REVIEW

Designing for a green chemistry future

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The material basis of a sustainable society will depend on chemical products and processes that are designed following principles that make them conducive to life. Important inherent properties of molecules need to be considered from the earliest stage—the design stage—to address whether compounds and processes are depleting versus renewable, toxic versus benign, and persistent versus readily degradable. Products, feedstocks, and manufacturing processes will need to integrate the principles of green chemistry and green engineering under an expanded definition of performance that includes sustainability considerations. This transformation will require the best of the traditions of science and innovation coupled with new emerging systems thinking and systems design that begins at the molecular level and results in a positive impact on the global scale.

The scientific question facing the chemical sector when designing for the future Earth is not whether products of the chemical industry will be necessary, because they surely will be. Rather, the question is, what will be the character, nature, and production processes of synthetic chemicals needed for a sustainable civilization? Chemistry has a long history of inventing essential and beneficial products and processes with extraordinary performance; however, this technological progress has often been realized using a narrow definition of function, which does not account for adverse consequences.

Today's chemical sector follows a linear path (Fig. 1, left), in which feedstocks, mostly fossil and finite in nature, are pushed through a production chain that relies on reagents that are designed to be highly reactive but are often also unintentionally persistent and/or toxic, which is consequential for worker exposure as well as accidental or intentional release (e.g., methyl isocyanate release in Bhopal, India, and dioxin spills in Times Beach, Missouri, and Seveso, Italy). Many of these processes generate waste (often itself toxic, persistent, and bioaccumulating), at rates higher than the intended product, particularly as product complexity increases (e.g., 5 to 50 times for specialty chemicals and 25 to 100 times for pharmaceuticals) (*1*). Similarly, the resulting chemical products are often designed for their intended use while relying on circumstantial controls to limit exposures to hazards that have often not been assessed, potentially owing to the historic lack of tools and models, as evidenced by the multitude of unintended adverse consequences (*2*).

Given the need for the many functions provided by the products of the chemical industry, the question, as we look to the future, must include two goals: How do we (i) keep and greatly expand upon the advances in performance while (ii) limiting or eliminating the detrimental impacts that threaten the sustainability of human and planetary well-being? Answering this question is an important and urgent scientific challenge. There is a plethora of achievements in the fields of "green chemistry" (*3*, *4*) and "green engineering" (*5*) that have demonstrated that more performance and functionality from our chemical products and processes can be realized while decreasing adverse impacts. These successes need to be made systematic and not anecdotal. To succeed, not only do the conditions and circumstances by which we make and use chemical products need to be altered but the inherent nature of the chemical products and reagents themselves across the entire value chain from feedstock to application also needs to be changed (Fig. 1). This requires changing the nature of the very definition of "performance" from function alone to function and sustainability, which can only be realized through thoughtful design of the intrinsic properties of the molecules and their transformations.

Call for design and innovation in an integrated systems framework

Pursuing improved design for sustainability in complex systems is acutely challenging when using a traditional reductionist approach (*6*). In the chemical sector, a reductionist focus on function has resulted in pharmaceuticals that not only extend and enhance life and well-being but also persist in our water after their useful life, causing exposure to unintended populations (*7*); agricultural chemicals that increase crop yields while causing fish kills and degrading groundwater (*8*); and chemicals that make materials durable and impart long-term performance but bioaccumulate in our bodies and in the biosphere (*9*). Despite many examples of the failure modes of the reductionist approach, we often continue to use this framework to address sustainability challenges, as evidenced by the focus on isolated, individual metrics (e.g., greenhouse gas emissions, energy or water consumption, and ecotoxicity) instead of on reframing sustainability as a multidimensional problem of nested complex systems (*10*).

