Invited testimony prepared by Dr. Julie Beth Zimmerman in response to H.R. 2051 - Sustainable Chemistry Research and Development Act of 2019

Madam Chairwoman, Members of the Committee:

My name is Julie Beth Zimmerman. I am on the faculty of Yale University as a Professor in the Department of Chemical and Environmental Engineering and the School of Forestry and Environmental Studies. Perhaps most relevant for this hearing, I am also the Deputy Director of the Center for Green Chemistry and Green Engineering at Yale. I have over 130 peer reviewed publications on the subject of sustainable technologies and have co-authored the textbook, Environmental Engineering: Fundamentals, Sustainability, and Design.

I am here to comment on the "Sustainable Chemistry Research and Development Act" and to provide my perspectives on why it is imperative to advance these important areas of green and sustainable chemistry.

History of Green Chemistry

In the 1990s, Green Chemistry was defined; the US Green Chemistry Program was launched; and the world has followed our lead with the International Union of Pure and Applied Chemistry, the United Nations Industrial Development Organization, and countless international networks have launched green chemistry programs over the years. The US is the world leader in green chemistry and must continue to remain so.

Definitions of Green and Sustainable Chemistry

While there have been isolated examples of making individual chemical products or types of synthetic methods more environmentally benign over the course of the past century[1, 2], a systematic approach to the design of chemistry aligned with sustainability was introduced in 1991, defined as "the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances"[3] and codified by a set of principles in 1998[4]. This approach known as green chemistry has been practiced in academia and industry throughout the world and has created a body of knowledge that is an important scientific foundation for the changes that need to take place in the move toward sustainability.

The term 'sustainable chemistry' has been introduced more recently and possesses numerous definitions[5-9] that have propagated by individuals, researchers, companies, trade associations, not-for-profit organizations, and governmental entities. While there are groups and individuals that say that green chemistry and sustainable chemistry are the same thing, there are others that propose substantively different definitions for sustainable chemistry from that of green chemistry[10].

Why are definitions important?

What is being proposed in all of these discussions and debates is a conceptual construct that can act as a framework for change from the status quo of traditional chemistry over the past two centuries. One essential element in the introduction of any new definition, especially of a concept, is clarity. Vague, nebulous, and plentiful definitions of a single concept are antithetical to bringing about the kind of alignment and focus that the new concept is trying to drive[11]. In other words, if people are confused about what sustainable chemistry even is, it is difficult to imagine that from that confusion will arise a clear path on how to attain it[11].

Green Chemistry has, from the outset, been known as "the chemistry of sustainability"[12]. Key to this is moniker is the obvious fact that **green chemistry *is* chemistry.** There are few people that would argue that a sustainable world can be achieved in the absence of green chemistry. However, it is equally true that green chemistry alone, no matter how fundamental, broad in reach and impact, is not going to be sufficient for achieving a sustainable civilization. Sustainable chemistry- genuine sustainable chemistry that is not merely a marketing phrase - cannot be conducted in the absence of green chemistry. This is clearly illustrated by the recent publication of "The Periodic Table of the Elements of Green and Sustainable Chemistry,"[13] (Appendix 1) where the "heart" of the table are the "Scientific and Technological Elements" which consist of the principles of green chemistry and green engineering[4, 14]; a reflection of the fact that the fundamental science is at the heart of the chemical enterprise[15].

If, as some have suggested, sustainable chemistry is merely using chemistry to address sustainability problems such as those addressed in the United Nations' Sustainable Development Goals (e.g.,climate change, energy generation, water purification, food production, or the manufacture of medicines) regardless of adhering to the Principles of Green Chemistry, would allow for the high potential of tragic unintended consequences. These are sometimes referred to as "doing the right things wrong"[16]. Therefore, any construct of genuine sustainable chemistry would need to recognize that Green Chemistry needs to be its centerpiece, heart and soul, central and essential element[11] and that systems level thinking and life cycle assessments are essential to the tasks at hand.

However, as we recognize that there is more to a sustainable world than just chemistry, we need to recognize that there are and should be many more aspects to sustainable chemistry than green chemistry[11]. These aspects should enable and empower the conduct and impact of the chemistry of sustainability. This requires an ecosystem of economics, policy, interdisciplinary engagement, equity, education, regulation, metrics, and awareness[11].

Green Chemistry Successes

Perhaps the most important thing to know about the developments around green and sustainable chemistry in recent years is the fact that it is an experiment that has worked perhaps beyond anyone's most ambitious predictions. What do I mean by "It worked."

1. The science has been at the highest standards of excellence. As an editor of the American Chemical Society's journal, "Environmental Science and Technology", I am tasked with judging scientific quality through a rigorous peer-review process. The field of green and sustainable chemistry has generated the high quality, world-class science, which has been recently summarized and synthesized in "The Green ChemisTREE: 20 years after taking root with the 12 principles"[15] (Appendix 2). The rate of the production of excellent research is increasing so rapidly that it is now difficult to provide comprehensive overviews of the state of the science. Metrics show that there are now more than 300 Green Chemistry-themed review articles that each have been cited at least 100 times[15].
2. Rather than simply being a way to do things cleaner, more efficiently, and more safely, green and sustainable chemistry's greatest strength has been achieving all of these things while inventing completely new innovative materials, molecules, and chemicals that increase performance, function, and competitiveness spurring new companies and enhancing profits of existing companies[17].
3. The breadth of applicability of sustainable chemistry positively impacts a wide range of sectors including health care, agriculture, energy, electronics, plastics and beyond. This is simply because of the fundamental nature of chemistry that transcends business boundaries.

Nothing to Fight to About

In an age where so much at the intersection of environment and business is controversial and contentious, it is refreshing and encouraging that green and sustainable chemistry is one area where there is almost nothing to fight about.

At a time when every environmental issue seems contentious and controversial, green chemistry has accomplished all of this success with astounding levels of strategic and systematic partnerships between environmentalists, business, and other stakeholders. Examples include the Green Chemistry in Commerce Council, the Green Chemistry Industrial Roundtables at the American Chemical Society and in my own Center at Yale where scientists work in close collaboration with businesses to transform science into solutions.

