Learning from the past and considering the future of chemicals in the environment

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Knowledge of the hazards and associated risks from chemicals discharged to the environment has grown considerably over the past 40 years. This improving awareness stems from advances in our ability to measure chemicals at low environmental concentrations, recognition of a range of effects on organisms, and a worldwide growth in expertise. Environmental scientists and companies have learned from the experiences of the past; in theory, the next generation of chemicals will cause less acute toxicity and be less environmentally persistent and bioaccumulative. However, researchers still struggle to establish whether the nonlethal effects associated with some modern chemicals and substances will have serious consequences for wildlife. Obtaining the resources to address issues associated with chemicals in the environment remains a challenge.

Synthetic chemicals have enabled marked improvements in food production and living standards (1). Although concerns exist about the many hundreds of chemicals in the environment, there are only a few, albeit notable, examples of chemicals actually harming wildlife populations (Fig. 1). These examples demonstrate that hydrophobic (lipophilic) chemicals can both persist in the environment and bioconcentrate, meaning that the highest exposures manifest in the longest-lived top predators. In addition, tests of acute toxicity on a limited range of laboratory-friendly species are not predictive for all species and effects, and chronic tests on a wider range of organisms are needed. Knowledge gained from such disasters should make the use of chemicals increasingly safer. However, our past failures suggest that we must be prepared for more surprises in the future.

Proportion of chemicals for which adequate environmental information is known

In places where data are accessible, such as the United States and Europe, the number of chemicals and substances on the market is believed to be around 75,000 to 140,000 (2, 3). However, empirical data on persistence are available for ~0.2%, bioconcentration data for 1%, and aquatic toxicity for 11% of chemicals registered in the European Union (4, 5), and similar data have been reported for the United States (2). In the absence of such substantive information for the majority of chemicals, computational predictive methods can provide some help in terms of risk assessment (2, 4). Nevertheless, the task is complicated by the formation of breakdown products in the environment, for which we have little to no information. An additional challenge to our efforts to assess risk from these many chemicals entering the environment is the potential for mixture effects. These effects may lead to higher impacts on organisms than would have been predicted on the basis of individual chemical-based risk assessments (6). Today’s research funding model tends to encourage widening and deepening studies on the current chemical, or group of chemicals, perceived to be of most concern, rather than supporting research on a larger proportion of the chemicals being discharged and considered potentially problematic (7).

Chemical risks are not equal, nor is exposure

Given the vast array of chemicals contaminating our natural environment, where should we focus our greatest attention? For instance, the risk of copper harming wildlife is reported to be five orders of magnitude higher than the risk from the drug atenolol (8) when comparing median exposure with median toxicity values for rivers in the United Kingdom. In other words, the risk of harm from atenolol is only 0.001% of the risk from copper. In fact, metals dominate the top 10 of 71 chemicals of concern studied in the United Kingdom (8) (Fig. 2) and are similarly highly ranked in China (9).

Chemical exposure from wastewater, which can be expressed as the extent to which the wastewater generated by an individual will be diluted by the natural river flow (10), is not evenly spread around the world. Depending on landmass, population size, and rainfall amount, some countries will face constant and widespread elevated exposure to chemicals in wastewater, whereas other nations will experience much less exposure (Fig. 3).

New chemicals and new places of concern

In modern society, chemicals are expected to serve a variety of functions; examples include...
medicines, flame retardants, and pesticides. We now recognize that the very properties that can make these chemicals work effectively can simultaneously be deleterious for the wider environment. For instance, as medical knowledge grows, the expectation for new pharmaceutical-based treatments for diverse health conditions will continue. A current example is the incentive for drug companies to devise more effective compounds to treat a range of age-related conditions (11). Additionally, ethinylestradiol has been a very effective oral contraceptive, but the combination of its potency and persistence has made it an endocrine disrupter in wild fish downstream of wastewater effluent (22). If some of the new pharmaceuticals act as agonists or antagonists on the endocrine system, then the estrogen-based disruption may expand to a wider variety of fish (13). On the subject of flame retardants, problems with the persistence and toxicity of polybrominated diphenyl ethers have led to a wider range of replacement candidate substances, including nonhalogenated organic or metal compounds with phosphate groups, hydroxide, or stannate groups (14). Finally, concerns over pesticide mobility, non-target toxicity, and persistence have markedly reduced the number of products for sale. The pest-control approaches of tomorrow are likely to be more precisely targeted to affect RNA interference, pheromones, and sterility. New flame retardants and insecticides should be much safer than older ones, but we must be alert to unexpected consequences, as have been observed for neonicotinoids (insect-specific post synaptic agonists). These compounds, once considered sustainable, are now known to cause population decline in wild bees (15).

