

Harnessing Computational Methods to Characterize Chemical Impacts on Biodiversity

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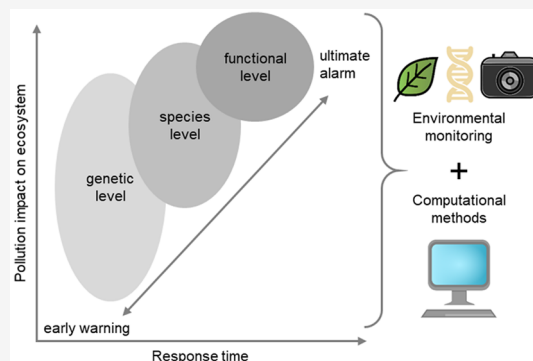
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ABSTRACT: Chemical pollution can threaten biodiversity at different levels, from genetically diverse populations (genetic diversity) to different species (species diversity) and ecosystem traits/interactions (functional diversity). Most assessments of chemical impacts on different biodiversity levels depend on wet lab and field experiments, including sequencing large numbers of organisms, environmental DNA approaches, single chemical–species–outcome toxicity tests, and trait-based methods. However, it is impossible to assess all chemicals, species, populations, and ecosystems using these methods. Therefore, we advocate that computational methods are necessary to characterize, quantify, and predict chemical impacts on biodiversity. We briefly introduce the current state of research into chemical impacts on genetic diversity, species diversity, and functional diversity and describe new opportunities for computational methods like data integration, machine learning, cross-species/cross-ecosystem extrapolation, adverse outcome pathways, and Bayesian methods to support research in these three areas. By harnessing data and methods currently at our disposal and preparing methods to take advantage of continuously emerging data sets, computational approaches can be paired with environmental monitoring so different levels of biological organization can serve as consecutive warning signs for chemical impacts on biodiversity. This will enable effective ecosystem protection measures to be better developed and implemented to prevent biodiversity loss from chemical pollution.

KEYWORDS: chemical pollution, genetic diversity, species diversity, functional diversity, new approach methodologies



THE NEED FOR COMPUTATIONAL METHODS TO ASSESS CHEMICAL IMPACTS ON BIODIVERSITY

Chemicals are released into the environment and pose a threat to ecosystem health. Most chemical risk assessments are based on testing a limited number of species, using a single compound approach.¹ However, mixtures of chemicals can affect endpoints at all levels of biological organization. Ecosystems can be composed of thousands of different species and genotypes with differences in susceptibility to chemicals that may yield different responses at the population and community level. Assessing chemical impacts at all levels of biological organization is essential because pollution has been identified as one of the five major drivers of biodiversity loss.² Yet, chemical pollution is understudied compared to other drivers,^{3,4} and research tends to be isolated from large-scale biodiversity assessments.⁵

A challenge in assessing the effects of chemicals on ecosystems is the complexity of chemical exposures and their interactions at different levels of biological organization. The Convention on Biological Diversity (CBD) defines three biodiversity levels: genetic diversity, species diversity, and ecosystem diversity (Table 1).⁶ Here, we focus on genetic diversity, species diversity, and functional diversity as we are

more interested in chemical impacts on biological levels of organization than on habitat structure/ecosystem conditions. These biological levels are interrelated, and chemical exposures can lead to cross-level effects. At the genetic diversity level, individuals within a species may respond differently to a chemical exposure owing to individual genetics, while at the species diversity level there are marked differences in species susceptibility to chemicals. Genetic diversity can also be related to species diversity wherein a reduction in population genetic variability can make a species more susceptible to a given chemical, and species diversity is related to functional diversity as changes in the abundance of some species can alter the interactions between species, resulting in structural changes in ecosystems and their functional traits.⁷

New approach methodologies (NAMs, Table 1) are crucial owing to the ethical and logistical (e.g., time and cost)

