Green Chemistry

CRITICAL REVIEW

View Article Online
View Journal

Cite this: DOI: 10.1039/c8gc00482j

The Green ChemisTREE: 20 years after taking root with the 12 principles

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Received 11th February 2018,
Accepted 21st March 2018

DOI: 10.1039/c8gc00482j

rsc.li/greenchem

The field of Green Chemistry has seen many scientific discoveries and inventions during the 20 years since the 12 Principles were first published. Inspired by tree diagrams that illustrate diversity of products stemming from raw materials, we present here the Green ChemisTREE as a showcase for the diversity of research and achievements stemming from Green Chemistry. Each branch of the Green ChemisTREE represents one of the 12 Principles, and the leaves represent areas of inquiry and development relevant to that Principle (branch). As such, in this 'meta-review', we aim to describe the history and current status of the field of Green Chemistry: by exploring activity within each Principle, by summarizing the benefits of Green Chemistry through robust examples, by discussing tools and metrics available to measure progress towards Green Chemistry, and by outlining knowledge gaps, opportunities, and future challenges for the field.

Introduction

In the nearly 20 years since the field of Green Chemistry was codified with the 12 Principles of Green Chemistry,[1] an enthusiastic global community has made countless contributions to advancing the field and realizing the potential benefits. Whereas in the early-to-mid 1990s Green Chemistry was rarely highlighted outside niche symposia and the publications of early adopters, now scientists have access to any number of high-impact and dedicated journals, handbooks

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The team of authors represents the Center for Green Chemistry and Green Engineering at Yale (the Center). The Mission of The Center is to advance sustainability by catalyzing the effectiveness of the Green Chemistry and Green Engineering community. The Center seeks to benefit Green Chemistry and Green Engineering by advancing the fundamental science and technology, training the current and future workforce, catalyzing implementation of effective science, technology, and policy, and raising awareness of the power and potential of these fields.

and encyclopedias, conferences, academic and professional training courses, software tools, databases, funding sources, and award programs. The level of activity within the community is such that sub-fields are beginning to emerge at the interfaces with toxicology, engineering, and other allied disciplines. It is becoming increasingly challenging to provide comprehensive overviews of the state of the science: citation metrics show that there are now more than 300 Green Chemistry-themed review articles that each have been cited at least 100 times. Nevertheless, here we endeavor to provide a perspective, not only reflecting the accomplishments of the past decades, but also looking forward to new, fertile ground for investigation. Our aim is to provide a useful orientation for newcomers to the topic, while also inspiring current practitioners to consider the remaining urgent and important intellectual challenges.

We use the 12 Principles of Green Chemistry as a framework for the discussion. Many will be familiar with the Principles as laying out the "what" and "why" of designing chemical products and processes that reduce or eliminate the use or generation of hazardous substances. The global community has filled in many of the gaps for "how", and here we will highlight examples of chemical reactions, processes, design strategies, and other tools that can be used to reduce the potential impacts of chemical products across their life cycle. Metrics to quantify advances in meeting these goals cut across all Principles and research topics, and indeed have been the focus of entire review articles and handbooks in their own right. Transparent and quantitative evaluation of putative improvements builds trust among inventors, end users, and the public. In the discussion below, for each Principle, we focus on the following:

• Potential impacts: Why is the chemistry important? Where is it found? What role does it play in environmental, economic, and social systems?

• Tools: How may a chemical practitioner go about realizing and advancing the potential benefits?

• Examples: What has been recently accomplished? Here, while it would be tedious if not impossible to give an exhaustive treatment, we have aimed to guide the reader toward more specific review articles and focus on a small number of case studies to illustrate the spirit of the Principle in action.

• Metrics: What techniques can be applied to evaluate new designs? What gains have been quantified from the advances in science?

• Implications: Where are remaining knowledge gaps? What opportunities and challenges remain?

The maturity of the field also inspired us to introduce the "Green ChemisTREE" metaphor (Fig. 1). Tree diagrams have been used in chemistry to celebrate the diversity of applications that can be supported by a particular raw material,[2] for example tracing a product back through its polymer, monomer, or other intermediate components and ultimately a resource such as crude oil, coal, natural gas, or minerals. Indeed, many variations on the theme have appeared in illustrations since the beginnings of modern chemistry (see the "Petroleum Tree"[2] and the "Coal Products Tree"[3]). Our goal is similar: to be concise, informative, visual, and encourage the viewer to reflect on what lies at the roots of progress in the chemical enterprise. Here, the branches of our Green ChemisTREE shown in Fig. 1 are each of the Principles of Green Chemistry with the leaves representing techniques available to the Green chemist – mechanisms, procedures, design guidelines, and other resources that can be used to realize the potential benefits of Green Chemistry (represented in text form in Table 1). The tree will continue to grow, of course; Green Chemistry has always been envisioned as a philosophy of continuous improvement. (Green) Chemists will constantly question what can be done better, what experiments and collaborations would be a step in the right direction, and how we know we have made progress.

Green chemistry principles

Principle 1: "It is better to prevent waste than to treat or clean up waste after it has been created."

The costs of chemical waste are a serious economic, environmental, and social liability, with even technologically advanced countries facing costs on the order of $1B per year for both legacy and ongoing activity. In addition to economics, there are impacts on ecosystems as well as the health of workers, surrounding communities, consumers, and the general public.[4,5] Waste prevention is a cornerstone of Green Chemistry; chemists' choices of raw materials, reaction pathways, protecting groups, catalysts, solvent systems, and separation methods may all lead to reduced waste generation and help mitigate these costs. In practice, this is a shift from conventional "end-of-pipe" or treatment and disposal methods in that the goal is for chemists to avoid waste in the first place, through innovative design. Techniques can be applied across the life cycle including during material acquisition, production, use, and end of life. Many of these strategies are the focus of specific Principles and will be discussed in detail in their respective sections. Broadly, the goals of chemical approaches to waste reduction are simplification, dematerialization, and closed loop systems.

To date, within the Green Chemistry community there has been significant emphasis on reducing waste during chemical synthesis through simplification and dematerialization, which are closely connected. A typical approach is one-pot synthesis which avoids isolation and purification of chemical intermediates, thereby reducing quantities of solvents and separation aids. In organic chemistry, this has often been accomplished through advances in catalyst design, for example selective activation of C–H bonds,[6,7] aryl–aryl bond formation,[8–11] and olefin metathesis.[12] Development and optimization of catalytic systems to improve selectivity in chemical reactions can improve multiple environmental outcomes, including waste reduction, and is further highlighted in Principle 9. Progress has also been made in designing chemical reactions where the reagents or products take on additional roles that would ordi-

Fig. 1 The Green ChemisTREE highlighting the areas of inquiry and progress relevant to each of the 12 Principles of Green Chemistry (as represented to a branch). Abbreviations: crit. – critical; eff. – efficiency; haz. mat. – hazardous materials; metr. – metrics; prod. – production; solv. – solvent; ADME-*a*bsorption, *d*istribution, *m*etabolism, excretion; HTS-high throughput screening; (Q)SAR-(quantitative) structure–activity relationship.

Table 1 Listed branches and leaves of the Green ChemisTREE (Figure 1), highlighting the areas of inquiry and progress relevant to each of the 12 Principles of Green Chemistry. Abbreviations: ADME-absorption, distribution, metabolism, excretion; HTS-high throughput screening; (Q)SAR-(quantitative) structure–activity relationship. (s) indicates a leaf shared between two separate branches

Prevent waste (1)	Atom economy (2)	Less hazardous synthesis (3)
• One-pot synthesis • Integrated processes • Self-separation • Molecular self-assembly (s) • Process intensification • Additive manufacturing • Waste as feedstock • Circular economy Ref. 1 and 4–37	• *E*-Factor (s) • Synthetic efficiency metrics • Reaction network optimization • Rearrangement reactions • Ring modification reactions • Coupling reactions • Aromatization reactions • Cycloaddition • Grubbs metathesis Ref. 1, 25, 26 and 38–73	• Lifecycle analysis (LCA) • Non-metal catalysis • Dialkyl carbonate reactions • C–H bond functionalization • Replace hazardous materials (s) • On-demand production of hazardous materials (s) • Hazard and risk metrics • Material efficiency metrics • Energy efficiency metrics • Green synthesis evaluation metrics Ref. 1 and 74–94

Design benign chemicals (4)	Benign solvents & auxiliaries (5)	Design for energy efficiency (6)
• Read across (s) • SAR/QSAR (s) • Reactivity parameters (s) • 2D/3D properties (s) • Metabolism (s) • Design guidelines (s) • ADME • HTS/*in vivo*/*in vitro* • Enzymatic models • Modes of toxic action • Adverse outcome pathways Ref. 1 and 95–152	• Water • Solventless • Ionic liquids • Sub- and supercritical fluids • Switchable solvents • Gas-expanded liquids • Bio-sourced solvents • Greener surfactants • Solvent selection tools Ref. 1, 51 and 153–215	• Self-separation • Mechanochemistry • Sonochemistry • Microwave irradiation • Photocatalysis • Electrocatalysis Ref. 1, 176 and 216–266

Use of renewable feedstocks (7)	Reduce derivatives (8)	Catalysis (9)
• Fermentation • Enzymatic processes • Biomass-to-chemical • Biofuels • CO_2 • New platform chemicals • Renewable platform chemicals • Integrated biorefinery Ref. 1 and 267–320	• Flow chemistry • Click chemistry • Electrosynthesis • Molecular self-assembly (s) • Molecular chaperones • Non-covalent derivatives Ref. 1, 51, 65 and 321–342	• Solid acids and bases • Clay/zeolithes • Enzyme engineering • Immobilization • Isolated enzymes • Biocatalysis • Nanocatalysis • Organocatalysis • Ultra-low loadings • Metal-organic frameworks • Abundant metal catalysis Ref. 1, 27, 51, 63, 83 and 343–405

Design for degradation (10)	Real-time analysis for pollution prevention (11)	Inherently benign chemistry for accident prevention (12)
• Read across (s) • SAR/QSAR (s) • Reactivity parameters (s) • 2D/3D properties (s) • Metabolism (s) • Design guidelines (s) • Prediction tools • Biodegradation databases • Molecular triggers • Degradable polymers • Green pharmaceuticals • Benign metabolites Ref. 1, 74, 105, 288, 295, 29, 325 and 406–457	• Continuous flow and analysis • Sensors • Chromatography • Spectroscopy • Computational advances Ref. 1, 313 and 458–491	• On-site production of hazardous materials • Reduced use of hazardous materials • Replace hazardous materials (s) • On-demand production of hazardous materials (s) Ref. 1 and 492–514

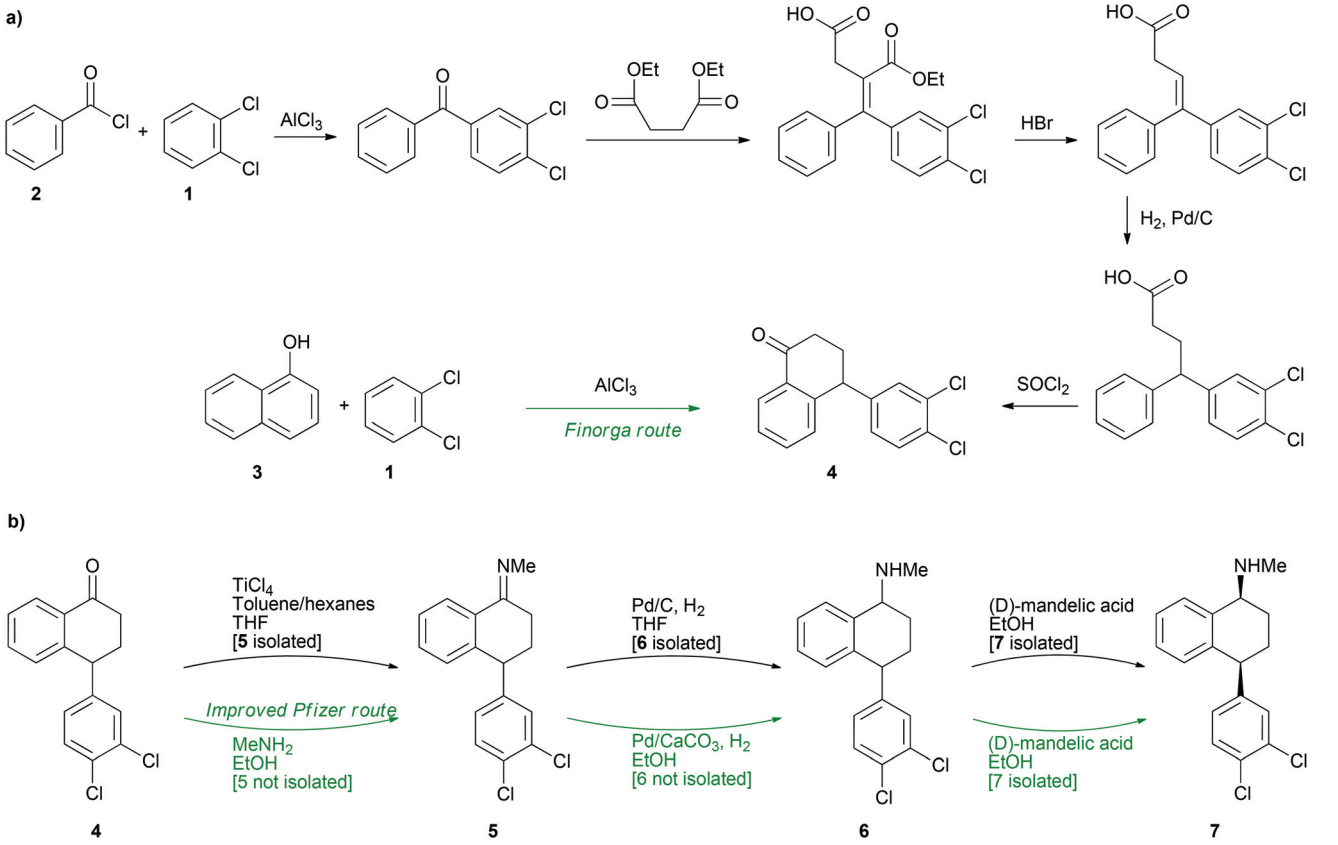
narily be performed by auxiliaries, for example molecular self-assembly or self-separation resulting in more autonomous reactions with fewer resources invested in driving the system.[13] Taking advantage of intrinsic physical and chemical properties and designing at the system level are key elements in the approach.[14]

