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Critical Perspectives

Chemical Mixtures and Multiple Stressors: Same but Different?

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Abstract: Ecosystems are strongly influenced by multiple anthropogenic stressors, including a wide range of chemicals and their mixtures. Studies on the effects of multiple stressors have largely focussed on nonchemical stressors, whereas studies on chemical mixtures have largely ignored other stressors. However, both research areas face similar challenges and require similar tools and methods to predict the joint effects of chemicals or nonchemical stressors, and frameworks to integrate multiple chemical and nonchemical stressors are missing. We provide an overview of the research paradigms, tools, and methods commonly used in multiple stressor and chemical mixture research and discuss potential domains of cross-fertilization and joint challenges. First, we compare the general paradigms of ecotoxicology and (applied) ecology to explain the historical divide. Subsequently, we compare methods and approaches for the identification of interactions, stressor characterization, and designing experiments. We suggest that both multiple stressor and chemical mixture research are too focused on interactions and would benefit from integration regarding null model selection. Stressor characterization is typically more costly for chemical mixtures. While for chemical mixtures comprehensive classification systems at sub-organismal level have been developed, recent classification systems for multiple stressors account for environmental context. Both research areas suffer from rather simplified experimental designs that focus on only a limited number of stressors, chemicals, and treatments. We discuss concepts that can guide more realistic designs capturing spatiotemporal stressor dynamics. We suggest that process-based and data-driven models are particularly promising to tackle the challenge of prediction of effects of chemical mixtures and nonchemical stressors on (meta-)communities and (meta-)food webs. We propose a framework to integrate the assessment of effects for multiple stressors and chemical mixtures. *Environ Toxicol Chem* 2023;42:1915–1936. © 2023 The Authors. *Environmental Toxicology and Chemistry* published by Wiley Periodicals LLC on behalf of SETAC.

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INTRODUCTION

Globally, ecosystems are influenced by humans at an unprecedented scale and magnitude (Steffen et al., 2015; Waters et al., 2016). The pervasive footprint of human activities has resulted in substantial losses of biodiversity and is affecting the functioning of ecosystems, making them potentially less hospitable for life (Barnosky et al., 2012; Steffen et al., 2018; 2018). Major anthropogenic stressors of biodiversity are habitat degradation through land/sea use change, overexploitation, climate change, and pollution with chemicals (Díaz et al., 2019). These stressors frequently co-occur spatially and temporally. Almost the entire ocean (97.7%) was subject to multiple stressors in a global analysis of 19 stressors (Halpern et al., 2015). Similarly, an analysis of German river monitoring data and four stressors found that in more than 95% of sampling sites two or more stressors occurred above thresholds for ecological risks (Schäfer et al., 2016). In a study on diatom, invertebrate, and fish communities in 434 US streams and on five stressors, 68% of streams had two or more stressors at levels suggesting adverse effects (Waite et al., 2021). Thus, multiple stressors are the new norm in ecosystems.

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Predicting the responses of organisms, populations, communities, and food webs to multiple stressors represents a major challenge (Figure 1), partly due to potential interactions between stressors that are widely occurring in ecosystems (Cote et al., 2016). An analysis of mesocosm experiments and of European monitoring data of lakes and rivers for 174 paired stressor combinations identified interactions in 33% of cases (Birk et al., 2020). Another study found that stressor interactions explained more than half of the variance in ecological status in over 50,000 European river subcatchments (Lemm et al., 2021). Experimental studies with aquatic and soil microcosms and with plant communities found that stressor interactions were more frequent when the number of stressors increased (Rillig et al., 2019; Speißer et al., 2022; Suleiman et al., 2022). Note that stressor interactions can also be a consequence of the statistical model used when diagnosing interactions and may not have a mechanistic basis (see *General mechanisms and identification of interactions with null models* section for details), although this still complicates prediction.

In real-world ecosystems, chemicals typically occur simultaneously as mixtures. For example, a screening of 2316 chemicals in Greek wastewater samples detected 398 chemicals (Gago-Ferrero et al., 2020). Of 970 target compounds, that is, chemicals selected for chemical analysis, 426 chemicals with approximately 30 different modes of action toward organisms were found in three Central European rivers (Busch et al., 2017). Studies in agricultural areas of Central and Eastern Europe found up to 50 pesticides, a group of chemicals designed to adversely affect organisms, in a single water sample from streams (Halbach et al., 2021; Moschet et al., 2014; Schreiner et al., 2021). Of 82 target compounds, 76 were detected in soils in regions with different land uses around Paris, France (Gaspéri et al., 2018).

A reliable prediction of chemical effects often requires consideration of the full mixture. Several studies reviewed by Posthuma et al. (2019) demonstrated associations between chemical mixtures and ecological responses. Bioassays with water samples from streams and rivers suggest that although many chemicals occur at low concentrations, they need to be considered to explain the response of the bioassays (e.g., Escher et al., 2020; Neale et al., 2020). Indeed, multiple chemicals with a similar mode of action, each occurring at low concentrations that would cause no or only negligible effects, may together exert a strong effect, which is called the

	Multiple stressor research tools and methods	Joint challenges & research gaps	Chemical mixture research tools and methods
Real world relevance	♦ Wide occurrence of multiple stressors ♦ Joint effects widespread	Simultaneous consideration of multiple stressors & chemical mixtures	♦ Wide occurrence of chemical mixtures ♦ Joint effects widespread
General approach	♦ Mix of controlled & more ecologically realistic experiments ♦ Focus on populations, communities & food webs		♦ Strong bias towards controlled experiments ♦ Focus on physiology, individuals & populations
Null models	♦ Significance testing ♦ Null models integrating communities developed	Too focused on interactions Null model selection	♦ Concept of Model Deviation Ratio ♦ Null models integrating chemical & non-chemical stressors ♦ Large databases on chemical effects
Stressor characterization	♦ Classification systems accounting for environmental context		♦ Costly ♦ Comprehensive classification systems at suborganismal level
Study design	♦ Factorial designs with few treatment levels ♦ Co-tolerance concept ♦ Metacommunity and source-sink concept	Extrapolation meta-populations, communities & food webs Temporal and spatial stressor profiles	♦ Regression designs ♦ Concept of equipotency
Process-based models	♦ Complex food web and ecosystem models	Adaptation to stressors	♦ TKTD and bioenergetic models
Data-driven models	♦ Large scale analyses	Simplification and aggregation	♦ Large scale analyses

FIGURE 1: Overview of the tools and methods of multiple stressor and chemical mixture research with joint challenges and research gaps. Idealized representation. Blue text highlights the tools and methods that are of particular interest for the other research areas.

"something from nothing" effect (Silva et al., 2002; Thrupp et al., 2018; Figure 2A). A large number of experimental studies in the laboratory, mostly with only two or three chemicals and single species, has found interactions between chemicals that likely have a mechanistic basis (Rodea-Palomares et al., 2015). A recent meta-analysis of mixture experiments including various chemical classes found on average 35% of interactions (Martin et al., 2021). Mixtures containing pesticides and biocides that frequently occur in ecosystems (Liess et al., 2021; Riedo et al., 2021; Wolfram et al., 2021), were particularly prone to exert interactions. In contrast to these experimental systems, several studies on pesticides in agricultural streams found that the highest estimated toxicity for a single pesticide in a sample, in other words ignoring mixture toxicity completely, was sufficient to explain the ecological response (Liess et al., 2021; Schäfer et al., 2013). Thus, experiments may strongly overestimate the relevance of interactions for real-world ecosystems.

Although multiple stressors are ubiquitous and often include chemical mixtures, biotic responses to them have largely been studied separately (but see, e.g., Burton & Johnston, 2010). This is despite the fact that chemical and nonchemical stressors act jointly, sometimes through mechanistic interactions, on organisms (Holmstrup et al., 2010; Laskowski et al., 2010; Liess et al., 2016). The lack of an integrative approach to studying both chemical and other stressors reflects the disciplinary divisions that exist between scientific communities in which (applied) ecologists and ecotoxicologists use distinct research topics, paradigms, journals, and conferences (Bernhardt et al., 2017; Hodgson, Halpern & Essington, 2019; Orr et al., 2020; Schäfer et al., 2016). Notwithstanding, to predict the responses of biological systems to multiple stressors and multiple chemicals as well as combinations of both requires an overarching framework that integrates and thereby benefits the associated research communities (Pirotta et al., 2022). Below we describe and discuss the approaches for multiple stressor and chemical mixture research and provide an outlook on potential synthesis in different domains (Figure 1).