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Table 1. Definitions of Terms Used throughout the Paper

| Term | Definition |
|-----------------------------------|--|
| Computational methods | Approaches to develop mathematical and computer-based models to understand and predict phenomena. ⁸ In the context of chemical impacts on biodiversity, these phenomena would be potential adverse effects from chemical pollution. ⁹ |
| New approach methodologies (NAMs) | Animal-alternative approaches to assess chemical hazard and risk. ¹⁰ NAMs include both <i>in vitro</i> and <i>in silico</i> (computational) methods. Here, we focus on computational methods. |
| Levels of biological organization | Structures identified by part-whole relationships with biological components at higher levels composed of biological components at lower levels. ¹¹ Here, we focus on the relationship between genetic diversity as the lowest level, species diversity, and functional diversity as the highest level. |
| Genetic diversity | Variation at the DNA level within a species (i.e., population-level genetic variability). ¹² While different susceptibility to chemicals includes variability based on life stage and environmental factors, here we focus on genetic susceptibility as a driver of population-level effects. |
| Species diversity | Describes the number of different species occurring in a community or ecosystem and their relative abundance. |
| Functional diversity | Describes the range and distribution of functional traits of organisms in a community or ecosystem. ¹³ The loss in species diversity due to different chemical and nonchemical stressors may or may not correlate with functional diversity ¹⁴ and therefore requires a separate assessment. |
| Ecosystem diversity | Covers both community-level and habitat diversity. Includes the interactions between organisms and the abiotic environment. ⁶ |