Strategic design of production processes can also lead to significant improvements. Process intensification focuses on

redesign for improved yield, product quality, and efficiency; this is often accomplished through reduction in process complexity, equipment units, or processing plant size.[14,15] The pharmaceutical industry has provided notable examples of waste prevention through process intensification and design of synthetic routes with step reduction in manufacturing of active pharmaceutical ingredients (APIs). For sertraline (a selective serotonin reuptake inhibitor sold under the tradename Zoloft®), a combined process was designed to simplify the original multi-step manufacturing process of the aryl-substituted tetralone precursor **4** to a single step (Scheme 1a), and an improved route to sertraline led to doubled product yield, decreased raw material input, improved energy efficiency, reduced water use, and elimination of several toxic waste products (Scheme 1b),[16–18] which was honored with a U.S. EPA Presidential Green Chemistry Challenge award.[19] Changes in the mechanism of material delivery have been shown to reduce the environmental footprint by incorporating more of the manufacturing materials into the final product. Examples can be seen in the metalworking and mold making industries, where waste is reduced by substituting traditional subtractive strategies (*e.g.*, selective removal of excess material through chemical etching) for additive ones (*e.g.*, 3-D printing).[14,20–22]

When the very generation of waste cannot be fully avoided, closed loop ("waste as feedstock") systems, recycling, and interconnection of multiple product streams can be highly effective in valorizing waste streams and making progress toward circular economies. While this is widely practiced in industry, especially at the level of commodity chemicals, it is an effective approach at any scale and important to consider in early design stages of new chemical products and processes. Recycle and reuse strategies are not free of economic and environmental costs, but life cycle assessment tools have shown that for many materials the benefits can far outweigh the impacts. Metallic chemistry is an example where the embedded energy, material, and water requirements for virgin material are especially high, and additional factors such as scarcity of supply and toxicity of waste streams are important.[24] Waste-as-feedstock research has made significant advances in valorization of renewable resources (see Principle 7), including municipal wastes and industry byproducts, in turn creating opportunities for low-footprint chemistry and diverting materials from landfill or incineration, each with their downstream adverse economic, environmental, and societal impacts.

Many methods for quantifying chemical waste and efficient use of materials are available to chemists. Some of these are



Scheme 1 (a) The initial multi-step synthesis for the aryl-substituted tetralone **4** from substrates **1** and **2** compared to the improved single-step Finorga route (green arrow) starting from **1** and **3**.[23] Adapted with permission of The Royal Society of Chemistry (b) comparison of Pfizer's previous and improved (green arrows) synthetic route for Sertralone **7**, starting from **4**.[18] Adapted with permission. ©2004 American Chemical Society.

discussed in more detail in Principle 2 below. One of the commonly used approaches is the Environmental (or Mass Efficiency) Factor, or *E*-factor, which enables simple comparison of processes by quantifying the mass ratio of waste to desired product.[25–27] *E*-Factor analyses are useful at lab and production scale and have also been used to identify trends in chemical industry, such as a general increase in waste for chemicals produced in smaller quantities. Commodity chemicals produced in complex, interconnected manufacturing plants tend to have a small waste footprint, whereas specialty chemicals may be associated with thousands of kg of waste generated per kg of product. Thus *E*-factors commonly vary over 5 or more orders of magnitude.[28–30]

Increasingly, it is recognized that more information besides absolute quantities of waste need to be taken into consideration; that is, the nature of the wastes (*e.g.*, the toxicity) is also an important factor in decision-making. Life cycle assessment tools are being used to identify key contributors to waste from chemical products and processes, and to prioritize targets for improvement. This wider, system-level view helps identify and balance potential tradeoffs, and helps chemists ensure that increases in reaction yield or material efficiency do not occur at the expense of offsets in different areas, *e.g.*, energy or water consumption.[31]

Further progress in waste elimination at source is likely to come through improvements in product design and alignment of chemists' activities with changes in infrastructure and consumer behavior. Decentralization of manufacturing and shifts to smaller and more flexible chemical plants can be expected to lead to new efficiencies,[32] for example through miniaturization and multifunctional reactors. However, there may also be new challenges in increased material flows within the broader economy as described by the "rebound effect".[33,34] This has not been thoroughly investigated for improvements in chemical technologies, though recent work has explored effects in the areas of biofuels[35] and consumer electronics.[36] In addition to cleaner manufacturing, chemists will need to anticipate product use and end-of-life scenarios to ensure that technologies are sustainable when integrated into larger systems. This concept of "circular economy" can be applied at the interface of chemistry and engineering, for example in greener electronic products; it requires a multi-prong strategy that goes beyond process efficiency, also taking into account material recyclability, design for disassembly and reuse, and technological innovations to maintain quality and performance standards.[37]

Principle 2: "Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product."

Efficient use of raw materials is a key approach to waste prevention (discussed in detail in Principle 1). The field of chemistry has long been concerned with synthetic efficiency as a practical matter of economics, and from the point of view of intellectual challenge and aesthetics, *i.e.*, "elegant" syntheses. Clearly these goals are synergistic with environmental concerns as well. Historically, chemists have used metrics such as product yield and selectivity as a gauge of success. More recently, the concept of atom economy was articulated,[38] and it has been widely adopted in Green Chemistry as a complement to the *E*-factor (see Principle 1).

Atom economy builds on the traditional concept of yield by dividing the molecular weight of the final product by the total molecular weight of all reactants, therefore taking generated waste into account. The details of stoichiometry and actual yield are straightforward to include, as Experimental Atom Economy and Percentage Yield × Experimental Atom Economy (%PE EAE), respectively (see Table 2 for details).[39] These calculations are among the simplest estimates of "greenness" of a reaction. A variety of other metrics have since been proposed, and these focus on various efficiencies such as carbon efficiency, reaction mass efficiency (RME), energy efficiency, as

Table 2 Metrics that measure aspects of a chemical process relating to the Principles of Green Chemistry

Metric	Equation	Description or limitation
Percent yield	$\frac{\text{actual yield}}{\text{theoretical yield}} \times 100\%$	Product yield *vs.* theoretical yield
% Atom economy[a]	$\frac{\text{MW atoms utilized}}{\sum \text{MW of reactants}} \times 100\%$	Theoretical reactant conversion efficiency
% Experimental atom Economy	$\frac{\text{theoretical yield}}{\sum \text{mass of reactants}} \times 100\%$	Experimental reactant conversion efficiency
%PE EAE	$\frac{\text{actual yield}}{\sum \text{mass of reactants}} \times 100\%$	Experimental product yield and reactant conversion efficiency
E-Factor[b]	$\frac{\text{waste produced}^{c}}{\text{actual yield}}$	Inclusion of wastewater may mask relevant synthetic route differences and obscure comparison
F-Factor	$\frac{\text{value of metric of interest}}{\text{functionality}}$	Compare the synthetic routes (*e.g.*, for chemicals) based on the same functionality, with the metrics of interest

[a] Expressed in stoichiometric amounts. [b] Theoretical *E* factors can be derived from the atom economy (*i.e.*, knowledge of the stoichiometric equation).[25] [c] [∑mass of raw material and energy input − actual yield].

well as considerations of cost, toxicity, human health impacts, ozone depletion potential, and greenhouse gas emissions.[40–44] Another alternative is the *F*-factor ("function") proposed by Poliakoff[45] to enable the comparison of products or different synthetic routes (*e.g.*, combinations of reactions) based on the level of product functionality. The value of *F*-factor can track any metric of interest (*e.g.*, human toxicity) in the course of achieving desired functionality in a product, or through specific synthetic routes.

However, there is not a single metric that can encompass all the aspects of Green Chemistry, and it is therefore important that the choice of metric(s) be based on the context of the intended evaluation.[46] For example, McElroy *et al.* proposed a tiered metrics toolkit to streamline the improvement of synthetic route designs at different stages of the pharmaceutical drug development life cycle.[47] Furthermore, in accordance with the discussion in Principle 1 above, waste and other environmental impacts extend beyond the manufacturing stage of a chemical such that synthetic efficiency should be interpreted in the context of overall life cycle benefits and impacts.[48]

The implementation of these new metrics has led chemists to build a "toolbox" of favorable chemical reactions.[25] Certain bond-forming and bond-breaking mechanisms are intrinsically more atom economical than others. For example, olefin metathesis is an elegant example of a selective class of carbon–carbon bond forming reactions with high atom economy.[49,50] Other examples of reactions with good atom economy include (1) rearrangement reactions such as the Claisen rearrangement,[51] the Cope rearrangement,[52] the Curtius rearrangement,[53] and the Schmidt reaction,[53,54] (2) coupling reactions such as the Suzuki–Miyaura cross-coupling,[26,55] (3) ring contraction/expansion reactions[56,57] such as the benzilic acid rearrangement[58] and the Buchner reaction,[59] and (4) cycloaddition/aromatization reactions such as the Diels–Alder cycloaddition[60] and the Biginelli reaction.[61] Further, catalytic reaction pathways are often important in enabling high atom economies and low *E*-factors.[38,56,62–64] This is discussed in further detail in Principle 9 below. Finally, strategies for protecting group-free synthesis also lead to significant benefits;[65] these are discussed further in Principle 8 below.

Chemical manufacturing often depends on multiple synthetic steps, requiring chemists to consider potentially large numbers of reaction networks that lead to a specific target or provide a material with a certain function.[66] One strategy to improve efficiency is through step-economy, *i.e.*, minimizing the number of reaction steps. Step-economical synthesis can be designed to target molecular structure or molecular function; however targeting function is advantageous as the target structure often remains flexible in that case, allowing for design of molecules that are synthetically more accessible.[67,68] The increasing availability of computational resources in chemistry enables routine implementation of useful metrics to optimize step economy, improve atom economy and minimize byproduct formation as well as more complex tasks such as optimization of reaction networks. For example, Computer-Aided Organic Synthesis (CAOS) models automate identification of synthesis networks that meet efficiency goals as defined by a variety of metrics.[69–71] The majority of existing CAOS models take a retrosynthetic approach, beginning with a search for an appropriate reaction for the last synthesis step of the desired product, then propagating the reaction network backward.[69–71] This approach, though effective, can place excessive demands on computing resources when the synthesis network is not step economical. Another challenge is the need for multiple "trial-and-error" attempts to increase chances of a global optimization. Recently, machine learning techniques have been incorporated into model development to improve search efficiency.[72,73]

As sophisticated efficiency metrics are increasingly adopted as a result of their integration in chemistry education, professional training, and publishing standards, those reaction types requiring more efficient synthetic strategies will become increasingly evident. Efficiency gains in chemical synthesis will be made as new raw materials are made available (*e.g.*, as a result of maturing biomass-to-chemical technology), catalytic systems continue to improve in scope and substrate compatibility, and advances in process chemistry are implemented (*e.g.*, combined processes and material recycling). But it will be important to quantify how improvements in synthetic efficiency affect other aspects of the chemical lifecycle. For example, impacts of biomass purification, or extraction of metals used to prepare catalysts, could more than offset the downstream benefits in chemical synthesis. Metrics beyond resource efficiencies (*e.g.*, mass, energy) should be employed to measure the environmental, health and safety implications of new synthetic strategies, for example through life cycle analysis (LCA). The extended metrics, coupled with a holistic evaluation approach, may mitigate unintended consequences of synthetic route designs and burden-shifting among "green" endpoints.

