aquatic risks (Liess et al., 2021), combined with cumulative and multi-stressor conditions like the Stress Addition Model (SAM; Liess et al., 2016) can drive ecological risks that are not captured by static assessment approaches (Liess and Gröning, 2023). Incorporating such temporal dynamics and combined stressor effects is crucial for improving the realism of ERA.

4.2. Integrating exposure pathways and mechanistic driver understanding of vulnerability

Despite clear advantages, coupling pesticide fate models with ecological and population models remains complex. High-resolution input data (land use, practices, soil, climate) are often missing or fragmented, and access to such data can restrict model development and validation. Most ecological models (e.g., ALMaSS; Poulsen et al., 2023; Topping and Duan, 2024) are calibrated for limited landscapes, which can only be extended with available data. Most of this data, particularly access to farm data, is often collected nationally, but is inaccessible. Examples here include the data collected under the CAP (Common Agricultural Policy) subsidy schemes in the EU and pesticide data gathered under the Sustainability Directive. Additionally, field monitoring remains critical to parameterize indirect effects (e.g., trophic cascades, competitive shifts) and ensure model realism. Field monitoring is costly and must be planned in concert with the application of modelling. Finally, constructing landscape scenarios, ranging from environmental contamination to exposure and then to effects on ecosystems, is also a challenge itself. They must remain realistic while being representative of regions, integrating processes operating with different characteristic time and space scales, as well as their feedback.

4.3. Toward a $Z = |4|$ conceptual tier

To support this integration, we propose formalizing $Z = |4|$ as a conceptual tier for next generation ERA (Tarazona et al., 2024). This tier explicitly couples mechanistic toxicology with spatial exposure and ecological dynamics by integrating information from NAMs, AOPs, and trait-based data. Rather than providing fully quantitative predictions, this tier supports the identification of vulnerable species, traits, and exposure conditions under realistic scenarios. It also enables iterative refinement by linking prospective modelling with retrospective observations, contributing to a more adaptive and transparent risk assessment framework.

4.3.1. The $Z = |4|$ tier: Exploiting the adverse outcome pathway (AOP) approach

The Adverse Outcome Pathway (AOP) framework provides a structured approach to link molecular-level effects to adverse outcomes relevant for risk assessment. Its main advantage in this context is that it enables comparison of substances acting through shared biological pathways, thereby supporting the assessment of combined effects across chemicals and stressors (Ankley et al., 2010; Kim et al., 2024; Hernández-Jerez et al., 2024). In addition, AOPs can focus on endpoints that are not routinely addressed in standard toxicity tests. These so-called non-conventional endpoints may include effects on physiological parameters linked to behavior, immune function, or DNA integrity. Such endpoints are often more sensitive than traditional apical endpoints while remaining causally anchored to higher-level biological outcomes. By capturing early key events at the molecular, cellular, tissue, organ, and individual levels, AOPs provide mechanistic insight into the processes underpinning advance physiological and ecological effects.

Incorporating these mechanistic features enhances transparency and strengthens causal inference between PPP exposure and ecological consequences, thereby improving the interpretability and relevance of ERA outcomes.

Beyond qualitative only approaches, quantitative AOPs (qAOPs) and qAOP networks (qAOPNs) incorporate dose–response and temporal data, enabling derivation of points of departure (POD) from normality and construction of quantitative Key Event Relationships (KERs) that define stressor-response and response-response relationships along the AOPs (Perkins et al., 2019; Paini et al., 2022). As qAOPNs capture convergence and divergence of toxicity pathways, they provide a framework to assess combined effects by chemicals acting through similar MOA (e.g. assuming concentration addition) or dissimilar MOA (e.g. assuming independent action) (Knapen et al., 2018; Villeneuve et al., 2018; Beyer et al., 2014). By linking qAOPs/qAOPNs with toxicokinetic (TK) and toxicodynamic (TD) modelling, and embedding these in spatially explicit exposure scenarios, ERA can move from deterministic risk thresholds toward probabilistic predictions of risk magnitude, variability, and uncertainty across landscapes and taxa.

4.3.2. *The Z = |4| tier: Predictions without well-described AOPs*

Although a well-characterized AOP represents the 'gold standard' for mechanistically connecting a PPP to its adverse downstream effects, developing a fully characterized qAOP is a resource-intensive process. So, although powerful, the AOP approach gets caught in the 'too many species' traps. For this reason, AOPs will likely be restricted to a relatively narrow range of PPP-species combinations (at least for the short to medium term). This is also true for our current approach to organism-level data on PPP sensitivity for non-target species (Z = |3|), largely because laboratory-based exposure experiments are performed on a narrow set of standard test organisms. However, genomic resources are expanding (Darwin Tree of Life Project Consortium, 2022), including for species with relevance to PPP-exposure (e.g., Perry et al., 2022), as are trait databases for species that occupy agricultural landscapes (e.g., Cook et al., 2022). These resources can be used to generate mechanistic-based 'weight of evidence' PPP sensitivity predictions for species performing key agricultural ecosystem-services (Fonte et al 2023).

