







## REVIEW

# Three perspectives on the prediction of chemical effects in ecosystems

Anke Schneeweiss<sup>1</sup>  | Noël P. D. Juvigny-Khenafou<sup>1</sup>  | Stephen Osakpolor<sup>1</sup>  |  
 Andreas Scharmüller<sup>1,2</sup>  | Sebastian Scheu<sup>1</sup>  | Verena C. Schreiner<sup>1</sup>  |  
 Roman Ashauer<sup>3,4</sup>  | Beate I. Escher<sup>5,6</sup>  | Florian Leese<sup>7</sup>  | Ralf B. Schäfer<sup>1</sup> 

<sup>1</sup>Institute for Environmental Sciences,  
University Koblenz-Landau, Landau in der  
Pfalz, Germany

<sup>2</sup>Institut Terre et Environnement de  
Strasbourg (ITES), UMR 7063, CNRS-  
Université de Strasbourg-ENGES,  
Strasbourg, France

<sup>3</sup>Syngenta Crop Protection AG, Basel,  
Switzerland

<sup>4</sup>Department of Environment and  
Geography, University of York, York, UK

<sup>5</sup>Department of Cell Toxicology,  
Helmholtz Centre for Environmental  
Research – UFZ, Leipzig, Germany

<sup>6</sup>Environmental Toxicology, Center for  
Applied Geoscience, Eberhard Karls  
University Tübingen, Tübingen, Germany

<sup>7</sup>Aquatic Ecosystem Research, University  
of Duisburg-Essen, Essen, Germany

## Correspondence

Anke Schneeweiss and Ralf B. Schäfer,  
Institute for Environmental Sciences,  
University Koblenz-Landau, Fortstrasse 7,  
76829 Landau in der Pfalz, Germany.  
Email: [schneeweiss@uni-landau.de](mailto:schneeweiss@uni-landau.de) and  
[schaefer-ralf@uni-landau.de](mailto:schaefer-ralf@uni-landau.de)

## Abstract

The increasing production, use and emission of synthetic chemicals into the environment represents a major driver of global change. The large number of synthetic chemicals, limited knowledge on exposure patterns and effects in organisms and their interaction with other global change drivers hamper the prediction of effects in ecosystems. However, recent advances in biomolecular and computational methods are promising to improve our capacity for prediction. We delineate three idealised perspectives for the prediction of chemical effects: the suborganismal, organismal and ecological perspective, which are currently largely separated. Each of the outlined perspectives includes essential and complementary theories and tools for prediction but captures only part of the phenomenon of chemical effects. Links between the perspectives may foster predictive modelling of chemical effects in ecosystems and extrapolation between species. A major challenge for the linkage is the lack of data sets simultaneously covering different levels of biological organisation (here referred to as biological levels) as well as varying temporal and spatial scales. Synthesising the three perspectives, some central aspects and associated types of data seem particularly necessary to improve prediction. First, suborganism- and organism-level responses to chemicals need to be recorded and tested for relationships with chemical groups and organism traits. Second, metrics that are measurable at many biological levels, such as energy, need to be scrutinised for their potential to integrate across levels. Third, experimental data on the simultaneous response over multiple biological levels and spatiotemporal scales are required. These could be collected in nested and interconnected micro- and mesocosm experiments. Lastly, prioritisation of processes involved in the prediction framework needs to find a balance between simplification and capturing the essential complexity of a system. For example, in some cases, eco-evolutionary dynamics and interactions may need stronger consideration. Prediction needs to move from a static to a real-world eco-evolutionary view.

## KEYWORDS

adverse outcome pathway, environmental change, evolution, forecasting, metacommunity, pollution, scale, toxicants

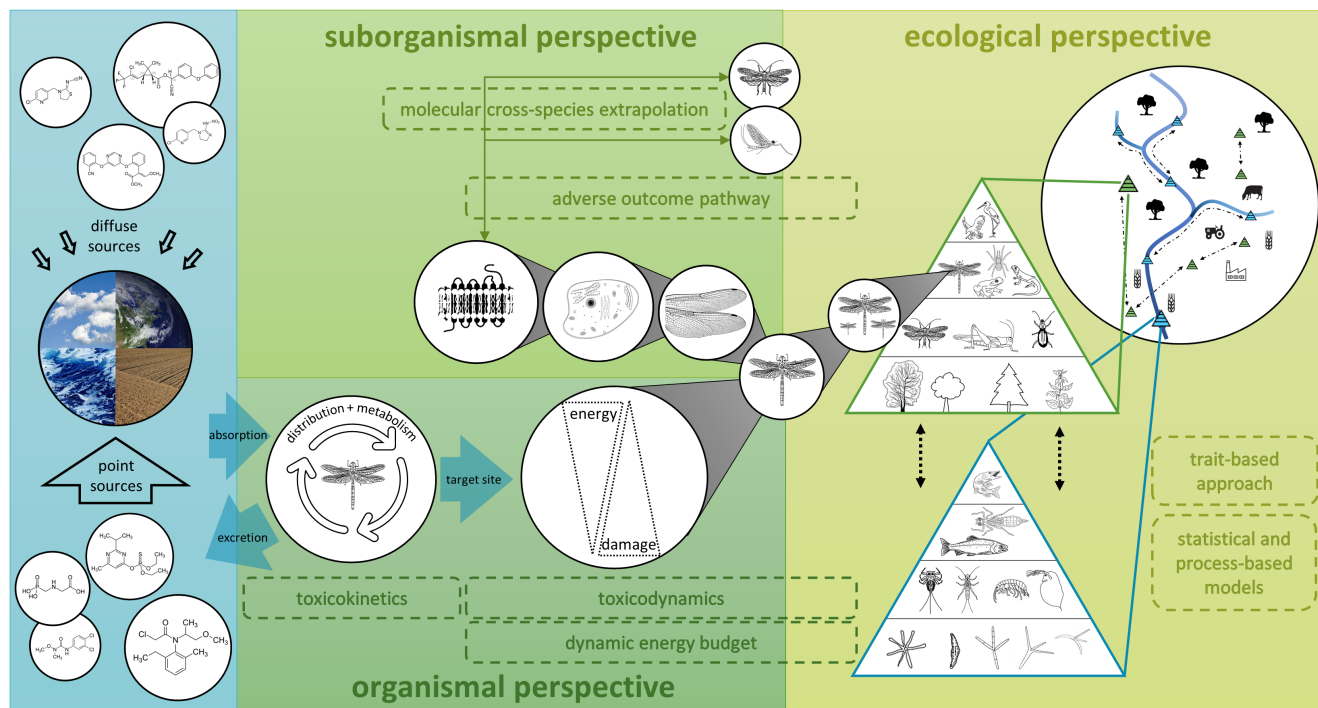
## 1 | INTRODUCTION

Studies around the globe have established associations of chemical groups of concern, for example, pesticides, pharmaceuticals and industrial chemicals, with population decline and biodiversity loss (Beketov et al., 2013; Brodin et al., 2013; Desforges et al., 2018; Kidd et al., 2007; Oaks et al., 2004; Rundlöf et al., 2015). Since 1970, synthetic chemical production has increased at a higher rate than other drivers of global change, such as CO<sub>2</sub> emissions or anthropogenic land-use change (Bernhardt et al., 2017). A recent study estimated more than 350,000 chemicals to be registered for production and use (Wang et al., 2020). In the environment, a wide range of chemicals of urban, agricultural and industrial origin can be detected, in particular in aquatic ecosystems that typically drain landscapes with diverse land use (Bradley et al., 2019; Moschet et al., 2014). For example, more than 400 chemicals with approximately 30 different modes of action (MoA) were found in three Central European rivers (Busch et al., 2016). A study on 19 agricultural streams in Eastern Europe found up to 50 pesticides in a single water sample (Schreiner et al., 2021). Simultaneous exposure to multiple chemicals can cause additive or synergistic effects compared with individual exposure (Cedergreen, 2014) depending on their MoA and interaction type. For example, mixtures including cholinesterase inhibitors or azole fungicides, both interfering with the metabolism of other chemicals, tend to induce synergism (Cedergreen, 2014). Thus, predicting the effect of chemicals on ecosystems requires consideration of potential mixture effects and, consequently, knowledge on all chemicals occurring in an ecosystem. However, most studies focus on target chemicals, i.e. chemicals of concern. These often explained only a minor fraction of the total measured effect in *in vitro* bioassays, suggesting that relevant chemicals might be missed by the current targeted chemical analysis (Escher et al., 2020). Non-target chemical analysis can cover a wider range of chemicals (Brack et al., 2019). However, even if the full spectrum of chemicals was detected and quantified, predicting their ecological effects would be hampered by the absence of ecotoxicological data for many chemicals (Posthuma et al., 2019; Schäfer et al., 2013; Wang et al., 2020). Overall, the large number of synthetic chemicals in the environment combined with limited knowledge on their occurrence and effects in organisms compromise our ability to predict chemical effects in ecosystems. This in turn hampers ecosystem management and conservation and may contribute to underestimating chemicals as one of the drivers of biodiversity loss (Groh et al., 2022; Schäfer et al., 2019).

