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Current Status and Future Challenges in Molecular Design for Reduced Hazard

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ABSTRACT: Synthetic chemicals and materials are the basis of our society and our economy. Yet, in spite of all the advances in toxicology that have helped us understand and even predict toxicity associated with industrial chemicals, fundamental scientific questions crucial to the development of safer chemicals are left unanswered. Alternative strategies, such as *in silico* toxicity predictions, are considered the next frontier in molecular design for reduced hazard; however, such strategies are still not sufficiently developed to meet existing needs. Design strategies need to incorporate information and data at the nexus of multiple disciplines. Critically, there is a need for the incorporation of toxicology into the design phase of the molecular design process. In this Feature, we discuss the current status and future challenges in molecular design for reduced hazard.

KEYWORDS: *Molecular design, Reduced hazard, Principles of Green Chemistry, Toxicology, Sustainable innovation, Eco-innovation, Sustainability, Synthesis, Systems thinking, Property-based guidelines, Design rules, Preventative toxicology, Green toxicology, Life cycle assessment, Building blocks, ToxCast, Tox21, NSMDS, MoDRN*

Synthetic chemicals and materials are the basis of our society and our economy. Yet, in spite of all the advances in toxicology that have helped us understand and even predict toxicity associated with industrial chemicals, fundamental scientific questions crucial to the development of safer chemicals are left unanswered. The potential threat that commercial chemicals can pose to our society and the environment through unintended biological activity has become increasingly clear in recent years. Whereas chemists have developed considerable expertise in designing chemicals for specific industrial functions, so far little progress has been made in minimizing the undesired biological and environmental behavior of commodity chemicals through systematic design tools. Of the 700+ commercial chemicals introduced to the US market each year, over 85% are approved for manufacturing despite the lack of experimental health and safety data.[1] The influx of newly introduced chemicals in the marketplace has outpaced adequate assessment of the hazards associated with these new materials, in part due to the number of new chemicals introduced daily and the prohibitive economic and social costs of toxicity testing, particularly *in vivo*.[2] Society thus bears the risk of any hazards to health or the environment, and these are usually only discovered after large quantities of the chemical have been produced and distributed or after sufficient time has elapsed for epidemiological evidence to mount.[3] Integrating next generation approaches to protect sustainably public health and the environment will become increasingly necessary with population growth and urbanization. Alternative strategies, such as *in silico* toxicity predictions, are considered the next frontier in molecular design for reduced hazard; however, such strategies are still not sufficiently developed to meet existing needs.[4] In this Feature, we will discuss the current status and future challenges in molecular design for reduced hazard.

Current Status of Molecular Design. A fundamental consideration of the chemical designer is the function of the target compound in the context of product development. This represents the "fit for purpose" consideration.[5] In contrast to an initial focus on structure, the "function-oriented synthesis"

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(FOS) approach places an initial emphasis on target function rather than structure.[6] According to Wender,[6] a central tenet of this approach is that a given function can be derived from a variety of structures and not just from the initial construct. Consequently, the goal of the designer becomes the conceptualization of simpler targets that are synthetically more accessible, and are in theory more sequence efficient. Within this paradigm, the focus turns from the original structure and the corresponding retrosynthetic analysis to a focus on function and "retrofunction analysis". The designer seeks to find the simplest substructure that provides the desired function. In medicinal chemistry, this subunit is called the pharmacophore, which is the unit of moieties that will provide the desired biological activity. In this general view, form follows function.[6] Ideally, a FOS approach would include reductions in hazard by design, in addition to improved sequence efficiency.