These 'weight of evidence' predictions are based on comparing differences across molecular biology/traits that are known to be pertinent to PPP sensitivity. Trait-based approaches consider traits that correlate with PPP vulnerability/sensitivity, and some data has been incorporated into PPP risk assessment via the SPEAR approach (Liess et al., 2008; Ganatra et al., 2021). These trait-based approaches can include both ecological/life history and organism-level traits (e.g., generation time and body size) along with sub-organismal traits (e.g., cuticle thickness and gut epithelium permeability) to predict exposure vulnerability and/or organism sensitivity (Rubach et al., 2011; van den Berg et al., 2019). Such data can be combined with molecular/bioinformatic data arising from the increasing availability of non-model organism 'omic' data (Blaxter et al., 2022). Specifically, such approaches assess interspecies variation in toxicokinetic and toxicodynamic components (LaLone et al., 2023). Toxicokinetic scores may be derived from metabolic enzyme complements (CYP450, glutathione pathways, ABC transporters), while toxicodynamic scores assess conservation of target receptors and downstream repair pathways. These layers can be combined into sensitivity rankings and validated through high-throughput assays (Haas et al., 2022; Bass et al., 2024). Such 'weight of evidence' prediction can also exploit existing well-characterized AOP knowledge, incorporating MIEs and comparing highly conserved KEs into cross-species comparisons (Rivetti et al., 2020). To this end, approaches such as 'SeqAPASS' (LaLone et al., 2023) and 'G2P-SCAN' (Rivetti et al., 2023; Schumann et al., 2024) have been generated to facilitate additional cross-species extrapolation of AOP data. Predictions of sensitivity at the Z = |4| level can feed into whole organism understanding. For example, neuroactive PPPs may disproportionately affect species that both possess a relevant version of the target receptor with high similarity to known target-species sequences, but that also depend on displaying complex courtship or predatory behaviors known to be mediated through the same receptor.

4.3.3. *The Z = |4| tier: Retrospective mechanistic-based ERA*

Sub-organismal 'biomarkers' can also be applied to retrospective ERA to: (1), rapidly quantify the direct effect of specific PPPs on non-target organisms in the field, allowing a comparison of the protective capacities of various landscape management strategies and, (2) informing the extent we need to study and quantify indirect effects (e.g., effects that cascade through trophic networks and host-parasite interactions). In combination with other relevant data (e.g., biodiversity change, animal stoichiometry, habitat use), the aim is to generate spatial impact maps across the agricultural landscapes, offering a more rapid assessment of the consequences of different agricultural practices. The induction of detoxification systems by PPPs (e.g., cytochrome P450 enzymes), or genes linked to damage repair, represent biomarkers of exposure and effect (Christen et al., 2019), supporting causal attribution of population decline. Retrospective integration of field data such as biodiversity trends, species weights, or habitat use into spatial impact maps would strengthen validation (and calibration) of predictions generated using data at the individual (Z = |3|) and sub-organismal (Z = |4|) level.

4.4. *Mechanistic-based landscape NGERA: Towards a systems-based approach*

Integrating mechanistic data into landscape ERA can improve biological relevance and support the transition towards more predictive and less animal-dependent assessments (Tarazona et al., 2025). However, such integration is currently constrained by data availability, model complexity, and the need for validation. In the near term, mechanistic approaches are therefore most useful for supporting interpretation, prioritization, and uncertainty analysis, rather than replacing existing regulatory methods. Progressive, stepwise implementation, supported by ongoing case studies and targeted model validation efforts, will be essential to ensure that these approaches are scientifically robust, transparent, and fit for regulatory use.

5. Near-term implementation (5–10 years)

While full implementation of landscape-based ERA remains a medium-term objective, several elements could be integrated into existing regulatory frameworks within the next 5–10 years. These include:

- Use of generic spatial exposure scenarios (e.g., grassland, arable land) harmonised across PPP, biocides, and REACH assessments to support cross-legislation alignment.
- Integration of existing emission scenario documents developed under the Biocides and REACH regulations into shared spatial exposure layers, enabling MSs to better monitor and estimate potential aggregation effects of a single substance authorized for different uses under different legislations.
- Application of aggregate exposure assessments for single substances across regulatory silos, building on existing substance-specific evaluations.
- Use of monitoring data from predefined areas of interest to support retrospective assessment and validation of predicted risks.
- Validate key model components through pilot case studies, including terrestrial and aquatic PARC sites, by the end of the PARC projects under realistic exposure and landscape conditions.

Together, these measures provide a pragmatic and stepwise pathway for integrating landscape-based ERA concepts into existing regulatory workflows, without requiring immediate, large-scale methodological overhaul.

CRediT authorship contribution statement

Ana Fernandez-Agudo: Writing – review & editing, Writing – original draft. **Annette Aldrich:** Writing – review & editing. **Johan Axelman:** Writing – review & editing. **Carole Bedos:** Writing – review & editing. **Pierre Benoit:** Writing – review & editing. **Colette Bertrand:** Writing – review & editing. **Olivier Crouzet:** Writing – review & editing. **Cécile Dagès:** Writing – review & editing. **Quentin Devalloir:** Writing – review & editing. **Yann Devos:** Writing – review & editing. **Jean-Lou CM Dorne:** Writing – review & editing. **Sabine Duquesne:** Writing – review & editing. **Andreas Focks:** Writing – review & editing. **Maria del Carmen Gonzalez-Caballero:** Writing – review & editing. **Matthias Liess:** Writing – review & editing. **Susana Loureiro:** Writing – review & editing. **Vanessa Mazerolles:** Writing – review & editing. **Michael Meissle:** Writing – review & editing. **Manuel E. Ortiz-Santaliestra:** Writing – review & editing. **Jes J. Rasmussen:** Writing – review & editing. **Raphaël Royauté:** Writing – review & editing. **Maj Rundlöf:** Writing – review & editing. **Ralf B. Schäefer:** Writing – review & editing. **Stephen Short:** Writing – review & editing. **Ayesha Siddique:** Writing – review & editing. **José Paulo Sousa:** Writing – review & editing. **David J. Spurgeon:** Writing – review & editing. **Pierre-François Staub:** Writing – review & editing. **Knut Erik Tollefsen:** Writing – review & editing. **Chris J. Topping:** Writing – review & editing. **Gabriele Treu:** Writing – review & editing. **Vera Zina:** Writing – review & editing. **Jose V. Tarazona:** Writing – original draft, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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Further reading

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