THE GENERAL APPROACH OF ECOTOXICOLOGY AND (APPLIED) ECOLOGY

Ecotoxicology is a relatively young discipline, which has partly inherited its methodological focus from (mammalian) toxicology, at least for research with an applied scope (Newman & Clements, 2008). Mammalian toxicology has a

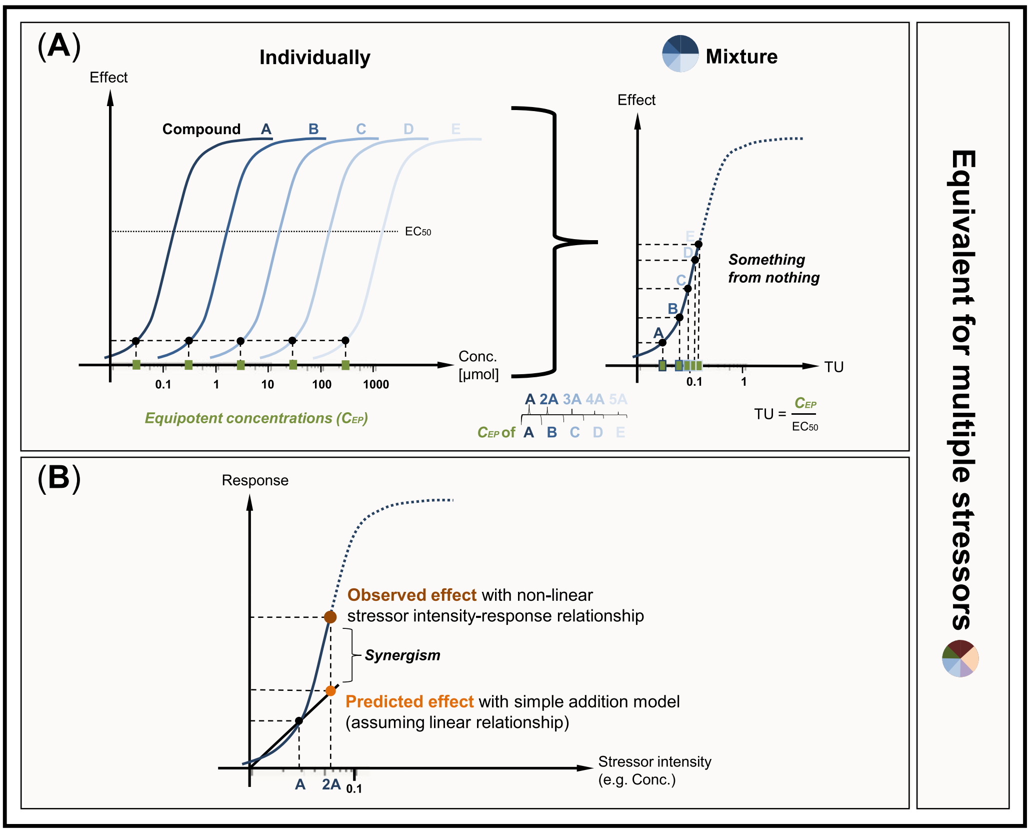

FIGURE 2: Illustration of several concepts related to stressor intensity–response relationships. (**A**) Concept of equipotency and the phenomenon of "Something from nothing" for five chemicals A to E. At the equipotent concentration level (C_{EP}), each compound causes the same effect in isolation. In the absence of interactions and assuming the same mode of action, compounds at equipotent concentrations in a mixture are perfectly exchangeable. This is illustrated by five compounds in a mixture at C_{EP} equalling five times the single compound A. (**B**) Predicted effect when assuming linearity and effect observed when the stressor intensity–response relationship is nonlinear. In this case, doubling the level of an individual stressor would be perceived as synergism when using a simple addition model.

strong focus on extrapolating chemical effects from a few selected species (e.g., rat, mouse) to humans (Abou-Donia, 2015), whereas a major part of ecotoxicological research aims to quantify the responses of a few selected species to (typically single) chemicals under controlled laboratory conditions, as a basis to evaluate the potential implications of chemicals in ecosystems (Cairns, 1986; Schäfer, 2014). Standardized experimental test systems with single, laboratory-adapted species and chemicals still form the backbone of current chemical regulatory risk assessment (Dale et al., 2008). Key applications of risk assessment include prospective chemical safety assessment (e.g., Registration, Evaluation, Authorisation and Restriction of Chemicals [European Commission (EC), 2006]), retrospective environmental quality assessment (e.g., European Water Framework Directive [EC, 2000]) and life cycle impact assessments. A literature analysis found that 53% of all studies on pesticide effects in freshwater ecosystems focussed on a single organism, the water flea *Daphnia magna*, which is a surrogate test species used to assess toxicity toward invertebrates (Beketov & Liess, 2012). Field studies on communities in real ecosystems constituted less than 1% of all studies. In situ bioassays, where organisms are deployed in ecosystems to assess the potential effects of chemicals, are more frequently conducted but typically also rely on individuals of a single species (Burton & Nordstrom, 2004; Sarkis et al., 2023). However, extrapolating results from single species experiments to ecosystems, for instance in the case of freshwater ecosystems with more than 100 000 known invertebrate species (Balian et al., 2008), remains a major challenge and was rated among the most important current research challenges in ecotoxicology (Van den Brink et al., 2018). Besides the inheritance of methods from toxicology, the ecotoxicological research's focus on single species and often single chemicals under controlled laboratory conditions is driven by its strong connection to regulatory chemical risk assessment. The regulatory frameworks differ between chemical groups (e.g., pesticides, biocides, nanoparticles), but generally rely on single species as representatives for whole organism groups and trophic levels, and simplified experimental designs that ignore additional stressors (van Dijk et al., 2021). This regulatory footprint is also visible in the strong focus of ecotoxicological modeling on individuals and populations (Larras et al., 2022).

Compared with a large part of ecotoxicological research, ecological studies more frequently use field experiments and surveys in ecosystems to establish links between stressors and ecological responses, although laboratory studies are also widely used in multiple stressor research. However, these studies have largely ignored chemicals as stressors except for nutrients (Bernhardt et al., 2017; Groh et al., 2022; Schäfer et al., 2016; Schneeweiss et al., 2023; Sigmund et al., 2023). For example, analyses of general and specific (e.g., freshwater) ecological journals found a comparatively low amount of studies on toxic chemicals, and related United States national project funding was negligible (Bernhardt et al., 2017; Persson et al., 2022; Schäfer et al., 2016). This is presumably owed to disciplinary division, that is, that toxic chemicals are regarded as the subject matter of a different discipline (Orr et al., 2020) and to the complexity of characterizing mixture exposures and related ecological effects, which requires sophisticated and costly methods of sampling and analyzing chemicals (see below; Sigmund et al., 2023). Moreover, the sheer amount and potential interactions between chemicals have for long complicated the identification of causal relationships and the implementation of eco-epidemiological approaches aligning applied ecology with ecotoxicology (Bro-Rasmussen & Løkke, 1984; Posthuma et al., 2020).

Overall, the above described research paradigms can historically explain the gap between multiple stressor research and chemical mixture research (Figure 1). A contemporary analysis of the state of progress in the respective disciplines follows and highlights domains with potential for synergy.

GENERAL MECHANISMS AND IDENTIFICATION OF INTERACTIONS WITH NULL MODELS

From a mechanistic perspective, stressors can interact twofold. First, a stressor can moderate the intensity of other stressors, hereafter called intensity interaction. For example, increased turbidity through sand input in experimental streams decreased the predation of invertebrates (Louhi et al., 2017). Second, the effect of a stressor on an organism, population, community, or food web may influence the effect of a different stressor, hereafter called effect interaction. For example, predation by fish modified the response of a zooplankton community to warming in a mesocosm experiment (MacLennan & Vinebrooke, 2021). In this context, chemical mixtures represent a special case of multiple stressors to which the same two types of interaction, that is, intensity and effect interaction, apply. A chemical can modify the concentration of a second chemical, for example nanoparticles modify pesticide concentrations (Seitz et al., 2012), and one chemical may influence the response of organisms to a second chemical, for example azole fungicides can reduce the biotransformation in invertebrates and thereby increase their sensitivity to pyrethroids (Cedergreen et al., 2017). Other factors such as the ecological context, for example the organisms involved and biological level, are relevant for prediction of stressor effects (Thompson et al., 2018).