Incrementally improving current products and processes through efficiency measures is the focus of many sustainability efforts in the chemical industry, but this approach will not be sufficient. Instead, we need transformative, disruptive innovations to sustainably provide desired functions. Systems must be considered in their entirety to identify solutions that do not shift impacts or cause unintended consequences elsewhere. The traditional reductionist approach, then, must be coupled with integrative systems thinking to inform designs for a sustainable future (*11*). For example, knowledge about the functional performance of a molecule is only a minimal requirement; knowledge about the potential hazards of the molecule is also needed. Instead of solving a singular challenge in ways that may exacerbate other challenges (e.g., trading off bio-based fuels for land-use pressures or competition with food), there is now the opportunity for so-called "nexus solutions" (*12*), that is, solutions that synergistically advance multiple sustainability challenges—for example, an earth abundant metal catalyst that splits water using sunlight, yielding hydrogen for energy storage and producing water when that hydrogen is combusted for energy recovery (*13*). Designing future fuels that are produced in a carbon-neutral way to reduce local air pollution emissions and increase engine efficiency is another example (*14*). Although there are current discussions on cascading nonlinear problems (e.g., increased fossil energy generation→greater water stress→refugee migration→civil unrest and military conflict), systems thinking and design targeting nexus solutions allow for the possibility of cascading nonlinear solutions: discreet and specific actions that create benefits that are multiplied and magnified (e.g., CO_2 utilization shifts a waste to a feedstock→the use of toxic reagents, such as phosgene, is avoided→CO_2 emissions decrease→the rise of CO_2 levels slows→global climate change is mitigated).

Expanding the definition of performance beyond technical function to include sustainability

Realizing the necessary changes to the chemical sector requires a redefinition of how the concept of performance has historically been measured. Since commercial synthetic chemistry was started in the mid-19th century with

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the introduction of Perkin's mauve dye, the criterion by which chemical products were judged was "performance." Performance has been almost entirely defined as the ability to efficiently accomplish a narrowly defined function (e.g., color for dyes, adhesion for glues, or the ability to kill pests for pesticides). However, the unintended consequences of this singular focus demonstrate the imperative that our definition of performance must broaden to include all of the aspects that we care about beyond function, particularly sustainability.

This expanded definition of performance requires chemical product and process designers to know not only the mechanisms of technical functional performance but also the mechanisms of harm that the substances can induce. This expanded definition of performance implicitly requires that anyone designing, inventing, and intentionally making a chemical product or process must have a working knowledge of the molecular hazard, be it a global, physical, or toxicological hazard. After more than a century of incidents and accidents that have resulted in adverse consequences to human health and the environment, the training for chemists that integrates toxicology deeply into the curriculum remains the exception and not the rule. Enabling the consideration of chemical hazards in the same manner as chemical performance will require that our education programs, like our technologies, expand the definition of function to include sustainability attributes.

The redefinition of performance also directly affects the business model of the chemical sector, because one part of the strategy of diminishing adverse impact is to reduce the absolute quantity of material needed, thereby reducing harm potential across the life cycle. The "F-factor" (*15*) partially captures the concept of maximal functionality: The notion is to maximize function while minimizing chemical or material mass, which is akin to the Moore's Law challenge for computing power (*16*). Of course, the notion of minimizing mass is intended as a proxy for limiting the amount of feedstock, processing and transport energy, manufacturing waste, end-of-life material for management, and, subsequently, the associated harm. This approach can be applied to whatever service is required—for example, color, lubrication, or cleaning—and will shift the profit imperative from selling as much material as possible to selling as much function as possible with a concomitant decrease in hazard. Such a paradigm shift is in accordance with the United Nations Industrial Development Organization's emerging emphasis on "chemical leasing" (*17*), or selling the function, rather than a quantity, of the chemical. This reduces costs of material production and values efficiency and efficacy in ways that maximize profits in alignment with sustainability (Fig. 1, right).