Principle 3: "Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment."

Principle 3 calls upon chemists to consider factors other than efficiency when evaluating environmental and social impacts. It is closely connected to Principle 4, which focuses on design of less hazardous products, and also takes into account the properties of precursors, side products, and waste. It encourages chemists to adopt concepts from allied fields (*e.g.*, toxicology, environmental chemistry, environmental engineering) and to consider implications across the entire lifecycle of a chemical or product. One of the fundamental underlying ideas of Green Chemistry is to reduce risk (as a function of hazard and exposure)[74] by reducing hazard. These hazards include not only various toxicological endpoints, but also environmental, physical, and global hazards; see Table 3 for examples in each category.[75]

To date, much work in Principle 3 has focused on reducing or eliminating chemical intermediates that are known to be particularly hazardous, especially in the context of manufac-

Table 3 Hazard categories and examples of potential hazard manifestations[75]

Human toxicity hazards		Environmental toxicity hazards	Physical hazards	Global hazards
Carcinogenicity	Immunotoxicity	Aquatic toxicity	Explosivity	Acid rain
Neurotoxicity	Reproductive toxicity	Avian toxicity	Corrosivity	Global warming
Hepatoxicity	Teratogenicity	Amphibian toxicity	Oxidizers	Ozone depletion
Nephrotoxicity	Mutagenicity (DNA toxicity)	Phytotoxicity	Reducers	Security threat
Cardiotoxicity	Dermal toxicity	Mammalian toxicity (nonhuman)	pH (acidic or basic)	Water scarcity/flooding
Hematological toxicity	Ocular toxicity		Violent reaction with water	Persistence/ bioaccumulation
Endocrine toxicity	Enzyme interactions			Loss of biodiversity

turing. This has often involved drop-in replacements for problematic reagents; for example, dimethyl carbonate has a more favorable environmental profile in methylation and carbonylation reactions compared to methyl halides, dimethyl sulfate, or phosgene.[76–78] Progress has also been made in finding alternatives to widely used intermediates such as organohalogens, and has often been achieved by improvement in catalyst design, particularly with respect to selectivity. In the case of C–H bond activation which is traditionally done through halogen-mediated functionalization,[79] direct and selective transition metal catalyst-mediated C–H bond activation methods have emerged as greener alternatives in that they prevent toxic by-products, with additional improvements in atom- and step-efficiency.[80–82] Catalytic methods themselves are continually improved, with particular focus on the use of less toxic and abundant metals (see Principle 9 for more details on catalysis).[83] In addition, *in situ* or on-demand generation and consumption of toxic compounds could be an alternative approach to reduce risks associated with synthetic routes (also see Principle 12), as was recently shown for phosgene in amide synthesis in a microflow system.[84]

While it is relatively straightforward to avoid specific chemicals or reaction conditions, there remain many challenges in developing less hazardous synthetic methods. One of the main difficulties is poor characterization of toxicity properties of intermediates or waste products; in practice these may be challenging to isolate and purify and traditionally chemists have not had incentives to do so. Further, even when toxic hazards are well understood, it is more difficult to quantify and make comparisons between processes. One of the earliest attempts to account for safety in chemical synthesis was the Environmental Quotient, a qualitative analysis that considered both the *E*-factor of a process and its inherent hazard.[85] Since then, more quantitative and robust measures have been developed, including the Environmental Assessment Tool for Organic Synthesis (EATOS), which considers not only the quantity of reactants and waste, but their relative toxicity impacts in a quantitative way.[86] Semi-quantitative analyses have also been introduced, including EcoScale, which scores the safety of each chemical within a process, in addition to other process details.[87] Formal life cycle assessment methodology is also increasingly used to evaluate chemical synthesis pathways,[88,89] although data gaps for toxicity of specific chemicals remains an ongoing concern. Furthermore, a study on cradle-to-gate LCA for 181 organic chemical syntheses found no correlation between the toxicity of the final product and the inherent toxicity of materials used in the reaction pathway (see Fig. 2).[88] As a result, focusing on a single synthetic step and its associated impacts would not be likely to accurately assess the potential hazards of a full synthetic pathway.[88]

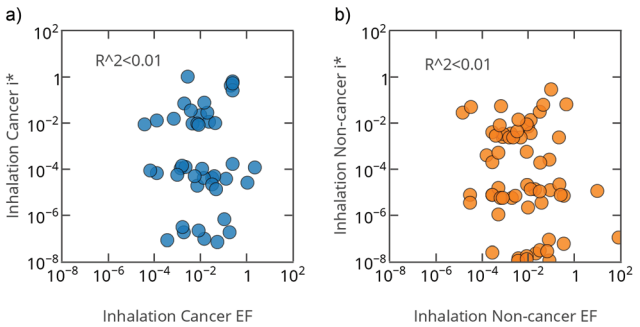


Fig. 2 Log–log scatterplots for (a) cancer and (b) non-cancer endpoints, of target chemical toxicity i (cases per kg emission) *vs.* life cycle inherent toxicity i* (cases per kg exposure) in organic chemical syntheses.[88] Reproduced with permission of the Royal Society of Chemistry.

Industry, NGOs, and government entities have created and adopted tools to assess relative hazard. For example, the public–private partnership "Life Cycle Initiative", hosted by SETAC (Society for Environmental Toxicology and Chemistry of the UN Environment Program), developed the USEtox model to assess human toxicity and ecotoxicity,[90,91] BASF introduced an eco-efficiency analysis tool to assess relative ecological impacts against cost-savings for businesses,[92] and recent work reviewed a total of 32 chemical characterization tools to evaluate their strengths and weaknesses.[93] Increased sharing of existing data on chemical hazards and harmonization of future data collection will be essential to provide chemical designers with even better tools to evaluate if a new process will reduce impacts on human and environmental health.[94]

Principle 4: "Chemical products should be designed to affect their desired function while minimizing their toxicity."

Principle 4 depends on direct collaboration between chemists and toxicologists as it requires knowledge of both chemical

function and toxicity properties,[95–97] as well as chemical and environmental engineers to mitigate or eliminate any of the other hazards laid out in Table 3. The aim is to identify hazardous substances and replace them with less hazardous ones through these collaborations. In a recent cross-disciplinary case study, several safer alternative plasticizers to phthalate esters were developed based on comparable or superior functionality,[98,99] rapid biodegradability,[100,101] and no signs of reproductive toxicity based on *in vitro* and *ex vivo* assays[102,103] and a subsequent *in-utero* exposure study.[104,105]

However, it is often difficult to identify readily-available alternatives that are safe, effective, and commercially viable. Many of the hazardous chemicals in commerce today do not have obvious substitutes for a variety of reasons including the lack of toxicity data on potential replacements, and this may lead to the replacement of one hazardous chemical with another through regrettable substitution.[106] To address this unintended consequence, rational improvements in the design of chemical alternatives can be aided by the establishment of molecular design guidelines to identify areas of chemical space with reduced hazard potential[107–109] while considering functional performance.

Given the ubiquitous societal exposure to chemicals, one area of that has received increasing attention is on strategies to inform the design of safer chemicals. Molecular design guidelines, along with other predictive toxicity models, are based on the premise that chemical structure and associated molecular properties are related to both chemical function and biological effects.[110] Methods to predict chemical activity from structure have been in use for over 100 years[111,112] and have been primarily implemented as structure–activity relationships (SAR) and read-across models.[113] A common design approach is the avoidance of toxicophores within the chemical structure based on structural alerts as applied in medicinal chemistry. The approach is a way to mitigate the risk of idiosyncratic drug toxicity, and indeed a recent analysis showed that a selected group of drugs associated with toxicity contained structural alerts, and showed evidence indicating that reactive metabolite formation was a causative factor for toxicity.[114] However, the analysis also suggested a need for a more integrated screening paradigm for chemical hazard identification in drug discovery. Improving pharmacokinetics and intrinsic potency as a way to reduce dose is still an important design approach for medical chemists (Fig. 3).[114]

More recently, advances in density functional theory (DFT) and computational power allowed for the development of molecular design guidelines based on three-dimensional chemical structure and physiochemical properties[115–120] and the inclusion of new molecular descriptors, such as chemicals' ionization potential, electron affinity, and site of electrophilic substitution in *in silico* models.[121,122] For example, acute aquatic toxicity models based on 3D reactivity properties have been shown to perform better than traditional 2D QSAR estimates in an external validations.[123]

Like all *in silico* tools, the efficacy and reliability of molecular design guidelines relies largely on the data quality used

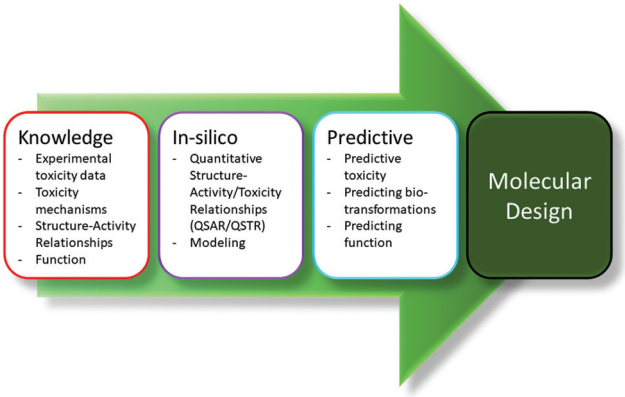


Fig. 3 A framework for molecular design leveraging knowledge from *in vivo* and *in vitro* toxicity data and mechanisms as well as molecular structure, property and function to develop *in silico* model to predict toxicity of new chemicals and inform safer molecular design.[95] Adapted with permission. ©2010 American Chemical Society.

to create the guidelines and the model's mechanistic relevance.[113,124–126] Thus, *in silico* models aim to incorporate modern understanding of chemical's absorption, distribution, metabolism, and excretion (ADME) within an organism. These mechanisms can be highly complex and depend not only on chemical structure and properties, but target endpoint, species, and individual variability.[124,127] Given this biological complexity, the concepts of adverse outcome pathway (AOP) and molecular initiating events (MIEs) have been introduced to help model biological cascades through key initiation and propagation steps.[128–133] From the chemical properties perspective, the processes can be divided into (1) how a chemical reaches the site of toxic effect (toxicokinetic) and (2) what biological interactions lead to adverse effects (toxicodynamic).[122,130] Three dimensional chemical features help create interpretable models for toxicokinetic and toxicodynamic effects[117,134–138] and can be further related to chemicals' modes of action to improve model performance and confidence.[123,139] One of the biggest challenges for molecular design is accounting for the diverse metabolic processes and their products. Metabolism involves hundreds of enzymes and varies substantially between species and individuals.[140–142] While many models for a single variety of cytochrome P450 (CYP) enzymes have been proposed, their efficacy is not perfect and other classes of metabolic enzymes must be explored further to better account for the metabolic complexity.[143–146]

While computational approaches to molecular modeling and design have gained popularity in recent decades due to the relative efficiency, cost-effectiveness, concerted data collection, and multiplicative increase in computing power,[121,147,148] Principle 4 is among the least developed Principles of Green Chemistry. Additional work is required to identify chemical structures and properties relevant to toxic endpoints and mechanisms of toxic action and to confidently expand molecular design guidelines to relevant areas of chemical space, specifically chemical function.[149] Fortunately, new medium

and high throughput screening (HTS) platforms are becoming more readily available.[121] Large *in vitro* data bases such as ToxCast and Tox21 are designed specifically to help elucidate modes of toxic action.[150–152] However, effective use of diverse data streams and computational methods will require greater cross-disciplinary integration, cooperation, and mutual effort to train new generations of chemists. Furthermore, as molecular design advances, it will become necessary to develop algorithms that enable transparent scoring and support decision-making when considering collections of endpoints related to persistence, bioaccumulation, and toxicity that may be difficult to compare directly.

Principle 5: "The use of auxiliary substances (*e.g.*, solvents, separation agents, *etc.*) should be made unnecessary wherever possible and innocuous when used."

Solvents are often the determining factor in the cost, environmental impact and safety of chemical and pharmaceutical processes.[153] Quantity often drives this phenomenon; in many chemical reactions and separation processes, the amount of solvent used exceeds raw materials, reagents, and products.[153] Conventional solvents with low molecular weight and high volatility have potential for greater exposures, increasing risk when they also have toxic properties.[154] For these reasons, solvent use minimization and substitution has been an active area in Green Chemistry.[155–158] Among the main strategies are use of water as solvent, EHS profiling of organic solvents, development of switchable solvents, sub- and supercritical fluids, ionic liquids, and solvent-less reactions. It is important to not only consider the solvents required for the transformations, but also the auxiliary compounds (*e.g.*, surfactants, chelating agents) that are often necessary to effectively carry out the desired reaction.