Predicting the impacts of chemicals in ecosystems is the key topic of the scientific discipline of ecotoxicology. Similarly, chemical regulation, operationalised as risk assessment and management, aims at protecting ecosystems from unacceptable impacts of chemicals. Protection goals typically target populations, communities, food webs and ecosystems (EFSA Scientific Committee, 2016; Forbes & Galic, 2016; Raimondo et al., 2019). However, ecotoxicology and chemical regulation have traditionally relied on summary statistics, so-called (no observed) effect concentrations ([NO]EC), derived from quantitative concentration–effect relationships established with single taxa and chemicals under controlled laboratory settings with

optimal conditions for the test species (Forbes et al., 2017). The effect is typically measured as mortality compared with a control (also called lethal concentration killing  $x\%$  of the test organisms, LC<sub>*x*</sub>) but can also relate to sublethal measures such as growth or reproduction (called effect concentration, EC<sub>*x*</sub>). For such data, simple mathematical models have demonstrated high predictability of toxic effects of mixtures (Kortenkamp & Faust, 2018). However, extrapolating such results to non-tested species and using them to predict impacts on spatiotemporally heterogeneous ecosystems remains a major challenge, which has recently been rated among the most important current research questions in ecotoxicology (Van den Brink et al., 2018). This challenge is due to organisms in nature being influenced by a range of environmental factors (e.g. pH, light) and multiple additional stressors (e.g. climate change, habitat degradation) (Birk et al., 2020; Côté et al., 2016) as well as complex eco-evolutionary dynamics in ecosystems driven by species dispersal, adaptation and species interactions such as predation or facilitation (Cadotte & Tucker, 2017; Govaert et al., 2021; Schäfer, 2019; Schiesari et al., 2018). Ecological studies have often dealt with such complexity by seeking to establish links between stressors and ecological responses based on field studies. Adopting this approach for chemicals is hampered by their sheer amount and potential interactions between chemicals in mixtures as well as with other environmental factors and stressors (Posthuma et al., 2020). Conversely, the reliance of chemical regulation on parameters such as experimentally derived (NO)ECs from few laboratory test species, coupled with a lack of mechanistic insight into the chemical MoA and ecosystem dynamics, has repeatedly led to ecological surprises in terms of unforeseen effects in ecosystems (Oaks et al., 2004; Rundlöf et al., 2015; Tian et al., 2021).

Here, we delineate three idealised perspectives that substantially contribute to date to prediction and cross-species extrapolation (Figure 1): (1) The suborganismal perspective, (2) the organismal perspective and (3) the ecological perspective. The suborganismal perspective uses molecular, cellular and biochemical information to predict chemical effects at the suborganism level, rarely resulting in robust links to organism-level responses (Section 2; Kramer et al., 2011). The organismal perspective mainly focusses on effects at the organism and population level and also attempts to integrate chemical absorption (here uptake), distribution, metabolism and excretion (ADME) processes (Section 3). The ecological perspective provides concepts to predict the consequences of organism- or population-level effects in complex ecosystems, focussing on processes and underlying mechanisms in populations, communities, food webs and ecosystems (Section 4). We describe the perspectives, highlight challenges and identify links between the perspectives that may foster prediction and cross-species extrapolation in the following sections. We focus on process-based and mechanistic approaches and pay only limited attention to approaches based on data-driven (e.g. based on statistics and machine learning) relationships, for example, interspecies correlation estimates (Dyer et al., 2006) or estimates based on species relatedness (van den Berg et al., 2021). In addition, our main focus is the prediction of ecological effects using biological approaches, whereas chemical-driven



**FIGURE 1** Simplified representation of the interrelationship between the different perspectives to predict the effects of chemicals on ecosystems. The dashed boxes illustrate associated approaches and tools.

approaches, such as quantitative structure–activity relationships that rely on the chemical structure and physicochemical substance properties for prediction (Barron et al., 2015), are certainly also interesting and relevant but beyond our scope.

## 2 | SUBORGANISMAL PERSPECTIVE

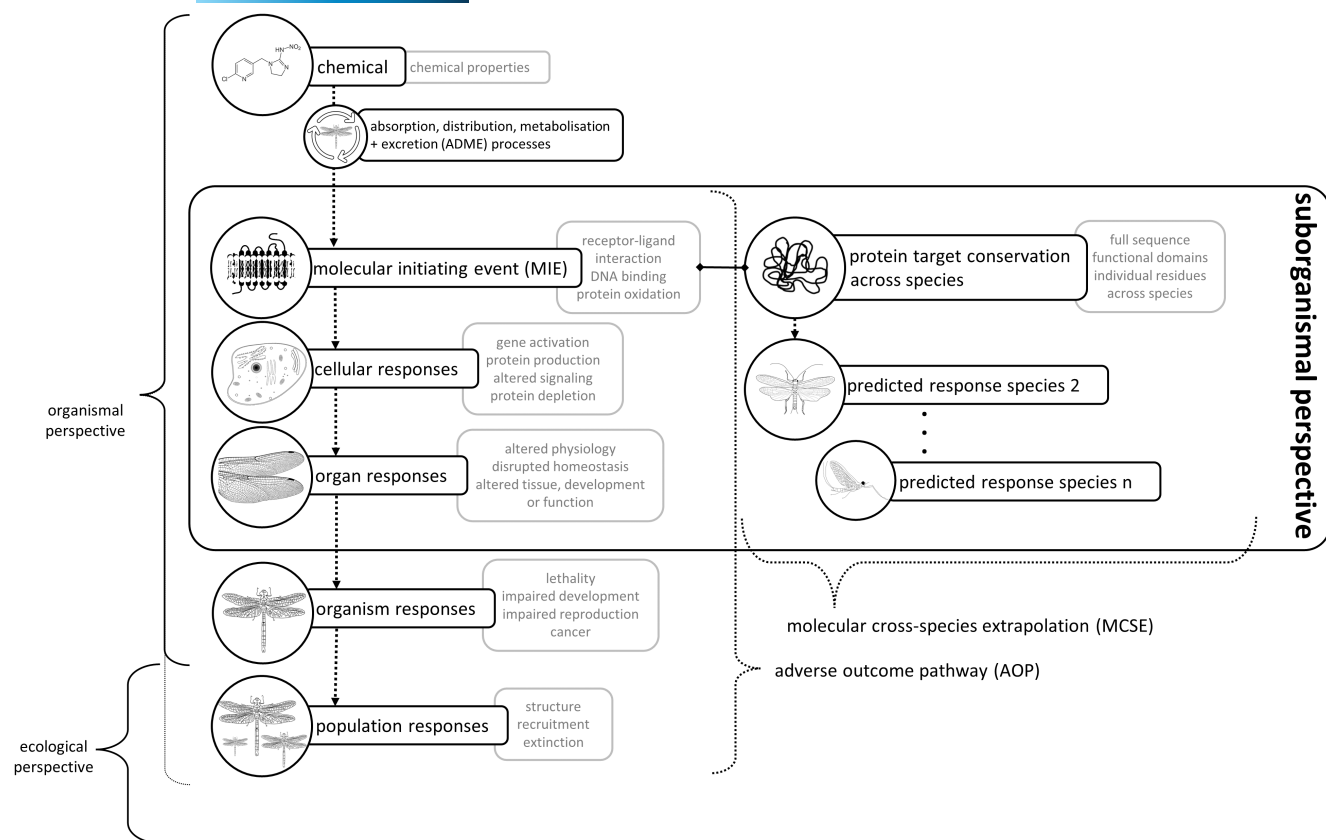
Although higher biological level effects are of ultimate interest in research and chemical regulation, they are always triggered by suborganismal processes such as a molecular initiating event (MIE). Responses to chemicals at the suborganismal level are largely considered as early warning signs of exposure or effects (Clements, 2000; Hagger et al., 2006). Although data from this level including single sensitive biomarkers are generally insufficient for robust effect prediction at the ecosystem level, they are pivotal for understanding mechanisms underlying chemical effects and represent a critical element of prediction and extrapolation. Since the early 2000s, a research area has emerged that relies on mechanistic understanding for the prediction of chemical effects through the use of emerging molecular, cellular and biochemical tools (de Nadal et al., 2011; Ouborg & Vriezen, 2007; Reusch & Wood, 2007).