In drug discovery, the optimization of function requires systems thinking and the evaluation of multiple factors such as receptor potency and selectivity, pharmacokinetics, *in vivo* potency, and importantly, safety as judged by metrics like the therapeutic index. Such optimization requires a holistic approach to design, and requires information and data from multiple disciplines. In practice, the designer can modify the target structure in an iterative process based on data that are generated during the optimization phase such as structure−activity relationships (SAR) or structure−property relationships (SPR). In addition to the biological data obtained from a screening cascade (i.e., receptor potency), optimization is based on the physicochemical properties of the target structure. Solubility, pK_a, partition coefficient (clog *P*), and melting point are examples of parameters that can be modified by the (medicinal) chemist in an attempt to optimize the early lead compound into a commercially viable product. The important point relevant to this discussion is that the iterative, data-driven, information-rich approach of compound profiling and filtering of drug discovery can be (and is) applied to other chemical optimization programs in other business sectors with the aim of reducing adverse effects by molecular design.[7,8] An example of a screening approach that is employed within the personal care and household products industry is from the Research Institute for Fragrance Materials, Inc. (RIFM), which supports applied research and distributes scientific data and safety assessment judgments to its corporate members. RIFM has developed a safety assessment process that is an iterative and tiered screening approach that assesses for human health and environmental safety.[9] The range of approaches to designing and identifying less hazardous chemicals varies widely by industry sector. Sectors that are engaged with chemicals meant to be biologically active such as pharmaceuticals and pesticides and sectors that make chemicals with high levels of human exposure such as cosmetics and cleaners often have very advanced methods that combine *in vitro*, *in vivo*, and *in silico* analysis and design tools where other sectors that make bulk industrial chemicals often have far more rudimentary approaches.

There is more, however, to compound design than product form and function. In today's business world, companies are adopting the three pillars of sustainability—profit, people, and planet—as an accounting framework for measuring their performance.[10,11] Sustainability is innovation's new frontier.[12] The adoption of the three pillars of sustainability by a company can be facilitated by the 12 Principles of Green Chemistry,[13] and critically, the implementation of safer chemical design concepts by the bench chemist or designer. Unfortunately, industry in large part has not adopted these concepts as a routine and necessary component of design;[14] however, there are increasing numbers of chemical companies focusing on the development of chemicals that are safer for human health and the environment. Sustainable innovation has been used interchangeably with the term eco-innovation, which is defined as "the production...of a product...that is novel to the organization...and which results, throughout its life cycle, in a reduction of environmental risk, pollution and other negative impacts of resources use...compared to relevant alternatives."[15] Molecular design that is based on the 12 Principles of Green Chemistry moves beyond baseline chemical and safety specifications to consider the environmental, economic, and social factors of sustainability.

The fourth Principle of Green Chemistry states, "chemical products should be designed to preserve efficacy of function while minimizing toxicity".[13] This essential and central principle is perhaps the least developed area of Green Chemistry. There are several reasons why the adoption of safer chemical design has not been widespread throughout the chemical industry.[14] A primary reason is that most chemists have not been introduced to the concepts of safer chemical design. Chemistry students rarely receive formal training in the design of commercial chemicals with reduced hazard.[14] Training in green chemistry and toxicology would provide practitioners with the skill sets and knowledge that would enhance their "green core competency." It has been stated that the green core competency of a company is defined as the collective learning and capabilities about green innovation and environmental management within an organization.[16] Consistent with this definition is the notion that knowledge resources and human skills, in addition to provisions and access to finance, are essential drivers to green innovation.[17] Green core competencies, specifically safer chemical design, can be enhanced with knowledge of the 12 Principles of Green Chemistry. Companies facing sustainability-related issues and challenges will require new core skills and competencies in order to successfully manage business sustainability and the related activity of eco-innovation.

In addition to a lack of training, there are other barriers to the adoption of safer chemical design by practitioners within industry. These barriers include (1) the availability (or lack of) methods, tools, and know-how that can be applied to rational design for reduced hazard; (2) an accepted definition, or perhaps standard, of a safer chemical;[14] (3) the desire to use drop-in replacements that may not be optimally less hazardous or more sustainable rather than design a novel chemical that can be resource intensive; (4) supply chain constraints, particularly for small businesses that may not have leverage to request that producers or suppliers provide safer chemicals or products; (5) creation of novel chemicals, unlike drop-in chemicals that are in commercial use, may require regulatory scrutiny; (6) TSCA regulation does not intentionally require chemical manufacturers to develop safer commercial chemicals.[18]