Green Chemistry occupies that precious niche of providing synergistic goals that the align goals of industry and environmentalists, profits and public health, the chemical enterprise and fence-line communities. **However, there is a problem**. With this successful experiment; with all of these success stories; with all of these achievements; green and sustainable chemistry is still the exception to the rule and is not being conducted systematically or at scale.

What the opportunities and challenges?

Why has green chemistry not yet reached its fill potential and what needs to change?

1. Knowledge base – While there are dozens of educational programs being offered at leading institutions across the country and across the world, they represent less than 10% of the chemistry departments. A general statement that is sadly true today is the people who are being taught how to make our molecules are not being taught how to make them in a sustainable or healthful way such that they are not toxic to humans or the environment.
2. General awareness – While those in the scientific community will likely know about the existence green chemistry, the vast majority of the retailers, product manufacturers, investment community, environmental groups, and the general public have virtually no awareness about the field. They have no idea of what is possible today much less what is possible tomorrow. They have no idea about the benefits they can achieve through its use. Consumers don't know what they can demand and expect.
3. Lack of incentives – If an academic researcher submits a proposal for grant funding for new molecules that are toxic or new methods of making chemicals that are wasteful, there is no disincentive. If a chemical producer wishes to manufacture a chemical product in a cleaner and

safer way but it requires capital investment to do so, there is little incentive.

4. Sporadic and unreliable research support – While it is true that when federal agencies are requested to report the amounts of funding that are supporting efforts in sustainable chemistry, there can appear to be significant expenditures, the truth may be less convincing. Because of the quirks of how agencies broadly define 'sustainable chemistry', many disparate programs may be bundled into this funding category inappropriately.
5. Nebulous and vague definitions. When sustainable chemistry is defined so broadly as to include all of work related to chemicals, health, and the environment, then this leads to a meaningless collection of disparate and disjointed work, much of which does not comply with the goals and definition of Green Chemistry. While we currently spend significant resources to characterize, monitor, assess the hazards and risks of chemicals to human health and the environment, that is not the same as creating, designing, inventing, developing, implementing and commercializing solutions. We would all agree that a diagnosis is not the same thing as a cure. And a cure is certainly not the same thing as prevention.

What needs to be done?

So what needs to happen in order for green and sustainable chemistry to become systematically integrated into the way that we design, make, use, and manage chemicals.

1. Awareness raising campaign
   - While it is not the job of the federal government to advance individual companies or sectors and certainly not to pick technological winners and losers; it can play an essential role in creating a general awareness of beneficial approaches that transcend specific companies and specific technologies. Green chemistry needs a greater general awareness of its benefits in order to reach its potential. This can be done by engaging the National Academies, informal science education programs such as museums and public libraries, and facilitating partnerships between Department of Commerce and relevant industry sector trade associations for the development of valid over-arching messages on green chemistry.

2. Training
   - Chemistry and chemical engineering departments need to ensure that a core competency of any student learning how to make and use chemicals is an understanding of their impact on humans and the environment and of the basic principles of green chemistry. Demonstration of this curriculum should be tied to eligibility of a department for research grants from the federal government.

- The Chemical Safety Board, National Institute for Occupational Safety and Health (NIOSH), and Occupational Safety and Health Administration (OSHA) should work with Green Chemistry practitioners to identify inherently safer alternatives for accident prevention and worker safety while training management and workers on how to do alternatives assessment when making product and process decisions. Subsequent recommended improvements for reduced risk and vulnerability should include safer chemistries thereby simultaneously advancing economic competitiveness and well-being for fence-line communities[18].

3. Interagency Advisory Committee and Research Funding
    - Establish an inter-agency Federal Advisory Committee Act group focused on aspirational sustainable chemistry design that would identify the desirable properties of sustainable chemicals and materials. These criteria would be able to specifically identify the attributes to answer questions including “What is a green plastic?”, “What are the design criteria for future agricultural chemicals?”, “What criteria should be used to distinguish which chemicals should be designed to be reused versus to degrade?” These criteria will be useful for numerous applications including for preferred purchasing programs within the Federal Government such that an organization would have to provide justification when not purchasing preferred products.

- At virtually no cost, the National Laboratories from the science agencies, such as Department of Energy, National Institutes of Health, United States Department of Agriculture, National Aeronautics and Space Administration, and Department of Defense could construct a database of patents and disclosures of green chemistry technologies. Making this publicly available could catalyze further discoveries as well as commercialization by researchers, entrepreneurs, and industry looking for green chemistry solutions.

- Establish a coordinated inter-agency research funding program focused specifically on green chemistry, rather than broad efforts sustainable chemistry or even more broad efforts on the nexus of chemicals, health, and the environment. The research and development supported under this program should span scientific research, foundational research, use-inspired research, applications research, and technology development.

- An inter-agency committee of the relevant scientific agencies should develop criteria by which advances in green chemistry technologies would be recognized by incentives including patent-life extensions. The result of these criteria would be made available to the Commerce Department's Patent and Trademark Office for incorporation into policy.

- The green chemistry criteria developed above would also be communicated to the Securities and Exchange Commission to form the basis of validating legitimate marketing claims for promoting products or processes.

4. <u>Recognition and facilitation of industry efforts</u>
   - Too often, companies especially those in highly regulated industries, e.g., pharmaceuticals, are required to go through extensive regulatory hurdles even when they are making extraordinary green chemistry improvements to their manufacturing processes. These hurdles to the implementation of green chemistry technologies and should either be modified or the companies should otherwise compensated for these significant costs in order to remove a barrier for these emerging technologies .

   - One provision of green chemistry is the use of waste as a feedstock for new materials. While there are significant advantages to this technology, regulatory barriers still exist for the beneficial use of many waste products. With the renewed attention on the 'circular economy', it will be essential that criteria be developed for the responsible broadening of the allowable categories of 'waste' materials able to be used for remanufacturing.