### 2.1 | Adverse outcome pathways for prediction

In this context, adverse outcome pathways (AOPs, Figure 2) represent an important concept that structures toxicological knowledge

originating from individual biomarkers as well as omics (e.g. genomics, transcriptomics, proteomics, lipidomics, metabolomics), thereby improving mechanistic understanding of all steps following chemical exposure from receptor to cell over organ to the whole organism (Ankley et al., 2010; OECD, 2013). AOPs describe the chain and network of events initiated by a chemical in an organism from triggering an MIE, cascading via key events to a physiological effect (Figure 2). Recent advances, such as in vitro testing, high-throughput screening, next-generation sequencing and omics-technologies, have simplified the identification of molecular target sites of chemicals, for example, DNA, membrane or specific receptors and enable simultaneous testing of many effects at cellular and tissue level (LaLone et al., 2018; López-Osorio & Wurm, 2020; Villeneuve et al., 2019). Statistical tools can help increase the interpretability and applicability of omics-based data for prediction, whereas multi-level analysis approaches may enable the integration of such data from multiple biological levels (see Murphy et al., 2018b).

However, only if (causal) relationships of suborganismal responses (e.g. MIEs) with apical organism responses (e.g. survival or reproduction success) (Kramer et al., 2011) or with physiological MoA (pMoA) as defined in bioenergetic models (Section 3, Murphy et al., 2018a, 2018b), can be established, AOPs can contribute to predicting effects at higher biological levels, for example, population, community, food-web or ecosystem level. Given the considerable efforts required, only a few such relationships have been established to date. For example, the relationship between effects on the vitellogenesis and fecundity (eggs/female/day) in oviparous fish enabled population-level predictions for endocrine-disrupting



**FIGURE 2** Main processes related to the suborganismal perspective. The box delineated by the solid black line depicts the main focus of the suborganismal perspective. Boxes in light grey provide more detailed information on terms. Arrows connect biological levels, whereas brackets indicate the processes and levels associated with the concepts of adverse outcome pathways illustrated based on Ankley et al. (2010) and molecular cross-species extrapolation and the other perspectives.

chemicals (Miller et al., 2007; for further examples see Kramer et al., 2011). However, these relationships need to be quantitative to predict effects at higher biological levels. Dose and time data on initial and maximum induction, adaptation and recovery is required from low to high biological level responses to build quantitative links (Wu et al., 2005). For example, molecular and biochemical responses seem frequently similarly rapidly induced as physiological, cytological or behavioural responses (Wu et al., 2005). Longer recovery time has often been found for population and community responses (Wu et al., 2005). Regarding the dose, for baseline toxicants, for example, cellular—and organismal effects occurred at similar critical concentrations (Escher et al., 2019; Lee et al., 2021). Quantitative relationships can differ by several orders of magnitude between chemicals (Kimber et al., 2011; Sewell et al., 2018), species and environmental contexts. Moving from the current mainly qualitative scope of AOPs to quantitative AOPs (qAOPs) requires the incorporation of dose and time information into thresholds triggering MIEs and the sequence of key events (Sewell et al., 2018). To date, only a few probabilistic and mechanistic qAOP models were developed for effect prediction, with divergent characteristics and outcomes (reviewed in Spinu et al., 2020), and a need for guidance on the development and evaluation of qAOP models remains, particularly for application in a regulatory context (Spinu et al., 2020). Generally, improved databases,

data-sharing initiatives, bioinformatics, data-mining tools as well as the use of standardised terminology will support the development of qAOPs based on existing data (Sewell et al., 2018) and the computational prediction of AOPs (Bell et al., 2016; Oki et al., 2016). qAOPs might allow the use of cellular-level data, which can be obtained efficiently from high-throughput assays, for the prediction of organism- and population-level effects (Ankley et al., 2010; Kramer et al., 2011; Villeneuve et al., 2019). In human toxicology, major developments are underway to use data from high-throughput assays as a robust anchor for higher-level (organ or organism) responses by establishing quantitative *in vitro* to *in vivo* relationships (Bell et al., 2020; Wetmore, 2015). Mammalian data can partly be extrapolated to other species with closely conserved pathways (see next Section 2.2), but generally the development of species-specific pathways in additional vertebrates, invertebrates and plants is needed (Villeneuve et al., 2019).

## 2.2 | Molecular cross-species extrapolation

Molecular cross-species extrapolation (MCSE, Figure 2) can help extrapolate chemical sensitivity across species by comparing molecular target sites of chemicals, e.g. receptor protein sequence

and conformation similarity among species. MCSE assumes that evolutionary conservation of molecular target sites implies chemical sensitivity (Gunnarsson et al., 2008). Where the structure and function of molecular target sites are similar across species, at least building blocks of (q)AOPs can be reused, which enables more efficient AOP development for new species (Ashauer & Jager, 2018). Unfortunately, information on structure and function is rarely available (LaLone et al., 2016), but advances in sequencing technologies and molecular methods may rapidly expand the available data. Moreover, advances in web-based tools for MCSE such as the US EPA Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) tool already enable the inclusion of some structural data of proteins (e.g. conserved functional domains and individual amino acid residue positions, Figure 2) (LaLone et al., 2013, 2016). Furthermore, a low degree of similarity in molecular target sites across species (e.g. using the tool SeqAPASS; LaLone et al., 2016) can already guide the selection of species for further laboratory tests (LaLone et al., 2013, 2018).

### 2.3 | Major challenges and current developments

Despite major advances, the suborganismal perspective remains insufficient to predict the effects of chemicals in ecosystems. The steps from chemical uptake to reaching a molecular target site (termed toxicokinetic [TK] process, i.e. ADME) and the adaptive capacity of an organism before an MIE is initiated are not considered by AOPs or MCSE and remain a main focus of the organismal perspective. To close this gap, different approaches have been suggested, such as high-throughput physiologically based TK models in human toxicology (Breen et al., 2021), the aggregate exposure pathway framework (Teeguarden et al., 2016), the combined measurements of external and internal concentrations (i.e. circumvent TK processes; van den Berg et al., 2021) and linking AOPs with bioenergetic models (Section 3, Kramer et al., 2011; Murphy et al., 2018a, 2018b).

Furthermore, suborganismal responses are usually recorded under standardised and simplified laboratory conditions, but the conditions in real systems can influence these responses. AOPs and MCSE consider usually a single chemical effect as independent of remaining physiological processes (Murphy et al., 2018a, 2018b). However, depending on resource availability and other moderating factors, energy can be allocated differently, which influences the overall response. Energy trade-offs between physiological processes, such as maintenance (including metabolism of chemicals), growth and reproduction, for instance under the impact of multiple stressors, are not considered. This limitation of AOPs could potentially be alleviated through integration with the organismal perspective (Section 3, Murphy et al., 2018a, 2018b).

In addition, both chemical effect prediction and extrapolation across species should consider that chemicals can have multiple and non-specific target sites. Besides, a single MIE can result in multiple outcomes and common key events can be involved in multiple AOPs resulting in non-linear, branching AOPs (Sewell et al., 2018),

with a high potential of reusing (q)AOP building-blocks. Finally, even if organism-level effects could be reliably predicted, prediction of higher-level effects up to the ecosystem level requires including ecological and evolutionary processes theoretically and empirically (Sections 4–6).

## 3 | ORGANISMAL PERSPECTIVE

Bioenergetic models, such as dynamic energy budget (DEB) models can extend the prediction from the suborganism level to the organism and population level and at the same time provide the necessary background on ADME processes when integrated into toxicokinetic–toxicodynamic (TKTD) models (Figure 3). They allow one to predict the effects of realistic time-varying exposures in the field based on responses recorded under constant exposure conditions in the laboratory (Sherborne et al., 2020). At the same time, they can translate complex exposure patterns into effects at medium biological levels (e.g. organism, population), thereby providing an important element of effect prediction (Ashauer et al., 2011, 2016).

