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Greening Chemistry and Ecotoxicology Towards Sustainable Environmental Quality

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Abstract

Pursuit of sustainable environmental quality is a noble goal, but global megatrends, highlighted by concentration of chemical use in cities faster than implementation of waste management systems, present emerging risks to public health and the environment. Step changes in global environmental assessment and management activities are necessary. Herein, integration of green chemistry with ecotoxicology, which has matured to a mechanistic science, promises to reduce exposures to hazardous substances and support pursuits of the United Nations Sustainable Development Goals. Integrative, comparative and predictive toxicology efforts, if advanced across models, species and scales of biological organization, can catalyze the work of chemists and engineers engaging sustainable molecular design for reduced environmental hazard.

I. Green Chemistry and Ecotoxicology on an Urban Planet

Don't get lost in the numbers. We live on an urban planet. Most people now live in cities, and in 2050, when ~9.8 billion humans occupy Earth, 70% of the human population will reside in urban areas – over one third of all people will live in China and India. By 2030, this global megatrend will be pronounced with 22 megacities in Asia-Pacific alone. Of particular relevance to urbanization, the United Nations Sustainable Development Goals (SDGs) for 2030 aim to protect the planet while delivering prosperity for all.[1] SGD 11, which focuses on sustainable cities and communities, specifically aims to "reduce the adverse per capita environmental impact of cities, including by paying special attention to air quality and municipal and other waste management." [1]

Achieving the SDGs will require unique partnerships. At a time when concentration of humans is occurring unlike any other time in history, resource consumption, including chemical use, is also being concentrated in cities, and it is happening faster than environmental management systems and environment and health interventions can be implemented.[2] Further, the global frequency and magnitude of disasters are increasing,[3] which presents ecological risks when these natural (e.g., hurricanes) and anthropogenic (e.g., chemical spills) events occur. It is therefore clear that advancing principles of green chemistry and green engineering are necessary to realize a number of the SDGs[2,4] by reducing chemical risks to public health and the environment. But we must do so through intentional integration of green chemistry with other disciplines required for assessment and management of environmental quality.

Defined as "The science of contaminants in the biosphere and their effects on constituents of the biosphere, including humans",[5] ecotoxicology is an exceptionally synthetic field, which draws from diverse disciplines in the physical and life sciences. Imbedded in numerous national and international policy instruments, translational science from ecotoxicology

is fundamental for prospective examination of new substances and retrospective field studies of ecological integrity to prioritization of chemicals for experimentation and contaminated sites for restoration. Ecotoxicological applications initially facilitated development of and are currently transforming the practice of environmental protection and pollution prevention. Notable contributions include implementation of a water quality based approach through the U.S. Clean Water Act and routine surveillance of environmental quality for protection of public health and the environment. Further, ecotoxicology provides a theoretical foundation necessary to realize common ecosystem protection goals, including ecosystem services and biodiversity. Historically considered as descriptive exercises by some, ecotoxicology has decidedly matured to a mechanistic science. For example, the adverse outcome pathway (AOP) framework, which links chemical properties with molecular initiation events that may or may not cascade across levels of biological organization to adverse outcomes at the individual and population levels, now represents a major trajectory in toxicology, yet originated from mechanistic ecotoxicology.[6] Similarly, problem formulation, which represents the initial step within an ecological risk assessment, a common translational exercise and ecotoxicology application, is increasingly integrated within human health risk assessment practice. [7]

As a graduate student I became fascinated during studies of the urban water cycle with ecotoxicology, environmental chemistry and risk assessment.[8] Little did I appreciate then that these interests would quickly lead to green chemistry. But when we identified bioaccumulation of human antidepressants and their metabolites in multiple fish species from an urban river for the first time,[9] attention from the scientific community and media followed.[8] Subsequently, during a 2003 interview on National Public Radio's *Science Friday* in the U.S., I was asked what can be done to lessen the impacts of pharmaceuticals (and more broadly other substances) in

urban areas. I submit now, as I did then, that green chemistry and engineering are critically important.

