Stoichiometric Ecotoxicology for a Multisubstance World

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Nutritional and contaminant stressors influence organismal physiology, trophic interactions, community structure, and ecosystem-level processes; however, the interactions between toxicity and elemental imbalance in food resources have been examined in only a few ecotoxicity studies. Integrating well-developed ecological theories that cross all levels of biological organization can enhance our understanding of ecotoxicology. In the present article, we underline the opportunity to couple concepts and approaches used in the theory of ecological stoichiometry (ES) to ask ecotoxicological questions and introduce stoichiometric ecotoxicology, a subfield in ecology that examines how contaminant stress, nutrient supply, and elemental constraints interact throughout all levels of biological organization. This conceptual framework unifying ecotoxicology with ES offers potential for both empirical and theoretical studies to deepen our mechanistic understanding of the adverse outcomes of chemicals across ecological scales and improve the predictive powers of ecotoxicology.

Keywords: nutrient ratios, elemental imbalances, toxicity, ecotoxicological models, multiple stressors

Ecotoxicology is the study of the harmful effects of chemical contaminants on individual organisms, populations, communities, and ecosystem processes (Cairns 1988, Baird et al. 1996, Calow 1996, Relyea and Hoverman 2006, Gessner and Tlili 2016, Walker et al. 2016). Ecotoxicologists have found that toxicity may be influenced by environmental factors such as ambient physicochemical conditions influencing contaminant bioavailability, organismal traits (e.g., differential metabolism or sensitivity, trophic guild), and food webs or ecosystem structure (Newman and Clements 2007). Although these findings are often incorporated into regulatory actions (Jager et al. 2006, Garner et al. 2015), many big-picture ecological theories that cross all levels of biological organization have been less commonly integrated into the field of ecotoxicology and subsequent applications during chemicals assessment and management (Forbes et al. 2017, Schmitt-Jansen et al. 2008).

How organisms obtain the nutrition and energy needed for maintenance, growth, and reproduction is a central concept in many ecological studies that examine organismal physiology (Wagner et al. 2013), food webs (Phillips and Eldridge 2006), biodiversity (Worm et al. 2002), and biogeochemical cycles (Sterner and Elser 2002). Given how nutrition can be an important driver in many ecological studies, it is no surprise that multiple frameworks are used to examine how diets affect organismal phenotypes. All nutritional ecological frameworks in the broadest sense examine how nutrition affects the physiology, behavior, life history, and ecoevolutionary responses of organisms and their interactions with the environment (Raubenheimer et al. 2009). Frameworks such as optimal foraging and nutritional geometry have a behavioral ecology foundation that focuses on optimizing fitness traits on the basis of food selection. Initially, nutritional geometry focused on controlled laboratory experiments to examine the optimal nutrition of two macronutrients (i.e., proteins, carbohydrates). More recent techniques have included adding a third nutrient to investigate more complex diets (Raubenheimer 2011); however, much of the work has focused on organisms and is not readily scaled to communities and ecosystems. Other frameworks, such as ecological stoichiometry (ES), track elements and have a foundational focus on ecosystem science (Sterner and Elser 2002, Sperfeld et al. 2017, Elser et al. 2000). Early work in this area focused on interspecific competition and biogeochemical cycles (e.g., Elser et al. 1998), whereas more recent work includes a focus on the physiological changes that occur because of element-limited diets (Wagner et al. 2013). Although ES is limited partly because some types of micronutrient limitation (i.e., essential fatty acids or amino acids) are not easily identified by studying elements alone,

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recent work has extended the ES modeling framework to incorporate concepts from nutritional geometry and has was shown that macronutrients can be used as currencies (Anderson et al. 2020). Overall, the relative ease of tracking elements through food webs that can span all spatial levels of organization from genes to ecosystems (Hessen et al. 2013) makes ES an ideal framework to examine how toxicants and elemental stress affect organisms and ecosystems.

At the most fundamental level, ES is the study of imbalances between the elemental composition of available resources and what is required for organismal metabolism (Sterner and Elser 2002). In essence, imbalances between multiple available elements and organismal requirements of those elements strongly affect the physiology of many taxa and result in widely variable growth, reproduction, and survival (Sterner and Elser 2002, Frost et al. 2005, Wagner et al. 2013). Stoichiometric effects on organisms in turn alter ecosystems and biogeochemical cycles (Elser et al. 1998). If the organism elemental requirements are imbalanced with the elemental supply ratios, it would alter the nutrition of the organism and affect their excretion elemental ratios. For example, imbalanced nitrogen (N) to phosphorus (P) supply ratios can alter the nutrition of zooplankton consumers and their N and P excretion ratios (Elser and Urabe 1999). ES examines the causes and consequences of elemental imbalances across biological levels by linking cellular processes and organismal metabolism to population dynamics, predator–prey interactions, and ecosystem function (Sterner and Elser 2002).

Because elemental ratios in resources vary widely and elemental limitation is widespread in nature, ecotoxicology may benefit from the incorporation of a stoichiometric perspective. Traditionally, toxicity experiments use nutrient-replete conditions, with the intention to eliminate nutrient limitation and elemental imbalances, because of the inherent assumption that nutrient limitation would interact with toxins or toxicants to alter results. Although nutrient replete conditions may not be commonplace in natural ecosystems, only a few ecotoxicology studies have examined toxicity–elemental imbalance interactions. When explicitly included in single-species toxicity testing, the effect of the contaminant has been found to vary when there are elemental imbalances between the test organism and its nutritional resources (e.g., Hansen et al. 2008, Fulton et al. 2009, Fulton et al. 2010, Lessard and Frost 2012, Bian et al. 2013, Conine and Frost 2017). Although this handful of examples demonstrate the possible uses of ES to improve our understanding of ecotoxicology, this past work represents only a small part of what could be a larger conceptually united subdiscipline: stoichiometric ecotoxicology. We define stoichiometric ecotoxicology as a subfield in ecology that examines how imbalances between organisms and their food resources interact with contaminant stress in all levels of biological organization. Furthermore, we define nutrients in this framework as elements that are conserved across all spatial scales from genes to ecosystems.

One area of stoichiometric ecotoxicology that could be especially useful but remains undeveloped is the application of formal mathematical approaches that couple mass balance constraints to ecological processes. Stoichiometric models track multiple elements to understand how elemental imbalances affect processes from cells to whole ecosystems across multiple levels of biological organization. For example, at the organism scale, mass-balance models couple information on physiological processes of multiple elements (ingestion and assimilation) to determine animal elemental demands and the optimal nutritional mixture needed for maximal growth (Sterner 1997, Frost and Elser 2002, Frost et al. 2006). In addition, organismal processes are incorporated in dynamical models that quantitatively link energy flow and elemental cycling to predator–prey interactions (Loladze et al. 2000, Muller et al. 2001, Elser et al. 2012). These models could be extended to examine the ecological effects of natural or anthropogenic contaminants by modifying parameters relative to chemical concentration or body burden. Similarly, classical ecotoxicological models can be expanded to incorporate stoichiometric constraints by modifying parameters related to nutrient limitations. Integrative modeling approaches would allow for examination of interactive effects of nutrients and contaminants on organismal physiological state, competitive interactions, and whole-ecosystem mass balance. In addition, these models may help determine critical contaminant concentration thresholds that regulate biomass, growth rates, ecosystem function, and the biological transfer of toxins through ecosystems (Andersen et al. 2004, Evans-White et al. 2009, Suzuki-Ohno et al. 2012). Current models are beginning to incorporate stoichiometric constraints to understand the ecological effects of chemical toxicity (Peace et al. 2016, Hassan et al. 2018, as is discussed below), and this effort calls for conceptual, theoretical, and empirical development.