In both multiple stressor and chemical mixture research, many studies have focussed on identifying cases of effect interactions. These manifest themselves as deviations of the observed joint effects from the predicted joint effects, where the prediction is calculated with a null model using the individual effects of the stressors. If the observed joint effect is larger and smaller than predicted, this is called synergism and antagonism, respectively (as compared with the null model). Synergism and antagonism occur widely and hamper prediction for both multiple nonchemical stressors (Darling & Cote, 2008; Dieleman et al., 2012) and multiple chemicals (Cedergreen, 2014; Martin et al., 2021), but also combinations of chemical and nonchemical stressors (Holmstrup et al., 2010; Laskowski et al., 2010; Liess et al., 2016). However, while mechanistic effect interactions manifest as synergism or antagonism, the diagnosis of synergism and antagonism does not necessarily indicate an underlying mechanistic effect interaction (Figure 1).

What constitutes synergism and antagonism depends on a null model that is used to predict the joint effect from the individual stressors (Dey & Koops, 2021; Piggott et al., 2015). Different null models are typically used in multiple stressor and chemical mixture research. In multiple stressor research, the majority of studies used a linear statistical model in data analysis such as analysis of variance. This implies using a simple addition model or, sometimes unknowingly, when log-transformed data are used (Griffen et al., 2016), a multiplicative null model (for details on models see Schäfer & Piggott, 2018). At the biological level of communities and food webs, the co-tolerance concept can assist in the selection of an appropriate null model (Vinebrooke et al., 2004). The concept provides hypotheses on the community outcome of multiple stressors based on the correlation of species tolerances to the individual stressors. For example, if all species in a community exhibit a negative co-tolerance, that is, tolerances to different stressors are negatively correlated, each stressor would affect different fractions of the community. The simple addition null model may then be most appropriate to predict the joint effect. By contrast, in the absence of co-tolerance, that is, tolerances exhibit no correlation, the multiplicative null model may provide the most appropriate prediction.

The multiplicative model is also frequently used in ecotoxicology, but under the name of independent action (Bliss, 1939), effect addition, or response addition. It has been developed with a focus on chemicals that act biochemically dissimilarly in an organism, whereas the model of concentration addition has been developed for chemicals that act biochemically similarly in an organism (Loewe & Muischnek, 1926). The predictions of concentration addition and independent action converge in the case of mixtures with many chemicals at low effect levels, for example up to 10% of the total possible effect, where the effect is typically mortality (Escher et al., 2020). Given the frequent similarity in prediction accuracy and that data is often lacking to fit an independent action model (see below for details), the concentration addition model has been suggested as the standard tool for chemical risk assessment in different regions such as the European Union (Frische et al., 2014), the United States (Belden & Brain, 2018), and China (Chen et al., 2020). Comparative discussions on null model selection are largely lacking in ecosystem management focusing on multiple stressors. Another model that is often used rather implicitly is the dominance null model. This model predicts that the joint effect equals that of the stressor or chemical with the highest individual effect, hence it ignores all other stressors and chemicals. Interestingly, a recent analysis found that for the combined effect of climate change and a second stressor in freshwater ecosystems, the dominance model best explained the observed effect (Morris et al., 2022), in particular when stressor intensities differed strongly. In addition, several studies on pesticides in agricultural streams found that the dominance model yielded similarly strong associations with ecological community metrics as the concentration addition for all detected pesticides (Liess et al., 2021; Schäfer et al., 2013). This was largely due to a strong difference in the toxic potency of the most toxic chemical compared with all other chemicals (cf. Price & Han, 2011). By contrast, a meta-analysis of studies with mortality as response found that the dominance model exhibited the highest bias (Dey & Koops, 2021), although no model performed best in both accuracy and precision. Overall, it remains largely open which null model yields the most accurate and precise prediction for a given multiple stressor scenario, while for chemical mixtures concentration addition represents a widely accepted standard model.

In contrast to multiple stressor research, for chemical mixtures a formalized method has been widely adopted to evaluate which size of departure between data and null model prediction constitutes synergism or antagonism, the so-called model deviation ratio (MDR; Belden et al., 2007). The MDR is obtained by dividing the null model prediction by the observed joint effect, where >1 is synergism and <1 is antagonism. Several meta-analyses and reviews employed MDR boundaries of 0.5 and 2 as matching with the null model (Belden et al., 2007; Cedergreen, 2014; Martin et al., 2021). However, narrower boundaries (0.83 to 1.25), translating into more cases of apparent synergism and antagonism, have also been used (Carnesecchi et al., 2019). The MDR approach has been criticized for only relying on the effect size and ignoring the dependence of the MDR on the sample size (Macacu & Guillot, 2020). In response, a statistical significance test incorporating the sample size has been suggested (Macacu & Guillot, 2020), where synergism and antagonism are a function of effect size and sample size. Conversely, many studies have criticized statistical significance testing because statistical significance is not necessarily biological significance (Cohen, 1994; Pernet, 2017; Schober et al., 2018) and a statistical interaction does not imply mechanistic interaction of stressors or chemicals. For large sample sizes, even minor deviations from a null model are statistically significant. By contrast, small sample sizes in factorial designs, which often apply to multiple stressor studies, lack the power to detect interactions, in particular when the observational error is relevant (Burgess et al., 2021, 2022). However, multiple stressor research largely relies on statistical significance testing to identify synergism and antagonism. An alternative to purely effect-size driven MDR boundaries and significance testing for both multiple stressor and chemical mixture research could be MDR boundaries based on standardized effect sizes such as Cohen's *d* or Hedge's *g*, which are frequently used in meta-analyses (Jackson, 2015).

While joint effects of multiple stressors are typically only predicted within the context of a specific study where individual and joint effects have been measured (Hodgson & Halpern, 2019), the joint effects of chemical mixtures are often predicted for exposure concentrations, for instance determined in field studies, in the absence of measured effects, using effect data from single species laboratory tests and a null model, typically concentration addition. The concentration addition model requires effect data for a defined effect level to benchmark and aggregate the toxic potency of different chemicals. In most cases the median effect concentration (EC50), defined as the effect concentration where half of the test population exhibits a specific effect, is used because it is available from public databases and, in case of missing data, tools such as quantitative structure–activity relationship models allow for reliable prediction (Astuto et al., 2022). Quantitative structure–activity relationships predict properties such as the EC50 for an organism for nontested chemicals based on mathematical relationships between the chemical structure and respective properties, established using experimental data. To use independent action as null model, in contrast, would typically require the full dose–response relationship to derive an effect for a given exposure concentration of a chemical. However, full dose–response relationships are comparatively scarce compared with EC50 data. Hence, the concentration addition model is commonly applied to evaluate the joint effects of a chemical mixture found in ecosystems (e.g., Ginebreda et al., 2014; Liess et al., 2021; Markert et al., 2020; Rorije et al., 2022; Schäfer et al., 2013). Although mixture predictions rather provide a crude proxy of risks to populations or communities (see *Process-based models for predicting ecosystem effects of multiple stressors and chemical mixtures* section), they can be useful to evaluate the relevance of a chemical mixture, for example through comparison with risk thresholds (Schäfer et al., 2016). Multiple stressor research would clearly benefit from the ecotoxicological approach to provide standardized effects data. Besides data compilation, which has been done, for instance, for temperature tolerance (e.g., Pottier et al., 2022), this would also require a move toward regression designs in multiple stressor studies that allow for establishing stressor intensity–response relationships (see *Experimental design in chemical mixture and multiple stressor research* section).

The general approach of screening for synergism and antagonism has been heavily criticized in multiple stressor research (De Laender, 2018; Griffen et al., 2016; Pirotta et al., 2022; Schäfer & Piggott, 2018; Segner et al., 2014; Simmons et al., 2021). The main criticism is that the classification of effects does not provide mechanistic understanding and that rather mechanistic models should be developed (as discussed in *Process-based models for predicting ecosystem effects of multiple stressors and chemical mixtures* section). Many studies have shown that the outcome of the classification depends on the study context including (1) the study design, in particular the chosen stressor intensities in factorial designs, (2) the level of biological organization, where, for example, additive effects on the population level become nonadditive through species interactions in a community (Thompson et al., 2018), and (3) the time point of classification because effect sizes and directions can change in dynamic systems (Baas et al., 2007; Brooks & Crowe, 2019; e.g., Streib et al., 2022). Thus, a nonadditive classification does not imply a mechanistic effect interaction. In response, recent developments include a null model for the community-level based on the simple additive model (Thompson et al., 2018) and concentration addition and independent action (De Zwart & Posthuma, 2005), a more widely applicable version of independent action for multiple stressors (Tekin et al., 2020), and new null model approaches with a stronger mechanistic basis such as the stressor addition model (Liess et al., 2016). Using the more widely applicable version of independent action strongly reduced the frequency of synergism compared with a simple additive null model and yielded predominantly additive and antagonistic interactions (Tekin et al., 2020). The stressor addition model provided better predictions than concentration addition and independent action models for studies combining a chemical and a nonchemical stressor, and was least biased in multiple stressor studies with mortality as response (Dey & Koops, 2021; Liess et al., 2016). Interestingly, the criticism on the classification of effects is much weaker in chemical mixture research than in multiple stressor research. This is likely because the vast majority of studies in chemical mixture research focuses on single species tests and bioassays (Cedergreen, 2014; Martin et al., 2021), where strong departures from the null model (typically concentration addition) are relatively likely to indicate mechanistic effect interactions of the involved chemicals. Overall, a stronger exchange on null models between multiple stressors and chemical mixture research might benefit both research areas.