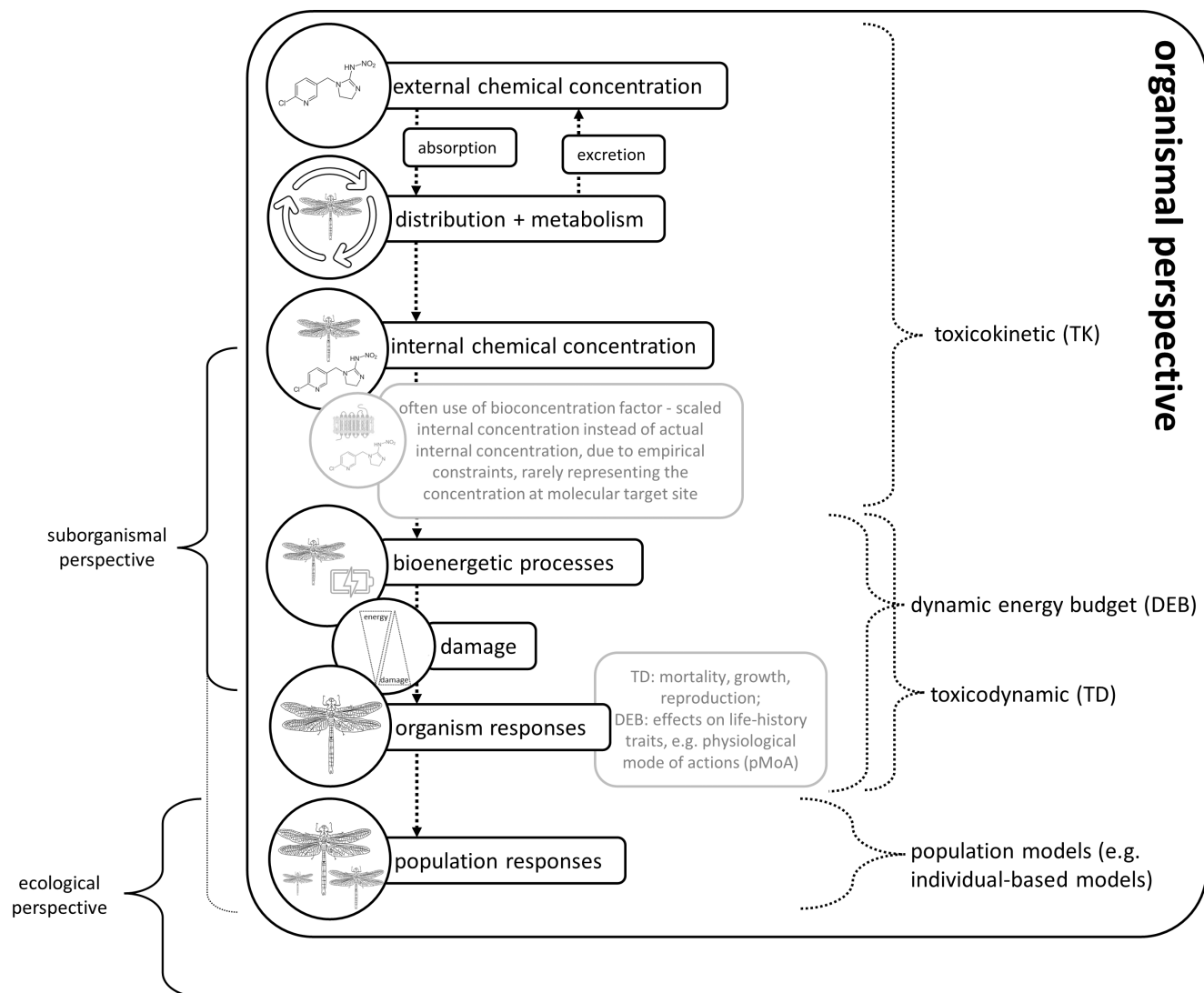
### 3.1 | TKTD models for prediction

Toxicokinetic–toxicodynamic models have a TK part that reflects the ADME processes of chemicals to predict a total internal concentration of a chemical in an organism (Figure 3). TK models can be modelled as one compartment (whole organism), multiple compartments (i.e. internal entities such as organs) or based on physiology (Grech et al., 2017) and are driven by chemical-specific (e.g. octanol–water partitioning coefficient) as well as organism-specific (e.g. lipid content) parameters. TD models focus on the effect of the concentration at a molecular target site on apical responses at the organism level, such as mortality, growth or reproduction (Figure 3). Here the derived TD model parameters can reflect biological processes and organism traits (Ashauer & Jager, 2018; Rubach et al., 2011). TKTD models allow for different complexities (e.g. include damage recovery) depending on the scope of prediction and data availability (Jager, 2020). This potential for different complexity has led to the emergence of a wide range of TKTD models. However, at least for the survival endpoint, they have been unified in the Generalized Unified Threshold model for Survival (GUTS), which models time-to-event or survival data (Jager et al., 2011). GUTS can be adapted to the available input data and to mechanistic assumptions when used to predict survival in a population. For example, the reduced GUTS (GUTS-RED), directly connects an external concentration to the scaled damage, without the need for internal concentrations (Jager, 2020; Jager et al., 2011).

### 3.2 | DEB models for prediction

A commonly used bioenergetic model framework is based on DEB theory (Jager, 2020; Kooijman, 2009). The DEB theory consists of





**FIGURE 3** Main processes related to the organismal perspective. The large box delineated by the solid black line depicts the main focus of the organismal perspective. Boxes in light grey provide more detailed information on terms. Arrows connect processes or biological levels, whereas brackets indicate the processes and levels associated with each approach and the other perspectives.

assumptions specifying how organisms obtain energy and matter from their environment to fuel their life cycle. The theory treats organisms as dynamic systems with explicit energy balances and can be applied to all species (Nisbet et al., 2000). Different variants of DEB models exist in ecotoxicology, which are coined under the term DEBtox or, according to a more recent publication, DEB-TKTD (Sherborne et al., 2020). Recent developments include a unified and simple DEB approach for practitioners (EFSA PPR et al., 2018; Jager, 2020; Sherborne et al., 2020). Generally, DEB-TKTD combines biological parameters of organisms (e.g. growth, feeding and maintenance) and chemical exposure over time (Jager et al., 2006). The modelling of bioenergetic processes allows one to capture (sub)lethal effects of chemicals on life-history traits of individuals. Structurally, the DEB-TKTD model consists of TK and TD parts. The TK part is similar to other TKTD models discussed above (Figure 3). By contrast, the TD part differs from TKTD models.

DEB-TKTD predicts the effects of a chemical inside an organism as stress costs of one of usually four pMoA (Figure 3), namely, assimilation, growth, maintenance, and reproduction (Ashauer & Jager, 2018), representing assimilation of energy from food, energetic costs for growing new body tissue, maintaining body functions including mitigating hazardous effects as well as producing offspring (Kooijman & Bedaux, 1996). Similar to GUTS, a reduced version (DEBkiss) of a full DEB-TKTD model has been developed, which simplifies bioenergetic processes and in turn requires fewer state variables and parameters (Jager et al., 2013). Another important simplification within the DEB-TKTD model framework is the introduction of 'compound parameters' (comDEB[kiss]), such as maximum length, which replace hard-to-measure 'primary parameters' (priDEB[kiss]) based on simplified model assumptions, for example, a constant ratio between size and maturity (Sherborne et al., 2020). For the simplest model variant (comDEBkiss), each

parameter relates to a measurable variable, and it can be fully parameterised based on standard laboratory tests, where growth and reproduction are measured over time (Jager, 2020; Sherborne et al., 2020). Generally, recent studies highlight the relevance of mechanistic understanding in DEB model parameters and processes for reliable prediction. If model parameters and processes have no phenomenological counterpart in the real world, they represent abstractions with unknown interpretability (Murphy et al., 2018a, 2018b) and uncertainty. For instance, population-level responses can differ strongly depending on the suborganismal mechanisms involved (Martin et al., 2014). One way to alleviate this might be to incorporate AOPs in DEB models (Murphy et al., 2018a, 2018b). For example, AOP key event responses could be integrated into a damage term that translates to DEB rates (Murphy et al., 2018a, 2018b). As mentioned in Section 2, AOPs and gene expression data could thereby gain higher predictive applicability.

### 3.3 | Major challenges and current developments

As outlined above, for both, TKTD and DEB models, simplified model variants have been introduced to achieve practical applicability for non-experts. However, it is challenging to find a compromise between depicting reality and keeping the model complexity (i.e. number of model parameters) and the data requirements computationally manageable. This compromise builds on assumptions, such as the constant ratio between size and maturity or the neglect of a reserve, ageing, body shape differences and starvation (Sherborne et al., 2020). For species or chemical MoAs where an assumption is not plausible, the model needs to be extended at the cost of simplicity (Sherborne et al., 2020).