The design of safer chemicals is not a new concept and indeed has been embraced by sectors like the pharmaceutical and pesticide industries, in part because of federal regulations that were introduced in the early years of the 20th century.[18] There are historical examples of how hazardous materials were transformed to less hazardous forms. A classic example is the invention of dynamite by Alfred Nobel who patented the

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invention in 1867.[19] Nitroglycerin is a highly explosive but unstable compound that has caused injury from unwanted explosions. Knowing these concerns, Nobel focused his research on improving the stability of nitroglycerin and went on to discover dynamite. He found that the adsorption of nitroglycerin to an inert substance like diatomaceous earth, along with the addition of stabilizers, provided dynamite that was safer and easier to handle. In effect, Nobel's discovery was an advancement based on formulation rather than inherent design based on structure. Nonetheless, his invention provided a chemical product with reduced hazard that was safer for handlers (workers) and it would change the progress of industrialization.

An example of molecular design for reduced hazard is taken from the pharmaceutical industry and has been highlighted by Williams and Naisbitt.[20] Clozapine is a dibenzodiazepine, antipsychotic drug whose use is complicated by the occurrence of a 1% incidence of agranulocytosis (Figure 1). Olanzapine is a

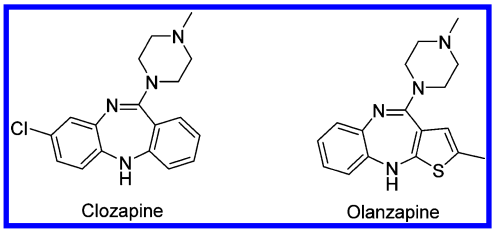

Figure 1. Chemical structures of Clozapine and its bioisostere Olanzapine.

thienobenzodiazepine analog in which a benzyl ring is replaced with a methyl-substituted thienyl moiety. Olanzapine has not been associated with a significant incidence of agranulocytosis. Here the design strategy for reduced hazard was the use of a bioisostere having similar biological activity as the original drug.

Other examples of design for reduced hazard to public health and the environment can be found in the Presidential Green Chemistry Challenge Awards.[21] We highlight recent awards as a way to exemplify the excellent work and progress in the area of molecular design for reduced hazard in recent years. In 2014, The Solberg Company was given the Design of Greener Chemicals Award for their design of the product called Rehealing Foam Concentrate.[22] The company developed a halogen-free foam concentrate that is an "innovative environmentally sustainable fluorosurfactant and fluoropolymer-free firefighting foam that is used to extinguish Class B fuels with no environmental concerns for persistence, bioaccumulation or toxic breakdown". The concentrate is a blend of hydrocarbon surfactant, water, solvent, sugars, a preservative, and a corrosion inhibitor.

A less recent but notable example of molecular design for reduced hazard is the work of Dow AgroSciences LLC, which won the Design of Greener Chemicals Award for the discovery of a new insecticide called spinetoram.[22] The company used an "artificial neural network" to identify analogs of a natural product called spinosad. The new pesticide retains the favorable environmental benefits of spinosad while replacing organophosphate pesticides for fruits, nuts, and vegetables. Spinetoram provides benefits to human health and the environment over existing insecticides. The company also developed a green chemical synthesis for the new insecticide.

The concept of safer chemical design is connected to the process of selecting alternatives to chemicals of concern. Alternatives assessment is "a process for comparing alternatives, usually to a chemical of concern and identifying those that are safer".[23] In 2014, the NRC committee on the Design and Evaluation of Safer Chemical Substitutions reported their 13-step framework for selecting alternatives to chemicals of concern.[23] The framework included several important unique elements or advancements, such as the recognition of the need for research and innovation in its framework. The committee highlighted the design of new chemical alternatives as an important type of innovation, and noted that the design of a new and safer chemical may be an option when an alternatives assessment does not identify a suitable replacement. The committee recommended that safety and ecological considerations be an integral part of early chemical design, which is at the heart of green chemistry.[24]