- Genuine and effective green chemistry solutions are being developed by scientists and industry every day and yet many are not revealed publicly because businesses are fearful of being accused of so-called, green-washing. The establishment of an interagency award recognizing green chemistry successes could build on the previous successes of the Green Chemistry Challenge Award. Broadening this award by formally mandating the participation of not only the Environmental Protection Agency, but also the National Science Foundation, Health and Human Services (National Institutes of Health and Food and Drug Administration), Department of Energy, Department of Commerce (National Institutes of Science and Technology), would make this a genuinely valuable tool for business and the scientific community.

- Establish a public-private partnership that includes scientists, the business community, and the investment community for the purpose of facilitating the commercialization of discoveries and support entrepreneurship. This fee-for-service organization should span the breadth of capabilities needed including laboratory facilities, business development, scale-up manufacturing, capital planning, customer testing, intellectual property protection strategy, and additional consulting/technical services that are necessary to move Green Chemistry discoveries through the pipeline to commercial products. Such an entity would be designed to be self-supporting after an initial phase based on royalties and license agreements from the technologies advanced through the organization.

In Conclusion

In conclusion, the powerful tool of green chemistry is essential to sustaining healthy people, a healthy planet, and a healthy economy. It must no longer be the exception to the rule but must become the rule itself; simply the way things are done.

Because, in the final analysis, while this is certainly about our immediate prosperity; more importantly, it is about our posterity.

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Appendix 1: The Periodic Table of the Elements of Green and Sustainable Chemistry

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The periodic table of the elements of green and sustainable chemistry

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Achieving a sustainable future will only be possible through the intersection of the best science and technology in combination with the societal, economic, policy, cultural, moral, and ethical ecosystem. Green chemistry and green engineering provide the scientific and technological foundation of the elements of green and sustainable chemistry while the other elements, relating to humanitarian aims, enabling system conditions, and noble goals, provide the imperative context. This alternative periodic table, strives to outline the range of aspects and tools that are available and needed to accomplish the daunting and necessary tasks of moving toward a sustainable tomorrow.

1. Introduction

Without the innovations of chemistry, sustainable development will be impossible to achieve. If the chemistry that humans use to pursue these innovations continues to be, itself, unsustainable, sustainable development will be equally impossible, particularly as global population, and subsequently societal needs, continues to increase. It is only through the combination of chemical innovations conducted in a sustainable way that progress toward the sustainable development goals (SDGs)[1] can be achieved. Green chemistry has often been known as "the chemistry of sustainability".[2–4] Sustainable chemistry is a term of more recent vintage that, in its most genuine usage, refers to a broader ecosystem beyond the science that includes education, economics, policies, management and other efforts that enable the science to be implemented and make a positive impact.[5] In this paper, we attempt to lay out a cohesive framework, "the periodic table of the elements of green and sustainable chemistry" (Fig. 1) that elucidates the various figurative aspects of the efforts to pursue chemistry that is directionally and qualitatively consistent with the pursuit of sustainability goals.

The tabular presentation of a complex topic is more than a familiar format for chemists during the sesquicentennial of Mendeleev's original publication. The metaphor of the elements and their relationship to molecules and materials is particularly appropriate when recognizing that just as elements can have multiple valence states and bonding can involve non-obvious molecular orbital interactions; so can the nature and interactions between these figurative elements of green and sustainable chemistry be complex and non-intuitive.

At the "heart" of this table are the "scientific and technological elements" which consist of the principles of green chemistry and green engineering;[6,7] a reflection of the fact that the fundamental science is at the heart of the chemical enterprise.[8] However, knowing that the science and engineering cannot operate alone, the area where the Main Group Elements would mostly reside are the conceptual frameworks and the economic and policy drivers that enable the greater enterprise. The group to the far left of the table are the "humanitarian elements" that emphasize the role that chemistry plays in meeting the essential needs of humanity and the biosphere. The group at the rightmost side of the table comprises the "noble elements" that identify the noble and aspirational elements of a vision of a sustainable civilization.

The table is meant to be an inclusive enumeration of the tools, strategies, efforts, and goals of chemistry and its enabling interconnections that work toward achieving a more sustainable civilization. Just as new elements have been discovered throughout the past 150 years, this table too will hopefully evolve and grow adding new dimensions and new possibilities.

2. Humanitarian

The UN Global Chemicals Outlook[9] predicts that the value of the chemical industry will double from US$5 trillion by 2030. This will bring benefits as chemical technologies are used to

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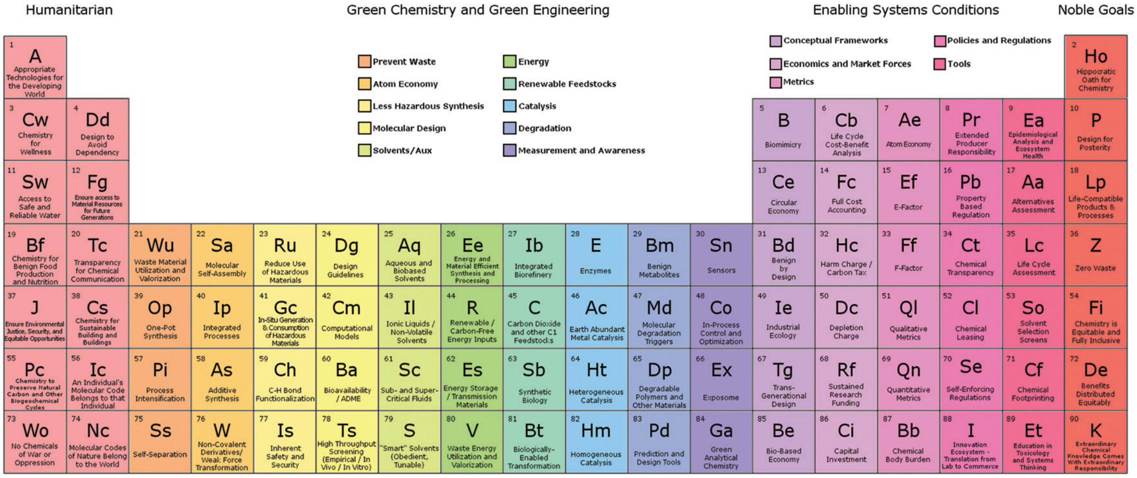