Environment and health disparities exist around the world. Though my initial green chemistry interests were shaped by studying urban rivers with instream flows dominated by or even dependent on effluent discharges from municipal sewage treatment plants, [10] it is important to consider that over 80% of global sewage goes entirely untreated and is returned to rivers, lakes and estuaries.[11] These reclaimed waters are subject to reuse by ecosystems and diverse human uses, including for terrestrial irrigation of agricultural fields and to support aquaculture.[12] Aquaculture is growing 3-5 x faster than terrestrial agriculture and must continue to increase to meet future global food demands,[13] yet emerging chemical contaminant exposures to wildlife and humans from such practices are routinely poorly characterized. [12] For example, existing environmental occurrence data for diverse classes of contaminants are often lacking for major geographic regions[14-18] where "nontraditional waters" from urban discharges are reused for aquaculture.[12] Implementation of wastewater treatment infrastructure and environmental management systems necessary to universally achieve SDG 11 and other goals will not be realized by 2030; therefore, green chemistry advances with ecotoxicology are essential to achieve a number of the SDGs and more sustainable environmental quality. It is not surprising that priority environmental quality research questions for integration of green chemistry and ecotoxicology were recently identified during Global Horizon Scanning exercises in Latin America[19] and in Europe.[20]

The fourth principle of green chemistry states, "Chemical products should be designed to preserve efficacy of function while reducing toxicity." [21] Unfortunately, as noted by Erythropel et al.,[22] principle 4 is one of the least developed 12 principles. However, chemicals labeled as

persistent organic pollutants, priority pollutants, persistent, bioaccumulative and toxic chemicals, and contaminants of emerging concern represent important opportunities for green chemistry. This is important because when problematic chemicals are identified by regulatory programs, then risk management in developed countries commonly includes removal of these substances from commerce. Ideally, undesirable properties of such compounds are determined prior to market introduction by businesses and government agencies. For example, persistence and bioaccumulation evaluations include parameters related to exposure, which should consider magnitude, frequency, duration and bioavailability. Toxicity information, however, is necessary to define hazard – chemical risk is of course a function of exposure and toxicity. Substitution of persistent, bioaccumulative and toxic compounds with alternative replacements that possess or are designed de novo with inherent properties yielding less hazardous profiles becomes a noble pursuit.[23,24] In particular, sustainable molecular design of substances with lower hazards presents profound opportunities to advance the science, fuel innovation and reduce environmental introductions of harmful substances.[25] Below I explore common attributes of environmental organic contaminants and identify several research needs associated with integration of green chemistry with ecotoxicology.

II. Persistence

Chemical persistence designations by regulatory agencies result from experimental studies or modeling predictions for specific chemicals relative to predetermined cut-off values. An organic chemical is often considered unacceptably persistent in water, soil or sediment if its environmental half-life ($t_{½}$) is greater than 60 days and is labeled as very persistent if the $t_{½}$ is > 180 days. It is

important to recognize that these cut-off values are not scientifically based per se, but instead represent policy decisions made pragmatically to partition the chemical universe among substances with relatively low to high environmental persistence profiles. In practice, however, whether such cut-off values remain appropriate has received less attention, particularly for urban regions.

Recall the surface waters mentioned above in which instream flows routinely depend on discharge from wastewater treatment plants. Though a number of these water bodies exist[10,26] and are now recognized as important systems for management given predictions of climate change[27], it is instructive to consider the current chemical persistence construct and the relevance of common cut-off values in these systems. The effluent-dominated Trinity River in Texas, USA, is essentially a de facto water reuse project because it connects two rapidly growing, highly populated urban areas in North America, Dallas/Ft Worth and Houston. River flows downstream from Dallas are > 98% wastewater effluent,[10] which then travel several hundred kilometers downstream to Lake Livingston, the first reservoir impounding the Trinity River downstream from Dallas and an important drinking water supply for Houston. Typical travel times in this system are ~2 weeks,[28] a much shorter period than typical regulatory t½ cut-off values of 60 and 180 days for chemical persistence in water.[29] Therefore, in a system like the Trinity, exposure of wildlife and other downstream uses over hundreds of kilometers to chemicals not presently identified as persistent by regulatory agencies are effectively so because of constant releases from upstream urban areas.