Nexus of Chemistry and Toxicology. In 2002, it was stated that a challenge to research in achieving green chemistry principles was "the development of preventative toxicology where increasing knowledge of biological and environmental mechanisms of action are continuously incorporated into the design of chemical products".[25] Fortunately today, there is an increasing understanding of the mode of toxic action and the underlying biochemical mechanism of action (MoA) of toxicity. This increased understanding is the result of advancements in computational modeling, systems biology, and high-throughput screening of compounds in receptor and toxicity-related assays.[7] The different mechanisms of toxicity of two commodity molecules, methanol and ethanol, are examples of our increasing understanding of the mechanisms of action and compound metabolism. Ethanol is metabolized to acetaldehyde and acetic acid, whereas methanol is converted to acutely toxic metabolites, formaldehyde, and then formic acid. Formic acid inhibits mitochondrial cytochrome c oxidase, which can cause hypoxia and metabolic acidosis resulting in optic neuropathy and permanent blindness.[26,27] The enzymatic metabolism of methanol to toxic metabolites is an example of toxification by the human body.

The increasing understanding of modes of toxic action and the underlying biochemical mechanisms of action of toxicity has led to an increasingly sophisticated *in silico* predictions of the potential for adverse effects. For example, the *in silico* prediction of Ames mutagenicity and CYP-inhibition outcomes have become more robust.[28] Our understanding has evolved from a whole organism level to the level of the organelle, while computational chemistry has advanced to solving problems at the level of enzymes, receptors and genes (Figure 2).

The *in silico* approaches to toxicity prediction of commercial chemicals have been recently reviewed.[29−32] Furthermore, the

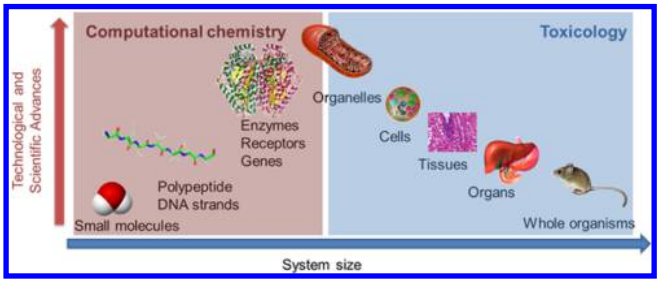

Figure 2. Technological and scientific advancement of computational chemistry and toxicology to the current level of enzymes, receptors, and genes at the cellular and organelle level.

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progress in computational toxicology that can be directly applied to advancing methods of toxicity prediction and molecular design has been reviewed recently.[33,34] An intention of *in silico* design and toxicity prediction is to reduce both the economic and ethical costs of *in vivo* screening for adverse biological effects by identifying chemicals of high concern. Companies are incorporating computational tools into their screening approaches and are evolving from the conventional approach based on animal-based, descriptive methods. The reader is referred to a recent article from The Dow Chemical Company[7] for a discussion of ongoing advances in predictive safety assessment in the chemical industry.

In 2007, the U.S. National Academy of Sciences released the report entitled "Toxicity Testing in the 21st Century: A Vision and a Strategy".[32,35] The authors of the report envisioned "increased efficiency in toxicity testing and decreased animal usage by transitioning from current expensive and lengthy *in vivo* testing with qualitative end points to *in vitro* toxicity pathway assays on human cells or cell lines using robotic high-throughput screening with mechanistic quantitative parameters".[35]

The committee's vision of toxicity testing (Figure 3) is a process that includes chemical characterization, toxicity testing,

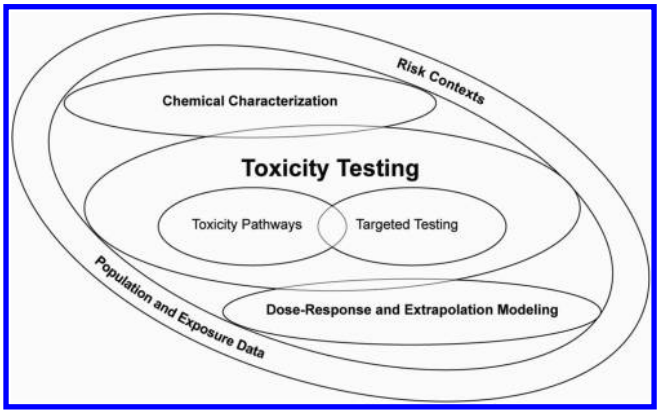

Figure 3. U.S. National Academy of Sciences Committee's vision of toxicity testing in the 21st century. Reprinted with permission from *Toxicity Testing in the 21st Century: A Vision and a Strategy*, 2007 by the National Academy of Sciences, Courtesy of the National Academies Press, Washington, DC.

