On the design of safer chemicals: a path forward†

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The need for chemists to design chemicals that not only fulfill their intended purposes but are of minimal hazard was recognized nearly a century ago. Over the decades regulations pertaining to the development of safer drug substances and pesticides have been promulgated, and caused changes in the relationships between industry, academia, government agencies, and how chemists are trained to develop new pesticides and new drug substances. This has led to the considerable progress that has occurred over the past 60 years in the development of safe and efficacious pharmaceuticals and pesticides. Progress in the design of safer commercial chemicals, however, has been comparatively slow, despite the many advances in: toxicological research; the elucidation of mechanisms of toxicity; and the identification of relationships between chemical structure, physicochemical and electronic properties with toxicity, environmental fate, or environmental hazard. While few would argue against the need for safer commercial chemicals, implementation of the design of safer chemicals as a paradigm has not advanced to the same extent as other approaches to preventing pollution. This article offers insights on how this paradigm can be advanced as an important component of sustainable development, and how those existing commercial chemicals for which safer, commercially viable alternatives are most needed can be identified and prioritized. One recommendation regarding prioritization is the use of information available in the United States (U.S.) Environmental Protection Agency’s (EPA’s) Toxics Release Inventory (TRI): the U.S.’ pollutant release and transfer register (PRTR). The TRI is an easy-to-use pollution prevention database tool used extensively for tracking the quantities of toxic chemicals annually released or otherwise managed as waste, and evaluating overall environmental performance by industrial facilities. Other PRTRs throughout the world have the potential to be used for identification and prioritization of chemicals as well.

Introduction

Contrary to the false but widespread belief that the designing safer chemicals paradigm evolved from the field of green chemistry, the importance for commercial chemicals to be designed such that they are of low toxicity and commercially viable was emphasized nearly a century ago by Alice Hamilton. Over the past 35 years many comprehensive treatises devoted to the design of safer chemicals have been published, and some chemical companies devote considerable resources to the development of safer commercial chemicals. Many specific and detailed examples on how time-honored approaches used by medicinal chemists to design safer, clinically efficacious pharmaceutical substances can be applied to the design of safer commercial chemicals are provided in publications by Ariëns and DeVito.

These examples illustrate use of: biochemical mechanisms of toxicity to infer molecular modifications that mitigate toxicity; qualitative structure–activity (toxicity) relationships; quantitative structure–activity (toxicity) relationships; isosteric substitution; and retrometabolic principles, among others, and provide structural representations of chemicals known or believed to be safer than other chemicals.

Yet for a variety of reasons, or more specifically because of a variety of impediments, the concept of designing safer chemicals has not yet been fully adopted by industry as a routine and necessary component of new chemical design. For optimal impact the concept must be accepted and applied as the general practice throughout industry in the development, production and use of commercial chemicals. Moreover, a concerted effort must be made on the part of governmental regulatory agencies, funding institutions and academic institutions to eliminate the many challenges that impede application of the concept or, as a minimum, help chemical companies surmount them.

The most intractable of the impediments to widespread adoption and implementation of the designing safer
New chemicals: that ever elusive ideal chemical. How do we know when we have one?

Exactly what is a safer chemical? What are its characteristics? How does one know when a new chemical is safe, or at least safer than another chemical? These fundamental but often overlooked questions must be addressed at the very beginning of the design phase of any new chemical substance. DeVito has put forth a list of characteristics (principles) that help answer these questions and that can be universally applied to the design of any new chemical.18 These characteristics are listed in Fig. 1, and are briefly discussed here. Insights on how some of these characteristics can be designed into a molecule are available elsewhere.2–13

Use potency. Good use potency, the very first characteristic of the ideal chemical (Fig. 1) is perhaps the one that is most often overlooked. This is because potency is usually thought of in the context of pharmaceutical agents and their ability to produce desired pharmacological outcomes. In regard to pharmaceuticals, potency is a measure of the quantity (dose) of a drug substance that is needed to elicit a given response (e.g., lowering of blood glucose concentration) to a given degree (e.g., to a blood level range of 85–100 mg dL−1) relative to the quantity needed for another drug substance to elicit the same response to the same degree and through the same pharmacological mechanism. The less quantity that is needed, the more potent the drug is said to be.

Many textbooks of pharmacology state that potency has little clinical utility or meaning other than to provide a means of comparing the relative activities of drugs in a given therapeutic category. That is, whether one drug is more potent (i.e., requires less of a quantity or dose) than another to effectively treat an illness is unimportant. This premise, however, ignores the clinical advantages that a more potent drug would have over less potent drugs in a given series in which the drugs were metabolized (bioactivated) to analogous toxic metabolites (e.g., an epoxide metabolite). In this not uncommon scenario, the less potent drug would require a greater dose to achieve the desired pharmacologic outcome, but the greater dose would correspondingly yield a greater quantity of the toxic metabolite and, therewith, the less potent drug would likely be more toxic than a more potent drug in the same series.

A more potent drug has environmental advantages. Since less of it is required to get the job done, smaller quantities of it need to be manufactured. It follows, at least in theory, that lesser quantities of feedstocks, solvents and other chemicals required for its manufacture are needed, resulting in less production-related waste. Over the past several decades there has been a general trend among pharmaceutical companies to design new drugs to have increased potency, longer durations of action, and require less frequent dosing over existing drugs. Table 1 provides examples of well-known, widely used drug products that illustrate this trend. The newer drug products in each of the pharmacological categories shown tend to be better tolerated and have largely replaced the older products.

While the impetus for this trend among pharmaceutical firms may not have been consciously rooted in green chemistry, the trend nonetheless has almost certainly reduced the quantities of production-related waste and environmental discharges of toxic chemicals, and is very much green chemistry. Take, for example, the sulfonylurea hypoglycemic agents shown in Table 1. These agents are used to control blood glucose levels in patients diagnosed with type-II diabetes mellitus. The potency of the newer agents, glyburide and glipizide, are approximately 100 times greater than that of tolbutamide, and need only be given once daily. Currently, approximately 29 million people in the U.S. have type-II diabetes mellitus.33 It is estimated that by the year 2050 nearly 60 million people in the U.S. will be diagnosed with the disease.33 Many of the...
29 million people afflicted with type-II diabetes use a sulfonylurea hypoglycemic agent to treat their illness. Based on the conservative assumption that about 14 million (~50%) of these patients use a sulfonylurea, this would mean that for tolbutamide, typically administered at 1500 mg per day, about 7658117 kg (16883260 pounds) would need to be manufactured annually to meet the needs of this patient population. Whereas for glipizide, typically administered at 5 mg per day, about 25537 kg (56300 pounds) would need to be produced annually. Most patients that use sulfonylurea hypoglycemic agents use either glipizide or glyburide because these drug products are better tolerated than the older agents of this class. The older agents of each category of drug products shown in Table 1, although once quite popular, are seldom used nowadays.