CHARACTERIZING STRESSORS AND THEIR MODES OF ACTION

Both multiple stressor research and chemical mixture research require a reliable quantification of stressors. Stressors can be separated into physical (e.g., warming, soil compaction, water flow velocity, fire, land use change), chemical (e.g., water reduction, nutrients, salinity, metals, pesticides), and biological (e.g., invasive species, disease) categories (Rillig et al., 2021), although overlaps exist (e.g., between chemical and physical stressors: microplastics, nanoparticles, and soot particles). Compared with the quantification of most physical and biological stressors and several chemical stressors such as nutrients, salinity, or water level, the labor and financial costs to comprehensively quantify toxicants are much higher (Sigmund et al., 2023). While costly measurement devices and sensors are by no means specific to chemical stressors (e.g., spectrophotometer for nanoparticles, weather stations, sensors for humidity or radiation), the sheer amount of potential chemicals and the fact that many of these are toxic in the smallest traces makes their quantification very costly because complex sample processing steps are often required (e.g., extraction from organisms or soils). Note that despite these efforts current mixture characterizations are rather incomplete, that is, they miss ecotoxicologically relevant chemicals (Escher et al., 2020). Moreover, compared with several stressors such as land use change and soil compaction that are press disturbances, several chemicals occur in pulses and thereby require a high temporal resolution of sampling (Rillig et al., 2021). For example, ecologically relevant pesticide concentrations in streams can exhibit a high variability over short time scales (e.g., hours and a few days; Leu et al., 2004; Stehle et al., 2013) and related automated sampling devices require strong technical expertise and are costly (Halbach et al., 2021; Moschet et al., 2014; Stravs et al., 2021). Overall, a major difference between multiple stressor research and chemical mixture research is that a comprehensive quantification of mixtures requires more labor and financial resources than most other global change stressors considered in multiple stressor research.

The classification of stressors including chemicals may support prediction of their effects. Chemical classification systems mainly rely on the so-called mode of action, although its definition and classification approaches differ in their focus. The focus can be on physiological effects, target site, or chemical structure and the level of complexity may vary strongly (Escher, 2013; Kienzler et al., 2017, 2019). While early classifications suggested four classes (inert, less inert, reactive, specifically acting; Verhaar et al., 1992), six broad and 31 specific modes of action have been suggested more recently (Martin et al., 2013). Modes of action are particularly relevant in the context of chemical mixtures because similarly and dissimilarly acting chemicals are assumed to be predictable by the concentration addition and independent action models, respectively. Physiological modes of action that focus on the energy processing in organisms (e.g., assimilation, maintenance, growth, or reproduction of an organism) may be useful to bridge the gap to multiple stressor research (Ashauer & Jager, 2018). Bioenergetic models could use these physiological modes of action to predict the joint effect of chemicals, nonchemical stressors, or combinations of both (Ashauer & Jager, 2018). By contrast, comprehensive classification schemes for nonchemical stressors in the context of multiple stressor research have emerged only recently, although their importance has long been recognized (Breitburg et al., 1998). Two very broad schemes discriminating three or four modes of action of stressors have been introduced (Galic et al., 2018; Schäfer & Piggott, 2018). Recently, Rillig et al. (2021) suggested a classification system with multiple categories including effect mechanisms, effect directions for different organism groups, and nature of the stressor (e.g., stressor is physical and is a particle, stressor is chemical and organic). A recent classification expands the stressor classification to the environmental context and also considers the sources of stressors, temporal and spatial profiles, and tolerances of major organism groups (Orr et al., 2022). This concept can feed into a more comprehensive risk assessment of multiple stressors that in addition to evaluating their mode of action classifies the environmental occurrence and organisms at risk. Finally, so-called threat webs have been suggested as a tool to identify the causal co-occurrence of stressors (Geary et al., 2019). An earlier study suggested the classification of stressors by frequency of occurrence in an ecosystem based on habitat types within an ecosystem (Burton & Johnston, 2010). Overall, ecotoxicological research has provided a comprehensive classification system for the mode of action of chemicals, which may inform further development in multiple stressor research. Conversely, chemical mixture research could benefit from multiple stressor research on how to consider environmental context when identifying potential realistic mixtures and organism groups at risk (for a case study see Bracewell et al., 2019).

EXPERIMENTAL DESIGN IN CHEMICAL MIXTURE AND MULTIPLE STRESSOR RESEARCH

Number of stressors and chemicals

A vast number of experiments has been conducted to study the effects of multiple stressors (see meta-analyses by Ban et al., 2014; Crain et al., 2008; Heugens et al., 2001; Jackson et al., 2016; Matthaei & Lange, 2016) and chemical mixtures (see meta-analyses by Belden et al., 2007; Cedergreen, 2014; Martin et al., 2021). Both research areas have been biased in their experimental designs toward strongly simplified scenarios (Hodgson & Halpern, 2019). For chemicals, the majority of mixture experiments has been performed with small mixtures under simplified conditions that deviate strongly from those found in real-world ecosystems (Martin et al., 2021). Specifically, they have been mainly conducted with (1) binary and ternary mixtures, (2) at equipotent concentrations, and (3) in the laboratory under controlled conditions using single species of plants or invertebrates and mammalian bioassays. Although a relevant fraction (e.g., 12%–36% depending on the group of chemicals in Cedergreen, 2014; 35% in Martin et al., 2021) of cases in the experiments exhibited synergism or antagonism, owing to the simplified experimental conditions this fraction may be overestimated compared with real-world ecosystems. However, this would not impinge on the general relevance of additive mixture effects (Posthuma et al., 2019). First, with typically hundreds of chemicals, the size of real mixtures is considerably larger than those considered in most experiments (Busch et al., 2017; Gago-Ferrero et al., 2020; Halbach et al., 2021; Massei et al., 2018; Schreiner et al., 2021). For a given effect level, departures from the concentration addition prediction generally decrease with an increase in the number of chemicals (Rodea-Palomares et al., 2015; Warne & Hawker, 1995), although as long as the number of chemicals remains relatively small (~10 or less), effect interactions may also increase (Chen et al., 2015; Rodea-Palomares et al., 2010; Tian et al., 2012). Second, most experiments used equipotent concentrations of chemical mixtures, that is, all chemicals constituting a mixture are present at concentrations that would, if the chemical occurred alone, trigger the same effect (Figure 2A). Deviations from null models for chemical mixtures typically peak at equipotency following the climax hypothesis (Lin et al., 2005; Tian et al., 2012). However, environmental mixtures depart strongly from equipotency (Geissen et al., 2021; Schäfer et al., 2013; Vallotton & Price, 2016; Weisner et al., 2021). For example, of 34 354 river water samples, only approximately 10% of chemicals contributed 90% of the predicted additive effect (Rorije et al., 2022). Finally, effect interactions are strongly species-dependent and may change with the effect level. For example, a ternary mixture of lipid regulators exhibited an antagonistic and synergistic interaction at low and high effect levels, respectively, in the bacterium

Vibrio fischeri (Phylum: Pseudomonadota), whereas the opposite pattern was found in a cyanobacterium (*Anabeana* spp.; Baek et al., 2019).