Humanitarian

Green Chemistry and Green Engineering

Enabling Systems Conditions

Noble Goals

■ Prevent Waste
■ Atom Economy
■ Less Hazardous Synthesis
■ Molecular Design
■ Solvents/Aux
■ Energy
■ Renewable Feedstocks
■ Catalysis
■ Degradation
■ Measurement and Awareness

■ Conceptual Frameworks
■ Economics and Market Forces
■ Metrics
■ Policies and Regulations
■ Tools

1 **A** Appropriate Technologies for the Developing World																	2 **Ho** Hippocratic Oath for Chemistry
3 **Cw** Chemistry for Wellness	4 **Dd** Design to Avoid Dependency											5 **B** Biomimicry	6 **Cb** Life Cycle Cost-Benefit Analysis	7 **Ae** Atom Economy	8 **Pr** Extended Producer Responsibility	9 **Ea** Epidemiological Analysis and Ecosystem Health	10 **P** Design for Posterity
11 **Sw** Access to Safe and Reliable Water	12 **Fg** Ensure access to Material Resources for Future Generations											13 **Ce** Circular Economy	14 **Fc** Full Cost Accounting	15 **Ef** E-Factor	16 **Pb** Property Based Regulation	17 **Aa** Alternatives Assessment	18 **Lp** Life-Compatible Products & Processes
19 **Bf** Chemistry for Benign Food Production and Nutrition	20 **Tc** Transparency for Chemical Communication	21 **Wu** Waste Material Utilization and Valorization	22 **Sa** Molecular Self-Assembly	23 **Ru** Reduce Use of Hazardous Materials	24 **Dg** Design Guidelines	25 **Aq** Aqueous and Biobased Solvents	26 **Ee** Energy and Material Efficient Synthesis and Processing	27 **Ib** Integrated Biorefinery	28 **E** Enzymes	29 **Bm** Benign Metabolites	30 **Sn** Sensors	31 **Bd** Benign by Design	32 **Hc** Harm Charge / Carbon Tax	33 **Ff** F-Factor	34 **Ct** Chemical Transparency	35 **Lc** Life Cycle Assessment	36 **Z** Zero Waste
37 **J** Ensure Environmental Justice, Security, and Equitable Opportunities	38 **Cs** Chemistry for Sustainable Building and Buildings	39 **Op** One-Pot Synthesis	40 **Ip** Integrated Processes	41 **Gc** In-Situ Generation & Consumption of Hazardous Materials	42 **Cm** Computational Models	43 **Il** Ionic Liquids / Non-Volatile Solvents	44 **R** Renewable / Carbon-Free Energy Inputs	45 **C** Carbon Dioxide and other C1 Feedstocks	46 **Ac** Earth Abundant Metal Catalysis	47 **Md** Molecular Degradation Triggers	48 **Co** In-Process Control and Optimization	49 **Ie** Industrial Ecology	50 **Dc** Depletion Charge	51 **Ql** Qualitative Metrics	52 **Cl** Chemical Leasing	53 **So** Solvent Selection Screens	54 **Fi** Chemistry is Equitable and Fully Inclusive
55 **Pc** Chemistry to Preserve Natural Carbon and Other Biogeochemical Cycles	56 **Ic** An Individual's Molecular Code Belongs to that Individual	57 **Pi** Process Intensification	58 **As** Additive Synthesis	59 **Ch** C-H Bond Functionalization	60 **Ba** Bioavailability / ADME	61 **Sc** Sub- and Super-Critical Fluids	62 **Es** Energy Storage / Transmission Materials	63 **Sb** Synthetic Biology	64 **Ht** Heterogeneous Catalysis	65 **Dp** Degradable Polymers and Other Materials	66 **Ex** Exposome	67 **Tg** Trans-Generational Design	68 **Rf** Sustained Research Funding	69 **Qn** Quantitative Metrics	70 **Se** Self-Enforcing Regulations	71 **Cf** Chemical Footprinting	72 **De** Benefits Distributed Equitably
73 **Wo** No Chemicals of War or Oppression	74 **Nc** Molecular Codes of Nature Belong to the World	75 **Ss** Self-Separation	76 **W** Non-Covalent Derivatives/ Weak Force Transformation	77 **Is** Inherent Safety and Security	78 **Ts** High Throughput Screening (Empirical / In Vivo / In Vitro)	79 **S** "Smart" Solvents (Obedient, Tunable)	80 **V** Waste Energy Utilization and Valorization	81 **Bt** Biologically-Enabled Transformation	82 **Hm** Homogeneous Catalysis	83 **Pd** Prediction and Design Tools	84 **Ga** Green Analytical Chemistry	85 **Be** Bio-Based Economy	86 **Ci** Capital Investment	87 **Bb** Chemical Body Burden	88 **I** Innovation Ecosystem - Translation from Lab to Commerce	89 **Et** Education in Toxicology and Systems Thinking	90 **K** Extraordinary Chemical Knowledge Comes With Extraordinary Responsibility

Fig. 1 The periodic table of the elements of green and sustainable chemistry.

improve infrastructure, human wellness, management of food and water resources, and shelter, particularly in the developing world. As quality of life increases, consumption of chemical-dependent products such as electronics, furniture, and personal care products is on the rise. With the high magnitude and pace of growth, it is critical that gains are not offset by impacts on human and environmental health. Sound chemical management practices are not implemented evenly around the world, and since chemical commerce increasingly depends on global and interconnected supply chains, significant harm results from exposures to pollutants.