Water has received significant attention as a green solvent since it is innocuous in comparison to many conventional organic solvents. Depending on local circumstances it may be easily accessible and inexpensive to employ. Many reactions originally developed in organic media can be performed in water, and the use of surfactants or other miscible organic co-solvents has widened the scope of chemistry in water to include oxidations, reductions, nucleophilic substitutions, and electrochemical synthesis.[51,159–161] While it is increasingly straightforward to adapt fundamental chemistry to aqueous solvent systems, there remain challenges with respect to life-cycle considerations including contamination and recycle/reuse issues, global imbalances in water quantity and quality, and potential socio-economic impacts of trans-national water flows "embedded" in finished products.[162]

Progress in solvent substitution for conventional organic solvents has been made by profiling commercially available liquids for health, safety, and lifecycle impacts. Main drivers are both academia[163–165] as well as the pharmaceutical industry,[156,166–168] and several solvent selection guides are readily available online.[169] This information has facilitated the identification of targets for replacement and careful consideration of candidates for substitution. For example, alternative solvent systems based on heptanes, ethyl acetate, and MTBE have been proposed to replace dichloromethane for use in column chromatography.[170] Solvent selection guides have been developed collaboratively with the goal of improving industrial processes including the efforts of the American Chemical Society Green Chemistry Institute Pharmaceutical Round Table.[166,168,169,171] Choices for solvent substitutes are expanding with advancements in biomass-derived solvents such as glycerol derivatives and 2-methyltetrahydrofuran.[172]

Development of novel solvents has also been an area of consistently high interest. It is advantageous to design solvents taking downstream process steps into consideration. This is exemplified by switchable solvents,[157] which consist of three principal classes. These are switchable-polarity solvents (SPS), switchable-hydrophilicity solvent (SHS) and switchable water (SW).[173–175] The common principle behind these materials is to enable the reaction in one mode, then switch modes facilitating the subsequent product separation process. For example, a SHS solvent system can be used to carry out an extraction without the need for a distillation step as shown in Fig. 4.[176,177] The technology has potential to reduce waste and environmental impacts that can result from use of multiple solvents in different steps of a process.

The use of subcritical and supercritical fluids[178,179] and gas expanded liquids[180–183] has been a major focus area for green solvents research. Within accessible subcritical/supercritical and gas expanded liquid regions, conditions can be fine-tuned to improve yield and energy efficiency while eliminating conventional organic solvents.[181] Supercritical CO_2 (sCO_2) is very attractive as a solvent because of its removal from reaction mixtures by simple depressurization. This can eliminate the need for energy-intensive distillation steps in a chemical process.[174] One of the largest applications of sCO_2 is extraction, especially in the food industry.[184]

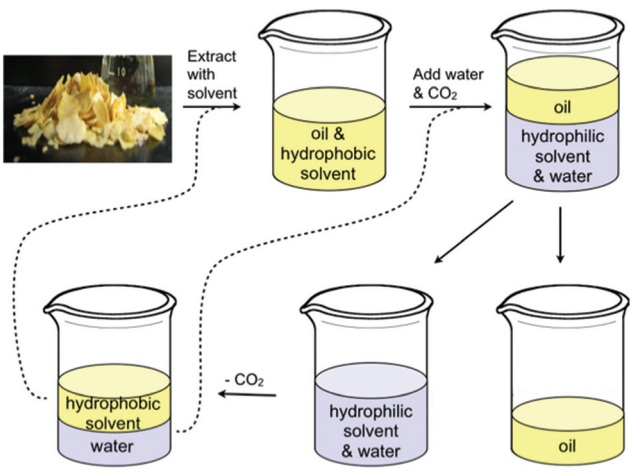


Fig. 4 The process by which a switchable-hydrophilicity solvent (SHS) can be used to extract soybean oil from soybean flakes without a distillation step. The dashed lines indicate the recycling of the solvent and the aqueous phase.[176] Reproduced with permission of the Royal Society of Chemistry.

Novel solvent systems have been advanced through use of room-temperature ionic liquids (ILs) for a wide range of applications.[185–188] ILs are organic salts composed of anions and cations. The major advantages of ILs as solvents include their extremely low vapor pressure (virtually eliminating inhalation exposures), their thermal stability, and the ability to mix and match libraries of anions and cations to obtain desirable properties.[189,190] This has led to the development of ILs comparable to common organic solvents such as acetone or ethyl acetate in a variety of applications,[191–196] and examples of IL use, application, and safety profiles have been frequently reviewed.[192,193,197–200] Given that a practically unlimited number of ILs is imaginable due to library mix-and-matching, no general conclusions can be drawn about metrics of concern. Rather, ionic liquids must be evaluated individually, or based on ion classes, for toxicity and biodegradability concerns,[194,197,201] as well as for their function, which can often go beyond the simple role of a solvent to also serve as reagent or catalyst.[194] It should also be noted that ILs are not intrinsically greener than traditional solvents, given that their production and disposal are usually more resource-intensive as compared to traditional solvents,[194] however, if used strategically, ILs can help make industrial processes greener, while also enabling unique process innovations.[198,202,203]

In addition to solvent substitution, there are ongoing efforts to eliminate the use of solvents altogether.[157,204] This is often accomplished with unconventional means of mixing or delivering energy to a system. For example, the use of ball bearings to mix solids at high speeds[205–207] shows much promise, along with microwave assisted reactions.[208,209] Microwave assisted synthesis promotes local heating through generating high frequency electric fields and allows for solvent-free conditions.[210] However, the field of solvent-less synthesis is still in its infancy,[211] and recent reviews by several leaders in the field pointed out the need for continued investigation into the mechanistic understanding of mechanochemistry, as well as improvements in reaction monitoring, product purification, scalability, energy consumption, and full LCAs.[205,211]

Naturally, when changing an important reaction parameter such as the solvent used, the replacement or addition of other auxiliaries might be necessary to carry out the desired reaction in these new conditions. An example for this is the development of new surfactants and chelating agents ("CO_2-philes") to expand the scope of possible reactions in supercritical CO_2,[212–214] Initially, the majority of these compounds were fluorocarbon compounds and therefore under scrutiny due to their tendency of being persistent in the environment, however, recent research led to the development of non-fluorous CO_2-philes.[213,215]

Principle 6: "Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure."

While catalysis has often been used as a highly effective means of reducing the energy requirements of a chemical transformation (see Principle 9 below), Green Chemistry has contributed to the development of techniques that reduce the overall energy requirement for chemical reactions, often focusing specifically on work-up and separation since these are often energy-intensive steps. Further, Green Chemistry has also benefitted from advances in unconventional energy delivery mechanisms, such as microwave irradiation, sonochemistry, electrochemistry, and photochemistry. Improvements in energy efficiency, milder reaction conditions, and shorter reaction times can lead to significant advantages particularly in large-scale processing where energy cost is substantial and uniform heating is challenging.[216,217]

Within chemical synthesis, the most energy-intensive steps are separating the desired product from the reaction environment including solvents, catalysts, or other auxiliaries.[218] Some estimates suggest that up to half of all US industrial energy use goes towards chemical separations, with distillations being the top contributor in the category.[218] This leaves vast opportunities to reduce energy use in chemical synthesis if chemical separations can be achieved without the need for such energy-intensive techniques such as distillations. As touched upon in Principles 1 and 5 above, many Green Chemistry efforts exist in this regard: for example, the use of a switchable solvent (shown in Fig. 4) allows for the separation of the desired product from the extraction solvent by the addition of water and CO_2.[176] Another approach is taking advantage of the change in solubility of a homogenous catalyst in reactants *versus* products to allow for its self-separation towards the end of the reaction (shown in Fig. 5).[219,220]

Under microwave irradiation, it is often observed that reactions that would require hours at elevated temperature can be completed in minutes.[221] The approach is compatible with a wide range of solvents including water, ionic liquids, and even solvent-free systems.[222] The reaction scope is wide, with recent improvements reported in diverse applications

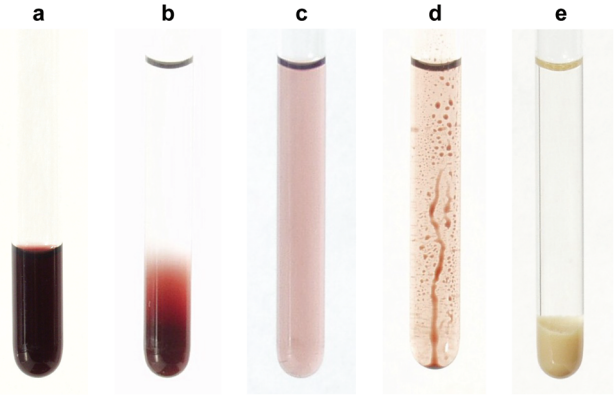


Fig. 5 Photographs of the catalytic hydrosilylation of $Et_2C{=}O$ by $[CpW(CO)_2(IMes)]^+[B(C_6F_5)_4]^-$: (a) ketone complex 4 W before adding $HSiEt_3$; (b) $HSiEt_3$ added, liquid not yet mixed; (c) mixed and homogeneous: (d) liquid clathrate formed. Reaction nearing completion; (e) end of reaction. Catalyst has precipitated.[219] Reprinted by permission from Springer Nature: Nature "A recyclable catalyst that precipitates at the end of the reaction", V. K. Dioumaev, R. M. Bullock ©2003.

including removal of pollutants and cross-coupling reactions.[223–225] The efficiency of microwave-assisted transformations as compared to "classic" organic heating methods such as oil baths is a topic of debate, however. The reported efficiencies can be higher or lower than conventional heating methods, and factors that impact this include the polarity of the solvent, the scale of the reaction, the type of microwave reactor used (single- *vs.* multi-mode reactors), whether or not the reaction vessel is open or closed, and of course the reaction carried out, which includes the absorbance characteristics of the reactants.[221,222,226] However, lower energy efficiencies in microwave heating compared to conventional techniques can often be balanced with shorter process times to yield lower total power consumption.[226] Ultimately, the determination of whether or not a process is more energy-efficient when performed with microwave heating than with conventional heating must carefully be assessed on a case-by-case analysis.[221]

Sonochemistry uses ultra-high frequency waves to resonate air cavities until implosion occurs, thereby converting electric energy into mechanical energy.[227] The energy release from implosions can heat the local environment to temperatures of up to several thousand Kelvins. While the fundamental mechanisms are still being investigated, such as the effects of wave amplitude, there is evidence of unique means to accelerate reactions.[228] For example, one study reported a 50-fold increase in reaction rate for the copper-catalyzed Ullmann coupling reaction in the presence of ultrasound irradiation due to several effects exerted on the copper particle size and surface.[229] Other applications for sonochemistry include combinations with other techniques to create synergistic effects, such as with microwave-assisted heating especially in heterogenous catalysis where sonochemistry impacts the surface of often-used metals,[228] as well as in microfluidic reactors, where sonochemistry can play an important role in avoiding solids buildup in process intensification.[230,231] Sonochemical oxidation has also been shown to efficiently degrade organic polymers and other pollutants.[227,232,233]

Efficiency gains from sonochemistry are not simple to quantify since the method is not often used as a drop-in replacement (such as for microwave-assisted reactions above), but a recent review highlighted that sonication pretreatment of biomass for biofuel production showed mainly negative energy efficiencies, meaning that the increase in yield is overcompensated by the energy needed for the sonication process.[234] The situation may be more favorable when pulsed ultrasound is used.[235] Further progress in this area and a clearer accounting of environmental benefits will require additional data comparing configurations of equipment as well as a better understanding of thermal control in sonochemical systems.