In the present article, we examine opportunities to develop stoichiometric ecotoxicology by coupling concepts and approaches commonly used in ES to ask ecotoxicology questions. In particular, we present a conceptual overview of the links between elemental stoichiometry and toxicology, discuss recent advances in stoichiometric ecotoxicology research, and explore possible areas of future development, including the development and application of new or modified mathematical models. Altogether we show the need and promise of stoichiometric ecotoxicology to provide the impetus for its future development.

The conceptualization of stoichiometric ecotoxicology

Although the potential value of examining interactions between stoichiometry and toxicology has been noted (see above), a next step is to further develop the empirical basis of stoichiometric ecotoxicology through the study of a diverse range of organisms, a broader range of toxic contaminants, and with more types of elemental imbalances. The underlying rationale and unifying concept of

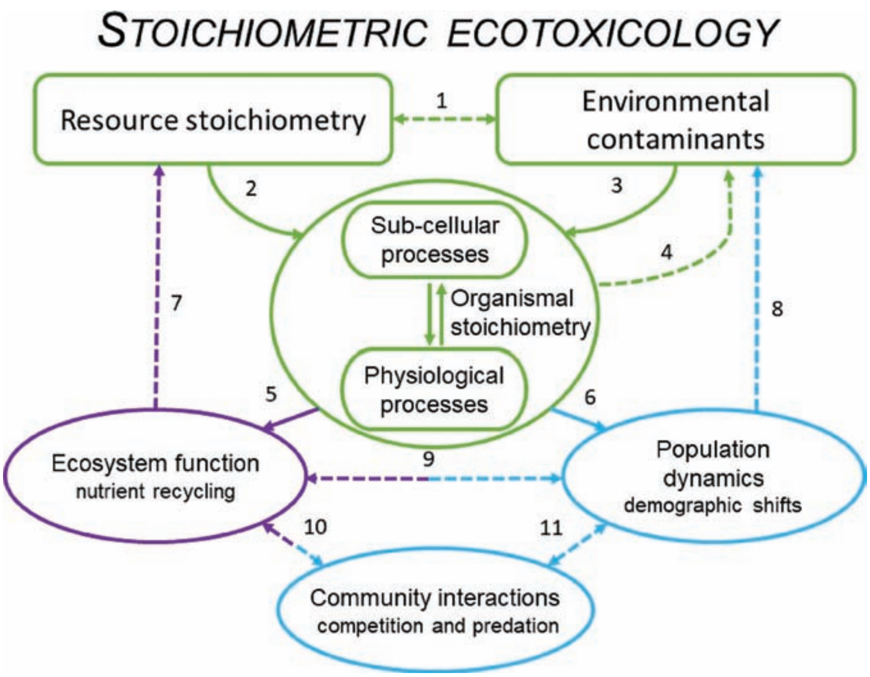

Figure 1. Possible interactions of resource stoichiometry (i.e., nutrient ratios in the environment) and environmental contaminants on relationships from the suborganismal level through ecosystem level. These effects include feedback loops within and between levels of organization. The colors represent three categories of interaction: organismal and suborganismal (green), population and community (blue), and ecosystem level stoichiometric ecotoxicology (purple). The dashed arrows represent indirect mechanisms or indirect feedback loops among components. The arrows are numbered and explained in the accompanying text.

this research field is that the supply of multiple resources can alter or be altered by the effects of chemical toxicity on organisms, populations, communities, and ecosystems (figure 1). As further development of this field will require examining these connections using a combination of empirical and theoretical approaches, a starting point is to identify the possible types and nature of interactions between toxins and toxicants and unbalanced elemental supply. In addition, this perspective is not specific to the taxa or trophic level, because we envision it being applied to toxicological research on all organisms including producers, consumers, detritivores, and predators. In the present article, we provide an initial overview of stoichiometric ecotoxicology and its potential applications across the various levels of biological organization (figure 1). Also, we have compiled a list of studies that implicitly or explicitly investigate the role of stoichiometric constraints on the response of organisms to diverse toxic substances, including pesticides, pharmaceuticals, essential and nonessential metals, and natural substances such as plant secondary compounds (table 1). These studies represent a starting point from which we identify the types of ecotoxicological questions that a stoichiometric framework allows us to ask at multiple levels of biological organization.

Organismal stoichiometry and ecotoxicology. Organismal physiology and life history are strongly affected by both available food resources (figure 1, arrow 2) and contaminants (figure 1, arrow 3), and these alterations to metabolism may interact to create more variation in toxicity. The nature of these interactive effects largely depends on the nutrients under consideration, the organismal traits, and the nature of the contaminant. For example, similar to the concentration addition mechanism of contaminant mixtures (Altenburger et al. 1996), if a toxicant and elemental stress affect the same metabolic pathways it could lead to an additive or synergistic stress response. In addition, exposure to toxicants may activate detoxification pathways within an organism that can involve the synthesis of compounds rich in carbon (C) or other elements. If these detoxification compounds mainly involve C, they may help alleviate elemental imbalances through disposing of excess C supplies that accompany elemental imbalances. Alternatively, excessive C demands could eventually lead to energy limitation and reduced nutrient use efficiency. If these detoxification requirements involve a non-C element in short supply, toxicity could exacerbate elemental limitation or impair repair in exposed organisms.

The presence of contaminants may also directly alter the nutritional quality of food resources available to both primary producers and consumers (figure 1, arrow 1). Numerous metals produce insoluble complexes with elements that are important nutritionally, such as P. For example, aluminum and phosphate form insoluble complexes, and so the presence of aluminum may reduce P supply and lead to skewed N:P ratios available to primary producers. This could result in increased P limitation of organismal growth and altered ecological processes (Kopácek et al. 2000, Clivot et al. 2014). Indeed, aluminum additions have been used to intentionally reduce P availability in lakes for 50 years, despite its known toxicity (Steinman and Ogdahl 2008, Brattebo et al. 2015).

Contaminants may also directly alter the C:N:P ratios of producers and consumers by altering their physiology (e.g., via increased maintenance costs associated with recovery from toxin exposure; figure 1 arrow 3). Das and colleagues (2014) found reduced C:P and N:P content of phytoplankton communities exposed to silver nanoparticles, whereas Cherchi and colleagues (2015) found opposite trends in the cyanobacteria, *Anabaena variabilis,* exposed to

Table 1. Examples of ecotoxicology studies that have examined stoichiometric mechanisms.