The following elements of green and sustainable chemistry are presented to emphasize core humanitarian aims and principles. Since chemistry has existed as a discipline, it has played a central role in meeting fundamental human needs. The development of water disinfection chemistry, for example, or the artificial fixation of nitrogen from air, were critical in sustaining growth and wellbeing as population growth outpaced resources. As we continue to press against the limits of natural systems it will remain a challenge to ensure basic needs such as food, water, security, and shelter for future generations. Green and sustainable chemistry should also strive to ensure that risks and benefits are equally shared among populations. In part that can be realized by improving equality and inclusion within chemical enterprise, and improving the transparency of communication to the general public. Green and sustainable chemistry respects human dignity, recognizing individuals' sovereignty over their personal molecular codes, and rejecting applications of chemistry that promote war, oppression, or personal degradation.

2.1 1, appropriate technologies for the developing world (A)

There has been a tremendous history of the invention and deployment of chemical technologies over the past two centuries that has transformed modern life for a segment of the global population. However, due to factors that include particular resource flows, capital flows, infrastructure requirements, human capital, and more – many of the technologies developed in the past and that are being developed today, are not benefitting or improving the well-being of a large percentage of the world's population.[10]

Developing appropriate technologies means understanding the context into which a technology is going to be deployed to ensure that it can bring benefit.[11,12] Designing a technology to be viable in the industrialized world or the developing world, a major metropolis or a tribal village, requires systems thinking and thoughtful design. Designing technologies for the appropriate context is a challenge that needs to be met if benefit is to be equitable.

2.2 3, chemistry for wellness (Cw)

Chemistry has been at the forefront of modern western medicines with the vast majority of effort focused on treating disease.[13] However, treating disease is not the same as preserving wellness. Chemistry has been at the forefront of increased food production. However, increased food supply and production of caloric content is not the same as the realization of access to nutritional health. Chemistry has been at the forefront of imaging, diagnostics, and sensors but measuring and monitoring a problem is not the same things as solving it or preventing it. Chemistry can play a role in significant and timely efforts to rigorously understand and deliver nutraceuticals, probiotics, and other beneficial supplements. There is also a need to elucidate opportunities to proactively enhance positive mechanistic pathways towards proactive health.

Chemistry has also been at the forefront of pollution and contamination of the geosphere, ecosphere and the biosphere because of the products it has and continues to produce and the way it produced them. All of these issues directly affect wellness. Chemistry can be designed to ensure that the nature of the material and energy basis of our society not merely accomplishes the goals of addressing problems after the fact but to avoid the problems and promote wellness by design.

2.3 11, access to safe and reliable water (SW)

One of the essential materials of life is water and access to it for drinking, sanitation, and hygiene is necessary for life, health, and well-being.[14] Chemistry has been critical in historical approaches to water disinfection and improving water quality from removal of harmful contaminants to addressing odor and taste concerns. Chemistry will be required to realize the future methods, process, and materials that enable healthful drinking water without the unintended consequences of harmful disinfection by-products. Equally important is the imperative of sanitation to avoid the spread of disease by exposure to pathogens. These services must be supplied in ways that are mindful of equity, safety, and dignity.[15,16] The water infrastructure and treatment needed to enable adequate potable (and non-potable) water will be dependent on chemicals and chemistry to ensure appropriate water quantity and quality for the intended use, be it drinking, sanitation, hygiene or another use.

2.4 19, chemistry for benign food production and nutrition (Bf)

While the great increases in the efficiency of food production have been astounding and life-saving, there have been unintended consequences for the over-use of fertilizers and the use of pesticides and herbicides that harm beneficial insects and plants and damage the ecosystem.[17]

Chemical alternatives, as well as non-chemical alternatives, are being developed and need to be implemented at scale. These range from targeted bio-pesticides[18] to herbicides that focus on specific pests and plants[19] to pesticides designed to degrade rapidly into non-toxic degradation products.[20] Integrated pest management systems have been shown to be efficacious and economically practical without the environmental damage.[21]

There is also significant and ongoing progress towards alternative protein and nutrition sources ranging from plant-based "meats"[22] to insect-derived products[23] to algal based foodstuffs.[24] Efforts to enhance the nutritional value of food, rather than emphasis on calories, will continue to make significant contributions towards the implementation of chemistry to provide more optimal food sources with lower environmental impact.

2.5 37, ensure environmental justice, security, and equitable opportunities (J)

Proximity to chemical manufacturing, processing and use has historically come with disproportionate risk to the surrounding communities and ecosystems;[25] this includes the exportation of banned chemicals and hazardous waste to communities with few other economic opportunities.[26]

Individuals should have the right to live in homes and communities that are not placed at increased risk due to transport or production of chemicals or inadequate protection of facilities. Use of highly hazardous chemicals increases vulnerability to accidents, natural disasters, or intentional acts of violence and terror. Adopting chemistries that are inherently benign is the most effective means of ensuring that communities are not placed at undue risk from the chemical enterprise. Case studies have shown that there are safer alternatives to toxic gases, VOCs, pesticides, and cleaning chemicals implicated in previous incidents.[27]

There should be no disadvantageous circumstances for individuals or communities living or working near chemical facilities. This is inclusive of legal emissions as well as unintentional chemical releases. Through the development of green and sustainable chemistry as well as community engagement, the historic adverse impacts of the chemical enterprise can instead provide desirable economic and safe opportunities in communities that have tended to be predominantly underserved and disenfranchised.

2.6 55, chemistry to preserve natural carbon and other biogeochemical cycles (Pc)

The integrated systems that are the basis of the planet's natural biogeochemical cycles, from carbon to nitrogen to water and beyond, are chemical cycles and chemical processes that are impacted by the human interferences and interactions with these cycles.[28] Human chemistry must be designed such that there will be no perturbation of the natural biogeochemical cycles and their interlinkages. Through thoughtful consideration of human material and energy utilization, there can be a preservation of the critical natural cycles essential to the preservation of life and all of its diversity on the planet.