dose response and extrapolation modeling, and human exposure data. Chemical characterization would include predicting properties and characteristics by using computational tools. Unfortunately, *in silico* toxicity predictions are still not sufficiently developed to meet existing needs.[4] Moreover, there is a need for more data that can be used to correlate chemical structure to adverse side effects via computational methods that in turn can be used to create *in silico* predictive toxicological tools and/or guidelines. To meet this need, the EPA has initiated several high-throughput toxicological screening initiatives. Toxicity Forecaster (ToxCast) is a part of the multiagency toxicity testing program called Toxicity Testing in the 21st Century (Tox21), and involves the National Institute of Health (NIH), the National Toxicology Program (NTP), the Food and Drug Administration (FDA), and the Environmental Protection Agency (EPA).[36] The ToxCast program is a multiyear effort launched in 2007 that uses high-throughput screening assays to profile compounds in cell-based and biochemical assays.[37] The intent of the program is to limit animal-based toxicity testing while quickly and efficiently generating large amounts of data as a result of screening large numbers of chemicals. The ToxCast data was added to the efforts of the Tox21 program, which has compiled high-throughput screening data on nearly ten thousand chemicals.

An intention of the EPA is to provide the data that is required by researchers to create and develop molecular design tools for reduced hazard. An example of this effort is a report that was recently published by Liu et al. on "Predicting hepatotoxicity using ToxCast *in vitro* bioactivity and chemical structure"[38] and by Shen et al., who investigated cytotoxicity using the ToxCast data set.[39] Such efforts are at the nexus of chemistry and toxicology.

The pharma industry has taken a "fail early strategy" when it comes to product development, and so it has put a focus on the potential toxicology liabilities of early leads within the discovery phase when drug leads are identified. This responds to late stage failures based on various reasons including unexpected adverse side effects that have been observed late in the discovery phase, or during the development phase of clinical trials[40] after investment of hundreds of millions of dollars, or even worse during the marketing phase when the patient bears the risks of any side effects. In response, project teams have developed screening cascades that filter out compounds based on the potential for adverse side effects. The screening cascade includes tools and models that rely on *in silico* evaluation, *in vitro* assays (e.g., cytotoxicity and off-target assays), and *in vivo* studies (e.g., maximum tolerated dose, metabolomics, chronic dosing). Compounds are deselected as negative data is collected from the screening cascade of assays and tests. In addition, there is an upfront assessment of potential leads. At the start of a program when multiple compounds are being considered for optimization, they are evaluated for their viability against a multitude of criteria. This is usually the first "gate" that compounds must pass before they receive company resources. The evaluation of molecules, referred to as starting points, are performed by "paper chemistry" before a compound is assessed in biological or physicochemical (wet) assays. The starting points are evaluated using cheminformatics that includes data mining for toxicity data that may be associated with a particular compound or class. Medicinal chemists utilize structural alerts based on substructures (e.g., electrophilic moieties like primary halides) or scaffolds associated with known toxicities or promiscuity to deselect compounds.[28,41] Green toxicology, like the pharma approach, introduces safety considerations into the earliest phase of chemical development and adopts the early toxicological screening approach that is utilized in the pharma industry. This approach provides a framework for integrating the principles of toxicology into the design of safer chemicals.[42]

For the practitioner, whether it is the synthetic chemist at the bench or the designer using a computer, there is a need for an interdisciplinary approach (systems thinking) that includes synthetic chemistry, toxicology, biology, pharmacology, and ecology. Chemists need to operate at the nexus of disciplines and fuse knowledge from multiple sources in order to design a chemical that has function without a negative impact on the environment and society throughout its life cycle. A knowledge of how chemical properties impact public health and the environmental will help chemists design molecules that perform their intended function and are safer for humans and the environment[30,43] Today's chemist should consider processes like bioconcentration, biodegradation, and bioavailability, along

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with environmental fate issues like mobility and persistence. These topics need to be incorporated into the curriculum of synthetic organic chemistry students, or made available as learning modules to today's practitioners.

