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Commentary

# Toxicology Advances for 21st Century Chemical Pollution

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**Pollution represents a leading threat to global health and ecosystems. Systems-based initiatives, including Planetary Health, EcoHealth, and One Health, require theoretical and translational platforms to address chemical pollution. Comparative and predictive toxicology are providing integrative approaches for identifying problematic contaminants, designing less hazardous alternatives, and reducing the impacts of chemical pollution.**

## Chemical Pollution and Grand Challenges

Despite growing awareness of the detrimental impacts of chemical pollution since the release of Rachel Carson's *Silent Spring* over 50 years ago, pollution remains a leading determinant for noncommunicable diseases and premature deaths globally.[1] Synthetic chemicals used in pesticides, pharmaceuticals, and residential and industrial settings are of particular concern because of rapidly increasing rates of production and diversification, complex human and environmental exposure scenarios, and a lack of universal pre-market toxicity evaluation. As a result, increasing volumes of synthetic chemicals with unknown human and ecological toxicity are entering water supplies, food production systems, the atmosphere, and cities and settlements throughout the world.

As agents of global change, synthetic chemicals have been increasing in both variety and volume at a more rapid rate than other stressors, including $CO_2$ emissions and nutrient pollution.[2] The chemical industry (the second-largest manufacturing sector in the world) is currently valued at >$5 trillion each year, and sales are projected to double from 2017 to 2030, as noted in the United Nations (UN) Global Chemicals Outlook II report. Between 2000 and 2017, the volume and capacity of chemical production grew rapidly in Asia, and most of the future chemical production will occur in emerging economies (Figure 1). Implementing environment and health protection systems that are effective and sustainable and achieving pre-market toxicity evaluations throughout global chemical supply chains present grand challenges of growing importance.

These challenges will most likely be exacerbated in the coming decades by rapid urbanization. An additional 2.5 billion people will live in cities by 2050, and the majority of growth is projected to occur in low- and middle-income countries, which are already disproportionately affected by the burden of pollution-related diseases.[1] Concentrated resource consumption and chemical use in cities result in concentrated waste streams from urban regions.[3] Currently, 80% of global sewage goes untreated,[4] and raw sewage and treated effluent discharges to surface waters of various quality are concentrated in cities. These waters are then reused for diverse purposes, including food production. The tightly linked food-energy-water nexus on which cities rely can therefore result in important human and ecological exposures to chemical pollutants, often of unknown toxicity.

Addressing global chemical pollution challenges, such as trajectories involving complex chemical mixtures, multiple stressors, and non-communicable diseases, requires systems-based approaches. In recent years, Planetary Health, EcoHealth, and One Health have emerged as multidisciplinary initiatives that embrace systems thinking to examine inherent connections across environmental quality, animal health, and human health in conceptually similar, though subtly different, ways.[5] Each of these holistic concepts focuses on the human-animal-environmental interface with a common goal of protecting health. Aligned with these initiatives, comparative and predictive toxicology—which have emerged from systems biology, computational chemistry, and pharmacology—are providing theoretical frameworks, translational methodologies, and interdisciplinary bridges to support and advance the goals of Planetary Health, EcoHealth, and One Health. Here, we explore advances in and applications of comparative and predictive toxicology and how these are accelerating progress toward the common goals of systems-based environment and health initiatives.

## Advances in Comparative and Predictive Toxicology

Toxicology has historically relied on descriptive *in vivo* studies with mammalian models (e.g., rodents) to support chemical assessments for protecting public health. However, such assessments can be costly, time consuming, and ethically challenged from an animal welfare perspective. Given that currently >350,000 chemicals and mixtures of chemicals are registered for production and use in commerce globally,[6] and these numbers are growing, safety evaluations must be performed in a timely manner. Simply stated, we cannot evaluate so many chemicals by using traditional mammalian toxicology methods because of time and financial-resource constraints. Addressing global pollution dictates more urgency.