Studies on multiple stressors exhibit similar shortcomings. Most studies have only considered two stressors, whereas in real-world ecosystems frequently a much higher number of stressors co-occur (Griffen et al., 2016; van Moorsel et al., 2023; Rillig et al., 2019; Suleiman et al., 2022). Recent studies with soil and aquatic microcosms demonstrated that increasing the number of stressors increases changes in the effect direction, thereby reducing the capacity for prediction (Rillig et al., 2019). However, an increase in the number of stressors was typically associated with an increase in the overall effect level. Here, multiple stressor research may benefit from the concept of equipotency in chemical mixture research. Although equipotency may be non-representative for real-world conditions, when increasing the number of stressors care should be taken to keep the effect level constant (Figure 2A), otherwise an increase in the effect size may simply result from a higher stressor intensity and would also be expected if the intensity of a single stressor increased. Furthermore, in the case of nonlinear stressor intensity–response relationships that are common, even an increase in a single stressor would yield to nonadditive responses when analyzing the data with a linear statistical model (Hunsicker et al., 2016; Pirotta et al., 2022). A modeling study demonstrated for different levels of biological organization that synergism and antagonism can simply result from nonlinear stressor intensity–response relationships without any underlying mechanistic interactions (Turschwell et al., 2022). Another major issue that is much more pronounced in multiple stressor than chemical mixture research is the restricted number of treatments levels, frequently just two or three, per stressor (Griffen et al., 2016). For example, less than 15% of studies in two meta-analyses of multiple stressor studies used five or more treatment levels of a factor, which are a minimum requirement to estimate stressor intensity–response relationships (Griffen et al., 2016; Matthaei & Lange, 2016). Thus, differences between studies in the classification of interaction types and effect directions for the same stressors may partly be the result of study designs with too few treatment levels, which also excludes the selection of some null models. Furthermore, this leads to between-study variance, translating into weak predictive power (Pirotta et al., 2022). Finally, many studies also lack realism by using simplified spatial and temporal stressor profiles, which is discussed next.

The temporal and spatial dimension of stressors and their effects

In multiple stressor and chemical mixture experiments, typically two stressors are applied simultaneously. Under more realistic real-world scenarios with desynchronized and dynamic stressors, the complexity of predicting effects is likely to increase (Fraker et al., 2022; Jackson et al., 2021). Stressors operate over different time scales, and long-term stressors that have been affecting ecosystems for decades, such as excessive nutrient input, may interact with pulsed stressors such as heatwaves. Pulsed stressors commonly occur at different magnitudes of stressor intensity and vary in their duration. Chemicals also exhibit pronounced temporal patterns. Given a continuous release, some chemicals exhibit relatively constant exposure (e.g., pharmaceuticals; Hernando et al., 2006), whereas others increase (e.g., novel chemicals), decrease (e.g., phased out chemicals), or show pronounced short-term or seasonal (e.g., pesticides; Halbach et al., 2021) trends. Comparatively few studies have manipulated temporal profiles of stressors, but these studies demonstrated that, among others, stressor duration, variability, timing, and time lag between pulsed stressors influence the overall impact (Bertocci et al., 2005; Bulleri et al., 2014; Fukami, 2001; Molinos & Donohue, 2010; Ostrowski et al., 2022; Verheyen & Stoks, 2019). Even long after a chemical or nonchemical stressor has disappeared, it may still influence the trajectory of ecological systems, which is called legacy or carry-over effect, and thereby determine how they respond to current and emerging stressors (Harding et al., 1998; Landis et al., 1996; Ryo et al., 2019).

The prediction of the effects of dynamic ocusisors is further complicated by the fact that the stressor order (e.g., order of chemical exposures) can determine the effects. For instance, if a species is negatively and positively affected by stressors A and B, respectively, first exposure to A would lead to stronger suppression than first exposure to B. Indeed, several studies on chemical and nonchemical stressors demonstrated that the stressor order can matter (Ashauer et al., 2017; Brooks & Crowe, 2019; Fukami, 2001; Rillig et al., 2015). The co-tolerance concept helps in assessing when stressor order matters (Flöder & Hillebrand, 2012; MacLennan & Vinebrooke, 2021). A negative and positive correlation of tolerance to stressors has been hypothesized to increase and decrease the relevance of stressor order, respectively (MacLennan & Vinebrooke, 2021). This concept easily translates to chemicals and may be useful for chemical mixture research. Conversely, toxicokinetic–toxicodynamic (TKTD) models are widely used in ecotoxicology and provide a mechanistic understanding of toxicity in organisms over time (Ashauer & Escher, 2010). They have successfully predicted the effects of different exposure profiles of chemicals on organisms (Ashauer et al., 2016; Bart et al., 2021), although mainly for single species. Toxicokinetic-toxicodynamic models and related bioenergetic models (details in next section) could be adapted for other stressors and then be useful for multiple stressor research (Goussen et al., 2020). Finally, a recent study introduced the concept of stressor action curves, based on the stressor addition null model, that successfully predicted synergistic effects for different sequential treatments of a chemical and nonchemical stressor on a single species (Schunck & Liess, 2022).

Most experimental studies are of short duration and thereby ignore the adaptive potential of stressed organisms (Boyd et al., 2018; but see Orr et al., 2021). While adaptation to stressors including chemicals has been found in many studies (Becker & Liess, 2017; Jeremias et al., 2018; Lasky, 2019), adaptation typically involves a trade-off that may compromise population viability (Siddique et al., 2020; Tikhonov et al., 2020). Meta-analyses of experimental studies with up to 1-year duration in different systems found contradictory results of the influence of experimental duration on the effects of multiple stressors (Darling & Cote, 2008; Lange et al., 2018). However, on longer time scales such as years, the effects of stressors dampened (Leuzinger et al., 2011). This may be due to adaptation, but also recolonization from other patches, which highlights the importance of the spatial dimension.

Similar to the temporal dimension, the spatial dimension of multiple stressors and chemical mixture effects has received little attention. Most studies have been conducted using spatially restrictive microcosms and mesocosms, thereby ignoring species dispersal (Nyström & Folke, 2001; Ryser et al., 2021; Schiesari et al., 2018; Streib et al., 2022). However, dispersal can be important because it may sustain populations in patches affected by stressors and thereby reduce the extinction risk, a phenomenon described in the source-sink concept and called the rescue effect (Furrer & Pasinelli, 2016; Gotelli, 1991; Pulliam, 1988). However, dispersal dynamics can also threaten the persistence of metapopulations. In case of too high dispersal mortality or stressor-driven population decline in too many patches in a landscape, this may deplete populations in connected source patches and eventually lead to metapopulation collapse (Amarasekare, 2004; Harvey et al., 2018; Spromberg & Scholz, 2011; Willson & Hopkins, 2013). Besides stressor effects, dispersal can also propagate the stressor itself. This is, for instance, important for chemicals that can enter food chains via bioaccumulation in dispersing organisms and consequently influence distant ecosystems (Schiesari et al., 2018). Several studies have shown that this mechanism also acts across ecosystems as cross-ecosystem biomagnification through the transport of chemicals via dispersing organisms (Laws et al., 2016; Previšić et al., 2021; Walters et al., 2008). Moreover, alien species, if they become invasive, are a biological stressor that may affect ecosystems far from the location of initial introduction (Early et al., 2016; Vilà et al., 2011).

The relevance of the spatial dimension for the propagation of stressors and their effects depends on the connectivity of habitats (Heino et al., 2021). The connectivity of habitats in a landscape is determined by the dispersal ability of organisms, the distance between habitat patches, and the influence of the landscape structure on dispersal, including dispersal mortality (Amarasekare, 2004; Streib et al., 2022). Physical structures in the landscape such as dams or roads can strongly constrain the movement of resources and organisms, thereby reducing habitat connectivity (Lange et al., 2018). Chemical pollution can also represent an "invisible wall" impeding dispersal of organisms (Schiesari et al., 2018). Stressors can also directly affect the dispersal ability of organisms through effects on their fitness.

While we have so far discussed the spatial dimension from the perspective of organisms, the stressors themselves often have different spatial profiles that determine the local co-occurrence in a habitat patch: while some stressors are very local (e.g., emission of chemical), others occur at the scale of landscapes or regions (e.g., heatwave, drought; Boyd et al., 2018; Brown et al., 2014; Morris et al., 2022; Streib et al., 2022). Chemicals can create spatial gradients of exposure in a landscape through a combination of transport processes and diffusion as well as processes decreasing their bioavailability such as degradation or binding to matter (e.g., soil, sediment; Schiesari et al., 2019). Understanding the spatial patterns of stressors is a necessary prerequisite to predict the identity of (multiple) stressors a population, community or food web is exposed to (Geary et al., 2019). The same applies to chemical mixtures.

Overall, both multiple stressor research and chemical mixture research have largely ignored the temporal and spatial dimension. This evokes questions on the degree of ecological relevance achieved. Both research areas would benefit from closer cooperation on how to integrate the temporal and spatial dimension into study design. The temporal dimension could be integrated by using realistic stressor dynamics (Gunderson et al., 2016) or through experimental designs that allow for subsequent parameterization of models that can predict the effects for different temporal dynamics (Bart et al., 2022; Goussen et al., 2020). The spatial dimension could be integrated by considering different habitat patches within an experimental unit (e.g., Turunen et al., 2018), but for very mobile (e.g., flying) organisms and organisms that are larger than arthropods, field studies and process-based models may be more feasible.