Electrocatalysis operates by applying a potential difference between a cathode and an anode in a conductive medium enabling electron transport, which can either be a solution-based supporting electrolyte or a conductive polymer. Electrochemical reactions usually do not require external heating or pressurization, but directly convert the applied electrical energy into chemical energy. The potential advantages of this approach have been explored for many environmental and renewable energy-related applications including organic synthesis,[236] biomass processing,[237–239] water treatment,[240,241] water splitting,[242–244] and CO_2 reduction.[245–247] Although mostly practiced in batch systems, electrochemical methods can be adapted to continuous processes to improve throughput for synthetic[248] or analytical applications.[249]

Photocatalysis can be practiced without any supporting electrolyte and can be done homogeneously, which allows for the use of enantioselective catalysts in fine chemical synthesis.[250,251] Heterogeneous photocatalysis benefits from progress in materials science, such as the use of semiconducting materials in a variety of redox transformations and environmental applications. Titanium dioxide shows useful activity as an oxidation catalyst and high efficiency in organic degradation.[252–254] Hematite can be used as a photoanode in water splitting.[255,256] Homo- and heterogeneous reduction of CO_2 has been reported.[257–260] Recent reports have shown plasmonic-metal nanoparticles to be highly efficient in capturing a wide range of wavelengths, enabling photocatalytic effects.[261,262] Limitations of photochemical methodology need further attention, particularly radical-initiated side reactions leading to reduced selectivity. Overall, there appears to be much unexplored potential for application of radiation in the UV, visible, and even IR range.[263] Further, recent advances in photocatalysis enable electrochemical reactions to be coupled to photocatalytical reactions. The two techniques can be complementary as they both achieve redox chemistry on a catalytic surface with a potential generated from an external source. Photo-assisted electrochemistry is applied in the renewable catalysis research community as a technology for water splitting or CO_2 reduction.[264,265]

For Principle 6, one of the cross-category research challenges is reactor design for unconventional delivery of energy, particularly at large scale. In many of the alternative systems described above, there remain challenges with respect to scale-up of the chemistry: thermal control, mixing characteristics, viscosity, and product separation are not always straightforward to adapt from lab-scale procedures. For microwave technology, strategies have been identified to facilitate larger batches and conversion of batch to continuous processing, though the inefficiency of converting electrical to microwave energy requires further attention.[266] This highlights the need for chemists to consider that adjustments made for larger equipment could have significant effects on overall lifecycle impacts. Similarly, integration of chemical plants and even geographical location can be expected to affect the overall environmental footprint. Global variability of impacts of different energy generation schemes, particularly in the context of the energy-water nexus and trends toward decentralized manufacturing, will require a careful accounting of resource flows. Such information will help measure the benefits of unconventional approaches beyond the basic time and yield metrics.

Principle 7: "A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable."

While the early chemical industry relied on renewable materials from wood, crops, animals and others,[267] the discovery, efficient extraction, and effective distillation of crude oil lead to the current reliance on mainly petroleum and natural gas.[268] However, limitations of geological resources, increased energy demand in rapidly developing nations, and the catastrophic impacts of CO_2 emissions on global climate[269] are driving a renewed interest in renewable resources. While the natural annual biomass production is on an enormous scale, only a small percentage of it is used for human consumption, such as food, fuel, or material applications,[268,270] and there are concerns about the impacts of competition between these end uses. Land transformation, water use, socio-economic impacts, and even CO_2 footprint relative to fossil resources are important considerations in biomass-to-chemical technologies.[271] While technology development is increasingly guided by life cycle assessment, many of these underlying concerns have driven an interest in renewable resources that are currently viewed as waste or low value, particularly agricultural residues.

At the level of chemical reactions, the biggest challenge in replacing petroleum oil derivatives with renewably sourced materials is their degree of oxidation as current industrial processes are mainly based on CO, hydrogen, and hydrocarbons such as ethylene, propylene, and benzene.[268] These compounds are subsequently converted into desired and more valuable compounds, which usually requires the addition of functional groups.[268] By contrast, renewable biomass in aggregate is *ca.* 75% carbohydrates or carbohydrate polymers (*e.g.*, starch, cellulose, hemi-cellulose, chitin), 20% lignin, and the remaining 5% consists of fats (triglycerides), proteins, and "vegetable secretions and extracts" such as terpenes and waxes.[268,272] The carbohydrate and lignin materials making up the vast majority of these materials already contain many (oxygen-rich) functional groups, as demonstrated by C : H : O ratios whereby crude oil contains 85–89% carbon, 10–14% hydrogen, and less than 1% oxygen while renewable resources contain only 50–75% carbon, 6–13% hydrogen, and 11–45% oxygen.[273] As a result, new processes have to be established to valorize these materials, including CO_2 which also meets the definition of "renewable". Analogous to the concept of atom economy, as discussed in Principle 2 above, the idea of "redox economy", or efficient delivery of hydrogen or other reducing equivalents, is a useful approach to evaluate chemical processing of renewable resources.[274,275]

Beyond the production of biofuels from renewable resources,[276–279] the main production strategies to produce bulk and fine chemicals are by biotechnological, chemical, and thermal means, or a combination of these.[268,273] Progress to date has led to identification of readily accessible intermediate "building block" chemicals, many of which are identical to important petrochemical feedstocks, or can be further transformed to molecules with identical applications.[270,280–287] On the other hand, bio-based feedstocks can also offer paths to diverse building blocks that are hard to obtain from petroleum, thereby opening new opportunities.[288] Examples of renewable building block chemicals from waste or low-value biomass residues include:

• Oxygenated C2–C6 small molecules (ethanol, 1,3-propanediol, butanol, lactic acid, succinic acid, 5-(hydroxymethyl) furfural from polysaccharides or glycerol [see Fig. 6 for an extended overview]);[268,280,281,287,289–293]

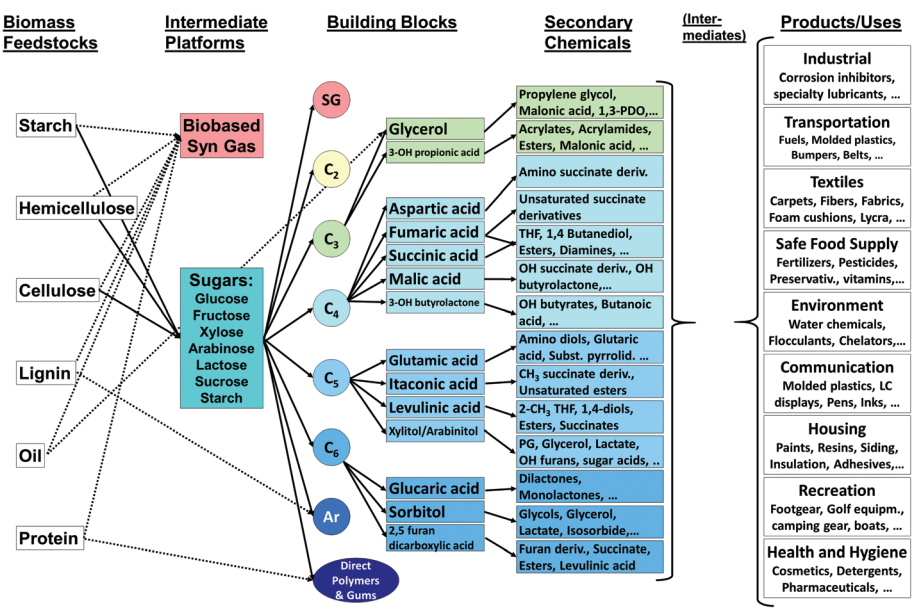


Fig. 6 An analogous model of crude oil through a petroleum refinery for products through an integrated biorefinery from renewable feedstocks. Adapted version focusing on the identified 12 top candidates for sugar-derived building blocks.[280] Courtesy of the Office of Energy Efficiency & Renewable Energy of the U.S. Dept. of Energy.

• Low molecular weight aromatic molecules from lignin;[272,294]

• Polyhydroxy alkanoates (PHAs) harvested from microbes;[295,296]

• Urea, cyclic carbonates, C1 small molecules (methanol, formic acid, formaldehyde), and C2–C3 olefins from gaseous CO_2;[268,297–302]

While current platform chemical production schemes from renewable resources have the potential to save fossil energy, they tend to be more energy-intensive than their petroleum-based homologues, often due to the energy-intensive step of water-removal.[303] However, when also taking into account the captured CO_2 during the plant's growth, these processes have the potential to reduce overall greenhouse gas emissions such as outlined for the production of methanol and ethanol from lignocellulose and sugar cane, respectively, in comparison to their petrochemical production route *via* naphtha cracking.[303]

Biotechnological means to produce compounds of interest are usually fermentative techniques using yeasts or bacteria, or the isolated enzyme responsible for the conversion.[304] Biotechnology has several advantages over "classic" organic synthesis, as structurally complex molecules can be produced in a single step, products are often pure stereoisomers, and side reactions rarely occur due to the specificity of the enzymatic conversion (more on biocatalysis also in Principle 9).[305] However, several drawbacks have slowed broader application of fermentation/enzymatic production: carbon sources are typically mono- or disaccharides, which either come from crops such as corn, cassava, and sugar beet, or have to be produced from lignocellulosic material, for example switchgrass or wood, adding a usually energy-intensive step to the process.[306,307] Additionally, microbial production yields are typically low compared to chemical synthesis, too high concentrations of product in the fermentation broth may result in toxicity to the microbes, and purification can be difficult especially when the product has to be extracted from within the cell.[308–310] Finally, enzymes that catalyze reactions not found in nature need further development, and competitive prices are hard to achieve for fermentation-based products compared to petroleum-derived products as the latter routes have many decades' advantage in optimization.[305,310] However, these challenges are being addressed, and include efforts in metabolic engineering to allow for enhanced production rates, higher yields, easier downstream purification, and easier access to non-native products.[310–312] Another interesting approach is to use a self-cycling fermenter to "synchronize" cell growth in order to increase microbe productivity.[313] An ultimate goal would be the co-production of food, fuel, and chemicals in a "biorefinery" configuration which has been proposed as a means of maximizing both economic and environmental benefits from bio-based resources.[293,310,314,315]

Recently, microalgae have been the subject of intense research interest due to high lipid and carbohydrate content and potentially increased productivity per unit of land and water compared to higher plants.[316] This has led to Green Chemistry-guided improvements in methodology for lipid extraction[317] and biofuel production.[318] As with many renewable resources, the processing and logistical challenges for algal biomass can lead to significant lifecycle impacts.[319] While not limited to algae, guidelines on green extraction techniques have been proposed as "the six principles of Green extraction".[320] Whereas the integration of processes is commonplace in the petrochemical industry, biomass processing can pose additional challenges due to wider variability of raw materials, within a class such as algae and between classes such as algae *versus* sugars *versus* lignocellulose.

Principle 8: "Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste."

Protecting group chemistry consumes additional raw materials, potentially increases the number of intermediate isolation or purification steps in a process (increasing solvent use and energy requirements), and typically contributes to waste streams.[1,65] Ideally, chemical synthesis should be carried out without protecting groups whenever possible. This can be achieved by taking advantage of non-covalent interactions or by improving reaction selectivity (chemoselectivity).[321,322] The latter is typically accomplished through catalyst design, but chemoselectivity can also be achieved by controlling reaction conditions.[323] In addition to selectivity and specificity, it is also helpful to identify reactions giving products that can be carried out without the need for chromatography, and easily recovered from solvent. So-called "click chemistry" provides a toolbox of protecting-group free synthetic methods.

Non-covalent modification techniques employ hydrogen bonding, pi-stacking, lipophilic–lipophilic interactions or electrostatic interactions to control the chemical and physical properties of molecules in a reaction.[324,325] One common approach, particularly in medicinal chemistry, is co-crystallization: structurally homogeneous crystalline materials containing two or more components present in definite stoichiometric amounts.[326] An example is the co-crystal of hydroquinone and bis-[*N*,*N*-diethyl]terephthalamide that lowers the solubility of hydroquinone.[327] Similar systems enable tuning of dissolution rate, bioavailability or physical stability of pharmaceuticals.[326] Ongoing research uses crystallography technique to better understand the complexity of co-crystal molecular interactions during combination and the mechanism of crystallization.[328]

Small molecule chemical chaperones can aid in self-assembly of supramolecular polymers through hydrogen bonding, pi–pi stacking interactions, host–guest interactions, and metal–ligand coordination. Molecular chaperones also allow for greener reaction conditions; in one recent example, a specific polymer synthesis was carried out in water rather than organic solvents taking advantage of self-assembly, and a molecular chaperone was subsequently used to reversibly deconstruct the polymer.[329] Catalyzed molecular assembly ("catassembly") has been used to aid reactions that would ordi-

narily be slower or require higher activation energy. Catassembly has also been a useful means of obtaining chirality. For example, chiral assemblies of π-conjugated carboxylic acids were obtained using carboxymethyl cellulose as catassembler.[330]

The use of catalysts to improve the environmental impacts of chemical reactions is one of the core Principles of Green Chemistry (see Principle 9, below). The use of catalysis to enable protecting group-free chemistry has been recently reviewed. One example of a catalyst-enabled approach is in synthesis of conjugated polymers *via* metal-catalyzed direct (hetero)arylation of aromatic compounds.[65,331] In these reactions, a C–C bond is formed by the condensation between an aryl halide (C–Br or C–I) and an aryl C–H bond. This eliminates intermediate steps, enables straightforward purification, and reduces waste.[331] Another interesting approach are *in situ* protecting groups which have been described for reactions in supercritical CO_2, where CO_2 not only acts as solvent, but also as temporary protecting group for amines by forming a carbamate.[332–334]

Another means of eliminating intermediate synthetic steps is electrochemical synthesis, wherein selective electron transfer aids in C–C bond formation or functional group interconversions for electroactive/electro-responsive reagents.[335] Redox-umpolung reactions (substrate functional group transformations due to electron transfer) facilitate significantly simplified reaction sequences.[335,336]

Flow chemistry has been used to reduce derivatization in chemical synthesis as well as in analytical methodology.[51,337,338] In syntheses, microfluidics in flow reactors can minimize side reactions by allowing for more precise control of mixing and thermal conditions. Flow chemistry can be used in conjunction with packed columns of immobilized reagents, catalysts, or scavengers to carry out multiple functions in a single, continuous process.[51]

The concept of "click chemistry" was coined by Barry Sharpless,[339] and is based on modular reactions observed in nature, where small units are subsequently joined to form larger structures. It recognizes that carbon–heteroatom bonds are often preferred over carbon–carbon bonds, and takes advantage of highly thermodynamically-favored "spring-loaded" reactions.[339] Since most click chemistry is carried out in water as a solvent, protecting groups for hydroxy (–OH) or amide (N–H) functionalities can be avoided.[339] A typical example would be the copper(I)-catalyzed 1,2,3-triazole forming reaction between azides and terminal alkynes without the need for protecting groups, that has been used productively in drug discovery (also see Fig. 7).[340–342]

When derivatization is unavoidable, it is straightforward to compare impacts of different strategies or avoidance of temporary modifications using atom economy and other waste metrics discussed in Principle 2. As we argued in that section, it is important for the chemist to consider that synthetic efficiencies may come at the expense of other lifecycle impacts. The same applies to protecting group strategies. Substituting a new starting material, catalyst, or solvent system in order to avoid a derivatization step may lead to shifting of environmental burdens between lifecycle stages. While expanding the toolbox of selective catalysis and "click" reactions is likely to improve the capability of synthetic chemists to design holistically improved chemical processes, this will require clear accounting for raw material sourcing, upstream processing, toxicity, and safety.