The inherent nature of tomorrow's chemicals and materials

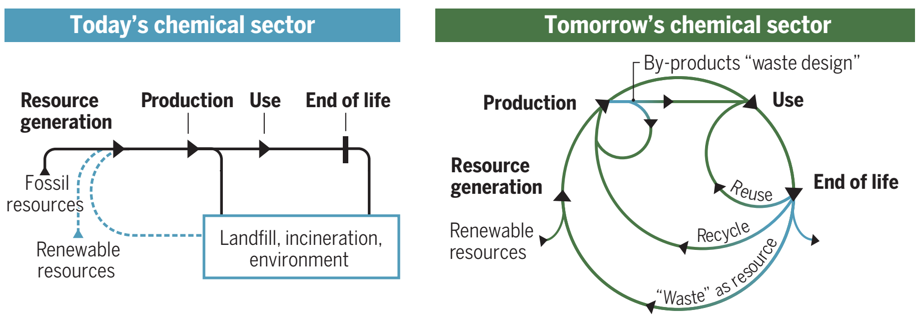
Tomorrow's chemical products should be designed to preserve efficacy of function while reducing or eliminating hazard (*3*). Here, hazard is defined broadly to consider physical (e.g., explosivity and corrosivity), global (e.g., greenhouse gases and ozone depletion), and toxicological (e.g., carcinogenicity and endocrine disruption) hazards. Chemical risk, defined as a function of both hazard and exposure, is often "managed" by solely focusing on limiting exposure to hazardous chemicals, for example, through the use of protective equipment or air emissions scrubbers. When exposure control mechanisms fail, the results can be catastrophic because the hazard part of the equation has not been addressed. The alternative approach of green chemistry is to shift the focus of risk reduction to reducing hazard. Notably, hazard is an inherent property of chemicals and is ultimately the result of a design choice. Accordingly, a shift to proactive design of chemicals and processes based on an understanding of the molecular mechanisms causing human and environmental toxicity as well as physical and global hazards more broadly is necessary (*18*). As such, an expanded definition of performance should include functionality as well as the inherent nature of the chemicals, including that they are nondepleting, nontoxic, and nonpersistent in the environment.

Nondepleting

Transitioning from fossil- to renewable-based chemistry must be thoughtfully designed within an integrated systems context to consider negative impacts that could be caused by land transformation, water use, or competition with food production. It is imperative that the important move to renewably sourced feedstocks is achieved using benign processes and includes a paradigm shift from linear to circular processes (Fig. 1). Thereby, materials that are currently regarded as low-value waste must be treated as a renewable feedstock in tomorrow's chemical sector (*19*). Examples of utilizing low-value "waste" include the conversion of lignin from papermill waste to produce vanillin and feedstocks such as catechol, phenol, or guaiacols (*20*) and the direct use of CO_2 to partially replace petroleum-based propylene oxide in the production of polyurethanes, which substantially reduces the carbon footprint and simultaneously improves other relevant environmental parameters (*21*, *22*). Going one step further, chemists need to consider "waste design": how synthesis routes can be adapted to avoid relying on treatment and disposal of by-products and instead include design decisions that render by-products useful as raw materials (Fig. 1) (*23*).

Nontoxic

The design of nontoxic chemicals can only be achieved through collaboration between



Mostly linear processes →	Circular processes
Fossil feedstocks →	Renewable feedstocks
Reactive, persistent, or toxic chemical reagents and products →	Benign chemical reagents and products
Catalysis using rare metals →	Catalysis using abundant metals, enzymes, photons, or electrons
Covalent bonds →	Weak, noncovalent interactions
Conventional solvents →	Low toxicity, recyclable, inert, abundant, easily separable green solvents or solventless
Material- and energy-consuming isolation and purification →	Self-separating systems
Large "waste" volume →	Atom-, step-, and solvent-economical processes
"Waste" treatment →	"Waste" utilization
Design exclusively for use phase with reliance on circumstantial control →	Intentional molecule design for full life cycle
Performance = maximize function →	Performance = maximize function + minimize hazards
Maximum chemical production for increased profit →	Maximum performance with minimal benign material use for increased profit

Fig. 1. Characteristics of today's and tomorrow's chemical sectors.

chemistry, toxicology, genomics, and other related fields. It is necessary to investigate and understand the underlying molecular mechanisms, including how molecules are absorbed, distributed, metabolized, and excreted from the body (ADME), and how physicochemical properties, including solubility, reactivity, and cell permeability, influence these events (*24*). Efforts to predict and model toxicity are ongoing, for example, based on molecular initiating events by examining structure-activity relationships [(quantitative) structure-activity relationships QSAR and SAR] (*24*). However, models rely on limited available toxicity data. Current efforts to generate this data include the ToxCast and Tox21 programs in the United States (*25*) and ToxRisk in the European Union (*26*).