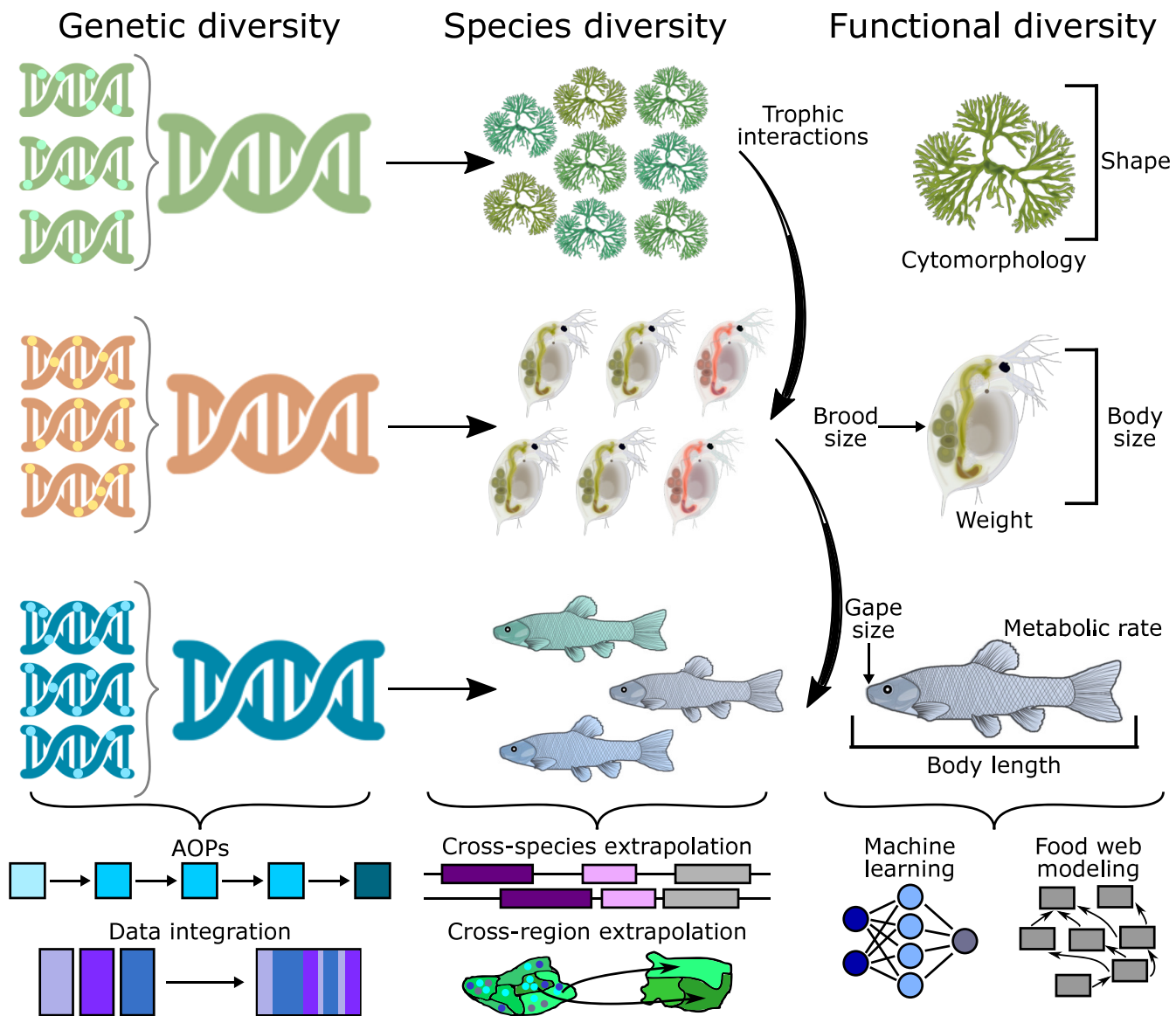


Figure 1. Overview of the different levels of biological organization and computational methods that can aid in the assessment of chemical impacts on these levels. Different points on DNA in the genetic diversity column depict variable genetic sequences within a population, while different colored organisms in the species diversity column depict distinct species present in different numbers. Note that some methods shown for distinct biological levels could also be applied to other levels (e.g., machine learning and data integration).

constraints of *in vivo* experiments. Therefore, just as human health assessment has increased the use of computational approaches to reduce *in vivo* testing and fill data gaps, so too must assessment of chemical impacts on biodiversity. However, the ecotoxicology community has been comparatively slow to implement computational methods, and NAMs have often been viewed with skepticism.¹⁵ Characterizing chemical impacts on ecosystems has lagged behind human health assessment as the same challenges in human health assessment exist for ecosystems (huge numbers of chemicals/mixtures, many possible toxicity mechanisms, and adverse outcomes), but they have the additional challenges of numerous species and ecological interactions. Therefore, novel computational methods must be harnessed to assess chemical impacts on biodiversity. The relationship between genetic diversity, species diversity, and functional diversity is depicted in Figure 1, along with potential computational methods detailed in the following sections that can be used to enhance assessment of chemical impacts on each level of biological organization.

Current Approaches to Assess Chemical Impacts on Genetic Diversity. Without adequate assessment of genetic diversity, chemical impacts cannot be characterized beyond the individual organism level, meaning potential impacts on biodiversity are unknown. Genetic variability is crucial to wildlife conservation, and its evaluation is needed to assess not only individual and population resilience, but also the level of adaptation possible for existing populations with current and changing chemical pressure.¹⁶ However, genetic diversity assessment has received less attention than other levels of biodiversity¹⁷ and is often disconnected from chemical risk assessment. For example, there are numerous research branches related to ecological genetics, including evolutionary genetics, population genetics, and functional genetics, with most fields focusing on the emergence of genetic variants to describe phylogenetic relationships or genetic diversity in the context of ecosystem conservation against stressors without specification.¹⁸ The field of ecotoxicogenomics has been proposed to integrate genomics techniques into ecotoxicology and environmental risk assessment and shows promise for mechanistic understanding of chemical impacts on organisms.¹⁹ However, incorporation of these approaches to assess differences in susceptibility to chemical exposures within a species is still limited.

The proportion of distinct populations maintained within species can serve as a genetic diversity indicator (other indicators discussed in ref 12), and genetic diversity assessment typically depends on sequencing large numbers of organisms in a given population.¹⁷ Sampling environmental DNA (eDNA) uses organism DNA in environmental samples to characterize individuals in a given ecosystem and has been used to estimate genetic diversity in populations.^{20,21} While this is a noninvasive approach to characterize actual genetic diversity in the wild, it is still most frequently used for species diversity assessment,²¹ with limited connections to chemical exposures. For example, some studies assess how chemical exposures drive genetic diversity alterations (e.g., how chemical contamination influences population genetics²²), but assessments of genetic susceptibility to chemical exposures inducing adverse outcomes in sensitive individuals are lacking. Other approaches to assess chemical impacts on genetic diversity include monitoring regions with chemical contamination (e.g., as has been done for endocrine disrupting chemicals²³). However, these

methods tend to focus more on adaptation than on the development of adverse effects, and field-based monitoring approaches are problematic for ecosystem protection as they depend on a species already under threat from chemicals. Alternatively, lab-based studies have been used to characterize genetic variants in populations and their response/tolerance to chemical exposures.^{24,25} While these approaches are useful for actual assessment of chemical impacts on genetically diverse populations, the number of species sampled is limited, making it difficult to know if the sampled genetic diversity for a given population/species is of a realistic range. Further, it is impossible to assess every population or species for their respective genetic diversity (either in lab or in field), let alone in combination with chemical exposures.