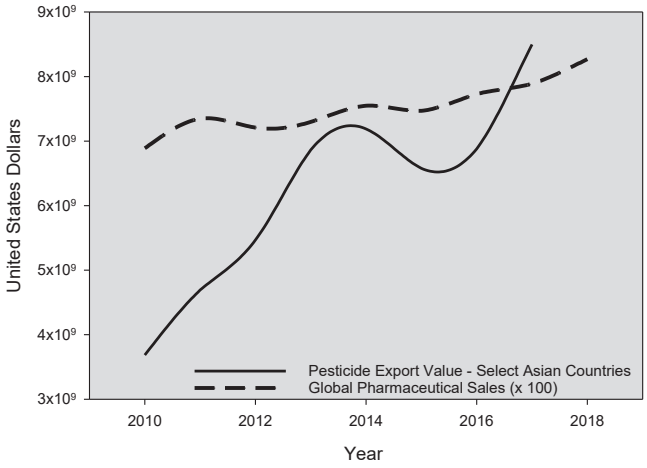


**Figure 1. Value of Global Pharmaceutical Sales and Pesticide Exports from Asia (i.e., China, India, Japan, Korea, and Vietnam) Are Increasing**

Data sources: http://www.evaluate.com/thought-leadership/pharma/evaluatepharma-world-preview-2019-outlook-2024 and http://www.fao.org/faostat/en.

Fortunately, advances in comparative and predictive toxicology—including research and regulatory shifts toward *in vitro* and *in silico* approaches and the increasing use of alternative animal models (e.g., zebrafish embryos)—are helping to address the ethical, economic, and time constraints of traditional toxicology while also advancing mechanistic understanding. Whereas comparative toxicology aims to understand chemicals that elicit common adverse outcomes across species, predictive toxicology routinely employs computational and other non-animal approaches to improve chemical hazard and risk assessments.[3] These advances are further permeating in ecological applications aimed at prospectively (i.e., before a chemical goes to market) and retrospectively (i.e., after contamination has occurred) assessing and managing the impacts of chemical pollution.

Comparative and predictive toxicology methods are gaining regulatory acceptance at the international level as a result of recent advances and human relevance. For example, the use of mammals for skin sensitization testing of chemicals has been common practice for many years, but earlier this year the UN Globally Harmonized Systems agreed that researchers can use data from non-animal tests to classify chemicals that corrode or irritate skin. And in Europe, *in vitro* testing has been used for identifying hazardous chemicals for diverse adverse outcomes and for selecting compounds in preclinical settings. These regulatory measures illustrate how comparative and predictive toxicology are facilitating transitions from traditional toxicology methods and are poised to address chemical pollution.

As a prime example, recent -omics advances are set to transform the process of decision making for environmental protection by more rapidly identifying new or existing chemicals that require management in a more cost-effective and timely manner. For example, concentration-dependent transcriptomics approaches with fish models provide efficient tools for prioritizing chemicals of concern and for making management decisions according to the responsiveness of evolutionarily conserved biological pathways in human cells and fish models.[7]

## High-Throughput *In Vitro* and *In Silico* Toxicology

In ecotoxicology and environmental toxicology, *in vitro* methods are now being used for metabolism studies to better elucidate chemical bioaccumulation in fish, an important component of environmental risk assessments for ecosystems and human health (i.e., ingestion of contaminated fish). As the science continues to develop, so has the ability to relate chemical concentrations that induce *in vitro* responses to *in vivo* exposure levels resulting in adverse human and ecological outcomes. For example, comparable with *in vivo* results,[8] toxicogenomic data generated *in vitro* are already yielding drug rankings and drug potentials to cause toxicity while guiding the selection of appropriate animal species with human relevance. Well-developed *in vitro* methods are also increasing confidence among scientists and regulators in the resource and ethical advantages of *in vitro* predictiveness and extrapolation to animals. Further, these methods offer valuable mechanistic information for training and testing a new generation of *in silico* models that use big data or modeling of molecular interactions to identify problematic chemicals and design less hazardous alternatives.[9]

Some of the most active comparative and predictive toxicology efforts in the US include the federal Toxicology in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) programs (http://www.epa.gov/chemical-research/toxicology-testing-21st-century-tox21). Through Tox21 and ToxCast, thousands of chemicals are being screened with hundreds of *in vitro* assays (largely adapted from drug-development and pre-clinical safety efforts) and zebrafish models for identifying chemical bioactivities. Such high-throughput information is supporting computational efforts to identify chemicals of potential concern. In addition, these and other toxicology advances are being leveraged for prospective evaluations of diverse substances—including ingredients in consumer products, industrial chemicals, and pesticides—for human and ecological hazards and during retrospective assessments (e.g., effect-directed analysis) for the identification of pollutants and other stressors in aquatic and terrestrial ecosystems.