Effect	Contaminant	Biological model or ecological process	Stoichiometric parameter	Study scale	Type of ecosystem	Type of approach	Reference
Effects of the contaminant on dissolved nutrient availability and stoichiometry							
	Aluminum	n.a.	Mineral nutrient stoichiometry	Ecosystem	Freshwater	Observational	Kopácek et al. 2000
	Aluminum	Microbial decomposers	Mineral nutrient stoichiometry	Community	Freshwater	Microcosms	Clivot et al. 2014
Effects of basal resources stoichiometry on contaminant bioavailability in the medium							
	Silver nanoparticles	Zooplankton	Mineral nutrient stoichiometry	Individual	Freshwater	Microcosms	Conine and Frost 2017
Effects of the contaminant on basal resources C:N:P ratios)							
	Triclosan	Plant	Primary producers C:N:P ratios	Individual	Freshwater	Microcosms	Fulton et al. 2010
	Atrazine	Periphyton	Primary producers C:N:P ratios	Individual	Freshwater	Microcosms	(Murdock and Wetzel 2012)
	Silver	Microbial decomposers	Plant detritus C:N:P ratios	Community	Freshwater	Microcosms	Arce-Funck et al. 2013
	Silver nanoparticles	Phytoplankton	Primary producers C:N:P ratios	Community	Freshwater	Microcosms	Das et al. 2014.
	Titanium nanoparticles	Cyanobacteria	Primary producers C:N:P ratios	Community	Freshwater	Microcosms	Cherchi et al. 2015
	Isoproturon, Mesosulfuron	Plant	Primary producers C:N:P ratios	Individual	Freshwater	Microcosms	Nuttens et al. 2016
	Chlorpyrifos	Insect	Animal C:N:P ratios	Individual	Freshwater	Microcosms	Janssens et al. 2017
Effects of resources elemental composition on consumers tolerance to contaminants							
	Fluoxetine	Zooplankton	Primary producers C:N:P ratios	Individual	Freshwater	Microcosms	Hansen et al. 2008
	Triclosan	Plant	Mineral nutrient stoichiometry	Individual	Freshwater	Microcosms	Fulton et al. 2010.
	Glyphosate	Zooplankton	Primary producers C:N:P ratios	Individual	Freshwater	Microcosms	Lessard and Frost 2012
	Uranium, Arsenic	Plant	Mineral nutrient stoichiometry	Individual	Freshwater	Microcosms	Mkandawire and Dudel 2012
	Silver	Plant	Mineral nutrient stoichiometry	Individual	Freshwater	Microcosms	Bian et al. 2013
	Imidachloprid	Zooplankton	Primary producers C:N:P ratios	Individual	Freshwater	Microcosms	Ieromina et al. 2014
	Metolachlor	Plant	Mineral nutrient stoichiometry	Individual	Freshwater	Microcosms	Brooks et al. 2015
	Atrazine	Phytoplankton	Mineral nutrient stoichiometry	Population	Freshwater	Microcosms	Baxter et al. 2016
	Silver	Macroinvertebrate	Primary producers C:N:P ratios	Individual	Freshwater	Microcosms	Arce Funck et al. 2016
	Silver nanoparticles	Zooplankton	Primary producers C:N:P ratios	Individual	Freshwater	Microcosms	Conine and Frost 2017
	Cadmium	Macroinvertebrate	Primary producers C:N:P ratios	Individual	Freshwater	Microcosms	Arce-Funck et al. 2018
Effects of resources stoichiometry on consumers bioaccumulation of the contaminant							
	Cadmium, Copper	Phytoplankton	Mineral nutrient stoichiometry	Population	Freshwater	Microcosms	Wang and Dei 2006
	Mercury	Zooplankton	Primary producers C:N:P ratios	Individual	Freshwater	Microcosms	Karimi et al. 2007
	n.a.	n.a.	Primary producers C:N:P ratios	n.a.	Freshwater	Theoretical model	Peace et al. 2016
	Cadmium	Macroinvertebrate	Plant detritus C:N:P ratios	Individual	Freshwater	Microcosms	Arce-Funck et al. 2018

Table 1. Continued.

Effect	Contaminant	Biological model or ecological process	Stoichiometric parameter	Study scale	Type of ecosystem	Type of approach	Reference
Toward the use of stoichiometric approaches including non essential, potentially toxic elements							
	Diverse metals	Macroinvertebrates	Primary producers Multielemental ratios		Freshwater	Observational	Karimi and Folt 2006
	Cadmium, Copper	Phytoplankton	Mineral nutrient stoichiometry	Population	Freshwater	Microcosms	Wang and Dei 2006
Interactive effects of contaminants and stoichiometry on ecosystem functions or processes							
	Zinc	Leaf litter microbial decomposition	Mineral nutrient stoichiometry	Community	Freshwater	Microcosms	Fernandes et al. 2009
	Silver	Leaf litter microbial decomposition	Mineral nutrient stoichiometry	Community	Freshwater	Microcosms	Arce-Funck et al. 2013
	Atrazine	Periphyton primary production	Mineral nutrient stoichiometry	Community	Freshwater	microscosm	(Murdock et al. 2013)
	Silver nanoparticles	Phytoplankton primary production	Mineral nutrient stoichiometry	Community	Freshwater	Microcosms	Das et al. 2014
	Silver	litter decomposition by macroinvertebrate	Plant detritus C:N:P ratios	Individual	Freshwater	Microcosms	Arce Funck et al. 2016
	Cadmium	litter decomposition by macroinvertebrate	Plant detritus C:N:P ratios	Individual	Freshwater	Microcosms	Arce-Funck et al. 2018
Effects of nutrient stoichiometry on the production of toxic compounds by organisms							
	Plant secondary compounds	Plant	Mineral nutrient stoichiometry	Individual	Terrestrial	Literature review	Bryant et al. 1983
	Cyanotoxins	Cyanobacteria	Mineral nutrient stoichiometry	Population	Freshwater	Microcosms	van de Waal et al. 2009
	Plant secondary compounds	Plant	Mineral nutrient stoichiometry	Individual	Terrestrial	Field experiment	Rivas-Ubach et al. 2012
	Cyanotoxins	Phytoplankton or cyanobacteria	Mineral nutrient stoichiometry	n.a.	Freshwater	Literature review	van de Waal et al. 2014
	Cyanotoxins	Cyanobacteria	Mineral nutrient stoichiometry	Population	Freshwater	Micrososm	(Wagner et al. 2019)
	Plant secondary compounds	Plant	Mineral nutrient stoichiometry	Individual	Freshwater	Microcosms	Nuttens et al. 2016

nanotitanium dioxide. Fulton and colleagues (2010) working on the aquatic macrophyte, *Lemna gibba*, showed that triclosan (a common antimicrobial agent) caused changes in tissue C:P ratios, depending on the N:P ratio of the culture medium. Exposure to ionic silver has also been shown to reduce leaf litter microbial conditioning, resulting in higher leaf litter C:N and C:P ratio (Arce-Funck et al. 2013). Nutrient stoichiometry has also been shown to alter the toxicity of contaminants to plants (Fulton et al. 2009, Fulton et al. 2010, Mkandawire and Dudel 2012, Bian et al. 2013, Brooks et al. 2015), especially through changes in growth rate (Brooks et al. 2015). Finally, even consumers can exhibit altered stoichiometry when exposed to contaminants as seen in the larvae of the damselfly *Enallagma cyathigerum* (i.e., a food resource for predators), which had higher N:P ratios when exposed to the pesticide chlorpyrifos (Janssens et al. 2016).