The concept of potency can be easily applied to many types of commercial chemicals. Here, potency could be defined as the quantity of a chemical required to fulfill some intended purpose to the same extent and by the same or similar molecular or physicochemical interactions as other substances. Take, for example, a congeneric series of fiber-reactive dyes under development to dye cotton fabrics a particular color. The substances within the series that can dye the same amounts of cotton substrates in lower quantities are the more potent of the congeners in terms of their ability to function as cotton dyes. All else being equal, the advantage of the more
potent dyes is that since less quantities are needed for use, less quantities need to be manufactured and, therefore, there is less potential for exposure to the dye and to the substances needed for its synthesis.

Use efficacy. Good use efficacy is another important characteristic of the ideal chemical. As with the term “potency”, “efficacy” is most often used in a pharmacological sense to describe a drug substance’s inherent ability to induce its desired pharmacological effect and how well it can do so without causing unwanted effects. Potency and efficacy are distinct, independent properties. As with potency, efficacy is quite applicable to commercial chemicals. In the above example of fiber reactive dyes, efficacy could be characterized as how well a dye in the congeneric series functions as a dye: i.e., how well does it impart the desired color? How is its fastness? Is it resistant to fading upon repeated washing or exposure to sunlight? Ideally, one would want to design a commercial chemical such that it is appreciably potent and efficacious.

Fiber reactive dyes that have both good use potency and superior commercial efficacy include bifunctional reactive dyes. This type of fiber reactive dye consists of two reactive groups that are separated from each other and serve to form covalent bonds with the fiber substrate (e.g., the hydroxyl groups within cellulose fibers of cotton). Fixation rates as high

Table 1  Examples of well-known pharmaceutical products that have increased pharmacologic potency and effect duration over previously developed products of the same structural class and pharmacologic mechanism

<table>
<thead>
<tr>
<th>Drug product generic name (brand name)</th>
<th>Structure</th>
<th>Year introduced in the US market</th>
<th>Typical oral dose and dosing frequency</th>
<th>Biological half-life (hours) (immediate release formulations)</th>
<th>Duration of effect (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylurea hypoglycemics</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tolbutamide (Orinase®)</td>
<td><img src="image1" alt="Structure" /></td>
<td>circa 1955–1960 19</td>
<td>500 mg three times a day</td>
<td>~5 h 20</td>
<td>6–12 h 20</td>
</tr>
<tr>
<td>Tolazamide (Tolnase®)</td>
<td><img src="image2" alt="Structure" /></td>
<td>circa 1965–1970 21</td>
<td>100 mg twice a day</td>
<td>7 h 20</td>
<td>12–14 h 20</td>
</tr>
<tr>
<td>Glyburide (Diabeta®)</td>
<td><img src="image3" alt="Structure" /></td>
<td>1984 22</td>
<td>2.5 mg once daily</td>
<td>10 h 20</td>
<td>up to 24 h 20</td>
</tr>
<tr>
<td>Glipizide (Glucotrol®)</td>
<td><img src="image4" alt="Structure" /></td>
<td>1984 22</td>
<td>5 mg once daily</td>
<td>4 h 20</td>
<td>up to 24 h 20</td>
</tr>
<tr>
<td><strong>H₂ receptor antagonist antiulcerants</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cimetidine (Tagamet®)</td>
<td><img src="image5" alt="Structure" /></td>
<td>1977 23</td>
<td>300 mg four times a day</td>
<td>2–3 h 24</td>
<td>6–12 h 24</td>
</tr>
<tr>
<td>Ranitidine (Zantac®)</td>
<td><img src="image6" alt="Structure" /></td>
<td>1983 25</td>
<td>150 mg twice a day</td>
<td>2–3 h 24</td>
<td>12–24 h 24</td>
</tr>
<tr>
<td>Famotidine (Pepcid®)</td>
<td><img src="image7" alt="Structure" /></td>
<td>1986 26</td>
<td>20 mg twice a day</td>
<td>2–3 h 24</td>
<td>12–24 h 24</td>
</tr>
<tr>
<td><strong>Aryloxypropanolamine-beta-blocking antihypertensives</strong></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Propranolol (Inderal®)</td>
<td><img src="image8" alt="Structure" /></td>
<td>1967 27</td>
<td>40 mg three times a day</td>
<td>2–3 h 28</td>
<td>6–12 h 29</td>
</tr>
<tr>
<td>Carvedilol (Coreg®)</td>
<td><img src="image9" alt="Structure" /></td>
<td>1995 32</td>
<td>6.25 mg twice a day</td>
<td>7–10 h 30</td>
<td>&gt;15 h 31</td>
</tr>
</tbody>
</table>
as 80% are achievable. Not only is less of a bifunctional dye needed for the intended purpose, but the high fixation rates of bifunctional dyes offer the additional benefit of having much less unused dyestuff entering waste streams. Moreover, they require less energy and less water consumption during application.\textsuperscript{34} Examples of bifunctional reactive dyes are illustrated below with structures 1 and 2. Compared to the dichlorotriazine (1), the monochlorotriazine–sulfatoethylsulfone containing dye (2) has significantly greater affinity for substrate fibers.\textsuperscript{35}

While not specifically referred to as efficacy of use, the importance of a determining whether a potential substitute chemical is at least as equally efficacious to an existing chemical used in a given application has recently been emphasized.\textsuperscript{17} Many examples exist in which a toxic chemical was replaced with a less toxic alternative without a full consideration of efficacy, and resulted in market failures such as poor performance or material incompatibility, or necessitated costly process and equipment changes.\textsuperscript{17} A furniture manufacturer, for example, substituted traditional fiberboard with a green board to eliminate formaldehyde-based binders. When laminated, the green board had inferior impact resistance and dented when heavy objects were placed on it.\textsuperscript{17}

Can be manufactured easily, efficiently, inexpensively, and greenly. The relevance of these characteristics to the ideal chemical are obvious. Ease, efficiency, cost and “greenness” of manufacture are often interrelated. A chemical that has many of the desirable characteristics of an ideal chemical will have limited commercial acceptance if its production requires the use of many other chemicals and many steps, as these requirements often lead to large quantities of production-related wastes and are resource intensive, which significantly adds to the cost of manufacture. There is a natural reluctance on the part of customers to switch from an existing chemical product that performs well to a new chemical that is purportedly superior but is unproven in the market place. This reluctance is only reinforced if the new chemical is more expensive.