PROCESS-BASED MODELS FOR PREDICTING ECOSYSTEM EFFECTS OF MULTIPLE STRESSORS AND CHEMICAL MIXTURES

To date, the focus on meta-analyses and on experiments with limited realism (see above) has delayed the development of a predictive understanding of the joint effects of multiple stressors and chemical mixtures in ecosystems. Process-based models may fill knowledge gaps of when and how chemical and nonchemical stressors interact to cause ecological surprises. They are the only tool that can capture all temporal and spatial scales as well as all biological levels, although not in a single model. Yet, this typically comes at the cost of uncertainty and complex model development requires a strong coordinated effort (Hodgson & Halpern, 2019). Most models can easily be adopted in different research areas because parameters and variables in mathematical equations are open to different interpretations. For example, a parameter that provides a mortality rate per unit increase of a variable could be interpreted as a response to both a chemical and nonchemical stressor. Several reviews have provided overviews on process-based models in ecotoxicology, with a general focus (Astuto et al., 2022; Larras et al., 2022; Schmolke et al., 2010) or with a focus on specific model types (Baas et al., 2009; Schmolke et al., 2017; Sherborne et al., 2020). However, reviews ocusing on community or food web models for chemical mixtures are lacking. Similarly, reviews on process-based models for multiple stressor research are rather scarce (but see Hodgson & Halpern, 2019; van Moorsel et al., 2023; Pirotta et al., 2022; Simmons et al., 2021), but a wide range of resources provides an overview of ecological models for different biological levels and purposes (Cabral et al., 2018; Grimm & Berger, 2016; Jopp et al., 2011; Jørgensen & Fath, 2011; Pilowsky et al., 2022; Vellend, 2016). Most modeling approaches, ranging from physiological to meta-ecosystem models, could be applied in both multiple stressor in chemical mixture research. In the present study, we focus on selected model types and challenges that could be fruitful for exchange between both research areas.

At the organismal to population levels, dynamic energy budget (DEB) models focus on the physiological effects of stressors, and how these affect populations and communities (Simmons et al., 2021). They have been widely applied in studies on the effects of chemical and nonchemical stressors as well as for combinations of chemical and nonchemical stressors (Goussen et al., 2020; Matzelle et al., 2015; Sokolova, 2021). Dynamic energy budget models for sublethal effects (e.g., growth, reproduction) of chemicals are often referred to as DEBTox models (Jager, 2020; Nisbet et al., 2000). For mortality as response, the abovementioned TKTD models are widely applied for chemicals. They rely on experimental data and can make educated extrapolations beyond the experimental conditions, for example different temporal exposure patterns, if observations from multiple time points are available (Ashauer et al., 2016; Jager et al., 2006). Moreover, their model parameters may be related to species traits and recent studies have shown their capacity to extrapolate effects to nontested species (Gergs et al., 2015, 2019; Singer et al., 2023). Toxicokinetic–toxicodynamic and DEBTox models can be used for simple and complex chemical mixtures (e.g., Ashauer et al., 2007; Baas et al., 2007; Bart et al., 2021), although mechanistic effect interactions are not considered (but see Cedergreen et al., 2017). The model approaches are open to nonchemical stressors if relationships between stressor intensities and effects over time are available. Overall, multiple stressor research could strongly benefit from the progress made for chemical mixtures with TKTD and bioenergetic models.

Experimental studies on multiple stressors and chemical mixtures have often ocusin on the response of a single species or taxonomic group, thereby providing limited insights into potential effects in food webs and on ecosystem functions (Martin et al., 2021; van Moorsel et al., 2023). Process-based models may in particular help to evaluate the effects of multiple chemical and nonchemical stressors on (meta-)communities, (meta-)food webs, and (meta-)ecosystems (Hodgson & Halpern, 2019). Understanding the effects at these scales and biological levels is complex because stressors may directly affect a range of species where the effect sizes likely vary strongly. In addition, stressors can indirectly affect a focal species, for instance by directly affecting its prey (Beauchesne et al., 2021). Trophic (Eklöf et al., 2013) and other (Kéfi et al., 2016) interactions generate a complex network of species interactions. These networks are typically well connected, such that direct effects of a stressor on a species propagate to other species (Zelnik et al., 2022). Importantly, indirect effects can overweight or reverse direct effects (Fleeger, 2020; Spaak et al., 2017).

Classic ecological models such as Lotka–Volterra or stage-structured population models have highlighted the relevance of considering species interactions when predicting the effects of stressors. For example, such models unraveled that the direction of stressor interaction on a population is driven by the shape of the density-dependence of population growth (Hodgson et al., 2017) and that species interactions interact with stressor intensity in determining effects on communities (Thompson Patrick et al., 2018).

Predicting the response of communities, food webs, or ecosystems to chemical or nonchemical stressors requires understanding the interactions of two complex networks. First, the network of direct effects on each species individually and, second, the network of all species interactions. This is further complicated because stressors can also affect species interactions, for example through changes in their behavior and development (Hanazato, 2001; Liu et al., 2022). Community ecology has concluded that obtaining a high-resolution species interaction network seems unsurmountable, even in the absence of stressors (Barbier et al., 2021; Weiss-Lehman et al., 2022). A way forward may be to replace the paradigm of high precision with high generality and focus on a "general" rather than a focal community. For example, the cavity method assumes identical species interactions and requires only certain statistical properties of species interactions to predict community dynamics (Barbier & Arnoldi, 2017). A related approach focuses on the average interaction strength between species and between stressors and species, and is likely to at least reliably predict the average effect of stressors on the community (Weiss-Lehman et al., 2022). Several other approaches can be used to tackle the challenge posed by the two complex networks. Rather than ocusing on species, trait-based approaches group the large number of species in communities and food webs, often based on a few core traits such as body size, resource uptake, and feeding preference (Allhoff et al., 2015; Kiørboe et al., 2018; Litchman & Klausmeier, 2008; Schneeweiss et al., 2023; Williams & Martinez, 2000). Furthermore, bioenergetic models have the potential to integrate metabolism with body size and density-dependent intra- and inter-specific species interactions to predict how chemical or nonchemical stressors affect the flow of biomass. Similarly, trophic network models can link species metabolism, consumption, and growth and could be used to predict how stressors affect species interactions and biomass dynamics across trophic levels (Simmons et al., 2021). Finally, size-spectra models can consider how stressors affect food webs based on an assumed inverse relationship between species body size and abundance, and size-dependency of predator–prey interactions (dos Santos et al., 2017; Jackson et al., 2021).

Several community, food web, and ecosystem models have been developed to predict the effects of multiple stressors. For example, a food web model and a complex ecosystem model were used to study the effects of fishing, acidification, and warming on the marine ecosystem (Cornwall & Eddy, 2015; Griffith et al., 2012). A network model predicted synergistic interactions of multiple stressors on several organism groups in a marine arctic ecosystem (Arrigo et al., 2020). A few ecotoxicological models for communities and food webs have been developed, as reviewed by Larras et al. (2022). Promising approaches that consider chemicals are the Streambugs model simulating populations of freshwater invertebrates in streams (Kattwinkel et al., 2016; Mondy & Schuwirth, 2017; Schuwirth & Reichert, 2013), the AQUATOX model simulating lake food webs (Park et al., 2008), and the ALMaSS modeling framework that has been used to simulate several terrestrial populations, including birds, invertebrates, and vertebrates (Sibly et al., 2009; Topping & Lagisz, 2012; Topping & Weyman, 2018). These models currently do not consider chemical mixtures, but their incorporation should require a minor effort compared with the general model development. Generally, if a reliable food web or ecosystem model was available for a specific research question or ecosystem under scrutiny, incorporating chemical and nonchemical stressors should be comparatively simple (for guidance on model selection see Geary et al., 2020).

To date, a key finding from the various modeling approaches is the context dependency of multiple stressor effects across different scales of time, stressor intensity, and biological organization. For example, a mechanistic model of two stressors showed that classification of their interactive effect depended on when it was measured, stressor intensities, and whether it was based on the physiological, population, or consumer-resource level (Turschwell et al., 2022). A major shortcoming of most ecological models used for multiple stressors and chemicals is the omission of stressor adaptation and thereby ignorance of eco-evolutionary dynamics (Boyd et al., 2018; van Moorsel et al., 2023). Notwithstanding, process-based models are valuable tools to integrate chemical and nonchemical stressors, formulate hypotheses, make predictions, and explain empirical results, including contradictions (Breda et al., 2022; De Laender, 2018).