Besides, another main challenge remains: For many taxa, key model parameter estimates required to build the model are lacking. Obtaining those by direct measurements in laboratory experiments after field sampling of the new species is resource-intensive and inappropriate for rare and endangered species (Petersen et al., 2008). Methods to reduce resource requirements in laboratory testing or to indirectly obtain key parameters for a model, such as parameter borrowing, pattern-oriented and artificial evolution approaches, are described elsewhere (Petersen et al., 2008). DEB model parameters have already been collected for more than 3200 species in the Add-my-Pet database (AmP, 2022), covering all major phyla (Lavaud et al., 2021). For species sharing the same receptor and pathway and compounds sharing the same MoA, model parameters should be the same and could be used for effect extrapolation to untested chemicals and species based on internal molar concentrations (Gergs et al., 2019; Jager & Kooijman, 2009). However, also the bioconcentration factor and the target site interaction efficiency of a chemical can make a difference in the outcome (Gergs et al., 2019; Jager & Kooijman, 2009), information that is rarely available. In addition, the actual internal concentration at the target site is difficult to measure for many species and the aggregation of ADME data for additional vertebrates,

invertebrates and plants, as realised for mammals/humans, is still pending (Villeneuve et al., 2019). Finally, extrapolation of chemical effect concentrations to untested species has so far only been done for survival data based on GUTS (Gergs et al., 2019), but not for sublethal responses (Sherborne et al., 2020). The cross-species parameter correlation method used in this extrapolation enabled the prediction of chemical effects for new species, however, its predictive capability at the population level involving an individual-based model was still insufficient and underestimated the actual effect (Gergs et al., 2019).

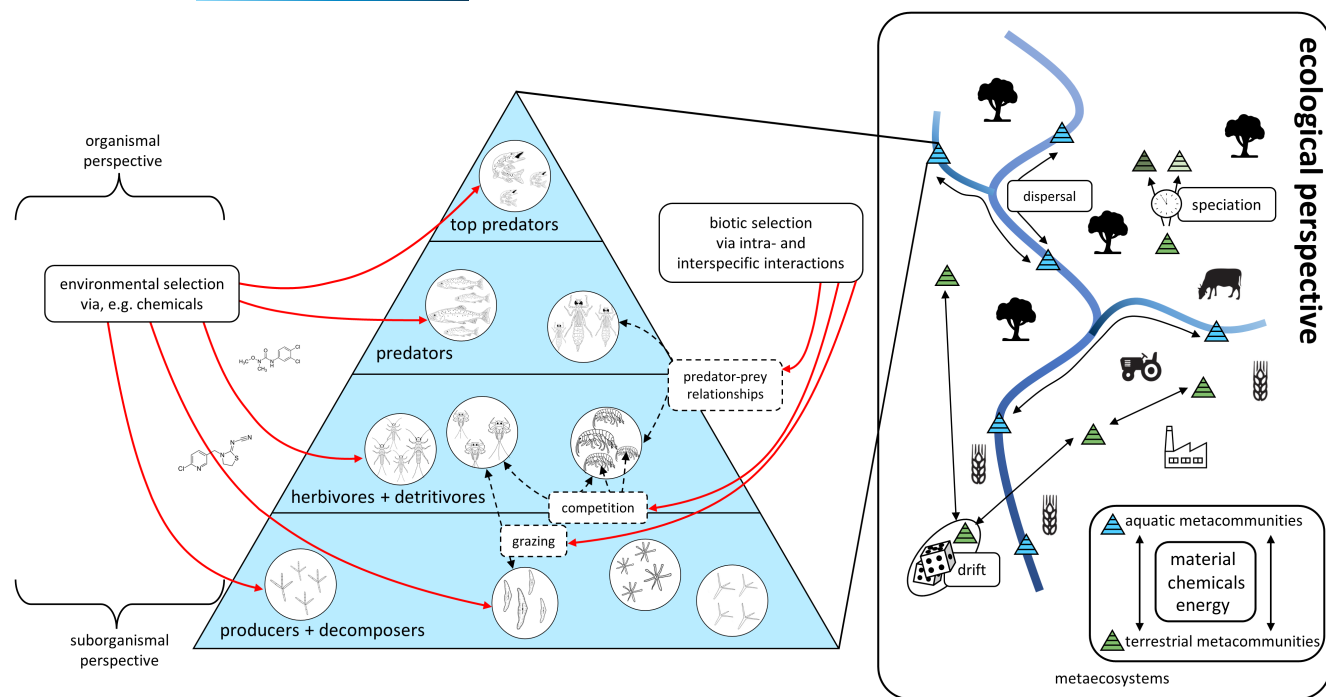
Starting in 1994 many studies with TKTD and DEBtox modelling applied a rigorous approach to the estimation of model parameters and their uncertainty by likelihood profiling (Bedaux & Kooijman, 1994; Kooijman & Bedaux, 1996). However, a more fundamental challenge was the propagation of uncertainty to the model outputs and subsequent predictions (Charles et al., 2022; Trijau et al., 2021). For the most common TKTD and DEB models, frequentist and Bayesian software packages have been developed in the last few years to solve this problem (Charles et al., 2022; Jager, 2021; Trijau et al., 2021). However, this remains a common challenge in community and ecosystem models (with some exceptions, e.g. Streambugs) (Mondy & Schuwirth, 2017; Schuwirth et al., 2015), which are required to extend chemical effect prediction to the community or ecosystem level.

Overall, TKTD and DEB models can strongly improve our understanding and capacity for prediction, but they are largely limited to the organism or population level in laboratory settings. Even perfect knowledge at the associated level would be insufficient to reliably predict chemical effects on populations in real-world ecosystems and necessitates an ecological perspective, outlined below.

## 4 | ECOLOGICAL PERSPECTIVE

A major aim of ecotoxicology and chemical risk assessment is to predict chemical effects at higher biological levels such as communities, food webs and ecosystems or biodiversity per se, which are generally within the domain of ecology. A rich but heterogeneous body of ecological theory has been developed to explain community, food web and biodiversity patterns and related processes at different spatial and temporal scales (Scheiner & Willig, 2011). In the last decade, generalising and unifying frameworks have emerged integrating previously separated lines of theory. Vellend's Theory of Ecological Communities identifies four processes that underly community dynamics (Vellend, 2010, 2016) (Figure 4):

1. Selection, which consists of a) environmental selection through environmental conditions including chemical pollution, and b) biotic selection through processes such as competition, predation or facilitation, that determine the occurrence and growth of a species in a habitat patch.
2. Dispersal, which determines the recruitment to and from habitat patches.



**FIGURE 4** Main processes related to the ecological perspective. The large box delineated by the solid black line depicts the components of the ecological perspective in a metaecosystem. Triangles represent metacommunities, the left triangle zooms into an idealised aquatic metacommunity, represented as trophic pyramid. Arrows depict a bi- or unidirectional exchange in materials, chemicals and energy (black) or impact (red). Brackets indicate the processes associated with the other perspectives.

3. Drift, in terms of stochastic processes that influence the development of populations and communities.
4. Speciation, i.e. formation of a new biological species, although mainly relevant on longer time scales.

#### 4.1 | Chemicals and ecological processes

Many studies demonstrated that the first three processes are highly relevant for predicting chemical effects on ecological systems (Figure 4). Direct chemical effects constitute a form of (environmental) selection. In addition, environmental conditions such as temperature, moisture or pH, besides potentially modifying chemical concentrations and interactions, determine the occurrence of a biological species in a habitat patch exposed to a chemical and its fitness (Laskowski et al., 2010; Niinemets et al., 2017). Biotic processes such as competition or predation/cannibalism have also been shown to increase the effect of chemicals or to delay recovery (Kattwinkel & Liess, 2014; Liess & Foit, 2010; Viaene et al., 2015). Dispersal contributes to recovery from chemical effects via recolonisation (Trekels et al., 2011), but can also lead to a transfer of chemicals between food webs and propagate effects to non-polluted habitat patches (Richmond et al., 2018; Schäfer et al., 2017; Schneeweiss et al., 2022). Only few studies have specifically examined the relevance of stochastic ecological drift for chemical effects. However, a modelling study demonstrated that incorporating stochasticity improved the prediction of experimental data (Erickson et al., 2014).