Has minimal hazard: minimal toxicity to humans and ecological receptors; minimal physical hazard; minimal global hazard. Many people naturally think of chemical safety from the context of human health, and automatically interpret “safer chemical” to mean a chemical that is or is expected to be of reduced toxicity to humans, usually in regard to some other chemical that fulfills the same commercial purpose. This occurs because we, as humans, tend to prioritize human health over that of other species in our environment.

This “human safety first” way of thinking is only natural and understandable, and not likely to change anytime soon. It is important to stress, however, that a safer chemical should not be thought of only as a chemical that has low toxicity in humans. “Safer” must encompass minimal hazard to humans, ecological receptors (e.g., birds, fish), and the global environment as a whole, as well as having less of a propensity for exposure of humans, ecological receptors, and the global environment. Regarding reduced propensity for exposure, this can be achieved if, or to the extent that, a chemical does not persist in the environment or bioaccumulate in food webs, or at least partitions to environmental compartments where it is rendered permanently unavailable.

The “safer chemical” is the chemical that causes minimal adverse impacts to human health, other forms of life, and the earth. It is a relative term, and should not be interpreted to mean that the safer chemical does not cause any adverse impact at any level of exposure, or is in fact totally safe or without risk. A safer chemical is one in which any adverse effects it may have on humans, other organisms, or the earth are tolerable, or at least more tolerable than the adverse effects caused by some other chemical under similar conditions of exposure.

The word “tolerable” as used in this context is complex. Tolerability of a chemical’s unwanted properties is something governmental authorities deal with on a day-to-day basis in making decisions as to: (1) whether to permit a chemical to be marketed; and (2) if marketing is to be permitted, what regulatory restrictions are needed to limit the use and waste management of the chemical in order to minimize exposure to it, without compromising the societal benefits the chemical may offer. In the end, the extent to which a governmental authority will tolerate a chemical’s unwanted properties and the risks it poses, and how the authority will regulate the chemical to mitigate the risks, is ultimately based on the importance of the chemical to society and societal values.

Society generally places greater value on protecting human life, especially the health of the unborn, infants and children, than on other forms of life, such as, for example, avian or aquatic life forms, or on protecting the planet. Therefore, regulatory authorities tend to be more concerned with (less tolerant of) the toxic effects a chemical may cause in humans, particularly fetuses, infants and children, than with effects on other forms of life. In the U.S. this is blatantly evident in the Food Quality Protection Act, as it explicitly mandates the U.S. EPA to consider the extra susceptibility and sensitivity that infants
and children may have to the toxic effects caused by pesticides, and to impose more stringent regulations on pesticide chemicals that may be especially harmful to infants and children as a result of prenatal or postnatal exposure.

Within the realm of human toxicity, cancer is probably the illness that is most feared by society, since it is a difficult disease to treat and cure, and often culminates in a slow, painful, emaciating death. Hence, chemicals that are known to, or even suspected of causing cancer are generally less tolerated and regulated more stringently than chemicals that do not cause cancer but may cause other toxicities that are associated with lower morbidity and mortality, and for which better treatment modalities exist (e.g., nephrotoxicity).

Chemicals that can or are believed to cause developmental toxicity are those that produce adverse effects on a developing fetus, infant, or child from exposure of either parent to the chemical prior to conception, during prenatal development, or post-natally. These chemicals are also of very high concern to society, and tend to be stringently regulated by federal authorities. With developmental toxicity there is also an element of additional societal concern because of the logical view that we should not transmit effects across generations, to progeny that are of course defenseless victims of our inability to make and use safe chemicals.

Toxicity to the central nervous system (CNS) is another highly feared illness. While often not fatal, it is usually long-lasting (if not permanent) and debilitating. Fetuses, infants and even children tend to be more susceptible and sensitive to chemical induced-injury to the CNS. This is because the brain cells and the membranes of the capillaries that surround and protect the brain cells (the blood–brain barrier) from toxic contaminants in the blood are not fully developed in infants and children.

Degrades readily in the environment to innocuous substances. There is further analogy with yet “extra” concern for toxic chemicals that may also persist in the environment and be transported great distances from their point of entry into the environment. Here the unifying general notion is that unsuspecting individuals located far from the discharge of the chemical are placed at risk, thus less able to defend than are the perpetrators. Mercury is a classic example of such a chemical. Mercury is extremely toxic to the CNS. Fetuses, infants and toddlers are especially sensitive and susceptible to the neurotoxic properties of mercury. Mercury also persists in the environment, and is known to bioaccumulate in the food web and biomagnify up the food chain.

Mercury metal is naturally found in fossil fuels. A major anthropogenic source of mercury emissions is from the combustion of fossil fuels in the production of electricity. Mercury oxides are thus formed and emitted to the atmosphere, where they can travel long distances and deposit to land or water bodies. Bacteria in soils and sediments transform the inorganic mercury oxides into methylmercury, a form of mercury that can be readily taken up by small animals and tiny aquatic organisms (e.g., algae and phytoplankton). Fish eat these organisms and build up (bioaccumulate) mercury in their bodies. As ever-bigger fish eat smaller ones, the methylmercury is concentrated (biomagnified) further up the food chain to human receptors.

Pregnant or nursing women exposed to methylmercury through their diet or otherwise also expose their developing fetus or breast fed infant to the chemical since methylmercury passes through placental membranes and enters the fetal bloodstream, and also enters breast milk. This is particularly problematic since fetuses and infants (and toddlers) are more susceptible and sensitive to the neurotoxic properties of mercury than are adults.