## Alternative Vertebrate Models

Because of their molecular, biochemical, and physiological similarities to humans, mammals (particularly rodents) have historically been used for biomedical research in general and toxicology in particular. But more recently, various fish species have been increasingly employed as vertebrate alternatives to rodents for toxicology, pharmacology, and etiology studies of human disorders. Notably, approximately ten new drugs discovered by zebrafish screenings have reached, or are about to enter, clinical testing thus far.[10] Fish are now commonly used in laboratory investigations, which are supported by well-developed comparative biology resources. Similar to *in vitro* tools, fish are more cost and time effective than mammals and aid in reducing animal welfare concerns. The more rapid development and reproduction of fish than of mammals provide clear benefits during high-throughput screening of a large number of chemicals.

Not only are fish pragmatic, ecologically important, and able to serve as a sentinel species, but also evolutionary relationships among fish and mammals allow fish models to provide advantages in molecular mechanistic studies because they offer opportunities for extrapolation across species. As noted above, recently developed diverse technical resources (such as sequenced genomes, DNA libraries, and available antibodies) further support using fish for biomedical studies. Fully established genome databases of zebrafish and the fathead minnow indicate high evolutionary conservation in comparison with the human genome. For example, 70% of protein-coding human genes are related to genes found in zebrafish, and many mutant phenotypes are similar to human clinical diseases.[11]

Evolutionary conservation of pharmacology and toxicology targets for chemicals among species has supported the development of various tools[12] (Box 1) to support the rapid and efficient evaluation of chemical toxicity. For example, Sequence Alignment to Predict across Species Susceptibility (SeqAPASS)[13] is an online tool that supports toxicological predictions across species and the identification of problematic chemicals. Such information can also aid the development and application of new comparative and predictive tools. One relevant example is transgenic fish models, which are being used as alternatives to transgenic mice in genome manipulation for comparative biomedical studies, functional genomic research, and comparative studies of relevance to human health and the environment.

Genetic engineering strategies combined with *in vivo* imaging of fish larvae are also allowing researchers to observe, in a non-invasive manner, real-time multi-scale responses to pharmaceuticals and chemical contaminants that would be difficult to detect with mammals. These transgenic fish models, when combined with *in vitro* bioanalytical tools and targeted and non-targeted analysis of chemical contaminants in the environment, present unique opportunities to diagnose specific sources and causative agents associated with chemical pollution. Thus, human health and ecologically focused studies with fish models are reciprocally benefiting each other, which is likely to further enhance protection efforts for public health and ecosystems from pollution.

## Future Perspectives

Addressing global chemical pollution in the 21$^{st}$ century presents a number of grand challenges for achieving the United Nations Sustainable Development Goals. Fortunately, recent developments in comparative biology, computational chemistry, and pharmacology are being translated to provide basic and applied environment and health information to decision makers and practitioners in government agencies and industries, particularly within the adverse outcome pathway (AOP) framework.[14] AOPs are conceptual models that can be used for understanding chemical activity and potential effects with available knowledge to describe causal linkages from molecular initiating events to adverse outcomes at the individual and population levels, which are relevant to chemical risk assessment. AOPs can also be extended to higher levels of biological organization and for examining cascading interactions among trophic positions.[15] When AOPs are conserved across species, comparative and predictive toxicology efforts promise to further develop coupled ecological and human health hazard and risk assessments. These efforts are particularly needed for chemicals of emerging concern, such as the per- and polyfluoroalkyl substances and diverse toxins from harmful algal blooms.

Efforts to prevent pollution are being informed by comparative and predictive toxicology advances for the identification of chemical bioactivity profiles, the evaluation of specific contaminants of concern, and the protection and restoration of ambient environmental conditions. Because environmental management systems and waste treatment infrastructure commonly found in developed regions are not being consistently implemented or are lacking in low- and middle-income countries, ''disruptive'' technologies (such as contributions from sustainable, green chemistry and engineering) will increasingly be necessary to reduce the environment and health risks from chemical pollution.[3] For example, the sustainable molecular design of organic chemicals[16] is fueling innovation by supporting the identification of problematic contaminants, supporting chemical substitutions, and rationally designing *de novo* substances that are less persistent, bioaccumulative, and toxic.

Ecosystems and human populations are consistently exposed to complex chemical mixtures and multiple stressors. We must better understand the cumulative risks of, and interactions among, chemical, physical, biological, and social stressors during development and implementation of management efforts to protect public health and the environment. For example, how chemical contaminants influence the susceptibility of plants and animals, including humans, to bacterial, viral, and parasitic infections is not being routinely examined. As we watch the current global coronavirus disease (COVID-19) pandemic unfold, non-communicable diseases resulting from pollution could elevate the impacts of respiratory viruses. Identifying mechanisms to facilitate cross-cutting research among infectious disease researchers and comparative and predictive toxicologists appears warranted.