Principle 9: "Catalytic reagents (as selective as possible) are superior to stoichiometric reagents."

The use of catalytic reagents is a means of achieving lower energy requirements, increased selectivity, reduced waste, and improved atom economy of chemical reactions, and thereby, catalysis touches on several of the other Principles of Green Chemistry. As a result, catalysts (in sub-stoichiometric amounts) are one of the most versatile tools available to Green chemists.[1,343–345] While it is common for catalysts to be optimized for turnover rates and selectivity, additional Green Chemistry considerations would include toxicity and hazard,[346–349] as well as relative abundance of metals used.[350–353] Recently, the term "metal criticality" was established to evaluate metals beyond their relative abundance to include environmental implications of mining operations, vulnerability to supply restriction, and supply risk.[354] Another creative approach is using plants for phytoextraction of metals from contaminated sites for subsequent catalytic use.[355,356] Improvements in catalyst systems have been aimed at enabling function under ambient conditions to minimize energy requirements. Increased stability, reduced loading, and recyclability are common goals. Strategies to meet these goals include immobilization, latency (stimulus-responsive catalysis), and undirected or tandem protocols. Another pivotal feature of catalysis is selectivity, which can be geared towards specific products (including regio- and enantioselectivity),[357–359] as well as to specific substrates even in unfavorable conditions, such as generation of hydrogen by splitting seawater.[360,361] In this section, several examples of catalyst systems in practice will be presented, including developments in homogeneous and heterogeneous approaches as well as biocatalysis.

Homogeneous catalytic systems have been relatively easy to characterize in terms of kinetics and intermediate species, compared to heterogeneous systems.[362,363] This has enabled fine-tuning of homogenous catalysts for continuous improvement in performance. For example, palladacycles have been one of the most studied catalytic systems since the 1980s and have since become one of the most efficient systems for C–C bond formation.[364,365] Recent reports show significantly improved turnover numbers while using ultra-low loadings (see Scheme 2 for an example of a Pd-catalyzed C–C coupling reaction).[366,367] Major trends in Green Chemistry have been aimed at obtaining high performance from non-precious metals, particularly abundant first-row transition metals such as iron, manganese, and copper,[351–353,368] and using biomimetic approaches such as enzymes as inspiration for synthetic systems to achieve similar reactivity and efficiency as

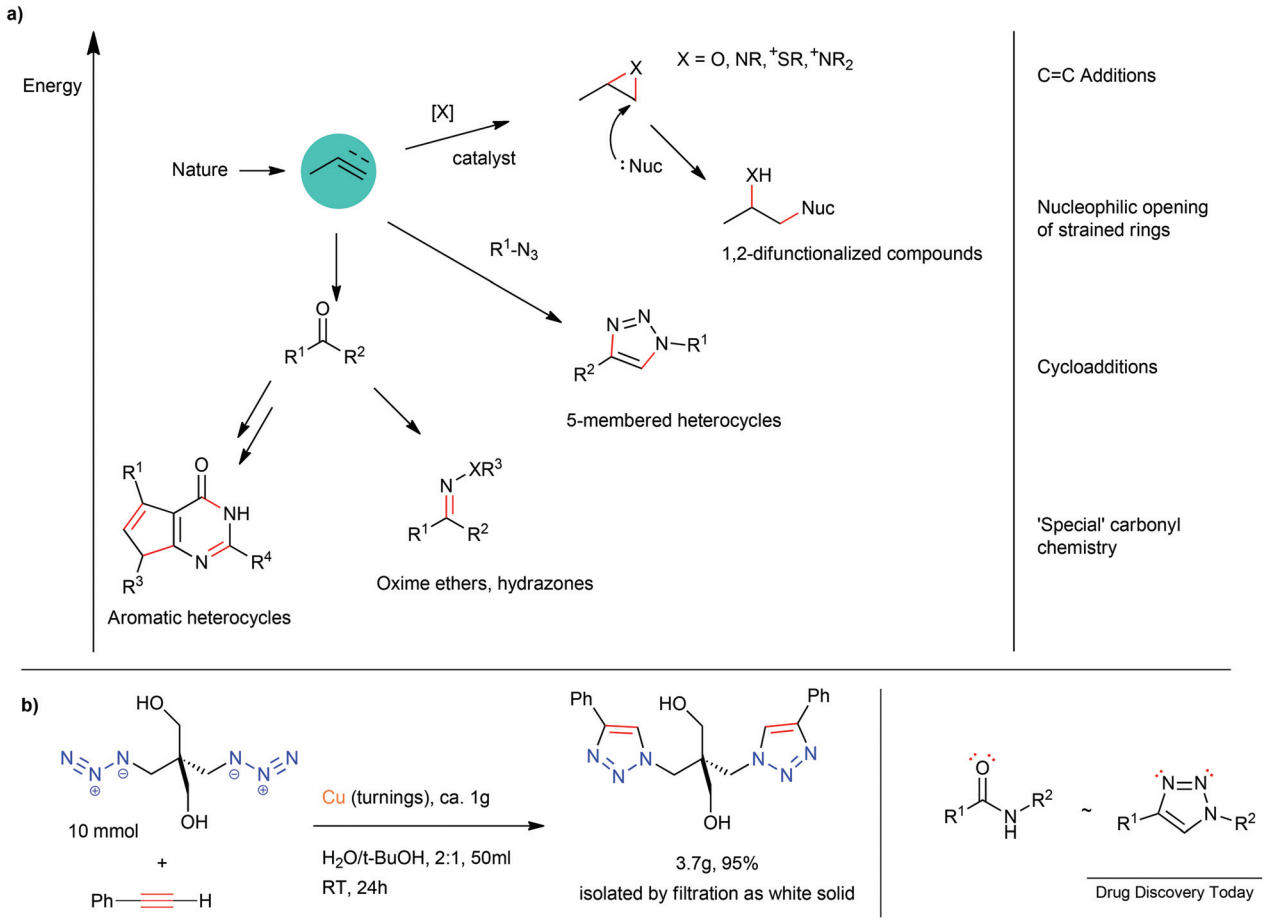
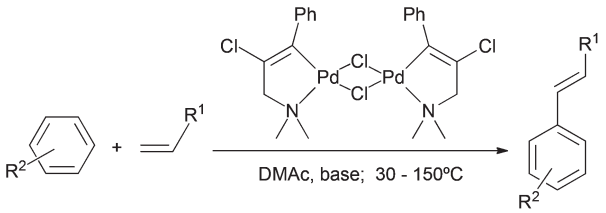


Fig. 7 Click Chemistry describes reactions that are modular, wide in scope, give high yields, create only inoffensive byproducts that can be removed without chromatographical methods, are stereospecific, simple to perform, and can be conducted in easily removable or benign solvents such as those shown.[317] (a) Linking reactions are energetically highly favorable, and unsaturated compounds provide the carbon framework. New groups are attached *via* carbon–heteroatom bonds (shown in red); (b) copper(I)-catalyzed coupling of azides and terminal acetylenes creating 1,4-disubstituted 1,2,3-triazole linkages, which share useful topological and electronic features with nature's ubiquitous amide connectors.[340] Reprinted with permission from Elsevier.

found in nature. Examples include the Fe-tetraamido macrocyclic ligand (TAML) activator for green oxidation processes,[369,370] and a Mn/Na-based catalyst for oxidative cleavage of 1,2-diols.[371,372] Performance enhancements of homogeneous catalysts have been gained through immobilization and simplifying down-stream separation and work-up.[373] This concept was recently demonstrated with ionic liquids, solid supports, and supramolecular architectures in conjunction with supercritical CO_2.[374,375] There have also been significant advances in organocatalysis, which uses no metals and can therefore lead to toxicological and economic advantages.[376,377] For example, one of the commonly used classes of organocatalysts is amino acids, which are mostly non-hazardous.[378] Ongoing research aims to increase the activity and efficiency of metal-free catalyst systems,[379] however, current challenges include high catalyst loadings[378–380] and the development of efficient methods for catalyst recycling.[381] Since the field is still developing, careful toxicity assessments must be integrated into the design of any new organocatalyst.[382]



Scheme 2 Palladacylces: examples of C–C coupling reactions using ultra-low loadings of palladium-based catalyst.[367] Reprinted with permission. ©2003 American Chemical Society.

Heterogeneous catalysts, though more difficult to study than their homogenous counterparts, have many advantages such as superior stability, ease of handling, and separation, and simplified recycling of the catalyst.[383,384] However, the use of abundant non-precious metals in catalyst design is increasingly of interest due to growing awareness of toxicity[346–349] and

scarcity issues of many metals throughout the life cycle.[350,352–354] Examples of heterogenous catalysts based on abundant materials include zeolites,[385,386] clays,[387,388] and solid acid or base catalysts; the latter two can offer increased safety compared to commonly used aqueous or liquid systems, in accordance with Principles 3 and 12.[383,389–393] Along similar lines, a class of robust silica-supported porous Brønsted acid catalysts has been developed that can be modified with different active metals to achieve specific transformations.[394,395] Nanoparticle catalysis has received attention in recent years, with a focus on non-precious metals such as nickel and copper,[83,396,397] however, there continues to be some debate about the potential environmental and human health concerns associated with the environmental fate and exposure of nanoparticles.[398–400] Further improvements in heterogeneous catalysis are likely to arise from advances in computational methods that enable detailed molecular surface characterization and better modeling of solvent interactions. Combined theoretical-experimental approaches may ultimately provide a level of fundamental detail and control over design comparable to what has long aided the development of homogeneous systems.

Natural catalysts such as enzymes and catalytic antibodies often outperform synthetic catalysts, both kinetically and in terms of selectively (*e.g.*, enantioselectivity).[401,402] Biocatalysis can usually be carried out under mild conditions (*e.g.*, ambient temperature and pressure, aqueous solutions, physiological pH) and the catalysts used are generally biodegradable, biocompatible, and renewable, making these catalytic systems highly attractive for environmentally benign processes.[27,51,345] Enzymatic processes exploit the chiral nature of enzymes in the formation of stereo- and regiochemical reaction products for application in synthesis of complex molecules with multiple functional groups.[403] Enzyme-based catalysts in chemical processes make use of unmodified or modified recombinant enzymes in whole cell processes or isolated chemical reactions.[63] Technology using isolated enzymes to control chemical synthesis is decades-old, yet recent advances in DNA technology and protein engineering have been crucial to improve the concept of directed evolution, such that enzymes can now be designed for a specific chemical synthesis process.[404] Enzyme design still lacks a complete mechanistic understanding of enzyme process and behavior, and numeric design models for enzyme activity are still not very accurate.[404] Many biocatalytic systems require additional research to improve stability which is limited by the "mild" reaction conditions mentioned above. Other challenges of biocatalysis include substrate or cofactor incompatibilities, inhibition, and reaction rate limitations caused by slow diffusion of the reactants into (and out of) the cells, which can be circumvented by the use of isolated enzymes.[404,405] Performance improvements are being sought through techniques such as immobilization, and the coupling of biological and chemical mechanisms, for example combining enzymatic processes with nanotechnology.[404]

Principle 10: "Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment."