Elemental resource supply affects the production of secondary toxic metabolites in plants and phytoplankton, which is further altered in the presence of anthropogenic contaminant exposure. Several studies have investigated the stoichiometry of plant secondary compounds, such as polyphenols (Bryant et al. 1983, Rivas-Ubach et al. 2012, Nuttens et al. 2016). For example, Nuttens and colleagues (2016) showed that higher N:P ratios in culture media led to lower concentrations of phenolic compounds in the aquatic plant, *Myriophyllum spicatum*, and that this effect disappeared when plants were exposed to the herbicide mesosulfuron. Elemental stoichiometry is also associated with eukaryotic and prokaryotic toxin production (van de Waal et al. 2009, 2014). As many of these toxins are N rich (i.e., low C:N), the concentration and supply ratios of C:N, and N:P influence the production of these toxins, with high N supply compared with demand increases N-rich toxin production (van de Waal et al. 2009, 2014). In turn, toxin production is sensitive to anthropogenic exposure. For example, *Microcystis* populations produce more of the cyanotoxin, microcystin-LR, when exposed to the antibiotic amoxicillin (Liu et al. 2014). These studies highlight the complex interactions between elemental supply ratios, secondary metabolic toxin production physiology, and their interaction with anthropogenic contaminant exposure.

Ecotoxicological investigations are often divided into two broad categories, studies of contaminant exposure (bioconcentration, bioaccumulation, biomagnification) and of contaminant effects (nonlethal and lethal), each of which can be influenced by stoichiometric constraints. The effects of elemental imbalances on metabolism could also alter the uptake (figure 1, arrow 3), biotransformation, and elimination of contaminants (figure 1, arrow 4) with implications for contaminant fate and toxicity. For example, the uptake of silver nanoparticles by algae, through an unknown mechanism, was higher under P-rich compared with P-poor conditions (Conine and Frost 2017). In this case, P-rich algae significantly reduced the toxicant concentration in water that, in turn, altered the toxic impacts on animal consumers. Contaminants may also alter the uptake of elements through modification of feeding behavior or digestive and assimilative processes (e.g., Frost and Tuchman 2005, Fulton et al. 2010). Several examples of this have been explored for *Daphnia*, which alters its feeding rates in response to P availability (Darchambeau et al. 2003, Karimi et al. 2007) and may therefore experience increased exposure to food-borne toxicants (Karimi et al. 2007). Stoichiometric constraints might also have indirect impacts on the bioaccumulation of contaminants by organisms. The bioaccumulation or bioconcentration of lipophilic toxicants can be affected by N or P limitation that cause the accumulation of lipid stores in both producers (Kilham 1998) and consumers (Wagner et al. 2015). Indirect effects have been investigated using both theoretical models (Peace et al. 2016) and experimental approaches (Wang and Dei 2006, Karimi et al. 2007, Arce-Funck et al. 2018). Those researchers concluded that well-balanced elemental resources increase organismal growth and dilute contaminants because of increased biomass.

Food quality and contaminants interact to affect the survival, growth, and reproduction of producers and consumers. For example, *Daphnia* feeding on a low P diet had a higher LC50 (lethal concentration required to kill 50% of the population) compared with those feeding on P-rich diets when exposed to fluoxetine (Hansen et al. 2008). Although it is unknown what mechanism provides this decrease in toxicity, it has also been displayed with *Daphnia* and other toxicants (e.g., glyphosate; Lessard and Frost 2012). However, elemental limitation does not always confer protection against toxicity in *Daphnia.* For example, elemental limitation increases toxicity when *Daphnia* were exposed to imidacloprid (Ieromina et al. 2014) and silver nanoparticles (Conine and Frost 2017). This food quality contaminant interaction is not specific to planktonic consumers and has also been found in a detritivore invertebrate, *Gammarus fossarum*. A higher tolerance occurred in *G. fossarum* consuming high P diets after an acute exposure to dissolved silver (Arce-Funck et al. 2016). Although feeding on high P resources during a chronic, environmentally realistic exposure to cadmium tended to synergistically increase the impact of the contaminant (Arce-Funck et al. 2018).

These examples highlight the need for controlled studies that examine each of the many factors (e.g., timing, nutrient, and contaminant concentration gradients, exposure duration) that may be important in understanding toxicity in a stoichiometric context. However, these examples also suggest that organismal responses to both stoichiometric and toxic stressors largely depend on the nature of the toxic compounds investigated, the duration of exposure, and the organism's biology. Coupled with these controlled studies, we see the importance of future studies aimed at understanding environmental gradients of chemical contaminants and complexity, particularly those substances with biological activities mechanistically capable of altering molecular targets (e.g., transporters, efflux pumps) and ecological functions in aquatic ecosystems (Rosi-Marshall and Royer 2012). Similarly, future studies could consider environmental gradients of elements, including conditions of elemental limitation and excess, that can alter growth rates, growth efficiencies, and the ability of organisms to withstand changes in maintenance requirements and other toxicant-induced stressors.

Ecotoxicology and the stoichiometry of populations and communities. Elemental imbalances in producers and consumers have strong effects on their population dynamics by altering population growth rates, maximum population size, and population permanency. Such stoichiometric effects could modify adverse outcomes elicited by contaminants at the population and community levels (figure 1, arrow 6). For example, populations of P-limited green algae are more sensitive to ibuprofen and less sensitive to common high blood pressure and epilepsy medications compared with P-replete algae (Grzesiuk et al. 2016). These indirect, elemental-driven differences in toxicity could alter biomass production in lower trophic levels and elemental food quality available for predators, which add to the direct effects of the elements themselves.

Different species are also known to exhibit varying sensitivities to elemental imbalances or contaminants, which will alter species composition in food webs and community-level interactions (figure 1, arrow 11). For example, antibiotic exposure of a microbial community found on decomposing leaves resulted in a community shift in favor of fungi over bacteria (Bundschuh et al. 2009). The antibiotic-exposed leaves with more fungi were then preferentially consumed by invertebrate shredders, which suggests interactive effects of elements and toxicants on the population and community dynamics of heterotrophic food webs (Bundschuh et al. 2009). Changes in population size either from poor nutrition associated with elemental imbalances or from chemical toxicity may also affect the total uptake and sequestration of contaminants with subsequent effects on the exposure of other organisms (figure 1, arrow 8). Based on our reading of the literature, community-level effects of stoichiometric toxicology are perhaps the least studied among the different levels of biological organization.