While the severe neurotoxic properties of mercury are independent of its ability to persist in the environment and bioaccumulate and biomagnify within the food web, these additional albeit non-toxic properties increase the likelihood of human exposure to mercury and, as such, augment its toxicity. It is important to stress that persistence and bioaccumulation are not in themselves universally undesirable properties of chemicals. There are many examples in which these properties are not only desirable, they are essential. Water is a good example. Water persists in the environment. According to the Old Testament, God made the earth’s waters on the very first day of the six days he used to create the earth. Water has persisted on earth ever since. Water also bioaccumulates. Approximately 60% of the mass of an adult human is in the form of water. It is good that water persists in the environment and bioaccumulates throughout the food web, as our very existence depends on it.

Thus in designing a safer chemical, it is reasonable to focus attention on human safety first. Particular attention should be given to designing chemicals that are unlikely to cause cancer, developmental toxicity or neurotoxicity to any degree. Chemicals should also be designed such that they do not persist for long periods in the environment, bioaccumulate significantly or biomagnify in the food web. While these properties by themselves are not harmful, they inherently enhance exposure to a chemical, and are undesirable if the chemical or any of its environmental degradates are toxic. A toxic chemical that also persists in the environment and bioaccumulates in the food web is generally of more concern than a chemical of equal toxicity that does not persist or bioaccumulate.

Does not require concomitant use of chemicals that are toxic. (E.g., use of the chemical does not require use of a toxic solvent). Clearly, any advantages or desirable characteristics that a new chemical may possess will be offset if the intended use of the chemical requires or involves the use of other chemicals, especially if the other chemicals have toxicities associated with them. Although a new chemical substance may have been designed to be non-toxic, its storage, transportation or use may require an associated substance that is toxic (e.g., a solvent such as carbon tetrachloride). Chemicals need to be designed such that their use requires few, if any, other chemicals, especially toxic chemicals. Even if a planned new chemical would require only one or two non-toxic chemicals for use application, consideration needs to be given during the design of the new chemical as to whether any downstream
changes in equipment, packaging, protective clothing, etc. need to be made in order for the new chemical and its associated chemicals to be used. The overall costs of such changes need to be weighed against the benefits offered by the new chemical in order to evaluate whether the new chemical is worth development.

**Offers clear and tangible environmental, human health and commercial advantages to an existing chemical or chemicals.**

The ideal chemical should not be a “me-too” chemical, meaning that it should not be just another chemical to be introduced into commerce that offers no advantages to other chemicals already in commerce and that serve the same use function(s). The ideal chemical must have clear, well-defined benefits and advantages. It must possess all or most of the characteristics discussed above.

**Existing chemicals. Where do we start?**

Which of the many chemicals used in commerce need to be replaced with safer substitutes? In the United States, the U.S. EPA classifies chemical substances as either “existing” chemicals or “new” chemicals. “Existing” chemicals are chemicals that were already in commerce in the U.S. when the Toxic Substances Control Act (TSCA) was enacted in 1976, or chemicals that (after 1976) have undergone premanufacture review by the U.S. EPA and subsequently listed on the TSCA Inventory. Currently, there are approximately 90,000 chemicals included on the TSCA Inventory. The bulk of these chemicals, about 62,000 or so, were grandfathered on to the TSCA Inventory in 1976 when TSCA was enacted.

Any substance that is not on the TSCA Inventory that is intended to be used in commerce in the U.S. is classified as a new chemical. Prior to manufacture (including import) of a new chemical for commercial use, a premanufacture notification (PMN) for the chemical must be filed with EPA under section 5 of TSCA. The EPA will review the new chemical submission for potential risks to human health and the environment, and will impose regulatory restrictions to mitigate any identified risks. The new chemical becomes an existing chemical after EPA has completed its review and the chemical is added to the TSCA Inventory. A chemical must be on the TSCA Inventory before it can legally be used in commerce within the U.S.\(^37\)

Section 5 of TSCA requires manufacturers or importers of a new chemical to notify EPA (i.e., submit a premanufacture notification, PMN) for new chemicals before manufacturing or importing the chemical. EPA has only 90 days (extendable to 180 days under certain circumstances) from the time of receipt of the notification to determine if an unreasonable risk may or will be presented by any aspect of the new industrial chemical, and make risk management decisions and take action to control any unreasonable risks posed by the chemical. If after 90 days the submitter of a new chemical is not notified by EPA of any regulatory restrictions or test requirements, the submitter can legally market or import the chemical.\(^37\)

TSCA departs from FDCA and FIFRA in regard to regulations of new chemicals in two ways. First, under TSCA, EPA does not approve or register a new chemical substance. It only imposes regulatory restrictions when deemed necessary before the chemical is marketed or imported to mitigate unreasonable risk. Secondly, and perhaps most significantly, section 5 of TSCA does not require any testing of a new chemical by a manufacturer or importer prior to its submission to EPA as a PMN. Since no testing is required, most manufacturers or importers do not conduct such tests on new chemicals or measure their physical properties, to supplement their PMN submissions.\(^37\)

Unlike submissions of new drug applications or new pesticide registrations, there is no burden of proof on the part of the submitter of a PMN to show that the new chemical is safe or, for that matter, efficacious. In fact, in reality, in order for EPA to impose regulatory restrictions on a new chemical submitted under section 5 of TSCA, the onus is on EPA to justify the restrictions. More simply, the submitter of a PMN is not required to prove or provide evidence that the chemical is safe, but EPA would have to have some basis for concluding that the new chemical substance is not or may not be safe in order to regulate it.\(^37\) Things may soon change, however. At the time of this writing TSCA is undergoing reauthorization. EPA may be given more flexibility to request safety data from submitters of PMNs under a reauthorized version of TSCA.