Effective exposure durations[30] of consumer chemicals are increased in these effluent-dominated and dependent systems because pseudo-continuous introduction rates from effluent discharges exceed instream rates of degradation for many chemicals. Yet unlike so many parts of the world with limited or absent wastewater infrastructure, the Trinity River system includes relative advanced secondary treatment infrastructure. Given global trends in urbanization and concentration

of chemical use coupled with limited wastewater treatment capacity, the current persistence paradigm appears quite meaningless for many urban areas. Environmental persistence determinations should thus be redeveloped (i.e. shortened) for these urban systems – this represents a timely and necessary research need for the development of less persistent chemicals. Further, research is needed to advance sustainable design of chemicals likely to be more rapidly biologically degraded in aquatic and terrestrial systems. Though green chemistry efforts to enhance biodegradation has been pursued, particularly for ionic liquids,[31] Green Chemistry Principle 10, or design for degradation ("Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment."),[21] remains largely understudied but can be informed with iterative toxicity assays during research and development.[32,33] Herein, engagement by computational and organic chemists with environmental chemists, engineers and ecotoxicologists is necessary to design substances more amenable to direct and indirect photolysis and to biodegradation, which could effectively reduce exposure magnitude and duration in urban aquatic ecosystems.

III. Bioaccumulation

Another opportunity for green chemistry with ecotoxicology is the need to design less bioaccumulative substances. Historically, lipophilicity was identified a key parameter to predict which organic contaminants were likely to bioaccumulate. Empirical bioconcentration relationships with log K_{ow} (octanol – water partitioning coefficient) for substances from various chemical classes were initially developed, then incorporated within quantitative structure activity

relationship models to predict bioconcentration factors (BCF). For example, a common BCF equation[34] is given in Eq. 1.

$$\log \mathrm{BCF} = (0.85 * \log K_{\mathrm{ow}}) - 0.7 \qquad \text{Eq. 1.}$$

By describing hydrophobic driven partitioning, this model accounted for absorption of nonionizable organics, but not chemical distribution, metabolism and excretion (ADME), which collectively influence bioaccumulation. Yet such advances by Veith and others were foundational at the time because empirical bioconcentration data did not exist for most contaminants. Unfortunately, this reality persists today, and even when bioconcentration data does exist for a specific chemical, it is rare to encounter such information for organisms from different trophic positions of representative food chains in terrestrial or aquatic habitats. Because these original approaches did not account for distribution, metabolism, excretion or biomagnification, factors that can increase or decrease risks to public health and the environment, uncertainties exist during bioaccumulative determinations. For example, compounds with high log K_{ow} values are historically predicted to have high BCFs, but are often more readily metabolized by fish.[35] Further, translating laboratory based predictions of bioaccumulation and biomagnification to the field has been identified as a pressing research need.[20] In addition, contaminant metabolism among species remains largely unknown for the chemical universe.[12]

Consider per- and polyfluoalkyl substances (PFAS) and pharmaceuticals as examples of contaminants inadequately assessed by traditional bioaccumulation approaches. Bioaccumulation of PFAS are importantly influenced by protein binding dynamics in aquatic organisms, diminishing the relative importance of traditional partitioning constructs to lipids. If quantitative

structure activity relationships (QSARs) based on log K_{ow} are applied to predict uptake and thus BCF values of PFAS in fish, then underestimation of bioaccumulation would result because protein binding is not considered and these substances fall outside the applicability domain of traditional BCF QSAR models. Similarly, it is important to consider elimination, not just uptake, of contaminants. In fact, BCF, as given in Eq. 2, is a kinetic relationship between uptake (k_1) and elimination (k_2).

$$\mathrm{BCF} = \frac{k_{1\ (uptake)}}{k_{2\ (elimination)}} \qquad \text{Eq. 2.}$$

In addition to metabolism, which is further discussed below, differential excretion profiles among PFAS can influence elimination and thus the magnitude of a BCF value for organic chemicals. For example, there is a marked difference in accumulation of PFOS (perfluorooctanesulfonate) and PFOA (perfluorooctanoic acid) by rainbow trout, apparently mediated through increased renal clearance of PFOA compared to PFOS by this common and commercially important fish model.[36,37] Unfortunately, such mechanistic bioaccumulation studies are not available for other PFAS and almost all other organic compounds, but designing substances that are more readily eliminated through biotransformation and excretion processes would markedly decrease bioaccumulative potential of industrial chemicals.