Moreover, stochasticity can profoundly modulate ecological dynamics (Shoemaker et al., 2020). Although the fourth process, speciation, is mainly relevant on longer time scales, evolutionary processes at the population level (e.g. natural selection, gene flow, genetic drift and mutation) can already occur at similar temporal and spatial scales as ecological processes (Govaert et al., 2021). This phenomenon is often termed 'rapid evolution' and its ecological and functional significance has been shown already several decades ago (e.g. Gorokhova et al., 2002; Reznick et al., 1997). With respect to pesticide impacts, multiple studies found evidence for rapid evolutionary adaptation and lower sensitivity (Bass et al., 2015; Hawkins et al., 2019; Lucas et al., 2015; Palumbi, 2001; Powles & Yu, 2010). This adaptation can lead to co-tolerance against similar stressors—but it may also result in higher sensitivity of species to other stressors due to performance trade-offs (Luijckx et al., 2017; Orr et al., 2021). Theory, experiments and prediction should, therefore, consider eco-evolutionary dynamics (Govaert et al., 2021), which would allow to move from a static to a dynamic prediction framework. Furthermore, genetic intraspecific variability, for example, cryptic lineages, showed differential sensitivity (Becker & Liess, 2015; Feckler et al., 2014; Sturmbauer et al., 1999), which hampers the transferability of experimental results based on individual clones or low-diversity laboratory populations to natural populations. Overall, the Theory of Ecological Communities provides the key ecological processes that need to be considered when predicting the effects of chemicals in ecosystems, yet the approach is abstract and makes no prediction on the relevance of each of



the processes for a specific ecosystem or species. A different amalgamating framework is provided by the Metacommunity Theory (Leibold et al., 2004). This explains and predicts patterns of community composition in connected habitat patches at local and regional spatial scales. Three of the processes (selection, drift, dispersal) outlined above are integrated with different weights into four non-exclusive paradigms of community organisation (for details see Leibold et al., 2004). Through the consideration of biogeochemical flows and complex food webs, this theory has been expanded to metaecosystems and meta food webs (Gounand et al., 2018; Loreau et al., 2003; Ryser et al., 2021) (Figure 4). However, this theory also rather provides predictions of general patterns from assumptions of the relevance of the individual paradigms than predictions of the community composition in a specific habitat patch or region. With respect to chemicals, this theory has been applied to establish a conceptual framework for chemical effects across ecosystems and to explain patterns observed in experiments (e.g. Peng et al., 2018; Schiesari et al., 2018).

## 4.2 | Use of traits in ecotoxicology

The trait-based approach, rooted in the so-called Assembly and Response Rule Framework (Keddy, 1992), has been most widely applied for explaining and predicting chemical effects in ecosystems. Loosely defined, traits are measurable characteristics of an individual (cf. Violle et al., 2007) and trait-based approaches aim at linking traits, instead of species, to environmental conditions at variable scales. Although it remains a challenge for ecologists to predict the specific set of species occurring in a habitat patch, trait-based approaches successfully predicted the trait composition of communities from environmental conditions (Shipley, 2010; Shipley et al., 2006). In the context of predicting the effects of chemicals, the sensitivity of a species to a chemical can be considered a trait. This trait forms the backbone of many applications in the context of ecotoxicology and risk assessment. For example, the sensitivity distribution across species, called SSD, is used to derive acceptable environmental concentrations of chemicals (Smetanová et al., 2014) and has been successfully linked to chemical effects in ecosystems (Posthuma & de Zwart, 2012). However, data on chemical sensitivity is lacking for most species. Hence, several approaches have aimed at predicting the chemical sensitivity trait, either by other traits (e.g. body size), phylogenetic relatedness or using tools related to the other two perspectives, i.e. suborganismal or organismal approaches (Malaj et al., 2016; Rubach et al., 2012; van den Berg et al., 2019, 2021). Although useful for filling data gaps, these approaches often depend themselves on input data that is scarce or associated with high uncertainty. Although not related to physiological sensitivity, several other traits can be used to assess the vulnerability of taxa (Figure 4; De Lange et al., 2009). Examples of such traits are habitat preference (determining exposure), dispersal capacity (determining recolonisation and avoidance of chemical exposure) and growth rate (determining recovery). Several studies used a combination of traits

to establish links between chemical pollution and species occurrence or community change (Badry et al., 2020; Delhayé et al., 2020; Kjær et al., 2021; Schäfer & Liess, 2013). Moreover, if links between traits that respond to environmental (including chemical) selection, so-called response traits, and traits that describe the effect of a species on ecosystem functioning, so-called effect traits, can be established, then these allow to predict changes in ecosystem functioning (e.g. Schäfer et al., 2012). Although trait-based approaches are valuable to identify vulnerable taxa and predict the trait composition of species in a habitat, their capacity to quantitatively predict the response to chemicals is hampered by data availability and insufficient consideration of eco-evolutionary dynamics.

Regarding data availability, traits with a strong mechanistic link to chemical effects, such as the capacity for production of heat shock proteins or the content of energy storage molecules (e.g. lipid, glycogen or proteins), average biomass or body size have rarely been measured for many organism groups that are particularly at risk from chemical effects such as invertebrates or fungi (Rubach et al., 2011). Measuring such traits would require major coordinated efforts, though the other perspectives might aid in predicting traits (Gergs et al., 2019; Pecquerie et al., 2011). Finally, intraspecific trait variation can be important (see for example De Laender et al., 2014) but, depending on the organism group, is often ignored due to a lack of data. Regarding eco-evolutionary dynamics, the trait-based approach is currently static in many respects. First, traits may vary over the lifetime of a species (Lancaster & Downes, 2010). Second, the average trait of a population may change with environmental conditions, which includes adaptation processes to chemicals (Dinh et al., 2016; Shahid et al., 2018), whereby the future response to the same or other stressors is moderated (Orr et al., 2021; Vinebrooke et al., 2004). Third, biotic selection and dispersal are often insufficiently accounted for in trait-based approaches (Cadotte & Tucker, 2017).

## 4.3 | Statistical and process-based models

A wide range of statistical and process-based models have been developed, rooted in a variety of ecological concepts and theories, that can predict the effects of chemicals. Joint species distribution models (JSDMs) are a group of statistical models that have attracted wide attention in ecology (Ovaskainen & Abrego, 2020). If larger monitoring data sets with measurements of species and chemicals as well as all relevant environmental factors are available, JSDMs can quantify the relevance of chemicals for the species distribution and predict the occurrence of species in non-measured patches in the landscape (Brown et al., 2018; Ovaskainen et al., 2017). The modelling requires knowledge on ecological processes such as biological interactions, which can be estimated from the data, though such estimates may not be reliable (Dormann et al., 2017, 2018). As larger field data sets are required, JSDMs are unsuitable for novel chemicals that have not been authorised for use. Many process-based models have been developed and used to predict the response of

populations, communities and ecosystems to chemicals (see reviews by: Galic et al., 2010; Rohr et al., 2016; Schmolke et al., 2010). Most of these models derive from classical ecological models and consider individuals as the smallest unit, thereby ignoring suborganismal processes related to the MoA (Accolla et al., 2020; Rohr et al., 2016). Notwithstanding, process-based models have successfully been used to quantitatively predict the responses of populations, communities and food webs to chemicals (Kattwinkel et al., 2016; Lei et al., 2008; Mondy & Schuwirth, 2017; Topping et al., 2003). The main challenge for process-based modelling remains model validation and the spatially explicit modelling of communities and food webs, which still faces conceptual, practical and partly computational constraints.

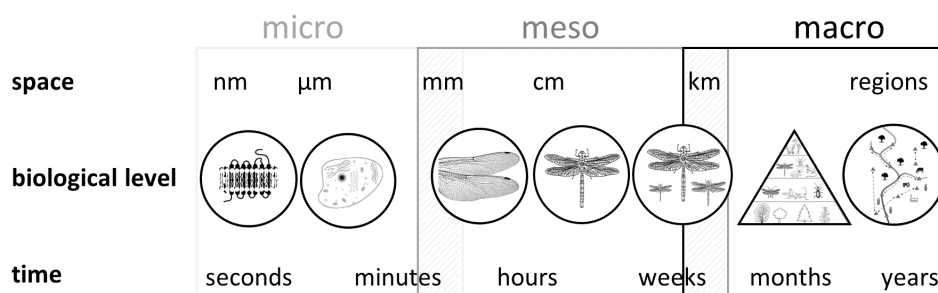
#### 4.4 | The challenge of multiple stressors

Chemical stressors often co-occur with other stressors (Holmstrup et al., 2010; Schäfer et al., 2016) and stressors can interact resulting in additive, antagonistic or synergistic effects (Piggott et al., 2015b). This represents a challenge to most ecological approaches. A link to the other perspectives may aid in predicting multiple stressor effects. For example, combining analytical and bioanalytical tools (e.g. in vitro bioassays) provides the opportunity to analyse mixtures of chemicals found in the environment for their combined risk and to identify risk drivers retrospectively (Escher et al., 2020). Furthermore, knowledge about a chemical's MoA and species sensitivity traits can guide model selection when trying to unravel mixture effects (Spurgeon et al., 2020). A few qAOPs assessed mixture effects and considered additional stressors (Chu, 2018; Spinu et al., 2020). Also bioenergetic models can incorporate mixture toxicity (Ashauer et al., 2007, 2015; Bart et al., 2021) including chemical interactions (e.g. synergism, antagonism) (Cedergreen et al., 2017) and provide a framework to deal with multiple stressors through the inclusion of other physical (e.g. temperature) or biological stressors (Galic et al., 2018; Goussen et al., 2020). However, data for relevant stressors, such as pH, nutrients or habitat degradation are largely lacking (Goussen et al., 2020). Finally, to reliably predict multiple stressor effects our understanding of the relative importance of stressors must improve (Goussen et al., 2020) including the

development of theoretical concepts (De Laender, 2018; Schäfer & Piggott, 2018).