There are two major misnomers regarding the TSCA Inventory. The first is that the TSCA Inventory is a list of toxic chemicals. The TSCA Inventory is not a list of toxic chemicals. Toxicity is not a criterion used in determining the eligibility of chemical substances for inclusion on the Inventory. Water, for example, is listed on the TSCA Inventory. The second misnomer is that every chemical included on the TSCA Inventory is currently used in commerce within the U.S. In fact, most of the approximately 90,000 chemicals on the TSCA Inventory are not used in U.S. commerce. The number of chemicals on the TSCA Inventory that are actually used commercially in the U.S. is probably a fraction of those included on the Inventory.\(^38\)

The TSCA Inventory, in simple but accurate terms, is merely a list of those chemicals that could legally be used in U.S. commerce. As for the toxicity of the chemicals included on the TSCA Inventory, some of the chemicals are quite toxic (e.g., benzene, potassium cyanide), many are not particularly toxic, or not at all toxic (e.g., water, dextrose, starch). In the European Union (EU) chemicals are regulated under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) by the European Chemicals Agency (ECHA). Under the REACH regulations, the burden of establishing safety of a chemical is placed on the companies that seek to manufacture, import, or otherwise use the chemical. The primary purpose of REACH is to improve the protection of human health and the environment from the risks that may be posed by chemicals, by the identification of intrinsic hazards and other undesirable properties sooner rather than later. To comply with REACH, companies must identify and manage the risks linked to the substances they manufacture and market in the EU. They have to demonstrate to ECHA how the
Medicine makes TRI data available through its ToxMap tool. An excellent source of information on chemicals known to be toxic and that are used by industry is the U.S. EPA’s Toxics Release Inventory (TRI) database. The TRI was established by the U.S. Congress under section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA), largely as a result of the tragic accidental release of methyl isocyanate that occurred in December, 1984 at a facility in Bhopal, India, and another serious accidental chemical release at a chemical manufacturing plant in Institute, West Virginia, in August of 1985.

These incidents underscored growing demands by communities, public interest and environmental organizations for information on the toxic chemicals being used and released by facilities in their communities. In response, EPCRA was enacted in 1986. TRI reporting began for calendar year 1987, with the first reports due by July 1, 1988. This information was made publicly available by EPA in June of 1989. This annual cycle of facilities reporting to EPA’s TRI Program, and EPA compiling and making the information available to the public has continued ever since. Since implementation of the TRI, more than forty countries have implemented their own pollutant release and transfer register (PRTR), and many of these PRTR systems were modelled from the TRI.

TRI data and information are used by many people and organizations, and for many diverse purposes. In addition to its use by the public, TRI data are used by the federal, state and local governments, for example, for prioritization purposes. EPA makes TRI data available shortly after it is submitted through a variety of means that include online query tools, complete data downloads, location-specific analyses, and data summary documents. The U.S.’ National Library of Medicine makes TRI data available through its ToxMap tool.

Over the years the TRI list of toxic chemicals and some of the TRI reporting requirements for facilities have been modified by EPA to reflect the concerns and needs of society and in response to petitions submitted to EPA to make changes to the TRI list of toxic chemicals. Examples of some of the more major changes are available. Currently, there are 675 discrete chemicals included on the TRI list of toxic chemicals, as well as chemicals classified in 30 chemical categories. Virtually all (if not all) of the chemicals included on the TRI list of toxic chemicals are also included on the TSCA Inventory. The U.S. EPA’s TRI-Chemical Hazard Information Profiles (TRI-CHIP) tool contains a variety of high quality toxicity data and information on the TRI chemicals.

The collection of TRI data is achieved by requiring facilities subject to TRI reporting that have ten or more full-time employees and that within a calendar year manufacture, process, or otherwise use a TRI-listed chemical in a quantity that exceeds a threshold amount to report to the EPA, and state and tribal governments. For a given chemical, facilities are required to disclose the quantities they: released onsite to air, land or water; recycled onsite; burned for energy recovery or treated onsite; or transferred offsite to other facilities or locations for treatment, recycling, storage or disposal during the calendar year for which the reporting threshold was exceeded. Releases to air include stack and fugitive emissions. Releases to land include, for example, disposal in landfills and injection into underground wells. Releases to water include discharges into rivers, streams or other bodies of water.

Facilities are required to submit their information by July 1st of the following year on the TRI reporting Form R: one Form R for each chemical for which an applicable reporting threshold was exceeded. Each year EPA’s TRI Program receives approximately 80,000 Form R reports from approximately 22,000 facilities.

When the TRI was originally implemented the only quantities of toxic chemicals that had to be reported were those released directly to the environment or transferred to offsite locations for treatment or disposal. Also, facilities had the option to report source reduction practices that reduced their waste generation and the affect these practices had on the quantities they released to the environment or transferred offsite.

A major change in the types of information required to be reported under TRI regulations occurred in 1990, with passage of the Pollution Prevention Act (PPA). In recognizing the potential of the TRI to be a powerful pollution prevention tool, the authors of the PPA expanded the information required to be reported by facilities under EPCRA section 313 to include information specific to source reduction and preferred waste management techniques. As described under section 6607 of the PPA, for a given chemical this additional information includes the quantities of the chemical that were recycled, used for energy recovery, or treated at the facility or elsewhere. The PPA also requires reporting of any source reduction practices (e.g., process modifications, substitution of raw materials) implemented at a facility during the reporting year. Data fields were added to the TRI reporting Form R for these additional required data elements.

Facilities may voluntarily disclose specific details on their source reduction practices, in the form of text, in section 8.11 of their Form R submissions. Disclosure of information in section 8.11 of the TRI Form R provides facilities with a unique opportunity to showcase their achievements in preventing pollution to the public and other users of TRI data and information. EPA has recently established an online tool where this pollution prevention data can be easily obtained and readily analyzed. The utility of the TRI dataset in assessing the environmental benefits of the green chemistry practices implemented by pharmaceutical manufacturing facilities has recently been demonstrated.

The most recent U.S. EPA TRI National Analysis report shows that in total nearly 11.55 billion kgs (25.5 billion pounds) of chemicals included on the TRI list of toxic chemicals were either released to the environment or otherwise managed as waste during 2014. Disaggregation of this total quantity into specific waste management practices is illustrated in Fig. 2.
Beginning with the 2014 reporting year, facilities that did not implement source reduction for a given toxic chemical have the opportunity to disclose (also in section 8.11 of the TRI reporting Form R) barriers to implementing source reduction practices. They do so by choosing from a pre-established list of categories of barriers to source reduction. Fig. 3 illustrates the barriers (reasons) facilities reported as to why they were unable to implement pollution prevention activities during 2014. For the 2014 reporting year, 72,246 of the TRI Form R reports received included waste quantities. Of these forms, 9,206 (13%) reported at least one barrier to source reduction, and 3,745 (41%) of the 9,206 Form R reports claimed “No known substitute or alternative technology” as a barrier. What is clearly striking, and perhaps disturbing, is that by far the most frequently encountered barrier is “No known substitutes or alternative technologies” to the toxic (TRI) chemical (Fig. 3). That is, many facilities seem to have to use toxic chemicals because they have no other choice.