Ecosystems and stoichiometric ecotoxicology. The field of ecological stoichiometry has long studied how changes in the elemental nutrition of animals could affect the rate and ratios of elemental cycling (figure 1, arrow 5), which feed back into the supply of elements available at the base of the food web (figure 1, arrow 7; Elser and Urabe 1999). Similarly, toxic chemicals may alter metabolic states or the elemental assimilation and excretion, with effects on the rate and ratios of elemental recycling (Taylor et al. 2016). Although this could be because of direct changes in organism metabolism, it may also be mediated through changes to populations (figure 1, arrow 9) or community composition (figure 1, arrow 10) as different life stages and species may have distinct stoichiometries (Back and King 2013, Bullejos et al. 2014).

The transfer of energy and matter across habitat boundaries, such as from aquatic to terrestrial communities is well documented. Classic examples include aquatic insect emergence being fed on by riparian spiders (Kato et al. 2003, Marczak and Richardson 2007) and birds (Murakami and Nakano 2002), or reciprocal transport from land to water by terrestrial insects feeding trout (Nakano and Murakami 2001) and hippopotamus transfer of savanna grassland nutrients to sub-Saharan African streams (Sabalusky et al. 2015). Given the breadth of knowledge linking nutrient availability to population and community structure, as is detailed above, it is apparent that C:N:P ratios of basal resources likely influence organism and material movement across habitat boundaries. Ecotoxicology can be linked to these subsidies as organically bound contaminants (e.g., PCBs, Walters et al. 2008, 2009) often accompany these movements of organisms. However, to date, few studies have investigated questions related to these potential connections (Fernandes et al. 2009, Arce-Funck et al. 2013) between biomass and composition of organisms and toxins or toxicants, and the nutrient stoichiometry of food resources. There is therefore a need to better understand how stoichiometric mechanisms may alter the results of ecotoxicological studies at the community and ecosystem levels.

Modeling advances in stoichiometric ecotoxicology

Throughout its history, mathematical modeling has been a powerful tool with aims to provide ways to organize ideas, develop hypotheses, and offer a qualitative understanding of complex systems while making useful predictions. Although traditional ecotoxicological mechanistic modeling efforts take a variety of approaches to predict the effects of diverse chemical contaminants on organismal responses (usually survival, growth, and reproduction), many models assume, implicitly or explicitly, a nutrient-rich environment in which elemental limitation is absent (Newman and Clements 2007). This assumption of a nutrient-replete environment likely reflects the norm for empirical ecotoxicity studies, as was noted above, where nutrient media (in the case of plants, cyanobacteria, and algae) or food (for invertebrates and fish) is sufficiently nutrient rich to not overtly stress model organisms. In contrast, ES models explicitly include elements to discover how the elemental composition of organisms shapes their ecology, population dynamics, and ecosystem function (Sterner and Elser 2002). These models have not generally considered contaminant effects on the causes and consequences of elemental imbalances on organisms. In the present article, we present brief overviews of models in these two fields, consider recent modeling efforts that aim to integrate them, and discuss future directions.

Ecotoxicological modeling. The development of ecotoxicological models over the last few decades has significantly contributed to interpreting how contaminants move and accumulate throughout aquatic foods webs, as well as how they affect organisms (Hallam and De Luna 1984, Mackay et al. 1992, Gobas 1993, Ankley et al. 1995, Kooijman and Bedaux 1996, Wang et al. 1996, Arnot and Gobas 2004, Arnot and Gobas 2006, Pieters et al. 2006, Ashauer et al. 2007, Ashauer and Brown 2008, Wang et al. 2008, Bontje et al. 2009, Borgå et al. 2014, Huang et al. 2014, 2015, Huang and Wang 2016). These models take a variety of approaches ranging from steady-state models of simplified systems with one to two ordinary differential equations to more complex size-structured systems of partial differential equations. Although some of these models focus solely on contaminant exposure (i.e., Arnot and Gobas 2006 balance uptake, assimilation, and elimination processes to model bioaccumulation and Wang et al. 1996 use kinetic models to predict the bioaccumulation of trace elementals in mussels), many models simultaneously model both contaminant exposure and effects (i.e., Huang et al. 2015 dynamically modeled contaminant concentrations in organisms and how these body burdens affected population dynamics). One of the best-tested modeling frameworks systematically applied in ecotoxicology follows dynamic energy budget (DEB) theory and has been included in international risk-assessment guidance for its relevance in analyzing ecotoxicity data (Jager et al. 2014a). Although DEB theory describes energy flows within an individual organism (Nisbet et al. 2000, Kooijman and Kooijman 2010), it aims to capture the quantitative aspects of metabolism and is explicitly based on the principles of conservation of energy and mass (Sousa et al. 2010). The model can be applied and adapted to any organism with changes in species-specific parameters. A recent Scientific Opinion article for the European Food Safety Authority noted the potential applicability of DEB models coupled to toxicokinetic or toxicodynamic effect models for regulatory risk assessment (Ockleford et al. 2018).

The Add My Pet online database serves as a curated and constantly expanding inventory of DEB parameters for thousands of species (www.bio.vu.nl/thb/deb/deblab/add_my_pet/index.html, 2653 species, November 2020). The standard model describes how an organism ingests food, assimilating some of the food as energy, and egesting the rest. Inside the organism, the assimilated energy is stored in reserve components from which the organism allocates energy toward two branches: growth and somatic maintenance and maturation or reproduction and maturity maintenance. The independence of the reserve dynamics of food availability is a key aspect of DEB theory and provides the individual with some protection against environmental fluctuations and some control over its own metabolism (Sousa et al. 2010).

Contaminant effects are integrated into DEB models (nicknamed “DEBtox”; see Jager and Zimmer 2012 and Jager 2016) either by allowing a toxicant to affect (change the value of) DEB parameters (e.g., Jager et al. 2014b) or through the addition of submodels that connect the DEB model to toxicant processes (Klanjscek et al. 2012, 2013). Moreover, DEBtox has been used to investigate the effects of multiple stressors at population and ecosystem scales. When stressors (e.g., food and contaminant) interact, they can have different effects (depending on the mode of action) at higher levels (individual, population, or ecosystem) compared with the stressor in isolation, as was demonstrated for *Daphnia* models by (Martin et al. 2014). It is unknown a priori if the effects will be additive, synergistic, or antagonistic (Galic et al. 2018). In Galic and colleagues (2017), for example, the exposure to toxicants targeting maintenance, feeding, and reproduction on a freshwater amphipod (*Gammarus pseudolimnaeus*) disproportionately weakened consumer–resource interactions under warming at the ecosystem level but had no effect at the population level.

Although these ecotoxicology modeling efforts have enhanced understanding and improved predictions of the adverse effects of contaminants, they may neglect to incorporate stoichiometric constraints. On the other hand, the following section describes stoichiometric modeling approaches, which have largely been developed without considering contaminant stressors.

Ecological stoichiometric modeling. An approach often used to study the effects of elemental imbalances on plants, animals, and microbes involves tracking the intake, acquisition, and release of multiple elements simultaneously. These models explicitly incorporate a mass balance perspective insomuch that elements acquired in excess of growth, reproduction, or maintenance will be released (Frost et al. 2004, Frost and Tuchman 2005). Following this, element-specific uptake or consumption can be coupled with elemental use for new biomass or maintenance to yield estimates of an ideal resource mixture that maximizes growth or reproduction (Sterner 1997, Frost and Elser 2002, Anderson and Hessen 2005). By altering the elemental mixture available for acquisition, these models yield predictions about the strength and direction of elemental constraints on organismal performance including slower growth, reduced reproduction, or alterations in nutrient release.