Nonpersistent

Tomorrow's chemicals must be designed to degrade easily and rapidly to nonpersistent compounds that do not adversely affect the environment. Recent examples include a rapidly degradable insecticide with very low toxicity to mammals (*27*), chemical modification to improve biodegradability of an otherwise environmentally recalcitrant beta-blocker (*28*), and rapidly biodegradable, nontoxic, and partially renewably sourced succinic acid–based plasticizer additives for polyvinyl chloride (PVC) polymers (*29*). An understanding of the molecular features and environmental mechanisms that lead to persistence are required to build predictive QSAR and SAR models (e.g., the U.S. Environmental Protection Agency's EPI Suite). It is crucial to routinely assess the potential persistence of synthetic compounds for every (newly) designed compound that will be ultimately dispersed in the environment (e.g., pharmaceuticals and personal care products) (*30*).

However, persistence may be a desirable attribute when considering the amounts of energy and molecular complexity embedded in a chemical compound and its synthetic route. An evaluation of whether this "investment" can be harnessed beneficially in a value-added application rather than pursuing a design for a degradation pathway is an important alternative consideration (Fig. 2). For renewably sourced and benign molecules with high levels of complexity and embedded energy and, importantly, that are not intentionally distributed in the environment, the goal should be reintegration into the value chain through reuse or recycle loops. However, if the molecule is intentionally or ultimately distributed in the environment, degradability is imperative, regardless of its complexity or embedded energy.

Redesigning the chemical value chain with nonfossil feedstocks

Today's chemical production relies almost exclusively on oil, gas, and coal as the sources of carbon. The petrochemical value chain that emerged in the second half of the 20th century forms a highly integrated network, sometimes referred to as the "petroleum tree" (Fig. 3). Petrochemical refineries produce less than a dozen building blocks, in particular, short-chain olefins and aromatics. Together with synthesis gas, which is a mixture of CO and H_2, these few compounds form the stem of carbon that constitutes the huge molecular diversity in branches, twigs, and leaves of more than 100,000 chemical substances in final products.