During much of the 20th century, rapid biodegradation of synthetic compounds was seen as negative as it signified "instability" and for many applications "stable" compounds were deemed necessary. However, several publicly visible examples of environmental harm from persistent chemicals such as pesticides[406] or surfactants[407] resulted in negative publicity and have driven efforts to develop biodegradable alternatives.[407] Today, Green Chemistry seeks to strike a balance between the stability of compounds during their shelf-life and intended-use phases, and their biodegradability when they enter the environment. When a compound enters the environment, the most important degradation processes are (a) biodegradation, (b) atmospheric oxidation, and (c) hydrolysis (see Fig. 8 for an overview of different environmental fates of contaminants).[408] A compound that is persistent, or pseudo-persistent,[409] will have more time to reach different environmental compartments and cause adverse effects during its lifetime. Given that risk is defined as hazard multiplied by exposure,[74] slow environmental degradation rates mean increased risk by increased possibility for exposure.

One of the core missions of Green Chemistry is to consider adverse effects of molecules on humans and the environment in the earliest stage, the design stage. With regards to the design of environmental degradation, several tools exist to support synthetic chemists. Among these are a number of databases containing information about known environmental fate of molecules. A recent review presents information on several biodegradation databases.[408] Notably, the University of Minnesota Biocatalysis/Biodegradation Database (UMBBD) includes data on the biodegradability of individual compounds by pure cultures, including enzyme and pathway information.[411,412] In turn, that information can be used to predict biodegradation pathways of similar molecules through the UMBBD Pathway Prediction System (PPS).[413] A similar prediction system based on known metabolism pathways is the CATABOL program,[414] and one of the early models focused on group contributions for aerobic biodegradaton.[415] These tools for predicting environmental fate are important to inform molecular design. There also exist "rules of thumb" for functional groups that render molecules particularly recalcitrant: halogenated molecules (except for iodine), quaternary carbons, tertiary amines, polycyclic structures with more than three rings, as well as heterocycles, and aliphatic ether bonds. On the other hand, the incorporation of ester bonds, amides, unbranched terminal alkyl chains, and phenyl rings generally improves the degradability of molecules.[407,408]

Furthermore, QSAR/SAR *in silico* models have been developed to predict environmental degradability based on the chemical and electronic structure and the physico-chemical properties of molecules (see Principle 4 for more details on QSAR/SAR). QSAR/SAR models have been developed to predict biodegradation,[416] atmospheric degradation,[417,418] and hydro-

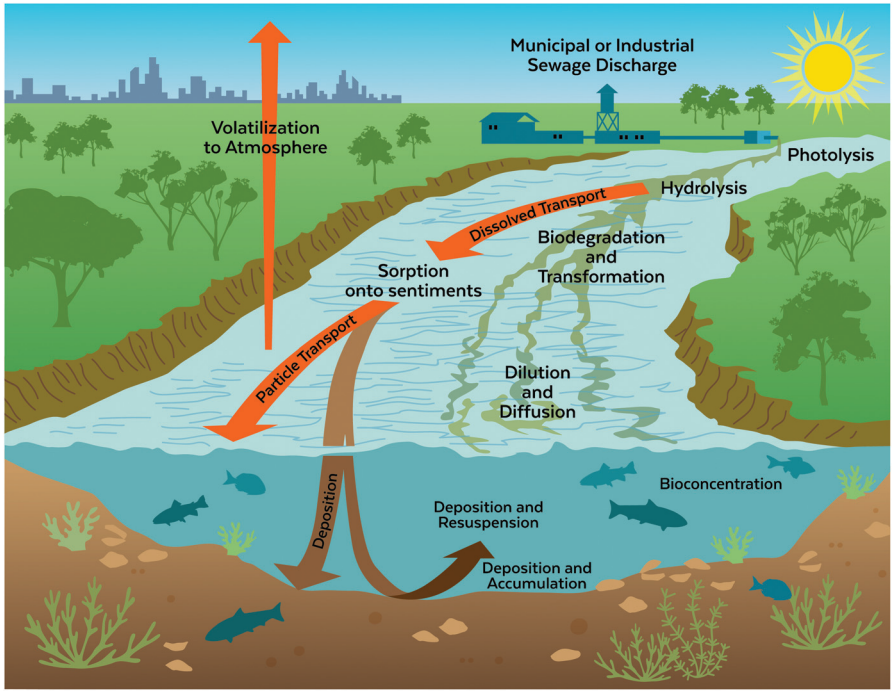


Fig. 8 Possible fate and transport of environmental contaminants.[410] Courtesy of the U.S. Geological Survey.

lysis.[408,419] The U.S. EPA EpiSuite™ software[420] contains programs to predict degradation by all three pathways, namely BIOWIN and BioHCwin for biodegradation, AOPWIN for atmospheric degradation, and HYDROWIN for hydrolysis.[408] Connecting such models to information on chemical toxicity will help identify degradation pathways that are potentially concerning, to avoid potential degradation/toxicity tradeoffs.

Many case studies are available that showcase the possibilities for improved biodegradation rates of a range of compounds while maintaining functional performance, including plasticizers,[100,102,421] alkylbenzene sulfonates and alkylphenyl ethoxylates,[407] ionic liquids,[408,422] antiseptics and musk fragrances,[408,423] and the beta-blocker atenolol.[424] Another idea to promote the degradation of chemicals is to integrate a "molecular switch" into compounds that would activate under specific environmental conditions,[425] which could be achieved, for example, using non-covalent derivatives.[325]

While the quick degradation of the parent compound is important, it is of similar importance to consider produced metabolites in terms of their degradation kinetics, but also their potential for human toxicity, ecotoxicity, or other adverse effects. Many examples exist where seemingly innocuous compounds, once in the environment, have been shown to break down to stable and problematic compounds. For example, the ubiquitous plasticizer di(2-ethylhexyl) phthalate (DEHP) is broken down to its monoester mono(2-ethylhexyl) phthalate (MEHP) in the environment, and the suspected endocrine-disrupting effect of DEHP likely stems from the metabolite MEHP.[426] Similarly, the commonly used nonylphenol ethoxylate surfactants are known to break down to nonylphenol in the environment, which is a toxic xenobiotic compound, as well as being a suspected endocrine disruptor.[427] Due to these problematic breakdown products, recent research has focused on renewable, degradable, and non-toxic plasticizers[105,421] and surfactants.[428]

Some of the most visible pollution of our times is plastic,[429] resulting from large annual consumption rates of the "big 6" polymers that account for 76% of all plastics produced globally [high- and low-density polyethylene (HDPE and LDPE, respectively), polypropylene (PP), and poly(vinyl chloride) (PVC), polystyrene (PS), and the polyester polyethylene terephthalate (PET)],[288] and the poor environmental degradation rates of these.[430,431] While efforts have been made to source the monomers for some of the "big 6" renewably,[288,432] recently several new and more biodegradable polymer classes have been developed with the intention to reduce the overall environmental impact of plastic waste.[431,433,434] While this is not an exhaustive list, these alternatives include starch and cellulose derivatives,[435] poly(lactic acid) (PLA),[436,437] poly(vinyl alcohol) (PVA),[438] poly(hydroxyalkanoates) (PHA),[295,296,439–441] poly (butylene succinate) (PBS),[442] and poly(caprolactone) (PCL).[443] While many of these have found a wide range of commercial applications, they cannot always serve as direct "drop-in" functional replacements for petroleum-based polymers. Use of the materials can require changes to processing conditions or methods for recycling or disposal of the material. For example, PLA has gained popularity as a replacement for PP or PS in liners for disposable coffee cups, yet processing changes had to be made to render it sufficiently heat-resistant.[444] PLA is biodegradable only in specific conditions,[445] requiring indus-

trial facilities. Overall, the needs for comparable functionality and suitable infrastructure to ensure biodegradation are complicating factors in polymer substitution and require consideration of the complete chemical lifecycles.

A frontier of design for biodegradation is in pharmaceutical chemistry: upwards of 3000 active pharmaceutical ingredients (APIs) are in use[446] and their production scale is in the range of 30 000 tonnes per year in Germany alone.[447] APIs have been detected in the environment, and their sources include improper disposal, incomplete metabolization in the body, waste streams from API production plants,[448] and their use in agriculture. From a biodegradation standpoint, API and API metabolites are a particular challenge due to their high chemical complexity and their design to allow for long shelf-lives.[449] In combination with the fact that APIs are biologically active by design, these compounds can pose a significant threat when released in the environment, as has been seen, for example, with antibiotic resistance,[448,450] or a massive decline in vulture population due to exposure to diclofenac.[451] Sweden is one of the first countries to have implemented a system that takes into account the potential environmental hazards of prescribed APIs to suggest the most functionally appropriate and environmentally-friendly medications to both doctors and patients.[452,453] Many reviews exist on the topic of Green Pharmacy,[447,454–456] and even a new journal on the topic was established.[457]

Principle 11: "Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances."

Principle 11 specifically highlights the importance of reaction monitoring in controlling chemical hazards and process safety. Further, analytical chemistry enables many of the other Principles of Green Chemistry. Real-time, in-process monitoring can be used to achieve waste prevention, improve synthetic efficiency, aid catalyst design, and support the use of unconventional or complex techniques such as solvent-free chemistry or biochemical processing. It is especially useful in optimizing the performance of continuous-flow reactors.[458] Hazard prevention arises through careful characterization of chemical reactions at production scale: through better understanding of reaction mechanisms and intermediates, and exploring interactions between process variables, it becomes possible to avoid problematic conditions such as overdosing of reagents, overheating (or overcooling), loss of selectivity, or decomposition of desired products. In most cases those deviations would ordinarily lead to chemical waste, pollution, or generation of toxic substances.

A wide range of monitoring techniques are available to chemists, either "in-line" (continuous sampling of all material, as in a flow configuration) or "on-line" (sampling of representative aliquots).[459] Many spectroscopic methods have been adapted for in-line measurement,[458] such as on a microfluidic "lab on a chip". Representative examples from the literature include UV/VIS,[460,461] IR and attenuated total reflection (ATR-IR),[462,463] Raman,[464,465] Mass,[466–468] and NMR spectroscopy (also see Fig. 9).[469–471] Liquid chromatography (LC) and gas chromatography (GC) are other important monitoring tools, however, these must be used on-line rather than in-line, and LC is often coupled with solid phase extraction (SPE) prior to injection, and mass spectroscopy post-separation.[472–474] Sensor technology plays an important role, for example monitoring headspace or dissolved gas concentrations by IR, luminescence, or electrochemical sensors.[475] While convenience and performance are continually refined, there is also a need for improved data processing including the use of feedback loops to automatically adjust and monitor reaction conditions.[458] Examples for the successful use of feedback loops include the optimization of various chemical synthesis parameters,[476–478] parameters for a methylation reaction in supercritical CO_2 using Matlab® code,[479] as well as LabView®-based self-optimization programs (also see Fig. 9).[313,469] Other interesting applications for real-time monitoring of chemical reactions include X-ray powder diffraction and Raman spectroscopy to monitor solventless mechanochemical reactions.[480,481] Many advances in process analytical technology emerge from collaborative efforts such as the IQ Consortium[482] and the Center for Process Analysis and Control (CPAC),[483] where tools are under development that are intended to be cost-effective, maintain operator safety, and minimize waste generated by the analytical measurements.