Elemental imbalances and their constraints across trophic levels have been incorporated into dynamical system models of population as well. Andersen (1997) took the classical Rosenzweig MacArthur variation of the Lotka–Volterra equations and incorporated nutrient-deficient growth by modifying the density dependence of the producer’s growth rate and the grazer’s growth efficiency. Following Andersen’s approach, Loladze and colleagues (2000) formulated a producer–grazer model (LKE model) of the first two trophic levels of an aquatic food chain (algae–*Daphnia*) that incorporated the assumption that both producers and grazers are chemically heterogeneous organisms composed of two essential elements, C and P. The model allows the P:C of the producer to vary above a minimum value but restricted the P:C variation in grazer biomass. Introduction of these stoichiometric constraints significantly affects the population dynamics and stability properties of the system, such as exhibition of the paradox of “energy enrichment” empirically supported by Urabe and colleagues (2002).

The growing library of models that have extended the LKE model under the theory of ES is mechanistic and robust. These models have incorporated dynamical consequences of elemental limitation (Loladze et al. 2000) and effects of elements in excess (Peace et al. 2013). They have also been expanded to incorporate multiple elements (Grover 2002, 2003, 2004) and two competing species (Loladze et al. 2004, Xie et al. 2010). They can explicitly track free elements in the environment (Wang et al. 2008, Peace et al. 2014), and determine important trophic transfer efficiencies (Peace 2015). The ES modeling framework has been expanded to include spatial dynamics (Rana et al. 2018), incorporate multistage dynamic processes (Jiang et al. 2019), and capture evolutionary dynamics (Yamamichi et al. 2015). These stoichiometric models incorporate the effects of both food quantity and food quality into a single framework that produces rich dynamics (i.e., stabilizing predator–prey systems) and allow more than one predator species to coexists on a single prey, producing multiple basins of attraction and bistability, exhibiting multiple types of bifurcations, and allowing evolutionary rescue. This ES modeling framework applies equally to phenomena at suborganismal levels as well as the whole biosphere level (Sterner and Elser 2002). Despite these advances, we have found that models developed under the ES framework typically disregard the effects of contaminants. The above brief summaries highlight the fact that many modeling efforts in ecotoxicology and ES have largely been developed separately. Below we discuss the opportunities for theoretical approaches to better integrate these two fields within single modeling frameworks.

Stoichiometric ecotoxicological modeling. Although there are modeling efforts that consider contaminant stressors along with element limitation (i.e., Bontje et al. 2009, Ankley et al. 1995), these models are not explicitly stoichiometric and do not allow for multiple elemental constraints where the element limiting growth can change with environmental element and light availabilities. In the present article, we propose integrative modeling frameworks with promising potential to explicitly incorporate elements and contaminants as well as integrative effects between them.

Existing theoretical frameworks in ES and ecotoxicology actually have similar structures but they use different perspectives. For example, ES uses an element perspective to develop mass-balance models of threshold elemental ratios (i.e., Frost et al. 2004, Frost and Tuchman 2005) and

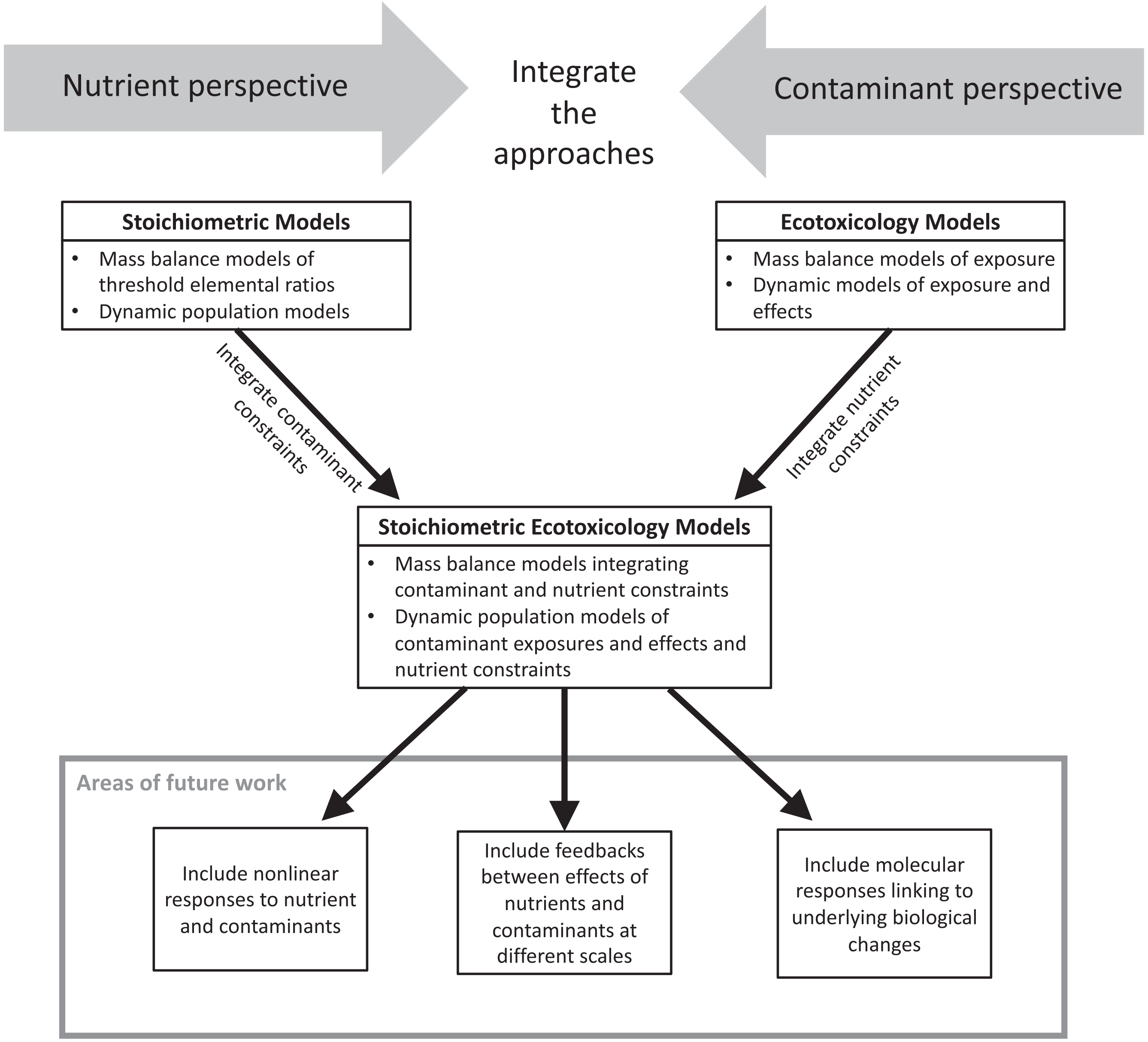

Figure 2. Proposed integrative modeling frameworks have promising potential to explicitly incorporate nutrients and contaminants, as well as integrative effects between them. Stoichiometric ecotoxicology models can then be extended to incorporate and guide areas of future work listed in the grey box.

ecotoxicology uses a contaminant perspective to develop mass-balance models of bioaccumulation (i.e., Gobas 1993). Although the mass-balance modeling approaches in the present article are similar, they employ different assumptions on parameters as the biological regulation of elements can significantly differ from regulation of contaminants. Both fields use dynamical population models, where ES uses a nutrient perspective to track essential elements throughout food webs and their influence of population dynamics (i.e., Loladze et al. 2000) and ecotoxicology uses a contaminant perspective to track the fate of contaminants throughout food webs and their effects on population dynamics (i.e., Huang et al. 2014, 2015). These modeling approaches can be unified by integrating contaminants into the ES models or by integrating nutrients into the ecotoxicological model as was shown in figure 2.