The good news is that examination of the TRI data and information indicates that source reduction activities were implemented during 2014 by many facilities in different industry sectors. Of particular note is the implementation of many source reduction activities by facilities in the “Paint, Coating, and Adhesive Manufacturing” sector [North American Industrial Classification (NAICS) code 3255] for toluene, xylenes, certain glycol ethers, dichloromethane, and methyl methacrylate. The same is true for facilities in the Pharmaceutical and Medicine Manufacturing sector (NAICS 3254) for dichloromethane and acetonitrile.

Interestingly, however, facilities in the Pharmaceutical and Medicine Manufacturing sector also reported many barriers to implementation of source reduction activities for acetonitrile. Facilities in the Plastics Product Manufacturing sector (NAICS 3261) reported a relatively high percentage of barriers to source reduction for toluene diisocyanates and other diisocyanates.

A large portion (87%) of the Form Rs submitted for reporting year 2014 that reported non-zero waste quantities also claimed no source reduction activities. Hence, while source reduction activities are being implemented by facilities on toxic chemicals, facilities still seem to be confronted with many challenges in implementing source reduction. Additional research is underway to characterize more precisely what these challenges are, and whether they exist across all sectors for a given chemical or only for specific types of sectors or facilities.

**TRI chemicals that are toxic substances control act (TSCA) work plan chemicals.** EPA has established a process for identifying existing chemicals that because of their toxicity or exposure potential warrant prioritization for further in-depth review and possible risk management action under TSCA. Currently, there are 90 chemicals that have been identified for additional review through this process. These chemicals are known as TSCA Work Plan chemicals. Of the 90 chemicals, 60 are included on the TRI list of toxic chemicals. The TRI database provides detailed information on: the quantities of these 60 priority chemicals that are released to air, land, and water, the locations of these releases, and by whom; the quantities that are treated, recycled, or burned for energy recovery; as well
as any source reduction activities that may have been implemented, or could not be implemented.

What is interesting (and sobering) is that the source reduction barrier “No known substitutes or alternative technologies” is claimed more frequently for the TRI chemicals that are also TSCA Work Plan chemicals than for the TRI chemicals that are not TSCA Work Plan chemicals. For the 2014 reporting year, of the 72246 Form R reports that included a waste quantity, 24586 (about 33%) were for TRI chemicals that are also TSCA Work Plan chemicals. Of these 24586 Form R reports, 3531 (14%) reported a barrier to source reduction, and 1555 (44%) of which claimed “No known substitutes or alternative technologies” (Fig. 4).

These facts are particularly significant given that the 60 TSCA Work Plan chemicals represent a small portion of the total number of chemicals included on the TRI chemical list, but the aggregated production related waste quantities reported for the TSCA Work Plan/TRI chemicals is disproportionately larger than that for the remaining TRI chemicals. As for the waste management quantities reported for these chemicals for the 2014 reporting year, 2222602613 kgs (4.9 billion pounds) were reported as total production-related waste. Of this total: 598670081 kgs (1.3 billion pounds) were released to the environment; 1133980925 kgs (2.5 billion pounds) were recycled; 181436950 kgs (0.4 billion pounds) were burned for energy recovery; and 308442812 kgs (0.68 billion pounds) were treated. Fig. 4 illustrates the barriers to implementing source reduction activities to the TRI chemicals that are also Work Plan chemicals during 2014 (see Fig. 3 for examples of the specific types of “other” barriers).

The same situation may very well exist throughout the world on these same chemicals. Many of the chemicals that are TSCA Work Plan chemicals and included on the TRI list of toxic chemicals are also included on the pollutant (chemical) lists of PRTR systems implemented in other countries or regions. Table 2 provides fifteen examples of chemicals or chemical categories that are TSCA Workplan chemicals and included on the TRI list of toxic chemicals, and that are also included on the pollutant lists of the PRTR systems of Australia, Canada, the European Union, and Japan. Also shown in Table 2 are the quantities of these chemicals that were released onsite from facilities in these countries during 2013.

So, where do we start? The TRI database is a rich source of information on many diverse toxic chemicals that are routinely manufactured, processed or otherwise used and released into the environment or otherwise managed as waste by facilities across the U.S. To answer the original question “Existing Chemicals, Where do we start?” we can start with the TRI list of chemicals. These are chemicals that are: toxic; manufactured, processed or otherwise used by facilities across industry sectors and in significant quantities; and released into the environment or otherwise managed as waste.

Moreover, the TRI chemical list offers an opportunity to apply the high-throughput screening (HTPS) data being generated by the U.S. federal government’s Tox21 program and the EPA’s ToxCast Program. Of the 675 chemicals included on the TRI list of toxic chemicals, 506 have been screened by the Tox21 Program. Of these 506 TRI chemicals, 298 have also been evaluated through EPA’s ToxCast Program. In short, a wealth of experimental toxicity, pharmacokinetic and HTPS data exists on the TRI chemicals. Much insight could be gained from an analysis and integration of the in vivo toxicity data, pharmacokinetic data and HTPS data, with the intent of elucidating structure–toxicity relationships and inferring rules that can be used to design new chemicals of reduced hazard that may serve as viable substitutes to the chemicals included on the TRI chemical list.

This effort will have international relevance. PRTRs contain a wealth of information applicable to sustainability analysis. Many of the chemicals that are included on the TRI list of toxic chemicals are also included on the lists of toxic chemicals established by other PRTR systems across the globe. There are efforts currently going on within the Organization of Economic Cooperation and Development (OECD) and other international organizations to harmonize and make comparable the information collected by the more than forty PRTR systems throughout the world, so that PRTR data can be analyzed on a global scale and used to assess progress towards global sustainability. The global sustainability analyses could be used to evaluate global trends, review trends in releases by country, evaluate impacts of environmental policies and programs, characterize waste transfers, gain insight into human and ecosystem health issues, identify additional priority chemicals, identify pollution prevention opportunities for industry, and review environmental performance and efficiency.
Change is needed in how chemistry is taught: the need for the “toxicological chemist”. Progress in the design of safer commercial chemicals has been quite slow in comparison to other subspecialty areas within the field of green chemistry. One major reason is that few, if any, universities or colleges offer formal academic programs in which instruction in biochemistry; toxicology; environmental sciences; and relationships between chemical structure and physicochemical properties with toxicity, environmental fate, and global hazard is given. The same is true regarding course offerings on commercial chemicals of concern, relationships between chemical structure and use function, and how all of the above interrelates within the realm of global sustainability.