2.7 73, no chemicals of war or oppression (Wo)

The history of the intentional use of weaponized chemicals is recognized as uncivilized and the continuation of the universal rejection of this practice is essential to a civilized society.[29] Likewise, the use of chemicals for carrying out the death penalty or for the oppression of individuals through chemical lobotomies or chemical castration must not happen. Designing, making, and utilizing chemicals for the purpose of mental or physical control over individuals is inconsistent with the peaceful uses of chemistry.

2.8 4, design to avoid dependency (Dd)

Some molecules can be addictive to humans. They can result in physical and neurological changes that result in dependency and its resulting impairment. Chemists have the duty to work at the highest levels on knowledge and awareness of the mechanisms of dependency in order to ensure that the molecules that are created do not result in human dependency and addiction.

Economic dependency is a separate yet important issue. Molecules should not be designed to be essential and inseparable to livelihood and wellness and embedded in systems that provide critical items like food, clean water, and medicine.

Chemical dependency is not limited to the human species but rather can also impact other living things both animal and plant. Dependency needs to be understood such that design for variety and resilience is pursued preferably.

2.9 12, ensure access to material resources for future generations (Fg)

The basic elements will largely not be created nor destroyed – with the exception of radioactive decay and escape of helium from our atmosphere. However, the ability to access resources that are fundamental to the chemical and material infrastructure of our society and economy can be greatly impacted and diminished through irresponsible use. The combustion of valuable fossil fuels, the dissipation of phosphorus, and the diffusion of rare earth elements will make the resource base of the future more difficult to access for future generations.

2.10 20, transparency for chemical communication (Tc)

The potential benefits and the potential harms that can be provided by chemistry are too immense and powerful to be cloaked in the darkness of jargon. Yet, as chemistry continues to evolve and become more sophisticated, the opacity of the science to the general public increases as well. The responsibility of molecular scientists – and scientists generally – is not merely to discover, invent, and understand, but rather to effectively convey that understanding as clearly and transparently as possible.[30] To be clear, this is not the same as 'as clearly and transparently as convenient'. The task of communication is not a secondary task but rather one of equal status in the scientific pursuit.

The lack of value placed on communication has resulted in alienation of the public from science and fear by the public of science.[31] The failure of scientists to effectively communicate has historically not merely damaged the scientific endeavor, it allows for anti-scientific rhetoric to fill the communication void. Of equal importance is the need for chemists to take an active role in raising awareness and providing education and training to enhance the benefits of this clear communication being received by an informed and increasingly sophisticated audience. The practice of green and sustainable chemistry depends on training at all levels, from K-12 to university and professional. Beyond the technical competency in chemistry required to maintain continuous innovation, it will be important to push at the conventional boundaries of the discipline. Educators can bridge core chemistry concepts with elements of green engineering, industrial ecology, toxicology, bioethics, public policy and other adjacent fields so that students will be well equipped for systems thinking as well as lifecycle, circular or cyclical strategies for chemical design.

2.11 38, chemistry for sustainable building and buildings (Cs)

The structures that are used to house people and their activities should be designed, constructed, and maintained to provide resilient protection while being conducive to health and wellness of the occupants and the surrounding ecosystems. From the molecular basis of the materials throughout their life cycle to the systems to provide the requisite water, climate control, and lighting, chemistry has a significant role to play in efficiently providing safe indoor environments for humans and their activities while considering the surrounding landscape. Further, buildings can be designed to be modular providing for future adaptions, deconstruction and reuse to avoid end of life material waste.

Provision of shelter depends on a wide range of chemistries including composition of structural and insulating materials, components of electrical and lighting technology, heating and cooling systems, water handling, and integration of buildings with the surrounding landscape. These services must be provided without damaging human health or environmental systems. For example, chemistry has a role to play in minimizing the climate impacts of concrete production, which account for as much of 5% of current global emissions.[32] Building materials and furniture should be designed to prevent chronic exposure to harmful chemicals, as has been experienced in formaldehyde-based resins and other releases of volatiles leading to "sick building syndrome".[33]

2.12 56, an individual's molecular code belongs to that individual (Ic)

Every individual possesses the unique molecular code that is the underlying basis of their individuality and their identity. Further, this code has the power and potential for understanding health and wellness in a fundamental way, at the molecular scale.[34] While this molecular code may contain information and functionality that can result in value, every individual is sovereign over their code and this sovereignty cannot be taken from them by others. As the ability to understand, manipulate, and utilize the various levels of this biological code increases, it will be ever more essential to guarantee that control of this code remains with the individual.

2.13 74, molecular codes of nature belong to the world (Nc)

No human wrote any of the genetic codes of Nature and no human or group of humans can own it. Humans played no role in the billions of years of the design of genomes, bio/geo material structure, natural transformations and self-assembly. The inventions of Nature belong to Nature. The codes of Nature belong to Nature. The act of a human recognizing its brilliance and deeming it a discovery is not justification to claiming ownership and control and in any way limiting access to this brilliance by everyone.[35]

2.14 Green chemistry and green engineering

In this section we group the principles of green chemistry and green engineering according to desirable environmental outcomes. It is important to consider that any individual technology or strategy should be used thoughtfully in the context of the broader lifecycle of a chemical, chemical process, or final product. The subsequent grouping of enabling systems conditions includes discussion of metrics and tools that can be used to prioritize "green" strategies and minimize the potential for environmental tradeoffs.

3. Prevent waste

Regardless of its nature, waste consumes resources, time, effort, and money both when it is created and then when it is handled and managed at end of life, with hazardous waste requiring even greater investments for monitoring and control.[36] As has been stated on numerous occasions, creating, handling, storing, and disposing of waste is necessarily an expense and does not add value in terms of innovation or performance. In processes of production, therefore, waste is always undesirable in all its forms.

Ideally, molecules, products, processes and systems would be designed to not create waste. That is, we should aim to eliminate the concept of waste by designing the outputs to be feedstocks elsewhere mimicking natural systems. Whether the waste is material, energy, space, time or the derivative of all of these, money, there are design strategies that can and are being implemented in green chemistry and engineering to eliminate the concept of waste.