DEB theory offers a modeling framework with the potential to analyze ecotoxicological issues in which stoichiometry plays an important role. This would require a more detailed or explicit stoichiometric framework than is currently incorporated in DEBtox studies. The standard DEB model is the simplest, nondegenerated, model among a family of models (Marques et al. 2018) that describes the full life cycle of an animal feeding on a single food source with constant elemental composition. Therefore, this model does not generally incorporate or examine stoichiometric mechanisms per se. However, multiple-reserve (instead of single-reserve) DEB models have been developed to consider stoichiometry explicitly. Kooijman (1998) proposed a generalizable model of two reserves, specifically citing applications to element-limited algal growth, such as the classic Droop models (Droop 1974). Sperfeld and colleagues (2017) described a DEB model with separate nutrient reserves (C and N) coupled with metabolic pathways that may be affected by changes in C or N mass balance. DEB models that consider stoichiometric constraints have been developed for a wide variety of applications, ranging from tracing isotope flows (Pecquerie et al. 2010) to describing the symbiosis between coral and photosynthetic algae (Muller et al. 2009, Cunning et al. 2017) to analyzing stoichiometric constraints on population dynamics (Kuijper et al. 2004a, 2004b, Kooijman 1998, Kooijman et al. 2004). However, to our knowledge, no study has used a stoichiometrically explicit DEB model to explain or predict ecotoxicological responses or adverse outcomes.

ES offers a complementary modeling framework to investigate the influence of elemental imbalances on responses of organisms to contaminants while simultaneously considering the effects of contaminants on ecosystem processes (Danger and Maunoury-Danger 2013). Toxicity could be incorporated into ES models by altering functions of organismal nutrient intake or by changing element–metabolism relationships with chemical exposure. For example, Frost and Tuchman (2005) used this type of model to demonstrate how reduced growth and increased element release rates from two benthic invertebrates resulted from lower assimilation efficiencies in animals consuming nutrient-poor leaf material grown under elevated carbon dioxide concentrations. Peace and colleagues (2016) and Hassan and colleagues (2018) developed models that incorporated the effects of concurrent element and toxicant stressors on population dynamics and the trophic transfer of toxicants. These authors dynamically model the bioaccumulation of toxicants under varying nutrient resources, capturing stoichiometric contaminant exposure dynamics, and incorporating the effects of toxicant and nutrient stressors into growth dynamics. In these models, elemental changes in the environment affect organismal growth rates and therefore population dynamics, which can drive changes in contaminant concentrations within the organisms. In addition, these authors captured and explored a phenomenon called the somatic growth dilution effect, observed empirically (Karimi et al. 2007), in which organisms experience a greater than proportional gain in biomass relative to toxicant concentrations when consuming food with high nutritional content versus low quality food. In addition to influencing life-history traits, specific contaminants can affect organism elemental composition (Danger and Maunoury-Danger 2013, Ni et al. 2017, Baudrot et al. 2018). Future model iterations should consider the impact of contaminants on organism elemental compositions. Although there have been few toxicological applications, ES models appear to have considerable potential to significantly improve our understanding of the effects that chemical contaminants have on organisms and ecosystems (Hansen et al. 2008).

Areas of future research

Organisms, populations, communities, and ecosystems all function in a world of contaminant and nutrient mixtures. With recent developments in the application of ES models, we are now at a point at which we can aim for a more mechanistic understanding of the combined effects of contaminants and elements at each level of biological organization. To achieve meaningful advances, some of the fundamental discoveries and models developed in the fields of ES and ecotoxicology should be considered and, if possible, merged into a unified framework, as is proposed in figure 2. These considerations could include determining nonlinear responses to elements and contaminants and their interactions, potential feedback loops between the effects of elements and contaminants at different scales, and integrating molecular responses to better link to and understand the underlying associated biological changes. The first steps would help define an integrated conceptual framework and inform specific research goals to advance our understanding of the effects of contaminant–nutrient combinations that more closely reflect natural environments.

Nonlinearities in the effects of individual elements and contaminants could alter our predictions of interactions between these substances. At the organismal level, nonlinear physiological responses to individual contaminants have been well documented for decades. A classic example is the hormesis response in which organisms exhibit a positive response to a contaminant at low doses and a negative, deleterious response at higher levels (Calabrese and Baldwin 2002). More recent work suggests biological adaptation as a potential mechanistic explanation for the otherwise phenomenological hormetic response (i.e., the U-shaped dose–response curve; Calabrese and Mattson 2017). Another landmark study examined and defined nonmonotonic responses to a suite of endocrine disrupting contaminants (Vandenberg et al. 2012). Classic models highlight nonlinearities in physiological responses to essential and nonessential metals (Karimi and Folt 2006). Recent work also suggests that nonlinearities are not limited to toxicants and can also occur in response to variable element (e.g., P and N) regimes. Specifically, high inputs of N and P can cause negative effects in forms that are not otherwise explained by other nutrient deficiencies and that would not be expected on the basis of ES theory (Costello et al. 2018). Additional studies are needed to understand the negative effects of high element doses, particularly as global element supplies continue to increase, and eutrophication of diverse ecosystems become more evident (Howarth 2008, Glibert 2017). Overall, nonlinear responses are neither rare, nor limited to certain types of substances, particularly when substances interact with multiple biological targets, and therefore have high potential to influence the combined effects of multiple nutrients and contaminants. Therefore, there is a need to develop predictive models that examine and explain the influence of nonlinear responses on the combined and interactive effects of multiple substances.

Nonlinear interactions and dynamics illustrate how complexities in the behavior and effects of elements and toxicants pose a challenge for how we distinguish among different types of substances. In some cases, substances considered to be elements function more like contaminants (Karimi and Folt 2006, Stumm and Morgan 2012). Several different classification systems exist that attempt to make clear, useful distinctions among types of substances on the basis of different characteristics. For convenience in the present article, we have used perhaps the most simplistic classification system, which is composed only of nutrients versus contaminants. However, developing a unified framework that combines knowledge from the ES and ecotoxicology fields requires us to revisit common classification systems in terms of how they may help us understand the behavior and effects of elements and toxicants in mixtures. This would help us organize and predict potentially complex, higher-order interactions among substances. Part of this framework could be mediated through a better understanding of the molecular components involved in the processes underlying element and toxicant effects as was described by the various DEB processes. Well-known examples of such systems include classes of metals (e.g., class A, class B); macroelements, essential trace metals, nonessential trace metals (Karimi and Folt 2006, Karimi et al. 2010); organic contaminant functions based on K_{ow} values; and contaminant functions based on specific molecular interactions. Moving toward a stoichiometric ecotoxicology framework requires us to define substances in ways that help us understand whether there are emergent patterns in how different types of substances interact and are organized at different scales.