Synthetic organic chemists, traditionally the principal architects of commercial chemicals, must assume the lead role in the design of safer commercial chemicals. What makes the synthetic organic chemist the most qualified individual to assume this leadership role is his or her ability to understand chemical reactivity at the molecular level. The basis of a chemical’s commercial utility, as well as whether it will be ultimately based on toxic effects is ultimately based on chemical reactivity at the molecular level. The basis of a chemical’s commercial utility, as well as whether it will be toxic or cause adverse environmental effects is ultimately based on how its molecules will interact with the molecules of other chemicals. These other molecules include those involved with the intended use of the commercial chemical, as well as those found in biological systems, such as macromolecules in humans, or molecules or atoms found in the environment.

But the academic training that chemists currently receive is not enough to enable them to design safer chemicals. Although chemists can collaborate with toxicologists, pharmacologists, biochemists, environmental scientists, and other chemists to design safer chemicals, a better scenario would be to have an individual who has a combined knowledge of these disciplines and is formally trained to integrate this knowledge and apply it to the design of safe, commercially useful chemicals. Garrett has described this hybrid scientist as the “toxicological chemist”. As part of the design of a new chemical, the toxicological chemist will consider both the function of the chemical in its industrial or commercial application, its potential for exposure and to cause toxicological effects in humans and the environment, and potential to cause global hazards.

The evolution of the toxicological chemist is similar to the evolution of the medicinal chemist, which occurred during the 1950s. Promulgation of the Federal Food, Drug and Cosmetic Act in the U.S. in 1938, specifically the pre-market testing it mandates, led to the publication of many studies that reported the metabolism, pharmacological and toxicological properties of many classes of chemicals undergoing evaluation as potential pharmaceuticals. This wealth of information enabled characterization of relations between structure, pharmacological activity, potency, efficacy, and toxicity of many classes of organic chemicals. Identification of these relationships would provide organic chemists with a rational basis from which molecular modifications expected to maximize the desired pharmacologic effect while minimizing toxicity could be inferred and used to design new molecules in which therapeutically effective was maximized and toxicity minimized.

The problem was that organic chemists, at the time the principle designers of pharmaceutical products, received none of the academic training in the biological sciences that was needed to enable them to analyze and interpret such infor-

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### Table 2: Onsite releases that occurred in different countries during 2013 of some chemicals that are on U.S. EPA’s TSCA work plan chemical list as well as the U.S. EPA’s TRI list of toxic chemicals and the lists of pollutants of the pollutant release and transfer registers of Australia, Canada, Europe, and Japan

<table>
<thead>
<tr>
<th>Chemical</th>
<th>United States TR† (kg)</th>
<th>Australia NPI‡ (kg)</th>
<th>Canada NPI‡ (kg)</th>
<th>EU E-PRTR§ (kg)</th>
<th>Japan PRTR† (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-Dichloroethane</td>
<td>188 177</td>
<td>265</td>
<td>154</td>
<td>754 832</td>
<td>203 559</td>
</tr>
<tr>
<td>Antimony and antimony compounds</td>
<td>3 186 945</td>
<td>7 687</td>
<td>2 877</td>
<td>60</td>
<td>338 710</td>
</tr>
<tr>
<td>Arsenic and arsenic compounds</td>
<td>114 675 287</td>
<td>121 353</td>
<td>54 072</td>
<td>115 636</td>
<td>985 078</td>
</tr>
<tr>
<td>Benzene</td>
<td>2 801 875</td>
<td>851 180</td>
<td>636 871</td>
<td>5 962 432</td>
<td>801 036</td>
</tr>
<tr>
<td>Cadmium and cadmium compounds</td>
<td>1 566 870</td>
<td>26 679</td>
<td>10 230</td>
<td>31 180</td>
<td>60 658</td>
</tr>
<tr>
<td>Chromium and chromium compounds</td>
<td>15 853 045</td>
<td>640 346‡</td>
<td>70 259</td>
<td>639 278</td>
<td>213 444‡</td>
</tr>
<tr>
<td>Cobalt and cobalt compounds</td>
<td>2 120 169</td>
<td>57 640</td>
<td>27 040</td>
<td>60</td>
<td>6830</td>
</tr>
<tr>
<td>Di(2-ethylhexyl) phthalate</td>
<td>36 092</td>
<td>146</td>
<td>606</td>
<td>25 320</td>
<td>61 087</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>1 551 782</td>
<td>324 101</td>
<td>74 979</td>
<td>2 854 336</td>
<td>10 990 462</td>
</tr>
<tr>
<td>Ethylbenzene</td>
<td>1 608 598</td>
<td>125 937</td>
<td>309 329</td>
<td>149 480</td>
<td>14 067 497</td>
</tr>
<tr>
<td>Lead and lead compounds</td>
<td>368 479 749</td>
<td>333 570</td>
<td>223 791</td>
<td>477 423</td>
<td>3 725 974</td>
</tr>
<tr>
<td>Nickel and nickel compounds</td>
<td>7 894 514</td>
<td>405 451</td>
<td>153 426</td>
<td>513 397</td>
<td>164 258</td>
</tr>
<tr>
<td>Tetrachloroethylene</td>
<td>436 707</td>
<td>21 799</td>
<td>118 143</td>
<td>459 842</td>
<td>885 534</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>920 530</td>
<td>25 621</td>
<td>38 224</td>
<td>111 418</td>
<td>3 036 415</td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>202 722</td>
<td>4859</td>
<td>403</td>
<td>617 936</td>
<td>155 647</td>
</tr>
</tbody>
</table>

† Onsite releases are defined as releases to air, water, and land. ‡ The most recent year of data for E-PRTR is 2013. Therefore, the 2013 data from the other PRTRs mentioned in this table were used. § Toxics Release Inventory. ‡ National Pollutant Inventory. ¶ National Pollutant Release Inventory. The European Pollutant Release and Transfer Register. ‥ All E-PRTR chemicals listed in this table are also covered by the Kiev Protocol. † Japan’s Pollutant Release and Transfer Register. † A release reported as 0 kg indicates that facilities claimed that they did not release the chemical on-site during 2013. They may, however, have reported other waste management quantities. ‡ Australia and Japan’s respective PRTR lists of pollutants do not include chromium metal (Cr6+).
mation, and integrate it with their training in organic synthesis to design new and improved drug substances. There was a need for a new type of organic chemist, a “medicinal chemist”: a chemist hybrid who received extensive training not only in synthetic organic chemistry but also in biochemistry, pharmacology and toxicology, and the relationships between chemical structure with physical properties, pharmacological action and toxicological effects. To address this need academic institutions that had chemistry programs developed curricula in which this training was provided, established medicinal chemistry programs, and began offering degrees in medicinal chemistry. Medicinal chemists are well prepared to design new clinically efficacious drug substances of low toxicity.