Prior to our studies with the urban systems and pharmaceuticals described above,[9, 38, 39] bioaccumulation of ionizable chemicals in the environment had received relatively limited attention.[40, 41] At first glance, increasing ionization by design appears to result in lower uptake and thus risks from bioaccumulation. However, our observations of ionizable pharmaceutical bioaccumulation by fish in urban rivers were interesting because: 1. the majority of human pharmaceuticals are ionizable compounds; 2. ionizable chemicals are typically less hydrophobic

than traditional nonionizable contaminants; 3. more pharmacokinetic information is available pharmaceuticals than other environmental contaminants; and 4. chemicals that are ionizable within environmentally relevant pH ranges found in surface water bodies represent an increasingly large piece of the global chemicals in commerce pie. Here again, because historic QSARs based on log K_{ow} were derived for nonionizable organics and lipid partitioning was presumed, ionizables fell outside the applicability domain of these traditional predictive approaches for bioaccumulation. We initially identified that bioaccumulation of ionizable base pharmaceuticals are not explained by lipid partitioning in fish.[39] Further, these substances do not appreciably biomagnify in surface waters,[42,43] partition in fish to a greater extent than predicted by log D_{ow} (octanol – water distribution coefficient) across pH gradients (in part due to differential protein binding[44]), and do not appear to be readily biotransformed *in vitro* by rainbow trout.[45] In fact, the importance of understanding bioaccumulation of ionizables has been identified as an important research need to reduce environmental risks of pharmaceuticals and personal care products.[46,47] Subsequently, bioavailability and bioaccumulation of ionizable environmental contaminants have received more recent attention.[48]

When BCF cut-off values used for regulatory determinations of potentially bioaccumulative chemicals are considered, global bioaccumulation approaches require further attention. A chemical is routinely considered bioaccumulative when its BCF is greater than 1,000 or it is identified as very bioaccumulative if the BCF is ≥ 5,000. But BCF values for the PFAS compounds described above routinely fall below these regulatory triggers, and ionizable pharmaceuticals with BCFs lower then these cut-off values have been observed in plasma of fish in urban coastal systems above human therapeutic plasma values. Such observations are important because internal doses of pharmaceuticals in fish, which often contain high

evolutionary conservation of pharmaceutical targets with other vertebrates, are linked to adverse effects.[49,50] Thus, as mechanistic bioaccumulation science moves forward for ionizables,[41] PFAS[36,37,51] and other organics, such advances present unique opportunities to again interface ecotoxicology and green chemistry by identifying attributes of molecules that are unlikely to bioaccumulate. It further appears clear that reducing uncertainties during bioaccumulation determinations through the design of less bioaccumulative substances presents critically important research needs for green chemistry with ecotoxicology.

IV. Toxicity

A noble goal for toxicology should be to render the practice of chemical product safety assessments unnecessary. This perspective may seem utopian, but worthy grand challenges can be perceived as such before being significantly engaged. Traditional approaches for risk assessment rely on developing an understanding of exposures and hazards for subsequent risk characterization. These estimations are then used to support environmental risk management activities; for example, implementing treatment technologies or remediating contaminated sites are common interventions. Risk management has thus focused on limiting exposures after a chemical has been developed and introduced to commerce, yet these traditional approaches are not globally effective - pollution is now recognized as a major environment and health priority.[52] Herein lies a promise for reducing risks to public health and the environment through the intentional reduction of chemical toxicity through substitutions with alternatives and by rational design of less hazardous substances.

Sustainable molecular design of chemicals with limited hazard profiles presents a profound opportunity for toxicology[23,53,54] and a grand challenge for achieving more sustainable environmental quality.[19,20] Of particular relevance to ecotoxicology, sustainable molecular design has been aided by identification of design guidelines for standardized acute and chronic aquatic toxicity endpoints[55-57] with recent efforts focusing on oxidative stress[58] and behavioral perturbations.[59] More intentional integration of computational chemistry within ecotoxicology is necessary beyond these initial efforts. For example, the Molecular Design Research Network (MoDRN; modrn.yale.edu), led by Paul Anastas at Yale University's Center for Green Chemistry and Green Engineering, represents a novel attempt to bridge disciplinary chasms toward advancement of sustainable molecular design.[60] These integrative efforts of green chemistry with ecotoxicology and other disciplines are important because toxicity is not a singular construct, but rather results from adverse outcomes associated with molecular initiation events following chemical interactions with biological targets.[6] Our contributions to MoDRN in general and sustainable molecular design for reduced toxicity in particular have been influenced by lessons learned from examining pharmaceuticals and the environment.[61]