An important area of research towards wider implementation of Principle 11 lies in the further development of sensors, such as electrochemical sensing (conductimetric, potentiometric or voltammetric) that offer qualitative or quantitative measurements of isolated species or analytes within complex matrices.[484] Electrochemical sensing offers particular versatility since it relies on the charge transfer phenomena associated with chemical transformations which is ubiquitous in chemical transformations.[484] Optical (colorimetric and fluorometric) sensors for a specific compound or broader applications have also seen a recent push in their development, including research towards their greener syntheses.[485]

Principle 11 has also been extended beyond process chemistry to encompass the environmental impacts of analytical methods more generally. Several comprehensive reviews discuss evaluation of techniques not just for time and convenience but also factors such as material intensity, hazard, energy requirements, occupational exposures (*e.g.*, emission of vapors to laboratory space), and fate of waste generated, per analytical sample.[486–489] There have also been efforts made to improve widely used techniques such as liquid chromatography; by modifying mobile or stationary phases, introducing additives, or using high-temperature separations, overall impacts can be mitigated.[490] In particular, the use of supercritical CO_2 instead of organic solvents has been successful in chiral separations, and improvements have been made toward achiral applications as well.[491] Overall, while much progress has been made in identifying methods that are in need of improvement and many alternatives have been made available, there remain challenges with respect to potential tradeoffs among solvent use, toxicity of reagents, energy input, and requirements for auxiliary materials. Analytical chemistry has

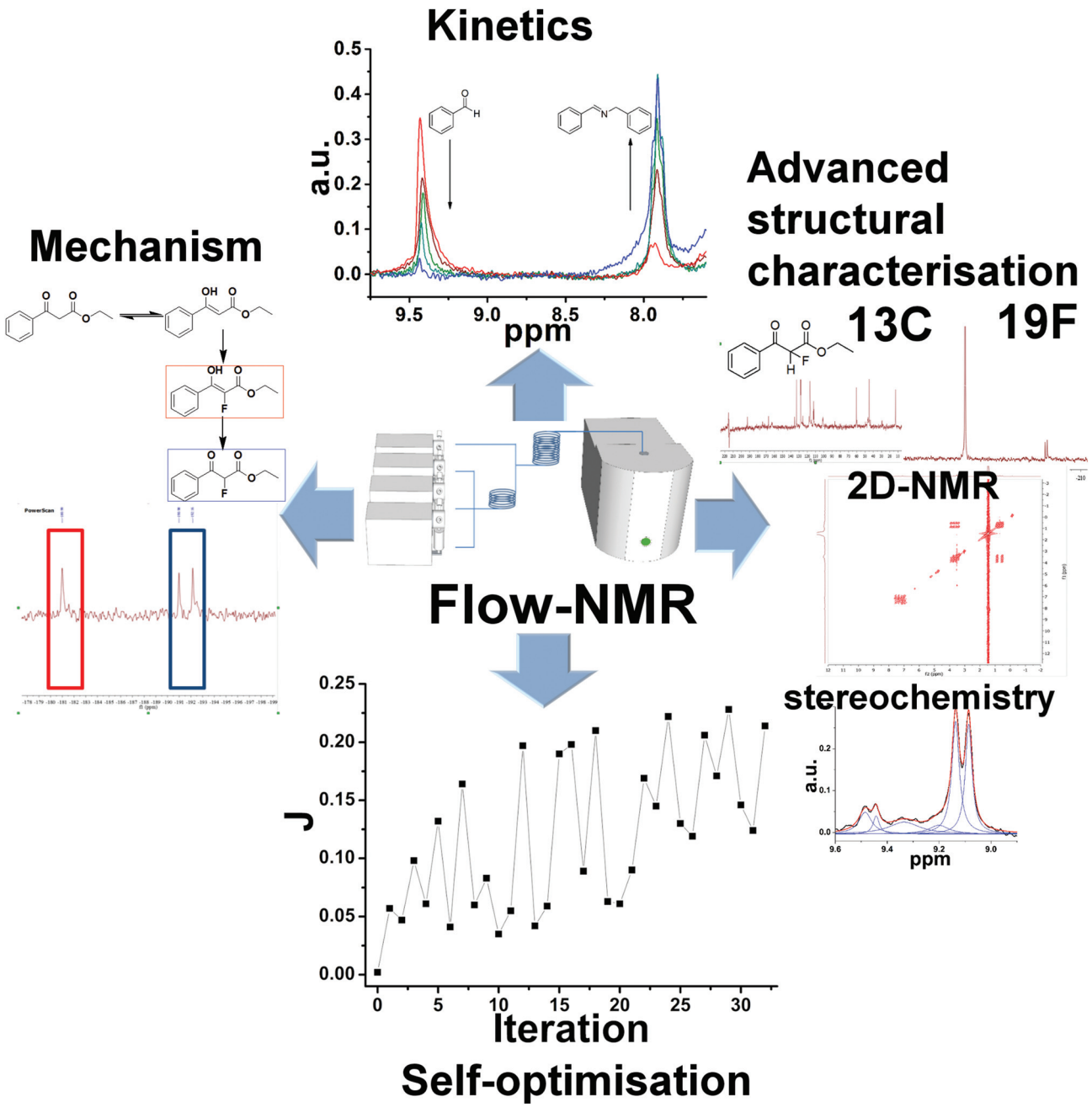


Fig. 9 An overview of real-time measurements made using an in-line NMR in a flow reactor setup to realize improved reaction yield, reduce waste, and enhance efficiency.[469] Published by the Royal Society of Chemistry.

received less attention from a "green" perspective compared to synthetic chemistry but it is likely to be improved by ongoing work in adjacent areas such as catalysis and chemistry of non-covalent interactions.

Principle 12: "Substances and the form of a substance used in chemical processes should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires"

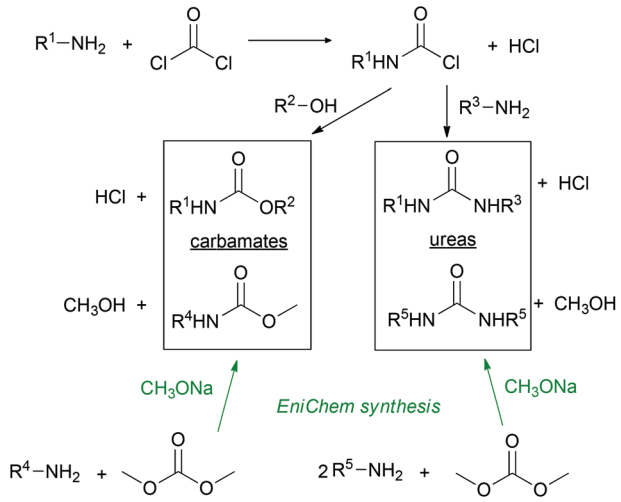
According to a survey by the ACS GCI Chemical Manufacturer's Roundtable,[492] Principle 12 is one of the most implemented Principles in the chemical industry, along with waste prevention (discussed in Principle 1). This is perhaps due to the high associated economic, environmental, and social costs of both chemical accidents and waste generation, and their relevance to powerful social drivers such as worker safety and national security.[493] Also, these Principles provide political and business incentives for scientific and technical advances reducing vulnerability, and the development of new tools to assess and implement chemical process safety. Ultimately, reducing or eliminating inherent hazard is achieved by the implementation of all Green Chemistry Principles, producing a fundamental

change that reliably lessens or removes accident risk within a chemical process and its life cycle.[493] In the same manner, accident prevention practices adopted by companies will ultimately lead to innovation with regards to hazardous chemicals.

The Inherently Safer Processes (ISP) philosophy was first articulated by Trevor Kletz: "What you don't have can't leak".[494,495] Since then, many efforts have resulted in safer processes, most of which have been combined in the book *Inherently Safer Chemical Processes* by the U.S. Center for Chemical Process Safety (CCPS).[496] The Occupational Safety and Health Administration (OSHA) as part of the U.S. Dept. of Labor released a "Transitioning to Safer Chemicals Toolkit" in 2013 that emphasizes the importance of reducing hazard over trying to control risk.[497] Further, following catastrophic chemical incidents, in 2013 President Obama issued an Executive Order to further reduce risk associated with chemical facilities in the USA (Exec. Order 13650: Improving Chemical Facility Safety and Security),[498] which led to amendments to the U.S. EPA Risk Management Program (RMP) regulations published in January 2017.[499] The amendments in the final rule consisted of requirements for large facilities to perform root cause analyses after releases or near misses, analyses of safer alternatives or technologies during process hazard reviews, and to implement better emergency responses and provide enhanced information to officials and the public.[499] However, the incoming EPA administration delayed the effective start date of these amendments to 2019;[500] an overview of the process can be found on the U.S. EPA website.[501] U.S. regulation is also in place to identify chemical facilities that may pose a risk to security under the Chemical Facility Anti-Terrorism Standards (CFATS);[502] the Chemical Security Assessment Tool (CSAT)[503] was developed and enhanced for determining which facilities are regulated under CFATS, based on their possession of chemicals of interest at or above a certain threshold quantity. This list of chemicals of interest is available online.[504]

An issue often raised with the implementation of ISP philosophy in industry lies in the lack of a consensus on safety metrics, which results in the absence of a common basis for decision-making.[505] Initiatives in this direction include the European INSIDE Project, a EU-industry collaboration concentrating efforts on front-end design stages of projects for safety improvements, resulting in INSET (INherent Safety, health and environmental Evaluation Toolkit) published in 2001.[506,507] In 2010, the MERITT (Maximizing EHS Returns by Integrating Tools and Talents) was published by the American Institute of Chemical Engineers (AIChE) to enhance EHS evaluation in process development.[508] Further, there has been a proliferation of different ISP metrics and assessment tools that have been reviewed.[505,509,510]

In 2016, Anastas and Hammond explicated the vital role that Green Chemistry can play within ISP, by (a) replacing hazardous substances in the chemical synthesis processes such as shown in Scheme 3, (b) limiting transportation of hazardous substances by switching to on-site production, (c) limiting storage of hazardous substances by on-demand production, and (d) reducing the reliance on irreplaceable hazardous substances. Further, an extensive list of examples is provided.[493] Additional chemical safety considerations and advances are reviewed in yearly "Safety Notables" since 2002 in the journal *Organic Process Research & Development*, see for example the 2014 [511] and 2016 [512] editions.



Scheme 3 An example of inherently safer chemistry: production of carbamates and ureas using dimethyl carbonate instead of phosgene which also eliminates HCl as a hazardous by-product, such as practiced for example by EniChem Synthesis S.p.A.[493]

Increased understanding of fundamental science and engineering is paramount to implementing inherently safer chemical processes. Analyses of accidents should be instrumental to inform design changes aimed at accident prevention.[513] Additionally, computational models offer opportunities to gain further insights into hazards of chemical substances (also see Principle 4) and processes, especially in various reaction conditions and in the presence of contaminants.[514]

Conclusion

Green Chemistry, now in its third decade, spans the diversity of chemical disciplines and allied fields. Here we have attempted to highlight the broad spectrum of original research and review articles from recent years, showing progress not only in academic research and fundamental understanding of chemical properties and mechanisms, but also entrepreneurial activity and implementation of improved processes in industry. The ChemisTREE diagram, organized along the 12 Principles, provides a convenient way of organizing the Green Chemistry "toolbox", orienting newcomers to the breadth of the field, and enabling an understanding of the foundation of the field as well as the variety of strategies available to advance Green Chemistry goals. Through Green Chemistry education, cross-disciplinary cooperative research, and new ways of collecting and sharing information, it will become more straightforward to design new reactions or technologies that avoid tradeoffs

between Principles or life cycle stages/impacts. Despite the breadth of scientific advances covered, there are tremendous opportunities and challenges that can be seen across the Principles and their manifestations (*e.g.*, the branches and leaves of the Green ChemisTREE):

• While the 12 Principles have been a useful framework, there needs to be a universal understanding that these are not twelve independent factors but rather an interconnected system by which design synergies and be imagined and realized. Only through this approach will new function and performance be realized for genuine transformative innovation and surpass the more modest goal of merely making the *status quo* technologies more efficient.

• It remains challenging to quantify environmental and social benefits that can be gained from a new laboratory-scale methodology. Without demonstration at larger scale or matching to analogous process chemistry technologies, discussion of "green" features tends to be limited to the few Principles that are most practical to demonstrate. Even for lower complexity or "drop-in" chemical replacements, if lifecycle data is not available it becomes more difficult to identify advances that are incremental, or truly transformational.

• Increased sharing of data would facilitate benchmarking of both existing and inventive technologies. Rapid development of electronic storage and communication capabilities in the past decade is likely to improve access to richer datasets. Advances in predictive modeling, machine learning, and artificial intelligence will enhance tools to inform greener design *a priori*. Review of collaborative approaches suggest that there remain challenges in organizing cooperative efforts that meet multiple goals such as longevity, authority, depth, and transparency.

• Adoption of Green Chemistry technologies is driven not only by technical advances but also public awareness, consumer behavior, and government policy. New technologies need to be carefully considered for the possibility of unintended consequences. Transparency in generation and communication of environmental and social metrics will be a key factor in building trust between chemical practitioners and the broader community.

As long as creativity remains an inexhaustible resource, the Green ChemisTREE will flourish. The field of Green Chemistry continues to grow in complexity, much like the tree that represents it, with solid roots already established. The potential for future benefit to society through the discovery and inventions driven by Green Chemistry are limitless.

The metaphor of the tree cannot be understated. A tree provides so much for so many: oxygen, habitat, shade, soil health, *etc*., just as the chemical enterprise touches so much of society and the economy. But just as a tree is dependent on the symbiosis of the greater ecosystem in order to survive, thrive, grow and continue its productive life, so it is with the green chemical enterprise. Those necessary interactions include a supply of educated and aware chemists, collaborators in the broad range of disciplines (including engineering, toxicology, biology, economics, and the humanities), recognition of value of sustainable products and processes by consumers, investment by businesses and venture capital, and stable funding of research. All of these elements will be needed to provide a world that functions in a manner that mimics nature and is

- healthful rather than toxic,
- renewable rather than depleting, and
- regenerative rather than degrading.

No tree stands alone in the forest. While the important scientific discoveries of green chemistry are central, essential, and crucial, in order to move to a truly sustainable civilization, they must be integrated with the ethical and societal imperatives that ensure that economic, policy, and cultural drivers are aligned toward systems conducive to life.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors would like to express their gratitude towards Dr. Evan Beach for the helpful suggestions and fruitful discussions. Further, the authors would like to thank Anna Wexler and the Yale School of Forestry and Environmental Science for the realization of the Green ChemisTREE figure.

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