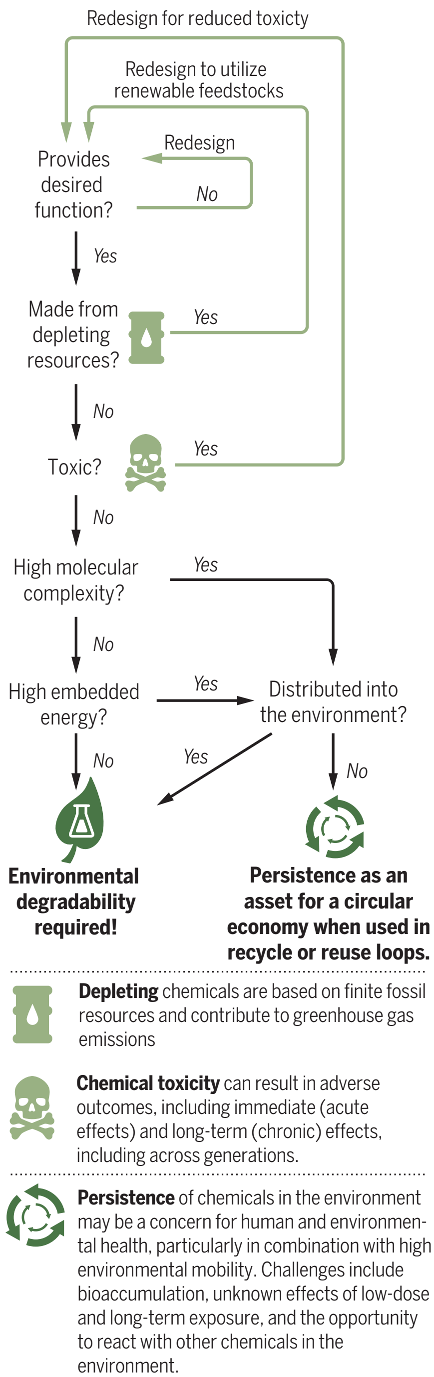


Fig. 2. Decision tree for chemical design.

The value generation of petrochemistry largely results from the powerful arsenal of synthetic methods for the introduction of functional groups into molecules. Consequently, the availability of starting materials and the desired product functions have a direct feedback connection with the development of chemical production routes and processes. Improvements in the corresponding synthetic methods will undoubtedly remain a major field of research with direct positive impacts on the environmental footprint of chemical products (Fig. 3, top, green arrows). Owing to the inherent problems of the depletion of a finite resource, connection to climate change, and inextricable links to toxic congeners, petroleum is not a sustainable option, and ultimately, the design of new value chains based on nonfossil carbon sources and energy from renewable resources will pave the way to closed carbon cycles. This paradigm shift, marking nothing less than the next industrial (r)evolution in chemistry, has already started (Fig. 3, bottom, green arrows).

Major scientific breakthroughs and innovations will be necessary to make the utilization of renewable carbon sources increasingly competitive. Advanced hydrogen technologies (*31*) and electrochemical processes (*32*) are actively researched to harness the required "decarbonized" energy. Among carbon sources, lignocellulosic biomass, one of the most abundantly available raw materials on Earth (*33*), and CO_2 (*34*) are available in sufficient quantities to achieve a "defossilization" of the chemical value chain. Recycled plastic material is another potential large-volume carbon source in the framework of a circular economy (*35*). In contrast to fossil resources made up from carbon and hydrogen only, these feedstocks comprise mostly highly oxidized and "overfunctionalized" molecules. Their transformation, therefore, requires innovative synthetic concepts and methodologies for the removal or reorganization of functional groups.

One option to deal with the challenge of complexity is to remove it—for example, through intermediate syngas production combined with the Fischer-Tropsch technology to produce a petroleum proxy as a drop-in replacement (*36*). Thereby, additional roots can be added to the petroleum tree from almost any nonfossil feedstock. "Green carbon" is then transported through all existing branches and leaves. Although this approach allows for repurposing established knowledge and infrastructure, it destroys and reassembles valuable functionality.

An alternative strategy is to take advantage of the inherent higher complexity of renewable feedstocks to open molecular shortcuts to the desired functional groups. For example, the production of important platform chemicals such as 1,3-propanediol or succinic acid by microbial fermentation of (waste) glycerol or sugars near room temperature in water is