New Opportunities to Assess Chemical Impacts on Genetic Diversity. In human health risk assessment, a population health-based approach has been emphasized to better account for chemical impacts on different individuals,²⁶ and computational methods to assess chemical impacts on genetically diverse humans have been increasingly developed. One approach uses existing adverse outcome pathways (AOPs) to identify functionally significant genetic variants implicated in regulatory regions of genes in AOPs to characterize genetic susceptibility to chemical exposures.²⁷ Another approach to characterize chemical effects on genetically diverse populations involves data integration to form new, putative chemical–genetic variant–outcome linkages (not starting from AOPs) to describe the pool of genetic variants potentially implicated in different chemically induced adverse outcomes.^{28,29} However, these computational methods have been limited to humans. We propose that these same approaches can be extended to nonhuman animals to assess chemical impacts on genetic diversity. For example, polymorphisms can be identified in key events of AOPs for nonhuman animals to predict downstream effects of genetic variability in response to chemical exposures. There are numerous databases that can be harnessed to characterize genetic variants implicated in different animal populations and predict the effects chemicals may have on these groups. For example, mice, rats, zebrafish, nematodes, and frogs have comparatively extensive data on genetic variability owing to their use as model organisms for humans (e.g., data in the Monarch Initiative³⁰). The potential overlap in genetic variants between human and nonhuman organisms has been explored to help characterize functional variants in humans based off of variants in nonhuman model organisms,^{31,32} and we propose these same approaches can be employed to characterize genetic variants in other species as well. While some of these species genetic variability may be more representative of lab settings than wild organisms, there is still merit in using inbred strains as these genetic data are often better characterized than wild populations.³³ By characterizing genetic variability across species (e.g., as orthologous variants in nematodes, mice, and humans have been compared³¹), patterns can be identified to help describe genetic diversity for understudied species and populations.

Current Approaches to Assess Chemical Impacts on Species Diversity. Species diversity is one of the most frequent measures for ecosystem protection across disciplines like ecotoxicology, sustainability science, and ecology.³⁴ Field-based methods for species diversity assessment have been developed to monitor species occurrence and abundance directly (e.g., data integrated by the Global Biodiversity

Information Facility, GBIF, <https://www.gbif.org/>), but largely lack standardization regarding sampling methods and site selection and have limited coordination with monitoring of chemical stressors. Therefore, we still have poor understanding of species diversity in different regions, and it is challenging to infer chemical impacts. Further, because monitoring studies are limited to whatever is seen by an observer at a given moment, this can lead to underestimating species abundance if rare species are not observed at their actual rate, overestimating species abundance if rare species are noticed more than common species, or missing species altogether if the time of observation does not align with an obvious life stage of an organism (e.g., aquatic larvae in a healthy insect population).³⁴

Metrics like species richness have been used as species diversity indicators (discussed in ref 34), and new lab- and field-based tools have been proposed to improve species diversity estimates from sample data and characterize impacts from chemical stressors. For example, ecotoxicogenomics methods and eDNA approaches are more frequently applied for species diversity assessment than genetic diversity assessment. In ecotoxicogenomics, methods using differential gene expression of species following chemical exposures can characterize different species sensitivity and tolerance to chemical threats (e.g., some species may have greater detoxification gene expression³⁵). Additionally, indicator species are frequently used to monitor ecosystem response to environmental changes like chemical pollution,³⁶ and multiomics approaches to monitor ecosystem health have been increasing.³⁷ eDNA metabarcoding can characterize multiple species from a single sample taken from an environment, meaning indicator species can be monitored in polluted ecosystems using this approach.³⁸ Species biomonitoring approaches (e.g., in the Water Framework Directive) have developed a suite of indicators to determine how species in a community may be altered with environmental change,³⁹ but these methods are not stressor specific, making it difficult to disentangle specific chemical effects or effects from complex mixture interactions in the environment.