A recent development in ecotoxicology to conceptualize big-picture impacts of contaminants has been made through the adverse outcome pathway (AOP) framework (Ankley et al. 2010). This framework could offer a way to classify substances in the context of stoichiometric ecotoxicology and connect biological scales. AOPs have been developed to conceptualize the knowledge linking a molecular initiating event of a contaminant to an adverse outcome at a relevant level of biological organization via key events and key event relationships. They can be used to link molecular responses to underlying biological changes, an area of future work identified in figure 2. Key events can occur at any level of biological organization and can be connected to DEB processes (Murphy et al. 2018a, 2018b). Traditional AOPs are chemically agnostic and encode causal, not quantitative, relationships. However, the development of quantitative AOPs (qAOPs) is an emerging field (Perkins et al. 2019). In qAOPs, quantitative key event relationships, such as dose–response and response–response relationships, can be influenced by ecotoxicological context through modulating factors (Conolly et al. 2017). Modulating factors alter quantitative key event relationship between two key events, such as to change the shape of a response–response relationship. Examples of modulating factors include the impact of environmental, genetic, disease, or nutritional variations on the key event relationship (Villeneuve et al. 2014). Informing appropriate modulating factors by nutrient–chemical interactions and relationships studied in stoichiometric ecotoxicology will serve to refine quantitative relationships in qAOPs. Connecting the established frameworks of DEB modeling and AOPs in circumstances where elements might behave as stressors (under nutrient limitation or in excess) or where contaminants behave as nutrients (e.g., hormesis at low doses) could improve the classification, downstream modeling, and prediction of emergent properties.

Future work is also needed to examine potential feedback loops among nutrient and contaminant exposures at different levels of biological organization. For example, contaminant exposure at the organismal and population level may influence element cycling at the ecosystem level by changing organism physiological processes (e.g., growth and excretion). In turn, element cycling may also affect contaminant toxicity, through somatic growth dilution and reductions in bioaccumulation (Karimi et al. 2007). To date, very little is known about the extent, strength, and type of such feedback loops and the circumstances under which they may occur. Such questions are particularly important to address to understand changes in contaminant and element inputs to ecosystems, including increases in nutrient pollution to aquatic systems.

There is also a need to examine the combined effects of element and contaminant exposure on organisms across age, size, or life stages. Mathematical models have been used to incorporate stage structure into population dynamics. Structured population models are able to incorporate additional complexity related to an additional variable, such as age, size, or life stage. These come in the form of discrete matrix equations (Leslie 1947), systems of ordinary differential equations, or continuous partial differential equations (Sinko and Streifer 1967). Within the context of ecotoxicology, systems of differential equations may include multiple compartments representing various stages of the life cycle and, correspondingly, different effects of toxicants on the stages of the life cycle. These models can include density-dependent effects of populations. It is straightforward to incorporate ecotoxicological effects for the various life stages in a matrix model (Emlen and Springman 2007, Erickson et al. 2014) or a system dynamics model (Weller et al. 2014). Furthermore, these models can easily be extended to model nutritional stress (Caswell 2006, Hanson and Stark 2011, Weller et al. 2014).

Continuously structured population models can be useful as they are more computationally stable when estimating parameters that are dependent on time or the structured variable. There are many continuously structured population models that incorporate food availability

(Ananthasubramaniam et al. 2011), and some that implicitly consider food quality (Nisbet and Gurney 1983). However, explicit modeling of stoichiometric constraints could be explored further within this framework. Ecotoxicological effects also could be integrated with continuously structured population models. Recently, however, Huang and Wang (2016) proposed a toxin-mediated size-structured population model allowing for different sensitivities to toxicants depending on size, age, and so on.

Incorporating stoichiometric ecotoxicology into management decisions. Advancing stoichiometric ecotoxicology promises to help reduce uncertainty during environmental risk assessment and management activities. This may be particularly true for extrapolations across laboratory to field scales of biological organization, which remain among the biggest research needs to achieve a more sustainable environment (Furley et al. 2018, Van den Brink et al. 2018). Brooks and colleagues (2015) recommended accounting for stoichiometric influences on aquatic ecotoxicology studies with plants and algae by balancing experimental pragmatism with environmental realism. Traditional ecotoxicology assays were developed to ensure sufficient growth of primary producers, which represents a common endpoint to understand adverse outcomes of contaminant exposures. To predict real-world outcomes, future research on ecotoxicology needs to be more representative of field-relevant elemental gradients. If nutrient assimilation and elemental ratios of lower trophic levels are modified, those changes will cascade into changes in interspecific competition, the efficiency of secondary production, and community composition.

We also propose better development and use of knowledge about how stoichiometric conditions influence the production of natural toxins by aquatic and terrestrial organisms. This is of particular relevance to ecological risk assessments in inland and coastal waters, where harmful algal blooms (HAB) can elicit profound impacts on aquatic life and public health and often surpass anthropogenic chemical risks (Glibert 2012, 2017). In fact, HABs are now recognized as transformative threats to water quality and confounders of environmental assessment and management efforts, which often rely on risk-based regulatory frameworks for the protection of public health and the environment (Brooks et al. 2016). Whereas ecological studies and monitoring activities have previously examined toxin concentrations, these efforts are routinely limited by the absence of robust analytical quantitation of diverse toxins produced by specific HAB species. This represents a critical consideration for water resource management because HAB forming species are assumed to be producing toxins even if measured toxins are below detection limits. These conservative measures decrease the exposure of toxins but may come at an unnecessary cost. Although water quality models can predict the occurrence, intensity, and severity of HABs, by not incorporating toxin production these models cannot predict the risks to human or ecosystem health. Developing predictive growth, toxin production, and comparative toxicity models across stoichiometric nutrient gradients are imperative for forecasting, diagnosing, and preventing ecological and human health risks presented by algal toxins (Brooks et al. 2016).

Conclusions

In the present article, we refer to the integration of ecotoxicology and ES theory as stoichiometric ecotoxicology. The conceptual framework for stoichiometric ecotoxicology that we have developed highlights the interactive impacts of elemental imbalances and chemical contaminants within and across scales from suborganismal to ecosystems. This conceptual framework was built from existing empirical and theoretical examples that link stoichiometry and toxicology. Although an increasing amount of stoichiometrically explicit models have provided insight into ecological interactions, there is much to be gained by incorporating concurrent nutrient and toxicant stressors into models formulated under the presented stoichiometric ecotoxicology framework. This unifying framework offers the potential to deepen mechanistic understanding of the adverse outcomes of chemicals across ecological scales and improve the predictive powers of ecotoxicology.

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