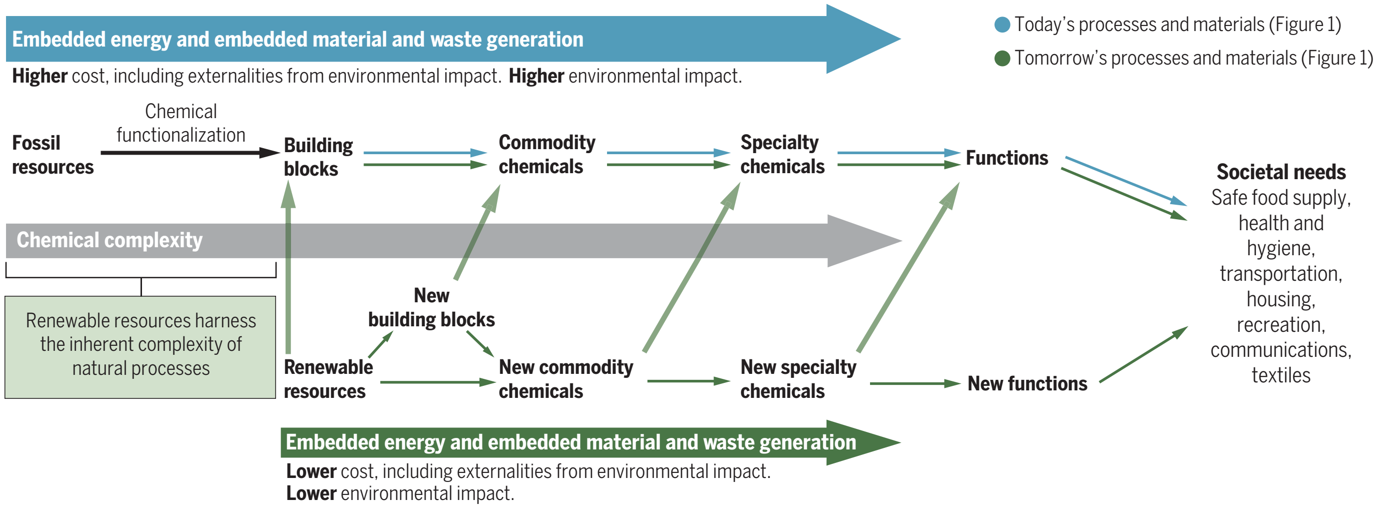


Fig. 3. Benefits of moving from fossil to renewable resources using greener transformation schemes and process chains in terms of embedded energy; embedded materials, including water; waste generation; and environmental and economic costs.

increasingly rivaling the multistep petrochemical routes (*37*). Similar considerations apply to the use of CO_2 that can be integrated into the value chain through existing large-volume base chemicals, methanol being one of the most promising options (*38*). Tailored chemo- and biocatalysts that can be adapted to variations in feedstock quality and fluctuations in energy supply, together with the development of highly integrated and energy-efficient purification processes, will be important scientific motors behind this development.

Perhaps to even greater advantage, renewable feedstocks provide entirely new chemical building blocks (*39*) that can drive the realization of improved functionality without the historic adverse impacts to human health and the environment. One molecule that has recently garnered interest is monosaccharide-derived furane dicarboxylic acid (FDCA), a possible building block for new polyester products such as containers for carbonated liquids (*40*). The incorporation of CO_2 directly into polymer chains of consumer products is already being industrialized (*21*). A growing number of new synthetic methodologies based on selective coupling of CO_2 and H_2 with other substrates illustrates their broad potential for construction of functional groups at late stages of product synthesis (*41*).

The necessary integration of the molecular and engineering sciences with the systems thinking on product performance is obvious in this area. This will enable integration of energy and material fluxes at the chemistry-energy nexus (*42*) and defines new opportunities for sector coupling of chemistry with, for example, agriculture, steel, or cement industries. Deconstructing a highly complex target molecule through "retrosynthetic analysis" to plan its assembly from existing building blocks and synthetic methods is a central pillar of today's synthetic organic chemistry (*43*). The same conceptual thinking can be transferred into a new design framework for synthetic pathways to improved target products from renewable feedstocks (*44*).

Conclusion

Einstein is famously quoted as saying "problems cannot be solved at the same level of awareness that created them" (*45*). The new tools and approaches we need include attaining mastery of weak-force interactions as a design tool, as we have realized with covalent bonds; designing complex, nonideal mixtures rather than synthesizing a single molecule to achieve function; understanding the molecular scale at the complete dynamic reality rather than as a simple, static snapshot; understanding and controlling long-range interactions for chemical reactivity at localized structures; and progressing from mathematical analysis of a series of experiments toward statistical mining of large and diverse datasets. As it is in nature, the concept of "waste" must disappear from our design frameworks, such that we instead think in terms of material and energy flows. Hazards to the inhabitants and systems of the biosphere by our chemical products and processes should be viewed as a critical design flaw and performance defined in terms of both primary functionality and sustainability.

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