Lab-based toxicology testing methods often assess species using one chemical—one species—one outcome assessment approaches. These methods are useful for building mechanistic knowledge of chemical effects on an organism, but it is impossible to conduct detailed assessments for the number of different species (including threatened or endangered species) and chemicals in circulation. While *in vitro* approaches can help expand one chemical—one species—one outcome assessments at the suborganismal level, their utility is limited for assessing sensitivity at the species level. However, these methods show promise for assessing chemically induced alterations in microbial and algal communities.⁴⁰

One computational method that is applied to harness chemical activity data and assess potential effects on species richness is the species sensitivity distribution (SSD) approach.⁴¹ SSDs integrate single-species effect data to infer the concentration of a chemical or a mixture of chemicals that affect a given percentage of species (i.e., potentially affected fraction). However, these methods depend on understanding the most sensitive endpoint for a species, do not directly address species loss, and may miss indirect effects that influence biodiversity (e.g., impacted food sources). Further, robust SSDs can often only be derived for a small set of chemicals because their construction is constrained by the limited number of species tested under laboratory conditions.

Semifield experiments, such as micro- and mesocosms, have been used to derive chemical threshold concentrations under more realistic conditions. They offer large benefits compared to lab-based single-species approaches or SSDs as they take into account species interactions (often in multiple trophic layers) and can be used to establish links between population and community-level effects and ecosystem functional parameters (e.g., oxygen production, organic matter decomposition rates¹⁴). Despite the number of micro- and mesocosm studies increasing in the last two decades, there have been few attempts to characterize chemical pressure on biodiversity loss in these experimental setups (but see ref 42). However, while semifield experiments offer the possibility to assess impacts on biodiversity and recovery after (several) contamination pulses and species generations so that adaptation and resilience of ecosystems to these stressors can be evaluated, these are impossible to conduct for all contaminant mixtures and ecosystem types. Therefore, additional computational approaches are necessary to expand our understanding of chemical effects on (less tested) species assemblages and ecological scenarios.

New Opportunities to Assess Chemical Impacts on Species Diversity. To expand data on diverse species' effects, cross-species extrapolation techniques harness existing knowledge of individual species for expansion to other species based on genetic homology, phylogenetic relatedness, or common biological mechanisms.⁴³ These methods either follow the one chemical—one species—one outcome approach, extrapolate the effects of multiple chemicals to one species (e.g., using quantitative structure activity relationships, QSARs), or can extrapolate effects of a given chemical on multiple species. Cross-species extrapolation research has been growing with approaches developed using linear regression models,⁴³ read-across-based methods,⁴⁴ or machine learning (ML).^{45,46} Through these extrapolations, data gaps can be filled so that chemical effects on a variety of species can be better characterized. For example, Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) is an online tool that uses a tiered approach to classify species similarity, starting from primary amino acid sequences through to conserved functional domains and likely protein conformations/interactions with chemical stressors.⁴⁷ Another tool, Genes-to-Pathways Species Conservation Analysis (G2P-SCAN), extrapolates chemical effects across species using conserved molecular targets and pathways.⁴⁸ There have also been initiatives to sequence large numbers of species, such as the Darwin Tree of Life project which is a collaboration between genomics institutes and biodiversity initiatives to gather whole genome sequences of all species in the United Kingdom.⁴⁹ Additionally, toxicokinetic–toxicodynamic (TKTD) properties are important to predict whole organism and/or tissue-specific concentrations of chemicals in different species—which can inform the potential for a chemical to lead to an adverse effect following exposure—and both individual species and multi-species models have been developed (see ref 50 for examples in fish). Therefore, as the amount of data on different species increases, it is essential that methods are in place to use these data as they emerge. For example, by filling data gaps for a variety of species, SSDs can be targeted to species assemblages representative of a given habitat, introducing the possibility of ecosystem-specific sensitivity and risk assessments.