Similar revisions must be made to the existing traditional approach to chemical education, at both the undergraduate and graduate level. Accordingly, academic institutions need to re-structure their course curricula for students who seek to have careers in industry developing new chemical products. Current course content needs to be streamlined, perhaps some courses could be eliminated, to make space for course work relevant to the design of safer chemicals.

Students need to receive instructions on how to:
- Design molecules to have low bioavailability;
- Avoid structural features or electronic characteristics known to bestow toxicity;
- Infer structural modifications or electronic characteristics expected to reduce toxicity;
- From mechanism of toxicity information;
- From structure–activity (toxicity) information.
- Use isosteric substitution of molecular substituents responsible for observed toxicity;
- Design molecules to decompose quickly to safe products in the environment.

Basic instruction in chemistry, biochemistry, physiology, toxicology, environmental science is critical. Instructions in these disciplines can be integrated into existing courses, or be offered as a new single course. Instruction in the relationships between structure or physicochemical properties with: commercial use efficacy; commercial use potency; toxicity; environmental fate and effects; and global hazard is needed. Instructions in these latter relationships can be blended into existing courses, or taught in the form of a single course. Fig. 5 outlines a year-long generic undergraduate course curricula on “toxicological chemistry”. This generic course could easily be expanded to a graduate level course, or series of courses.

Conclusion

The ultimate goal of the perspectives discussed above is to achieve a state of sustainability, through uniform integration of the “benign-by-design” concept into every aspect of the science and technology employed in the design, manufacture and use of chemicals in our society. To reach this goal, there must be changes in existing paradigms, infrastructures, research in toxicology, and approaches to chemical education as well as changes in emphasis, attitudes, and practices by individuals and organizations throughout the public and private sectors. While acute toxicity (or other extreme hazards) are already considered by all, except the least responsible, to be basic functions to be taken into account in deciding on the production or use of a chemical, more subtle effects may not be. This holds for chemicals that have long been in use as well as new molecular entities.

As discussed throughout this paper, opportunities for chemical selection (and hence amelioration of harmful chemicals entering the environment and impacting on ecosystems) reside in the chemical producing industries. But such opportunities also reside in the chemical using industries. Most consumer products are formulated, or fabricated, from a mixture of chemical components chosen to impart specific properties or functions. Usually, there are a number of possible chemicals to choose from that will provide the desired function. But how does one go about choosing a chemical product that, all things considered, is the safest, most affordable, most efficacious, and that customers would want to use? Clearly, integrating consideration of toxicology data and efficacy into this process, alongside cost and availability, requires these data to be accessible, not costly to use and, preferably, standardized.

Other factors need to be considered as well in regard to product design and product selection. Consideration of the inputs, outputs, efficiencies of manufacturing processes, potential human health and environment impacts from the manufacture, use, and waste management of a chemical (life cycle assessment) is necessary. Moreover, robust frameworks or constructs need to be available that will enable one to apply these factors, and use and interpret the above information to make informed, rational decisions regarding chemical design (for the chemical producer) and product selection (for the chemical user). Fortunately, such frameworks are available, and several green chemistry metrics are available to assess and compare the efficiencies (“greenness”) of synthesis pathways.

The opportunity now exists to advance the designing safer commercial chemicals paradigm to being the general practice throughout the chemical industry. Over the past 60 years or more there has been a tremendous amount of research focused on what makes a toxic substance toxic. This research has included the measurement of pharmacokinetic, mechanistic, and structure–toxicity data, as well as robust toxicological assessments on widely used commercial chemicals. This information serves as the foundation for inferring the structural modifications that reduce toxicity and that can be incorporated into new chemical analogs. Also, computational chemistry, molecular modeling and HTPS are assuming an increasingly important role in understanding the basis of chemical–biomolecular interactions. Improvements in computer graphics, computational power, and software have led to a better understanding of the three-dimensional aspects of ligand–receptor interactions and specificity, and have greatly assisted medicinal chemists in the design of new clinically efficacious agents.
and pesticide chemists in the design of safer pesticide chemicals.

These advances in computational power greatly facilitates interpretation and utilization of the enormous amount of toxicological and other information on existing commercial chemicals that has been generated in the past, and continues to be generated at a rapid rate. There is no reason why this same computational power cannot be used to make facile and efficient use of the enormous amount of pharmacokinetic, mechanistic, structure–toxicity, HTPS, and toxicity data already available for many classes of commercial chemicals to design safer alternatives.

To design commercially viable compounds that don’t cause harm, we must take the above research into account and use it to our advantage through the computational power that is now at our disposal. In addition, the resultant data must be easily accessible, preferably centralized, and subject to quality control (or at least quality assessment) to encourage integration, alongside function, into the basic design and choice of chemical products.

**Fig. 5** Generic course curricula for training of toxicological chemistry.
As we move further into the 21st century, it is clear that we have the tools and the resources to further unlock the secrets of molecular toxicology and to integrate this knowledge with our understanding of the relationships between chemical structure and properties with industrial application. What is needed now is the collective resolve of individuals and organizations in both the public and private sectors to build the proper infrastructure, use the enormous amount of pharmacokinetic, toxicological, and HTPS data with the computational tools now in-hand, and make the necessary changes to effectively implement the concept of designing safer chemicals widely and routinely throughout industry.

Disclaimer

The views, conclusions, and opinions expressed in this paper are entirely those of the author, and do not necessarily reflect those of the United States Environmental Protection Agency, nor does mention of any chemical substance or commercial product constitute Agency endorsement or recommendation for use.

Competing interest

The author declares no competing financial interest.

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