Property-Based Guideline and Design Rules. The characteristics of an "ideal compound" have been recently described by DeVito[14] The ideal compound is constructed on safer design concepts, and has minimal toxicological, physical, and global hazards. With respect to minimizing human toxicity, a goal of designers of nontherapeutic commercial molecules is to minimize exposure and biological activity. This perspective has been discussed in a recent review[30] and has led to design rules or guidelines to avoid environmental toxicity. Specifically, rules have been developed with the intention to reduce and ultimately avoid aquatic toxicity. The safer chemical space to minimize aquatic toxicity has been defined by log $D_{o/w} < 1.7$, $\Delta E > 6$ eV, and $V < 620$ Å^3.[44] With respect to the avoidance of human toxicity, the primary defense is to avoid absorption and systemic exposure. However, this is not sufficient. For high reactivity chemicals, absorption is not required to cause adverse effects as dermal contact is sufficient. Thus, the inherent hazards of chemicals must be avoided by design, that is, chemicals should be benign by design.[45] Human absorption of a chemical can occur via the skin, lungs and GI tract. Manipulation of physicochemical properties can minimize the absorption of chemicals via these routes of exposure. But if there is absorption, the design goals include reducing distribution, reducing bioactivation (or increase deactivation), accelerating excretion, and finally eliminating any potential toxicodynamic interactions responsible for specific toxicity.[30]

The manipulation of physicochemical properties can also minimize toxicity.[46] Large lipophilic compounds, particularly those with a low polar surface area, tend to show adverse effects. That is, high-clog P/low-TPSA compounds are approximately 2.5 times more likely to be toxic than be nontoxic.[47] There is a need for additional design rules and guidelines that are based on the electronic properties of the compound, rather than solely on structural features, (i.e., alerts) and on a deeper understanding of the biochemical mechanisms of action of toxicity.

NSMDS and NCCLC Programs. The U.S. Environmental Protection Agency (EPA) and the National Science Foundation (NSF) Divisions of Chemistry and Chemical, Bioengineering, Environmental, and Transport Systems (CBET) came together to encourage synergistic research activities and to enhance cooperation among multidisciplines in the area of safer chemical design.[48] The agencies separately funded awards for "Networks for Sustainable Molecular Design and Synthesis" (NSMDS) in 2013 with a total funding amount of $18.9 mil.[48] NSMDs are groups of two or more researchers working in trans-disciplinary fields to promote the development of safe and sustainable chemicals as well as safe and sustainable synthetic procedures. Research findings are expected to result in chemicals that are safer throughout their life cycle, from conception to production, use and end of life phases. Education and outreach of the Networks are important aspects of the initiative, and it is expected that the basic research from the Networks will be translated into social and economic benefit.

The NSMDS research teams are expected to communicate with the research networks from the EPA/NSF funded "Networks for Characterizing Chemical Life Cycle" (NCCLC).[49] The purpose of the NCCLC is "to encourage synergy and enhance cooperation in examining the life cycles of synthetic chemicals and materials as they relate to their manufacture, use, transport, and disposal or recycle".[49] The NCCLCs will promote development of trans-disciplinary, systems- and molecular-level understanding of the life cycle of important synthetic chemicals.[49]

It is also important to highlight the mission of the EPA's National Center for Computational Chemistry (NCCT), which is to determine how to change the current approach that is used for the evaluation of chemical safety.[50] NCCT scientists are incorporating advances in biology, biotechnology, chemistry, and computer science to identify important biological processes that may be disrupted by chemicals. It is hoped that the integration of such information will help prioritize chemicals based on potential human health risks at reduced cost and less time, while reducing the amount of *in vivo* testing.[50]