As with genetic diversity assessment, AOPs can be used to expand assessment of chemical impacts on species diversity. By

nature, AOPs describe sequences of events without stressor specificity. Therefore, by identifying AOPs with conserved impacts across species, chemical threats can be extrapolated. Additionally, based on conserved key events or biological mechanisms, AOPs can be extrapolated across species as well. While the number of AOPs is still relatively small to describe the full spectrum of biological effects across all species (459 AOPs as of January 2024), there have been numerous calls for computational methods to develop AOPs,^{51,52} suggesting the number will increase in the future (there were only 274 AOPs in January 2020⁴³).

ML-based methods can be used by integrating existing chemical toxicity test data for different species to predict chemical impacts both for new chemicals and new species. For example, ML models have been developed to predict chemical toxicity to different fish taxa using experimental *in vivo* fish toxicity data with specific chemical (e.g., physicochemical properties, molecular descriptors), species (e.g., organism taxonomy), and experimental descriptors.⁴⁵ While these methods are still challenged by data sparsity and high variability in input data (e.g., from diverse original testing conditions), this is a promising method for expanding chemical–species–outcome coverage. However, rigorous testing and validation of ML models with benchmark data are crucial for the advancement of these methods.⁵³ Other species-specific parameters like ecological trait data, TKTD parameters, and/or dynamic energy budget parameters (e.g., the Addmy-Pet database http://www.bio.vu.nl/thb/deb/deblab/add_my_pet/) can also be used to improve ML-based extrapolations, thus reducing the need for additional animal testing.^{46,54,55} Further, as other approaches improve (e.g., identification of common protein markers across species or AOPs), so too can ML methods become more robust and reliable.

While the focus of most computational approaches assessing species' sensitivity to chemical exposures characterize sensitivity across species rather than changes in abundance, one preliminary approach to estimate how chemical exposures may alter species abundance is the mean species abundance relationship (MSAR).⁵⁶ Preliminary estimates of species abundance can also be developed using probabilistic approaches to model different ratios of species abundance to assess potential biodiversity impacts. Other approaches can harness existing data sets on species occurrence (e.g., data in GBIF) to build ML and/or statistical methods to predict species occurrence (or distributions of occurrence) in different ecosystems (i.e., cross-region extrapolation). Such approaches have been applied to study how different global climate change scenarios will affect species distribution,^{57,58} but there has been limited effort to include chemical contamination into these projections that go beyond land-use indicators.

ML models can also be used to integrate data from mesocosm experiments to determine ecosystem-level responses to different chemicals and to infer how chemicals with similar or different toxic modes of action will affect them.⁵⁹ The data sets generated in micro- and mesocosm experiments can also be used to parametrize and calibrate food web models that allow testing different species and chemical exposure combinations.⁶⁰ The idea of developing 'virtual mesocosm experiments' (i.e., based on dynamic species biomass modeling) has been put in practice to answer theoretical questions;⁶¹ however, the implementation for chemical risk assessment so far remains limited. Further,

these modeling tools also present opportunities to explore relationships between chemical (and nonchemical) stressors and indicators of ecological quality and diversity, so that mechanistic links can be better established.

Current Approaches to Assess Chemical Impacts on Functional Diversity. Chemicals can reduce the performance of species carrying specific functional traits, thus affecting the functional diversity of ecosystems. Such loss can be translated into broader alteration of ecosystem function and effects on important ecosystem services such as nutrient recycling, carbon sequestration, and many others. In developing trait-based approaches to monitor chemical impacts on ecosystems, basic challenges include which traits are most relevant for ecosystem function and what metrics can be used to characterize alterations in those traits.^{62,63} Indicators for functional diversity include measures of functional redundancy (i.e., analogous traits in different species of an ecosystem that contribute to the same ecosystem function),⁶⁴ and direct field-based measurements of ecosystem functions are frequently used to characterize changes in ecosystem traits. For example, oxygen concentrations can be monitored to approximate respiration rates in rivers and streams,⁶⁵ while leaf-litter breakdown rates and microbial activity can be monitored to assess functional integrity of streams based on how leaves are processed by stream communities.⁶⁶ These approaches can also be used as indicators of chemical pollution. Microbial respiration and decomposition rates have been monitored to determine the effects of wastewater on microbial communities and organic-matter processing,⁶⁷ and leaf-litter breakdown rates have been found to correlate with structural changes in streams contaminated with pesticides.⁶⁸ These methods show promise for direct biomonitoring of contaminated sites over large spatial scales; however, they cannot be used for prospective risk assessment.