DATA-DRIVEN MODELS FOR LARGE SCALES IN THE AGE OF BIG DATA

The increasing availability of global- and continental-scale data from ecosystems including data on climate, species occurrence, and a range of stressors in concert with increasing computational power opens new avenues for large-scale data analyses (Dafforn et al., 2015; Pirotta et al., 2022). Data-driven approaches have been used for multiple chemical and nonchemical stressors to study effects on ecosystems at large spatial and temporal scales. Global data on a range of land use-related stressors and from terrestrial field studies allowed the effects on different dimensions of terrestrial biodiversity to be quantified (Newbold et al., 2015). Several studies analyzed the relationship of chemical exposure, aggregated with mixture models like concentration addition, with ecological indices or community composition of different organism groups, highlighting the ecological relevance of chemical mixtures (De Zwart et al., 2006; Lemm et al., 2021; Malaj et al., 2014; Posthuma et al., 2019). Furthermore, long time series have allowed the response of ecosystems to multiple global change factors over time to be analyzed (Fraker et al., 2022; Vaughan & Gotelli, 2019). The divide between multiple stressor and chemical mixture research is fading in these studies. Multiple recent studies have considered the effects of chemical mixtures in concert with those of nonchemical stressors on ecosystems at regional, national, and continental scales (Grizzetti et al., 2017; Lemm et al., 2021; Posthuma et al., 2019).

These large-scale data analyses confirm the prediction of process-based models that the response to stressors is context-dependent. For example, data analyses demonstrated that the relative importance of chemical mixtures and nonchemical stressors but also of stressor interactions varies spatially and temporally at a given scale (Grizzetti et al., 2017; Kefford et al., 2023; Lemm et al., 2021; Posthuma et al., 2019). Considering this scale is important when interpreting the results of such studies because the temporal and spatial scale can determine the shape and importance of stressors and their interactions (Fraker et al., 2022; Mack et al., 2022; Pirotta et al., 2022). Moreover, to conduct large-scale analyses often requires simplifying assumptions and data aggregation, and this may result in biased estimates of individual stressor effects and interactions (Jähnig et al., 2020). For example, to avoid the "curse of dimensionality," which implies severe loss of statistical power when establishing stressor–response relationships for individual chemicals, chemicals have often been aggregated into a single mixture metric. This prohibits detecting and considering potential interactions between individual chemical and nonchemical stressors. In addition, aggregating data on ecological communities into broad biodiversity metrics can mask the decline of species that are relevant for long-term community persistence (Jähnig et al., 2020). Nevertheless, findings from large-scale empirical studies can support prioritization of management efforts and evaluation of the efficacy of past policy and management efforts (Hallmann & Jongejans, 2021).

ELEMENTS OF A JOINT FRAMEWORK

Current political frameworks such as the European Water Framework Directive and the Kunming–Montreal Global Biodiversity Framework aim to restore and conserve considerable fractions of Europeans freshwater ecosystems and global ecosystems, respectively. This requires scientific frameworks that provide reliable prospective (enabling protective measures) and retrospective (enabling restoration measures) assessments on the response of ecosystems to chemical and nonchemical stressors. Such assessments are particularly pressing in face of increasing climate change impacts on ecosystems as well as likely increasing chemical pollution given a projected approximate doubling of chemical production within a decade (Naidu et al., 2021). Below we outline elements of an overarching framework that considers both multiple stressors and chemical mixtures, and that is based on the tools and methods discussed above (Figure 3). The framework can serve three functions: (1) supporting an integrative assessment of the effects of chemical and nonchemical stressors in case studies, (2) providing elements that can structure reflection and communication of uncertainties in cases where an integrative assessment is beyond capacity, and (3) urging future synthesis projects

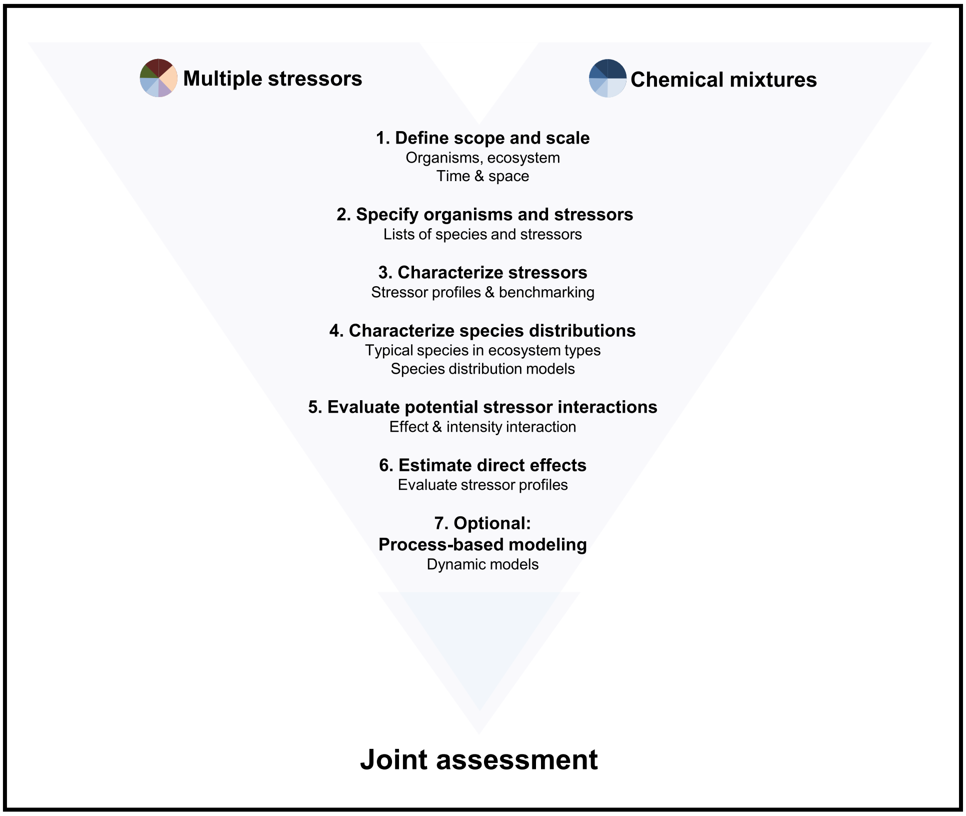

FIGURE 3: Elements of a framework for a joint assessment of the effects of multiple stressors and chemical mixtures.

to move beyond simple aggregation of potentially biased individual studies.

Define scope, biological level, and scale

Any joint assessment of the effects of chemical and nonchemical stressors requires a definition of the scope, biological level, and scale: (1) Type of (meta-)ecosystem. This defines the general environmental context (e.g., stream, agricultural soil). (2) Organism group(s). (3) Biological level. Typically ranging from populations to meta-ecosystems. (4) Temporal and spatial scale. This defines the ecological and stressor complexity, which ranges from a single population or community in an isolated patch with constant stressors and a short duration to multiple connected food webs in a landscape (meta-food webs) with strong temporal dynamics and associated stressors with varying spatial and temporal profiles over longer time scales. (5) Retrospective or prospective, if prospective define point in future. (6) Level of aggregation. This defines the acceptable level of simplification. It ranges from highly aggregated metrics for organisms (e.g., total abundance or biomass) and stressors (e.g., mixture metric) to lowly aggregated, that is, highly resolved, information for organisms (e.g., haplotypes of all populations) and stressors (e.g., concentrations or intensities for each).

Supporting Information, Table S1, provides an overview of how these definitions correspond to data typically generated with the methodical approaches discussed above. This first step defines the overall complexity and thereby determines what is achievable in understanding and prediction under the current state of knowledge. With increasing scales and biological level and the higher aggregated the metric used and the availability of data for organisms, most likely only a qualitative prediction can be achieved. We suggest that any study should reflect how their scale impacts the assessment. For example, a sufficiently long temporal scale was key to unravel stressor interactions between climate change, acidification, and UV-B radiation in lakes, where studies with a more limited scale may have incorrectly attributed ecological effects primarily to acidification (Schindler et al., 1996).