The modern economy has been transformed by globalization. As a result, much chemical production has been transferred to Asia (16), where chemical sales are now 168% of those in the United States and Europe combined (Fig. 4). However, in some cases, weak regulation or uneven local enforcement has led to severe pollution hotspots. Examples include atmospheric contamination with chlorofluorocarbons coming from the Shandong and Hebei provinces of China (17), gross perfluorooctanoic acid pollution from a vast Chinese manufacturing site (18), and water contamination with antibiotics from a manufacturing plant in India (19). Unfortunately, successful management of industrial waste, and pollution more generally, is far from straightforward. Setting water quality targets is a good step, but such benchmarks are successful only where independent regulators take consistent, high-quality measurements and are supported by an independent judiciary, on both the local and national scale. The degree to which environmental protection is improved by centralization or when it is devolved to local administrations is debatable (20). In the case of local governance in China, there is evidence for uneven application of regulations (21, 22). Protection is also boosted by a national commitment to transparency, in which scrutiny by the public, environmental nongovernmental organizations, and journalists is accepted. Nevertheless, this approach has not been adopted globally (23, 24).

Reasons for optimism
Progress in regulation and management of chemicals in the environment
Chemical regulations in the 1960s and 1970s concentrated on remediating past pollution and controlling the emission of a limited number of pollutants. The approach today is becoming forward-looking to ensure that new chemicals poised to enter the market will conform to minimum human safety and environmental standards. Examples include the Toxic Substances Control Act (TSCA) in 1976 (Public Law 94–469) in the United States, as well as Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (EC 1907/2006) in the European Union. Still, because many chemicals entered the market before these laws were enacted, a retrospective authorization process is trying to catch up. Although not perfect, the establishment of regulations such as TSCA and REACH set an important precedent: The onus to demonstrate that a chemical is safe for humans and the environment should lie with the manufacturer. In Europe, the phrase used to describe this concept is “no data, no market” (25).

Analytical developments, knowledge of undesirable chemical characteristics, and alternatives to animal testing
Developments in analytical chemistry continue to drive down limits of detection. With the use of nontargeted screening (NTS) methods, it is becoming possible to search for and tentatively identify all molecules present in a sample, both known and unknown (26). NTS has been applied to reveal the range of compounds in urban runoff water (27), to investigate unusual pollution incidents, and to identify the industrial premises responsible for such incidents (28). Recently, historic analytical raw data from previous studies have been used to retrospectively analyze “new” pollutants that were not originally targeted in these studies (29). These new approaches will help make the environment more transparent with respect to chemical contaminants.

There is now much shared knowledge on the undesirability of properties such as hydrophobicity and persistence in chemicals intended for discharge to the environment. In the consumer goods industry, recognition of poor biodegradability has led to the replacement of branched alkylbenzene sulfonates by linear forms, long-chain dialkyl quaternary surfactants by ester-based quaternaries, nonylphenol ethoxylates (which also have toxicity concerns) by alcohol ethoxylates, and musk xylene by macrocyclic musks. Although not driven primarily by environmental...
Concerns, an increasing proportion of newly registered pharmaceuticals are the so-called “biologics.” For example, 12 of the 30 new drugs registered for the German market in 2016 (noted by the German Pharma Association) and 75 of the 200 recent top-selling retail drugs in the United States (30) are made from biological materials such as proteins, genes, allergens, and cells. These substances are not considered to pose the persistence issues of small synthetic molecules.

Understandably, ethical concerns have arisen about subjecting large numbers of animals to laboratory toxicity tests for the many thousands of chemicals yet to be registered, and these concerns have encouraged the development of toxicity and exposure models (2). Computer models have been used to help predict which chemicals will be of greatest concern (in silico risk assessment)—in other words, those that will be persistent, bioaccumulative, and toxic (PBT). In a survey of 95,000 chemicals, a model predicted that only 3 to 5% were likely to be PBT (4).

Better wastewater treatment and international chemical initiatives

Shifting from primary wastewater treatment (settling) to secondary treatment (biological) and increasing biological treatment time in secondary treatment from simple methods such as trickling filters to activated sludge (31, 32) have considerable benefits for general water quality and chemicals reduction. The widespread adoption of the activated sludge process (ASP) in towns and cities around the world, with a biological treatment time of 8 hours or more, has done a great deal to protect rivers from the worst consequences of high chemical exposures. In China, it is now reported that the water distributed to 94% of urban population receives wastewater treatment, with 81% undergoing advanced processes such as ASP (33). Introduction of these methods can substantially improve water quality and, hence, biodiversity as compared with previous, less efficient treatments (33). As a society, we now have the capacity to introduce stringent tertiary treatment to eliminate almost all organics from wastewater effluent, as is being done in some parts of Switzerland (34).

Developed and developing countries share many of the same chemical challenges. This is particularly true with regard to many persistent pollutants, which know no boundaries. It is encouraging to see international agreements on persistent organic pollutants (Stockholm Convention), mercury (Minamata Convention), hazardous waste disposal (Basel Convention), and certain hazardous chemicals and pesticides (Rotterdam Convention). Sensible advice on managing chemicals, with respect to legal, economic, technical, and voluntary instruments and the adoption of safer alternatives, is now available to all countries (35).