Advances in comparative and predictive toxicology are providing mechanistic insights and tools for designing less hazardous chemicals before they enter commerce, identifying problematic substances currently in production, and diagnosing causes of chemical pollution. As

**Box 1. Select Online Resources for Comparative and Predictive Toxicology**

**EcoDrug**

The EcoDrug database (http://www.ecodrug.org/) includes information on the evolutionary conservation of human drug targets in >600 eukaryotic species. It supports the identification of these targets for >1,000 drugs and the exploration of integrated ortholog predictions for drug targets across taxonomic groups.

**SeqAPASS**

SeqAPASS (http://www.epa.gov/chemical-research/sequence-alignment-predict-across-species-susceptibility) extrapolates from data-rich organisms (e.g., humans, mice, rats, and zebrafish) to thousands of non-target species to evaluate their specific potential chemical susceptibility. Sensitivity of a specific species to a chemical is determined by a number of factors, including the presence or absence of proteins that interact with chemicals. It evaluates similarities of amino acid sequences and protein structure to identify whether protein targets are present for chemical interaction in other species.

**CompTox Chemicals Dashboard**

The Computational Toxicology (CompTox) Chemicals Dashboard (https://comptox.epa.gov/dashboard) is an online tool that integrates diverse information, including physicochemical properties, environmental fate and transport, exposure, usage, *in vivo* toxicity, and *in vitro* bioassay information, for >875,000 substances. It provides a resource to aid the rapid and efficient evaluation of chemicals.

**AOP Wiki**

The Adverse Outcome Pathway (AOP) Wiki (https://aopwiki.org/) is the primary repository of qualitative information for the international AOP development effort coordinated by Organisation for Economic Co-operation and Development (OECD). It describes an AOP in terms of key events (KEs), which represent measurable steps along a pathway, ranging from a molecular perturbation to an adverse outcome for an organism or population. KEs are connected via KE relationships (KERs), which capture evidence supporting the AOP in a structured way. The AOP Wiki provides access to AOP information via an online interface that supports browsing and searching for AOPs, KEs, KERs, and stressors known to perturb the AOPs.

**OECD QSAR Toolbox**

The OECD Quantitative Structure Activity Relationship (QSAR) Toolbox (http://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm) was developed to facilitate the accessible and transparent use of QSAR models. It provides a decision support system for chemical hazard assessment. It aims to avoid duplication of animal toxicity testing, promote intelligent testing strategies, predict chemical toxicity of categories, and support green chemistry and sustainable development.

**The Monarch Initiative**

The Monarch Initiative database (https://monarchinitiative.org/) uses semantics to integrate cross-species gene, genotype, variant, disease, and phenotype data. It provides a platform for exploring phenotype-based similarity across species and performing inter-species gene-phenotype anchoring analysis.

such, these toxicology advances are simultaneously building integrative foundations to advance the goals of the Planetary Health, EcoHealth, and One Health initiatives in addressing global pollution. However, strategic cooperation at both the educational and research levels, including non-traditional partnerships, is needed to foster connections and to integrate often disparate disciplinary pursuits via systems-based approaches.

Toxicologists and chemists need to more closely engage the broader Planetary Health, EcoHealth, and One Health communities to define and manage the growing global threats from chemical pollution. This need has been evidenced in part through the Global Horizon Scanning Project, an initiative with the Society of Environmental Toxicology and Chemistry (and the American Chemical Society in North America) that has engaged scientists, engineers, and stakeholders around the world to identify priority research questions aimed at achieving more sustainable environmental quality.[17] Most, if not all, of these key research questions are relevant to Planetary Health, EcoHealth, and One Health; however, a number of priority research questions are directly related to comparative and predictive toxicology. These research questions largely focus on chemicals and other environmental stressors, and rather than being moon shots, they will require shorter-term multidisciplinary team projects to reverse engineer progress toward addressing a number of grand challenges for public health and ecosystems. Key research questions from six continents[17] highlight comparative and predictive toxicology connections with global environment and health challenges, as well as sustainable, green chemistry and engineering opportunities. Clearly, these timely research needs should be addressed through systems-based initiatives.

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