Specify organisms and stressors

The next step is to specify the organisms (e.g., the species making up a community) and stressors, potentially starting with a conceptual model (for details see Suter et al., 2002). Three basic cases can be delineated (cf. Schneeweiss et al., 2023): (1) Organisms known (e.g., list of terrestrial arthropod species) and stressors known (e.g., list of chemicals and nonchemical stressors). (2) Organisms unknown (e.g., unknown composition of terrestrial arthropods) and stressors known. In this scenario, typical species of the selected organism groups in an ecosystem could be used (e.g., Jupke et al., 2022, 2023; Rodwell et al., 2018). Otherwise, databases and literature may allow the typical species occurring in the ecosystem under focus to be defined. If the purpose is restoration, lists of expected species in the absence of stressors could be used. (3) Organisms unknown and stressors unknown. In this scenario, typical stressor scenarios for a specific ecosystem scenario are largely lacking (Geary et al., 2019; Orr et al., 2022), but relevant chemical and nonchemical stressors can be extracted from (spatiotemporal) databases and publications (e.g., Domisch et al., 2015; Kriticos et al., 2014; Newbold et al., 2015; Poggio et al., 2021). For organisms see previous case.

This step combines information on all stressors, irrespective of whether they are chemical or nonchemical, although they may be aggregated into different metrics.

Characterize stressor profiles and benchmarking

The chemical and nonchemical stressor profiles need to be characterized, which includes the intensity and, depending on the scope and scale of the assessment, the spatiotemporal dynamics of each stressor. If data on the stressor intensity (e.g., concentration for chemical, nutrient level) and temporal or spatial dynamics is required, these may be obtained from (spatiotemporal) databases (Dafforn et al., 2015), monitoring databases from governmental authorities, or publications. Overall, this results, unless the spatial dimension is beyond scope, in maps of stressor intensity for each stressor, potentially for different time points. Previous studies have mainly focussed on the spatial dimension and typically used simplified proxies for stressors (e.g., van Gils et al., 2020; Grizzetti et al., 2017; Lemm et al., 2021; Vörösmarty et al., 2010), but temporally resolved data on some environmental factors (see datasets in Lehner et al., 2022) and chemicals (e.g., Wolfram et al., 2021) are already available and may be used to construct spatiotemporal profiles.

Subsequently, the absolute level of stressor intensity should be benchmarked to obtain a relative level, which is required for different null models and enables stressor ranking and prioritization. Benchmarking requires data on standardized effect levels for the organisms in focus (e.g., thermal maximum resulting in adverse behavioral changes in fish [CTmax], EC50). This is widely available for chemicals, but quite rare for nonchemical stressors, except for temperature (e.g., Pottier et al., 2022; see *General mechanisms and identification of interactions with null models* section). Data scarcity will often dictate to benchmark against representative species for an organism group, but if data allows, concepts such as species sensitivity distributions or sensitivity rankings provide community-level benchmarks for chemical and nonchemical stressors (Collas et al., 2018; Posthuma et al., 2019; Rubach et al., 2010). In the absence of data, environmental quality targets or classes may be used to assign qualitative levels of relative stressor intensity (e.g., Schäfer et al., 2016), where so-called safety factors that are frequently used for chemicals need to be accounted for. Benchmarking will convert the output for stressor intensity (e.g., maps over time per stressor) into species- or organism-group-specific outputs of relative stressor intensity.

Finally, to later evaluate the effects (see *Data-driven models for large scales in the age of big data* section), stressor intensity–response relationships should be available or at least data that allow stressor intensities to be translated into potential effects per organism under focus (for a qualitative assessment see Bracewell et al., 2019).

Characterize species distribution

Depending on the spatial and temporal scale of the study, data on occurrence of species over time and space may be required. For highly resolved spatial assessments, species distributions can be obtained via species distribution modeling (Ovaskainen & Abrego, 2020) or from spatiotemporal databases (e.g., Global Biodiversity Information Facility, 2023). Otherwise, aggregated spatial units such as ecosystem typologies may simplify this task, where several typologies provide lists of typical species occurring in an ecosystem type (e.g., Jupke et al., 2022; Rodwell et al., 2018).

Evaluate potential stressor interactions

To consider stressor interactions in the assessment will in most cases be hampered by data scarcity. Where robust knowledge, accounting for context-dependency (e.g., on stressor intensities) and species-specificity, of a stressor interaction is available this can be considered as relative or absolute change in effects or stressor intensities (see next step). Through selection of the null model the probability of overseeing important interactions can be reduced (e.g., the stressor addition model rather overestimates the joint effect; Dey & Koops, 2021). The integration of chemical and nonchemical modes of action in a joint classification system, for example physiological modes of action (see *Characterizing stressors and their modes of action* section), could in the future provide a theoretical foundation for the identification of effect interactions.

Estimate direct effects on organisms

The estimation of direct effects contains three elements: (1) Evaluate temporal stressor profiles with respect to the organisms under focus. Only where the variability in the stressor is high at time scales shorter than the generation time of organisms does it need attention (for details see Jackson et al., 2021) in terms of evaluating effects at different time points. Whether stressor order matters may be decided based on concepts such as co-tolerance and stressor action curves (see *The temporal and spatial dimension of stressors and their effects* section). (2) Evaluate spatial stressor profiles with respect to organisms under focus. Again, only where spatial variability would result in variable exposure of a species does it need attention in terms of evaluating effects at different locations. (3) Estimate the direct joint effect of all chemical and nonchemical stressors based on a null model (see *The temporal and spatial dimension of stressors and their effects* section), and consider superimposing potential interaction effects. This step will typically produce an effect estimate for each species or related aggregated units such as organism groups. If time and space are considered these effect estimates would be made for different time points and mapped spatially. Depending on the scope of the assessment the multiple layers of effect estimates could subsequently be aggregated across species, time, and space (e.g., maximum or mean stressor effect; for a probabilistic approach see Meent et al., 2020), which is likely appropriate where effect estimates are relatively constant over time and space (Vos et al., 2023). The effect estimates can directly be used in decision making (e.g., stressor prioritization), tested in experiments, or used in data-driven analyses of various kinds (e.g., testing the outcome against species and stressor distributions in another region). They may also guide the calibration of process-based models as described below.

Optional: Prediction of effects with process-based models

In all cases where the definition of scope and scale require a dynamic (i.e., different time points) and spatially resolved (i.e., variable exposure) assessment, process-based models are likely needed to make predictions (see *Process-based models for predicting ecosystem effects of multiple stressors and chemical mixtures* section). Whenever multiple time points are considered and multiple populations are involved, species interactions and thereby indirect effects become relevant (see *Process-based models for predicting ecosystem effects of multiple stressors and chemical mixtures* section). This may in turn require a high level of aggregation of organisms and stressors to keep the modeling feasible. Complex temporal stressor profiles will typically require the use of bioenergetic or TKTD models, potentially integrated in more complex models reflecting higher biological levels (e.g., food web model). Complex spatial stressor profiles will typically require landscape and ecosystem models that also consider dispersal besides species interactions (Vos et al., 2023). These models can also deliver results on potential recovery for stressor mitigation scenarios and thereby inform management.

CONCLUSIONS

The historical divide between ecotoxicology and (applied) ecology has lead to the development and use of different methods and tools in multiple stressor and chemical mixture research. Given similar challenges such as diagnosing interactions within and between multiple stressors and chemical mixtures, characterizing chemical and nonchemical stressors including their modes of action, and designing experiments that consider the spatiotemporal complexity of stressor profiles, the integration of the different methods and tools would likely advance both research areas. Process-based models and data-driven approaches are in particular open for joint development as well as for enhancing mechanistic understanding and predictive capacity with respect to the joint effects of chemical and nonchemical stressors. Our framework provides elements toward an integrative assessment of chemical and nonchemical stressors. While its application may exceed the capacity of many individual studies, its merit lies also in structuring reflection and communication of uncertainties that arise from ignoring certain elements. For example, this may result in acknowledging uncertainties in how chemical mixtures or other stressors contribute to diagnosed effects (Birk et al., 2020), although in other cases it may be clear that stressors such as direct resource extraction strongly dominate other effects and detailed assessments are not required (Caro et al., 2022; Jaureguiberry et al., 2022). The integrative assessment would comprehensively inform environmental quality management, whereas several current assessments, for example in the context of the European Water Framework Directive, are separated between chemicals and other stressors with different approaches, making the assessments partly incomparable (Brack et al., 2017). Finally, our framework may urge synthesis projects to move toward more comprehensive and integrative approaches, for instance when aiming to assess the influence of different chemical and nonchemical stressors on biodiversity loss. The rapid expansion of novel computer-based and molecular approaches, and the growing availability of high-resolution environmental and ecological data is likely to strongly reduce the effort required to apply this framework.

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