In addition to the bioaccumulation efforts described above, our observations of human pharmaceuticals in fish from an urban river prompted studies aimed at understanding adverse outcomes these exposures presented to wildlife.[8] To do so we leveraged mammalian pharmacology and toxicology information to examine biological "read-across" hypotheses,[45,49,62-69] based on evolutionary conservation of hundreds of pharmacological targets across vertebrates.[70-71] Because biological activities of pharmaceuticals are vastly more understood than other classes of environmental contaminants, this afforded unique opportunities to employ these rationally designed compounds as chemical scalpels to define evolutionary

conservation of toxicity pathways across species.[2] Such contributions have collectively been advancing comparative physiology, pharmacology and toxicology and providing interdisciplinary bridges for One Health related research.[2] For example, exciting recent developments, including SeqAPASS[72] and EcoDrug,[73] are facilitating cross species extrapolations, and can support toxicology to become an even more integrative discipline. Thus, lessons learned during drug development, including avoidance of properties resulting in undesirable side effects, are poised to continue to support the design of less hazardous substances when green chemistry is interfaced with ecotoxicology.

Much like leveraging mammalian pharmacology and toxicology data for comparative research, other cross-disciplinary interfaces have employed existing chemical property and hazard information to prioritize substances for study, reduce animal testing and identify problematic substances for substitution. Here again, such efforts have also recently been identified as important research needs to achieve more sustainable environmental quality.[19,20] We find utility employing probabilistic environmental hazard assessment (PEHA) approaches with environmental exposure and chemical toxicity distributions to identify data gaps, evaluate exposure patterns among environmental matrices and geographic regions, determine differential sensitivities among in vitro and in vivo toxicology model systems, and explore chemical properties of interest or specific chemicals of concern.[8,14-18,67,74-78] Examining acetylcholinesterase inhibitors and various classes of surfactants with PEHAs, Williams et al[78] specifically identified ecotoxicology opportunities to reduce animal testing, to characterize relative hazards among surfactant classes, and to refine risk assessment within the European Union's REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulatory framework. Building from these earlier experiences, we recently performed the

Cleaning Product Ingredients Safety Initiative, which complied a highly unique mammalian toxicology database for cleaning products,[79] and then leveraged this information to identify novel data-driven uncertainty factors and thresholds of toxicological concern for diverse chemical classes and product uses.[80-81] Hazard assessment methods developed by Wang et al[80,81] can specifically enhance screening-level hazard and risk assessments when toxicity data is limited or unavailable for specific chemicals, and support chemical substitution decisions during alternatives assessments. Future research is needed, however, within green chemistry and ecotoxicology to extend these efforts to other chemical classes and uses.

V. Concluding Remarks

Existing chemical risk assessment and management programs may seem like sisyphean pursuits. Though accomplishments of chemicals management programs are fundamentally important, hazardous compounds have continued to slip through the regulatory cracks, particularly when inappropriate tools are employed for chemical safety assessments. More chemicals are introduced to market than can robustly be evaluated for risks to public health and the environment, and most chemicals have zero empirical exposure or hazard data to robustly characterize risks. When new classes of chemicals of concern are identified, a vicious cycle is realized. It should thus not be surprising when the next class of emerging environmental contaminants, like PFAS or pharmaceuticals, are reported as new challenges. This scenario is compounded by the urbanization global megatrend that is resulting in increased access to and concentration of chemical use, and then contaminant releases from cities faster than environmental management systems and interventions can be implemented around the world.

Herein, sustainable molecular design promises to reimagine the historic assessment and management paradigm through a public health inspired construct. By enhancing biodegradation and reducing inherent toxicity, cumulative risk reductions from chemical exposure represents opportunities in complex scenarios, including chemical and waste challenges that are becoming palpable in urban regions of developing countries. Because ecotoxicology has matured to a mechanistic science, this synthetic discipline is now poised to facilitate sustainable molecular design and more sustainable development, but only if cross-disciplinary engagement occurs over the next decade. It won't be easy. Ecotoxicology is increasingly bifurcating between mechanistic studies at the molecular level extending to individual adverse outcomes in the laboratory and studies at higher levels of biological organization (populations to ecosystems) in the field. And there remains occasional misinterpretation among basic ecotoxicological studies and translational applications within practice exercises. Step changes with systems approaches and integrated multidisciplinary research programs (e.g., MoDRN) from the lab to the field are necessary if more sustainable environmental quality is to be realized, particularly within urbanizing regions. Fortunately, integrative, comparative and predictive toxicology efforts, if advanced across species and scales of biological organization, are positioned to catalyze the work of chemists and engineers engaging sustainable molecular design studies. Strategic investment will be required to stimulate cross-disciplinary research programs and ultimately achieve the SDGs and related protection goals for public health and the environment.

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