Reasons for pessimism
Continuing uncertainty over the importance of nonlethal effects

Once we move away from apical end points (lethal or end points that disrupt reproduction or growth), it remains a matter of speculation as to whether the response to a chemical observed in the laboratory really translates to harm for individuals or populations in the wild. In theory, the detailed mechanistic detection of an adverse outcome pathway (AOP) predicts harmful effects ranging from the molecular level up to the population level (36). AOPs have been used to confidently predict population effects on fish from endocrine disrupters (37), yet these effects have not been observed in the field (38). Whether the development of AOPs will aid in the environmental risk assessment of chemicals is presently unclear. Similarly, the question of whether gene, protein, or metabolite expression studies can, on their own, predict actual impacts on wildlife populations or food webs (39) remains to be answered.

Data quality and the relevance of research topics

It is now widely accepted that a high proportion of published research is not reproducible, a situation sometimes called the reproducibility crisis (40–42). Reasons may include perverse incentives on scientists to publish “exciting” research and a general lack of training for researchers (43). Two common associated problems are poor experimental design and bias (44). In ecotoxicology, many scientists conduct their research on animals that are not routinely used in regulatory tests and that other researchers rarely use.

The focus of public concern over chemicals is unpredictable. This can lead to sudden demands for information, which can overwhelm other research areas. Inevitably, many fundable topics will have to be dropped so that resources can be concentrated in an area of new concern. One area of marked growth has been the study of nanoparticles and the environment: A search for this topic on Web of Science revealed an increase from 36 papers per year in 2000 to 4200 per year in 2017. Yet many studies appear to show a modest relative risk, at least for common metal-based nanoparticles (8, 45). Another example may be the study of bisphenol A (BPA), an additive used in many plastic items, which has been shown to exhibit weak estrogen activity. Many hundreds of studies on BPA’s presence and possible harm to the environment have been published (a September 2019 search of Web of Science with the terms “BPA,” “effect,” and “environment” revealed 630 papers). Yet the evidence that BPA is adversely affecting wildlife is essentially nonexistent (46). On the other hand, there are many thyroid, cardiovascular, antiepileptic, and muscle relaxant drugs for which few, if any, studies of possible effects on aquatic wildlife have been carried out.

Perhaps surprisingly, the focus of research into chemicals in the environment is not necessarily linked to their relative risk. For the top 20 highest-risk chemicals in British rivers (Fig. 2), publications related to their environmental risk varied between 7531 for lead to only 2 for the anionic surfactant alcohol ethoxysulfate in the period 2015–2019 (Fig. 2).

This area of science is prone to the “bandwagon” effect, by which many papers only demonstrate what we already know. Did we need ≥250 papers to tell us that ethinylestradiol poses a risk to fish? Everything we need to know to protect the environment was communicated in the first half a dozen papers. A current trend is this desire to search for increasingly more subtle effects, such as the expression of one or a few genes being altered, when the consequences of those effects are entirely unknown.

Risk assessments are falling further behind, and scientists tend to stay in their silos

Thorough risk assessment is costly and may require decades of research. Given
the range of species and number of end points that could be examined, it seems certain that we will never catch up by using traditional approaches (47). If this assertion is correct, then persevering with the current testing strategy does not seem appropriate. Ethical objections to the use of animals, particularly vertebrates, in tests are increasing, yet we continue to add more tests to the Organisation of Economic Cooperation and Development (OECD) battery of accepted (eco)toxicity tests. Efforts to rethink how the environmental risks of a chemical can be assessed, with an expanded role for predictive modeling of harmful properties, are ongoing, but regulators remain cautious about relying on such information (49).

The study of chemicals in the environment appears to revolve largely around the two disciplines of ecotoxicology and environmental chemistry. In their publications, ecotoxicologists commonly state that “effects were observed at environmentally relevant concentrations,” whereas environmental chemists are often tempted to assert that their “highest measured concentrations exceeded reported effect (toxic) concentrations” (49). Such statements imply that chemicals are harming the environment, possibly to a serious extent, on a daily basis. However, it is unclear, based on the evidence of ecotoxicology and environmental chemistry alone, whether we are exaggerating the dangers and thus overregulating or, alternatively, underestimating risks (as has been proposed from mixture effects) and thus failing to protect (47). Additionally, a third community of scientists—ecologists—has much to offer, in theory, in assessing chemical impacts on wildlife. The presence of long-term wildlife monitoring is vital for such research, but we see surprisingly few examples of collaboration between ecologists, ecotoxicologists, and environmental chemists. Ecologists have highlighted alarming declines in some wildlife populations (50, 57), and, despite many confounding variables, long-term ecological data can be extremely compelling toward establishing a link between competing arguments, such as those concerning neonicotinoids and bees (25, 39). To determine the true harm of chemicals, these different scientists will need to collaborate closely (52).

Outlook

Adapting to the immensely difficult societal and environmental challenges of tomorrow will undoubtedly require new chemicals and chemical solutions. The production of chemicals, their diversity, and their use around the world has never been greater. Our ability to manage the risks is finely balanced, with reasons to be both pessimistic and optimistic. Unfortunately, the sheer volume of chemicals on the market, and presumably also entering the environment, currently outpaces our ability to assess the risks. Although there are no guarantees, our past knowledge combined with in silico modeling of hazards will be beneficial in gauging relative risk. Provided that long-term wildlife monitoring efforts are maintained, particularly in areas with the greatest chemical exposure, we may have some confidence that our use of chemicals is sustainable.
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