## 5 | THE SCOPE OF PREDICTION—A QUESTION OF SCALE

Prediction can have different scopes including biological levels, environmental contexts, as well as spatial and temporal scales (see scenario-based guide to prediction in the Supplementary Data, Text S1; Figure S1). The three perspectives focus on different biological levels, which typically imply a certain spatial and temporal scale (Figure 5). The suborganism level is rather associated with small spatial and short temporal scales. Changes in populations, organisms or in parts of organisms, which is the focus of the organismal perspective, typically cover larger (mm to m) and longer (hours to weeks) scales. Community, foodweb and ecosystem levels usually cover large spatial and long temporal scales (Figure 5). However, the scale is also influenced by the type of organism and chemical. For example, microorganisms have much shorter generation times than macroorganisms. Thus, chemical-driven changes in an individual mammal can persist longer than changes in (meta-) communities of microorganisms. Accordingly, temporal and spatial scales of (eco)toxicological test methods, of species traits and of stressors are interrelated, resulting in several species groups being underrepresented in certain test methods (Schuijt et al., 2021). For example, in vitro bioassays have been realised mainly for mammalian cell lines, whereas whole organism tests as well as biomarkers mainly for selected fish and invertebrate species (Schuijt et al., 2021). To assess the effect of chemicals on underrepresented species groups (e.g. fungi), extrapolation approaches (e.g. MCSE, trait-based) are certainly fruitful, but further test systems still need to be developed. Similarly for chemicals, test systems (e.g. high-throughput in vitro tests) for several major MoA still need to be developed (Schuijt et al., 2021; Villeneuve et al., 2019). Overall, prediction for larger spatial and temporal scales (e.g. regional level over months to decades), for example with larger-scale process-based models, is particularly challenging because empirical data on chemical effects often originates from experiments on much smaller spatial and temporal scales (Schneider, 2001). This means that calibration and parameterisation



**FIGURE 5** The expression of spatial and temporal scales varies between the biological levels and is also influenced by the type of organism and chemical. This illustration is simplified.

may be biased. Simultaneous recording data at multiple biological levels and over large and long scales may provide empirical relationships on which models can be built (see Section 6).

## 6 | DATA AND EXPERIMENTAL ADVANCES TO IMPROVE PREDICTION

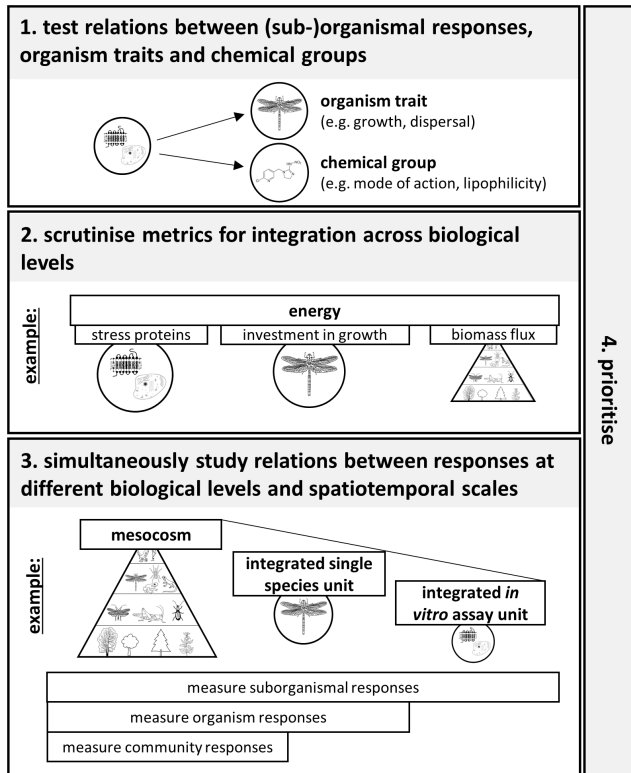
Each of the three perspectives provides essential elements for the prediction of chemical effects in ecosystems. Strengthening the links between these perspectives would considerably foster predictive modelling of chemical effects in ecosystems and effect extrapolation between species. A major prerequisite is data that simultaneously cover different biological levels as well as spatial and temporal scales. Below, we outline promising approaches and associated types of data that would strengthen the links between the perspectives as well as focus and coordinate the effort in data collection:

*First, record suborganism- and organism-level responses to chemicals and test for relationships with chemical groups and traits of organisms (Figure 6[1]).* Traits have been relevant predictors of variability in chemical sensitivity at the level of organisms or populations (van den Berg et al., 2021; Wiberg-Larsen et al., 2016). Yet, suborganismal processes involved in chemical uptake, transformation and effects may also relate to organism traits (Gergs et al., 2015, 2019). Moreover, expression profile data (omics), which are important for constructing the cellular portion of AOPs, might vary in tissues as a function of chemical MoA and selected organism traits (e.g. metabolic rate) and grasping such relationships would contribute to a fundamental understanding of toxic effects (López-Osorio & Wurm, 2020). Although trait data has increasingly become available for various taxa, substantial work remains to standardise trait data (Gallagher et al., 2020) and data on traits that are likely mechanistically involved in chemical effects are still scarce. Prioritising traits and potential relationships with (sub-)organismal responses based on expert knowledge for a specific ecosystem type (e.g. marine, terrestrial), chemical MoA and organism group, would limit the required measuring effort (Kearney et al., 2021; McGill et al., 2006). Pioneering studies have focussed on easily measurable traits such as body mass that is strongly related to the metabolic rate (Baas & Kooijman, 2015; Gergs et al., 2015; Ryser et al., 2021). Even purely correlative relationships between (sub-)organism responses with chemical MoA and traits would foster our predictive capacity (Kramer et al., 2011; Murphy et al., 2018a, 2018b) and extrapolations across species. Studies recording responses to chemicals at different (sub-)organism levels would ideally be done under variable spatiotemporal and environmental conditions to evaluate the generality of potential relationships, including with traits (McGill et al., 2006).

*Second, scrutinise metrics that are measurable at many biological levels such as energy for their potential to integrate across levels (Figure 6[2]).* Analysis of bioenergetics has been suggested as a common currency to integrate across biological levels given that generic energy flow rules apply universally and that bioenergetics is involved in the regulation of structural and functional responses

at all levels (Fischer et al., 2013; Forbes et al., 2017; Forbes & Galic, 2016; Segner et al., 2014; Sokolova, 2021). At the suborganism level, proteins associated with the protection from stress (e.g. heat shock proteins), antioxidant, pro- and anti-apoptotic proteins may indicate stress-induced bioenergetic state transitions (Reusch & Wood, 2007; Sokolova, 2013). Similarly, biomarkers such as the aerobic scope (difference between maximum and basal metabolic rate), energy reserves, energy uptake, mitochondrial capacity or cellular energy allocation can be measured (Goodchild et al., 2018; Schuijt et al., 2021; Sokolova, 2021). At the organism level, the investment in growth or reproduction may indicate bioenergetic stress responses (Schuijt et al., 2021; Segner et al., 2014), whereas on the population level population growth rate, density, age structure and biomass are potential candidate metrics (Forbes et al., 2017; Schuijt et al., 2021). At the community level, the measurement of energy budgets of a representative sample of individuals requires a high replication in experiments due to the invasiveness of the method. However, this could allow the use of energy budgets in process-based community models, thereby establishing links between the organismal and the ecological perspective. At this level, energy fluxes could be measured as biomass flux, directly (e.g. trapping organisms and organic matter) or indirectly using trophic relations established with stoichiometry and stable isotope measurements (Graf et al., 2020; Kato et al., 2004; Paetzold et al., 2005). The latter would prohibit downscaling to the energy budget of individuals. Structural metrics such as species abundance, diversity and biomass or the trophic organisation are usually assigned to the community level, while functional metrics such as primary production and element cycling rates are assigned to the ecosystem level (Schuijt et al., 2021). The bioenergetic-AOP framework quantitatively links energetic responses across biological levels (Goodchild et al., 2018). Thereby, correlations have been found between cellular energy allocation and whole-organism growth, metabolic rate and the scope for growth as well as with the non-traditional response of locomotion, enabling the incorporation of suborganismal insights into bioenergetic models. Further relationships (preferably causal, quantitative) between energetic responses from different biological levels could strengthen predictive ecotoxicology.