3.1 21, waste material utilization and valorization (Wu)

Waste is a human-centered concept. In Nature there is, for all practical purposes, no waste. In Nature, organisms and geosystems evolve to utilize the "waste" of one process to nourish, sustain, and strengthen another. While the history of human-designed chemical systems has been linear (*e.g.*, take-make-waste), there is a recognition that genuine elegance requires the building of circular systems where materials and energy flow in cycles as they do in Nature. This would require the developing the tools, techniques, and approaches for "designing waste" such that the "waste" itself is considered an additional product of the system.

These approaches of chemical waste valorization have found large-scale application in a variety of settings from individual product manufacturing processes to entire mega-scale factories to urban and regional networks.[37] Transforming waste into a value-added product is a science in its infancy and it will need to develop considerably in sophistication and scale in order to displace the wasteful linear processes that have historically dominated.

3.2 39, "one-pot" synthesis (Op)

When chemical transformations have taken place historically, they have often required many steps, especially for complex molecules such as those in the field of pharmaceuticals. Each time there is a multi-step synthesis, there is the need for separation, isolation, and purification that results in loss of material, increased energy usage, and time lost.[38] "One-pot" synthesis, by contrast, refers to transformations carried out in a single reaction vessel without isolation. Designing a process this way result in significant efficiencies and waste reduction.[38] The challenge is to avoid tradeoffs such as increased usage of toxic substances or decreased product quality. When done correctly, decreased steps and decreased reaction vessels can provide significant benefits.

3.3 57, process intensification (Pi)

Traditional methods of chemical manufacture have intrinsic inefficiencies that result in wastes of materials, energy, time, and space. This occurs when an overall process is split into large numbers of 'unit processes' of reaction, separation, and purification. When these steps can be combined the benefits are not only waste reduction but also lower capital and operating costs and increased inherent safety. The concept of having small continuous-flow 'reactors' that can achieve scale-out by increasing the number, so-called "numbering up", can have advantages over traditional "scaling up" of bulk processes.[39,40] Microreactor technology aids in multicomponent reactions, or reaction telescoping, in which multiple chemical steps may be carried out within a single reactor network.[41]

3.4 57, self-separation (Ss)

The chemicals and materials enterprise is one of the great consumers of energy in industry. One very large piece of this energy consumption is the operation of separations.[42] Separations includes many elements of isolation, purification, and some kinds of cleaning. In addition to the energy that is input into the traditional separation systems, the embedded energy that is contained within the solvents that have often been used in separation systems is also very significant.

The development of systems that can be designed to facilitate "self-separation" can decrease energy and material usage when done properly.[43] Designing a molecular product to separate from its reaction matrix or enabling an impurity generated in a process to self-separate due to intrinsic factors can have sustainability advantages.

4. Molecular transformation

The modern miracle of chemical enterprise is the ability to transform the materials that occur naturally in the world into new materials with new properties and performance that would not otherwise exist. History has shown there are thoughtful and wise ways to engage in molecular transformation and there are methods that are profoundly toxic, wasteful, and depleting. The new emerging synthetic methods that have been demonstrated in the field of green chemistry come from thoughtful life-cycle design and often use Nature and biological systems as an inspiration, mentor, and guide.[44] Through this type of thoughtful design, we move from a narrow definition of mere efficiency to one of holistic productivity.

4.1 22, molecular self-assembly (Sa)

The process of intentional bond-making has been one of the most important accomplishments of chemistry.[45] Historically, this process has often been forced through the use of energy or reactive reagents to occur at the time, place, and rate that is desired. The more complex the molecule, the more steps and energy that has often been employed.

Looking at natural and biological systems, there are many examples where complex molecules with extensive stereochemistry and intricate ring systems are realized through molecular self-assembly that takes place upon appropriate stimulus.[46] This can be achieved in human-designed synthesis as well. It is, of course, always important to not merely design a self-assembling molecule by shifting the energy and reagent inputs to another part of the product life-cycle such as its precursors.

4.2 40, integrated processes (Ip)

Long chains of unit reaction processes can have significant disadvantages for energy and material waste due to the separation, isolation, and purification steps usually encountered after each step.[47] These separations are amongst the most energy-intensive aspects of a process. In addition, there are almost always material losses due to transfer between unit processes. By designing processes to be integrated to the highest feasible degree there can be significant advantages not only for energy and material efficiencies, but also for the time that is required to transfer between vessels and the reduced worker exposure that can be obtained.

Integrating not only individual processes, but numerous processes can also be valuable to accomplish goals such as utilization of waste heat/material from one process as a feedstock for another.

4.3 58, additive synthesis (As)

In an addition reaction, all atoms of the reactants are incorporated into the final product whereas elimination and substitution reactions inherently generate waste as part of the nature of the reaction.[48] The use of addition reactions can allow for significant decreases in the waste generated intrinsic to the synthetic method. By building up a molecule atom by atom or fragment by fragment one uses only what is necessary to construct the target. Addition reactions must be used thoughtfully to avoid shifting the burden of waste from one step to another step or another part of a process. The additive concept translates beyond the molecular scale to materials and manufacturing applications where environmental benefits are similarly significant.[49]

4.4 76, non-covalent derivatives/weak force transformation (W)

Chemists have spent more than two centuries pursuing mastery of bond-making, with great success. However, it is also true that Nature accomplishes much of its performance and functional modifications, not through covalent bonds but rather through weak-force interactions.[50] These weak forces engage at the time and place necessary to impart the properties temporally as needed. Weak forces are also used to guide synthetic pathways in Nature.

While humans have been increasingly aware of the essential importance of weak forces, there has not been the pursuit of mastering these powerful tools such that they can be used as design levers to create the kind of functionality that is desired.