The Molecular Design Research Network (MoDRN) is a research project that is funded by the NSMDS program (ID Number 1339637). MoDRN is an initiative from the Center for Green Chemistry and Green Engineering at Yale University and is a multi-institute collaboration of four universities, namely, Baylor University, University of Washington, George Washington University, and Yale University. The overarching goal of MoDRN is to elucidate design guidelines systematically for reduced likelihood of adverse oxidative stress pathways implicated in human toxicity end points in order to evaluate readily the potential hazards of existing chemicals and inform the design of safer next-generation molecules. This effort will require the development of novel computational strategies for *in silico* evaluation in concert with *in vitro* and *in vivo* biological assays to enable an iterative process to move toxicity predictions toward greater accuracy and robustness. The existing *in silico* approaches to toxicity prediction varies widely in accuracy for various end points due to the inherent complexity of toxicity pathways and limited availability of quality data sets. The MoDRN computational−experimental screening approach will allow for rapid, iterative strengthening of *in silico* models and propagation of practical and teachable design guidelines based on robust models. The development of these guidelines are critical to *a priori* molecular design for safety and will reduce reliance on predictive *in silico* assessments of chemical toxicity of structures *a posteriori*. The MoDRN project provides a unique opportunity to bring cutting edge green chemistry and safe chemical design principles to practitioners in the field.

Future Challenges. Although the design of safer chemicals has been adopted by certain industrial sectors like pharmaceuticals and pesticides, molecular design for reduced hazard as a field of academic inquiry is still an emerging area of research, development, and commercialization. As our understanding of the mechanisms of action of toxicity grows, the work of the designer will be more clearly defined in the sense that the MoA will help refine the problem to be addressed at a molecular level. However, the challenges and the complexity will often make clear that a design solution may not be apparent with current understanding.

There are a number of future challenges facing scientific community in achieving molecular design for reduced hazard. Some of these challenges are technical whereas others are logistical and cultural.

1. It will be necessary to tackle the issue of safer design when human exposure is inherently required. The use of

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chemicals for therapeutics has and will continue to be a significant challenge.
2. Designing at the nexus of multidisciplines, including chemistry and toxicology, will face the challenges of terminology, methodology, and perspectives that need to be addressed through enhanced collaborative efforts.
3. The education of current and next generation chemists in the molecular design concepts and toxicology needs to be improved significantly because the vast majority of current curriculum largely ignores the topics.
4. There will need to be broader adoption by practitioners, particularly those working in industrial laboratories, whose primary goal is to produce a chemical for sale in the marketplace. Although historically, these issues were often relegated to controlled exposure or controlled use scenarios to reduce exposures and thereby manage risks, the historic failures of such approaches inherently requires advancement of alternative strategies.
5. Information on the life cycle assessment (LCA) impact associated with building blocks will be needed by the chemical designer. Designers need to know whether or not selected building blocks, and their preparation, are associated with human health concerns and environmental hazards. Otherwise, it is possible to produce a safe target molecule that causes larger problems elsewhere in the life-cycle. There is also the need to transition to biobased feedstocks.
7. More research must be done to develop the design of degradation potential and reduced bioaccumulation into novel chemical structures.
8. The development of "preventative toxicology" where increasing knowledge of biological and environmental mechanisms of action are continuously incorporated into the design of chemical products.
9. The importance of policy mechanisms to facilitate innovation and design of less hazardous substitutes.

CONCLUSION

The simultaneous evolution of the tools, understanding, and awareness in the fields of chemistry and toxicology has allowed us to have the possibility of genuine *de novo* design of molecules with a decreased probability for hazard to humans and the environment. Progress cited above is already being made and the future potential is significant. Through computational chemistry coupled with high-throughput and mechanistic toxicology, even great insights into design are likely.

Perhaps the greatest challenge is to encourage and ensure the adoption of these insights into their design protocols by practitioners. It is sadly true that while we focus on the cutting edge future research needed, the current well-established knowledge that would inform the design of safer chemicals is still yet to be systematically integrated in practice. This design imperative needs to be implemented in order to make a positive impact.

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