*Third, conduct complex experiments to simultaneously study responses to chemicals at different biological levels and spatiotemporal scales.* The ultimate challenge is to evaluate if and how low-level responses manifest themselves in higher-level responses. A combination of micro- and mesocosm experiments, covering a range of environmental and biotic selection factors would help to link different biological levels. For instance, different biological levels over time and space could be manipulated. Such experiments include nested designs that contain experimental subunits from different biological levels, by e.g. including single species subunits in multi-species mesocosm experiments to quantify the effects of a chemical in the absence of interspecific interactions (Figure 6[3]). Species for such subunits could be selected to cover a wide range of traits. The results could also foster cross-species extrapolation based on traits (van den Berg et al., 2021). Single and multispecies



**FIGURE 6** Overview of the four main aspects to improve prediction of chemical effects in ecosystems.

micro- and mesocosm experiments have been proven to be valuable tools to understand the response to a perturbation within a local spatial scale (Beermann, Elbrecht, et al., 2018; Beermann, Zizka, et al., 2018; Piggott, Salis, et al., 2015; Piggott et al., 2015a). To link local processes to a landscape context, another experimental design represented by linked experimental units has been successfully implemented in the laboratory using vial microcosms for aquatic (Altermatt et al., 2015) and terrestrial (Gilarranz et al., 2017) units (Figure 6[3]). These designs can be further extended, theoretically and empirically, to include cross-habitat exchanges that enable to monitor flows of energy, material and organisms (dispersal) as well as changes in the genetic and trait composition of patches, simulating real-world meta-community or -ecosystem dynamics (Harvey et al., 2020; Ryser et al., 2021). Furthermore, repeated experiments could highlight consistency or changes in chemical effects over time and space (Belanger et al., 1994; Schreiner et al., 2018). Finally, disentangling eco-evolutionary dynamics and interactions, as mentioned in the following aspect of this section, will require large, collaborative experiments such as described in Govaert et al. (2021).

Within these experimental designs, a wide range of data from different biological levels can be collected allowing to screen for links between the perspectives. For example, omics data can be collected in experiments of most levels of complexity (i.e. ranging from single-species laboratory to multi-species mesocosm experiments), but also in field surveys (Van Aggelen et al., 2010; Williams et al., 2011). Data from complex experiments with multiple factors of environmental and biotic selection or from field surveys covering a wide range of

conditions allow to evaluate, how these higher levels influence the suborganismal response (Figure 6[3]). The sampling plan should be informed by the scale of the response and may require high temporal resolution sampling of suborganismal responses (Figure 5). Recorded response data should be supplemented by detailed information on the test organisms (e.g. age, size, sex, origin) as well as on the experimental conditions (e.g. pH, temperature) to enable a wide range of predictions and modelling. Finally, experiments would be most informative if following a gradient design with a high number of chemical concentrations to establish robust concentration-response curves (Kramer et al., 2011; Kreyling et al., 2018).

Fourth, identify those processes most critical in light of the biological level and spatiotemporal scale of prediction, as well as in light of the taxa, chemicals and potentially characteristics of the (eco)system under scrutiny (Figure 6[4]). Important processes and missing data might be identified and prioritised, respectively, in a collaborative effort, for example in workshops with participants from multidisciplinary backgrounds (Forbes et al., 2020). Also novel data science tools including artificial intelligence might strongly expand our prioritisation capacity in future (Pichler et al., 2020; Scowen et al., 2021). For example, the AOP framework should aim at 'informed simplicity', i.e. capture the essential, measurable events that lead to a relevant organism-level toxicity endpoint rather than a comprehensive description of all biological aspects involved (Knapen, 2021). Similarly, depending on the application, reduced DEB and TKTD variants, that can easily be applied, may be sufficient. For the ecological perspective, several approaches allow to prioritise critical processes and, if necessary, to simplify (e.g. aggregation; for details, see Supplementary Data, Text S1). An example of a process that has rarely been considered within any of the perspectives, but can be relevant at all biological levels and may provide links between them, is evolutionary adaptation. An example of such a link are potential relationships between genes responsible for adaptation and fitness-related phenotype metrics such as shifted survival time, time to first brood or total number of offspring (Kramer et al., 2011). Novel evolutionary genomic techniques, such as restriction site-associated DNA sequencing (RADseq), shotgun population variation profiling (PoolSeq), transcriptome sequencing (RNAseq) or whole-genome resequencing, can identify genetic locations of adaptation even for non-model species, which lack prior genomic information (Weigand & Leese, 2018). Specific traits may help identify species with high adaptation potential, such as high de novo mutation rates, as mutations may emerge faster in species with large populations, short generation times and regular exposure (Doria et al., 2022; Hawkins et al., 2019). In addition, CRISPR-Cas9-based reverse genetic approaches in conjunction with in vitro metabolism and genome scans enable to test the relevance of certain genes for resistance (Denecke et al., 2017; Douris et al., 2020; Wang et al., 2018). Adaptation data from the (sub-)organism level may be further linked to changes in the diversity and frequency of species on the community and ecosystem level. DEB models have the potential to analyse the evolution of organismic traits and to identify adaptations including underlying mechanisms (Beaudouin et al., 2012; Goussen et al., 2015). If there

is strong indication of rapid adaptation of specific taxa to selected chemicals in the environment under focus, eco-evolutionary dynamics and interactions should be quantified and integrated into the prediction framework, otherwise they may be neglected. Ultimately, the challenge is to reduce the uncertainty in predicting chemical effects in ecosystems while maintaining or making feasible the data collection effort and model complexity.

## 7 | CONCLUSION

Ideally, a prediction framework would trace the chemical from its uptake into an organism and its transformation, over the triggering of biochemical reactions inside the organism to physiological effects and the propagation to the population, community, food web and ecosystem level (Figure 1). Yet, each idealised perspective captures only a part of this framework (Figure 1). The perspectives are complementary and rather reflect different phenomenological approaches than scientific disciplines but still have own scientific concepts and communities. Each of the perspectives has its own scale, which also delineates its limitations for comprehensive prediction (Figure 5). Our predictive capacity for effects of chemicals generally decreases with increasing biological levels, given the emergent dynamics inherent to ecological systems at the level of communities, food webs and ecosystems. Predictions seem feasible on a rather coarse level when focussing on organism groups, traits, compound groups and qualitative responses (e.g. sensitivity categories) (Bracewell et al., 2019; Halstead et al., 2014; Rumschlag et al., 2020). However, quantitative predictions (e.g. of densities) become almost impossible when dealing with specific organisms (intraspecific trait variation) and chemicals in a complex system, a circumstance that is shared with ecology (Ovaskainen & Abrego, 2020). Overall, a balance has to be found between simplification and capturing the essential complexity of a system, aiming at 'informed simplicity' for modelling complex systems (Knapen, 2021). The effort in data collection must be focused and coordinated. In this context, novel data science tools including artificial intelligence might strongly expand our capacity in future (Pichler et al., 2020; Scowen et al., 2021). We emphasise that the three idealised perspectives that substantially contribute to date to the prediction of chemical effects and effect extrapolation across species are still largely separated. We see the potential that theoretical and empirical links between the suborganismal, organismal and ecological perspective could enhance predictive modelling of chemical effects in ecosystems and extrapolation between species.

## AUTHOR CONTRIBUTIONS

This review was produced in group work. Anke Schneeweiss and Ralf B. Schäfer wrote the main part of the original draft and incorporated the reviewers' suggestions. All authors contributed to the general conceptual development, writing of selected parts and reviewing of the manuscript.

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## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

## DATA AVAILABILITY STATEMENT

No data were collected or analysed as part of this study.

## ORCID

Anke Schneeweiss  <https://orcid.org/0000-0003-1282-4552>

Noël P. D. Juvigny-Khenafou  <https://orcid.org/0000-0002-8001-8782>

Stephen Osakpolor  <https://orcid.org/0000-0002-8977-3020>

Andreas Scharmüller  <https://orcid.org/0000-0002-9290-3965>

Sebastian Scheu  <https://orcid.org/0000-0002-7444-2595>

Verena C. Schreiner  <https://orcid.org/0000-0001-8732-3766>

Roman Ashauer  <https://orcid.org/0000-0002-9579-8793>

Beate I. Escher  <https://orcid.org/0000-0002-5304-706X>

Florian Leese  <https://orcid.org/0000-0002-5465-913X>

Ralf B. Schäfer  <https://orcid.org/0000-0003-3510-1701>

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