In the lab, different bioassays can be used to monitor functional traits to inform ecosystem function. For example, the relationship between insect herbivores and plants can be tested through choice and no choice assays to monitor changes in both herbivore feeding behavior and plant defenses following ecosystem disturbance.^{69,70} The *Gammarus* feeding assay can be used to monitor the behavioral response of gammarids to environmental contaminants, which is crucial as macroinvertebrate feeding is a rate-limiting step in organic matter decomposition in streams.⁷¹ However, as with assays for other levels of biological organization, the utility of short-term bioassays to predict long-term effects from chemical pollution is limited.

Databases of functional trait data for different species have been developed for use in ecological monitoring, conservation, and management including plants,^{72,73} invertebrates,^{74–77} and fish.^{78,79} These resources can be used to computationally model the relationship between different environmental factors, species distributions, and species traits.⁷⁴ Multivariate analyses and ML have been used to identify functional diversity patterns that are directly related to toxic pressure and nonchemical stressors.^{80,81} For example, multimetric indices have been developed by incorporating biological metrics based on taxonomy and life history traits that respond to different pressure categories (e.g., water quality and habitat degradation) to be included in biomonitoring approaches.^{82,83} However, the use of this information to infer functional diversity loss or ecological function impairment by chemical pollution remains largely unexplored.

New Approaches to Assess Chemical Impacts on Functional Diversity. To expand the computational utility of data on functional traits, comprehensive databases should be developed covering different taxa levels and geographic regions. For example, the freshwaterecology.info database incorporates data on over 20,000 European freshwater organisms ranging from fish to phytoplankton with information on species traits and ecological preferences regarding habitat and morphology provided.⁸⁴ As data on different species distributions and functional or biological traits are clarified, patterns can be identified to build cross-chemical and/or cross-species extrapolation of functional traits using the same approaches applied for extrapolation-based species diversity level assessments (e.g., ML or read across of field-based data).

As with species diversity assessment, limited knowledge of ecosystem composition is a challenge for characterizing the functional traits in a given ecosystem. Therefore, the same approaches for cross-region extrapolation of species composition should also be applied for functional diversity assessment to build knowledge of at least the main community features and mechanisms present in different ecosystems. Combined biomonitoring and ML approaches can also be used to both characterize and assess changes in the taxonomic makeup and morphological trait composition of an ecosystem. For example, image-based ML methods have been used to characterize species in a given region and monitor morphological traits (e.g., body size).^{85,86} By monitoring these features in pristine and polluted environments and/or monitoring changes in these features with increasing chemical pollution, the relationship between chemicals and functional traits can be clarified and the corresponding data can be harnessed to expand ready-to-use databases of biological trait data and functional descriptors for the aforementioned computational methods.

Representative ecological scenarios and/or food web models relate species interactions between different trophic levels (e.g., feeding traits). By modeling the flow of effects from chemical exposures across trophic levels, changes in the functional trait composition of an ecosystem can be characterized. For example, the AQUATOX model combines multiple trophic levels of an aquatic food web and models potential organic toxicant effects.⁸⁷ While these types of models can characterize possible changes in structure and function of an ecosystem following chemical exposure, there are relatively few models available owing to the difficulty in characterizing different species interactions, particularly with spatiotemporal variability of exposure defined. So far, such food-web models are mostly deterministic and lack a comprehensive uncertainty assessment (but see ref 88 for a step in this direction).

Incorporating stochastic modeling approaches could help to predict a possible range of chemical effects in lieu of data representing reality. For example, geographic variability in effects from chemical exposures have been predicted for humans by using regional demographic data with TK models⁸⁹ and for earthworms by combining behavioral trait data with TKTD models and environmental data.⁹⁰ By following these approaches using variable data input representing a range of possible species TK traits and/or chemical exposures, potential changes in species' functional traits for specific geographic regions can be predicted. A straightforward approach to account for intraspecies variability and demographic stochasticity is Individual or Agent-Based Modeling.^{91,92} So far, these have mostly been used on a population level (e.g., see ref 93), but in principle they can be combined to model food webs, and

Bayesian inference can be joined with these models to infer parameters from data and quantify uncertainty.⁹⁴

CONCLUSIONS AND WAYS FORWARD

Assessing potential chemical impacts on biodiversity is crucial as more than one million of the planet's plant and animal species are threatened with extinction in the coming decades.² We propose that combined environmental monitoring and enhanced computational methods can enable genetic diversity, species diversity, and functional diversity impacts to serve as consecutive warning signs of chemical pollution impacts on biodiversity. Generally, genetic diversity impacts from chemicals can affect the most sensitive individuals but may not always translate to changes in species diversity, whereas changes in functional diversity represent extreme pollution events. This is because functional redundancy within communities and potential species turnover in response to stress could otherwise help protect ecosystem functions against stressor impacts.¹⁴ Therefore, new computational methods to assess chemical impacts on these levels of biological organization can be joined to ecosystem monitoring to help identify and differentiate between an early warning sign (i.e., genetic diversity impact) and an alarming pollution event (i.e., functional diversity impact) in different ecosystems.

We propose that computational methods like data integration, ML, and Bayesian methods show promise for assessment of chemical impacts on different levels of biological organization. Further, some methods could be used to assess chemical impacts across levels. For example, AOPs can cover the genetic and species diversity level, and incorporation of population and community dynamics could allow biodiversity projections. ML models could also be used to characterize different levels of biological organization that are more likely to be damaged due to chemicals with specific modes of action (e.g., by using mesocosm data sets as input, e.g.,⁵⁹) or to predict multilevel changes (e.g., how genetic susceptibility to a chemical stressor promulgates into a change in ecosystem function). Further, TKTD modeling approaches can cover a variety of biological levels as varying TK properties can serve as a proxy for genetic diversity based on population-variability in chemical metabolism,⁹⁵ and clarifying potential differences in TK properties is an important component of cross-species extrapolation⁹⁶ (e.g., General Unified Threshold model for Survival (GUTS) integrates TKTD models to estimate survival, which can predict impacts both within and across species⁹⁷). While computational methods come with their own inherent challenges (e.g., a lack of mechanistic explainability in ML depending on the model used), these methods can be complemented with experimental demonstrations and/or well-structured knowledge connections to increase confidence in new models or improve interpretability. For computational methods to predict chemical impacts on biodiversity to be realized, the four main needs are:

- Methods to quantify uncertainty and establish causality. For example, Bayesian inference is a useful approach to incorporate limited data with limited prior knowledge (e.g., mechanistic understanding regarding causality) to make the best possible predictions with the information at hand and quantify uncertainty around these predictions.⁹⁸
- Enhanced collaborations between chemists, toxicologists, geneticists, ecologists, and data scientists. For

example, initiatives like PrecisionTox⁹⁹ and the International Consortium to Advance Cross-Species Extrapolation in Regulation (ICACSER)⁹⁶ both bring together scientists from different fields and expertise with a focus on improving regulatory acceptance of computational methods for chemical safety.

- Coordinated data production, systematic experimental designs, and standardized data quality checks to increase data usability combined with standardized procedures for model comparison to guide model selection.
- Terminology, methods, and output from different fields must be harmonized to avoid parallel work and improve cross-feeding of new information.

We expect that data availability will be the biggest challenge in moving computational methods for assessment of chemical impacts on biodiversity forward and highlight the importance of standard data generation approaches and enhanced assessment of understudied species and chemical groups to combat this challenge. Even if we are missing data to make robust computational approaches a reality, now is still the time to conduct preliminary analyses and prepare frameworks so that methods are already established when the relevant data becomes available. Further, as artificial intelligence continues to develop, numerous aspects of toxicology and ecology could be enhanced (reviewed in refs 100 and 101, respectively). For example, ML models can guide the prioritization of experimental data collection and support systematic review of information to predict chemical risks.¹⁰²

KEY MESSAGES

- (1) Computational methods can enhance assessment of chemical impacts on genetic diversity, species diversity, and functional diversity.
- (2) Combined environmental monitoring and enhanced computational methods can enable different levels of biological organization to serve as consecutive warning signs of chemical pollution impacts on biodiversity.

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Notes

The authors declare no competing financial interest.

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