5. Less hazardous synthesis

While efficiency has historically served as a proxy for sustainable practices in the chemical enterprise, it is imperative that the goal of reducing the quantity of material and energy consumed is closely coupled with considerations related to the nature of that material and energy. Using less may not have the beneficial effects of reducing the overall hazard of the synthetic process depending on the nature of the feedstocks, reagents, and auxiliary chemicals.[51] It is imperative that these inputs and outputs, in addition to the intended product, are as inherently benign as possible. Further, the conditions under which synthetic processes are carried out should also be considered when pursuing the goal of a more sustainable chemical enterprise.[52] This offers benefits from environmental and human health perspectives in addition to a reduction in vulnerability to chemical accidents and sabotage.[27]

5.1 23, reduce use of hazardous materials (Ru)

The use of hazards – physical (*e.g.*, corrosivity, reactivity, explosivity flammability), toxicological (carcinogenicity, reproductive and developmental including endocrine disruption, neurological), or global (*e.g.*, ozone depletion, GHG's) – can be minimized or eliminated throughout the entire life-cycle of a chemical process.[6] Utilization of hazardous chemicals can be avoided through substitution of alternatives that have been designed for reduced hazard or, at a minimum, assessed and understood to have reduced hazard by comparison to what it is replacing.

Throughout processes, the feedstocks, reagents, solvents, catalysts and other substances can be replaced such that negative environmental and human health consequences can be minimized.

5.2 41, *in situ* generation and consumption of hazardous materials (Gc)

Reactivity is an essential part of chemical transformations and is also closely associated with the hazardous nature of many substances. One strategy that can be employed to avoid exposures of workers or nearby communities to toxic/reactive reagents, is to generate and consume them in the processes without any significant accumulation of these substances.[53] Through '*in situ*' generation, the substance needs only to be generated in minuscule quantities for the short time it is needed before it is consumed that reaction.

5.3 59, C–H bond functionalization (Ch)

Substitution and elimination reactions are inherently inefficient synthetic transformations at the molecular level. While these types of reaction provide access to countless molecules, they generate stoichiometric amounts of a "leaving group" that must be separated and recovered or treated as waste. In organic chemistry, one of the most useful alternatives is catalytic C–H bond activation. Ongoing research is aimed at improving selectivity and performance of systems that enable C–H functionalization in a highly controlled manner.[54]

5.4 77, inherent safety and security (Is)

Chemists and chemical engineers know the properties, structures, and conditions that underlie explosivity, flammability, and corrosivity. Designing molecules such they are not capable of ignition, combustion, or explosion is something that is within the skillset of chemistry today.

While safety has been a concern of the chemical enterprise for much of its history, this has often been accomplished through protection from the consequences of these physical hazards when they occur rather than through molecular design for reduction of intrinsic hazard.[27] These design tools can protect from accidents as well as terrorism and sabotage vulnerability.

6. Molecular design

The basis of our society and economy are synthetic chemicals and materials. While there have been significant advances in toxicology associated with identifying, and in some instances predicting, industrial chemicals that are likely to cause harm to human and ecosystem health, the gains in informing the *a priori* design of chemicals with reduced hazard to humans and the environment have been elusive.[55] To realize the goal of designing chemicals that are safe and functionally relevant, there is a need to create an interdisciplinary body of knowledge that sits at the nexus of computational chemistry, mechanistic toxicology, and big data analytics among others. It is only when we change the inherent nature of the chemicals and materials that are foundational to quality of life that we can truly advance towards a sustainable future that is no longer reliant on costly regulatory and technological controls of circumstances in which hazardous chemicals can be used and managed.

6.1 24, design guidelines (Dg)

Design is intentional. If a chemical contains a hazard that is not intended, it is a design flaw. Yet, many of our made-made chemicals contain hazards to humans or the biosphere by accident or lack of thoughtful design.

As we understand the underlying basis of hazard to human health and the environment at the molecular level, we can design to avoid it. As we understand the properties which enable chemical accidents and other adverse consequences, we can and must design to avoid these outcomes where possible.[56]

6.2 42, computational models (Cm)

With increasingly deeper molecular-level understanding of the nature of chemical hazard comes increased potential for the use of computational models to assess, predict, and design out hazards from the chemicals we use and produce. The wide range of physical/chemical properties that are the underlying basis for toxic mechanisms of action, exposure pathways, transport and fate, *etc.*, can be evaluated *in silico* with greater accuracy and the insights derived from these evaluations can be used to avoid the adverse consequences that have marked the less-desirable aspects of the history of the chemical enterprise.[57]

6.3 60, bioavailability/ADME (Ba)

At the foundation of protecting living things from toxicological impacts is the concept of ADME (absorption, distribution, metabolism, excretion). By understanding the molecular parameters that control the stages of ADME, substances can reduce a chemical's bioavailability—its ability to access a biological system. The insights from pharmaceutical research in trying to maximize bioavailability have provided intellectual tools that can be used in all aspects of the chemical enterprise in thoughtful design for hazard reduction.[58]

6.4 78, high throughput screening (empirical/*in vivo*/*in vitro*) (Ts)

Empirical testing of the toxicity of a chemical is an essential part of the deep understanding of the potential consequences of a chemical. As we move away from animal testing due to ethical and financial drivers, the development of bioassays is increasingly important. The bioassays emerging not only cover a large number of biological processes and toxicological endpoints, but also can be done within a high throughput framework. Through these high-throughput screening assays, there can be extensive amounts of data generated providing insights into the concerns that may be associated with a chemical or alternatively, inform safer design of future chemicals.[59]

7. Solvents and auxiliary chemicals

The cost, environmental impact, and safety of a chemical process is often driven by the solvents and other auxiliary chemicals.[60] It is interesting to note that the amount of solvent and auxiliary chemicals used often exceeds raw materials, reagents, and products, particularly in the case of separation and purification processes.[61] Once again, while quantity of these chemicals it is an important consideration from a perspective of material and energy efficiency, it is the nature of our historic solvents that has posed the greatest challenge to the environment and human health. Conventional solvents have generally been volatile, increasing likely exposures; hydrophobic, serving as long term sources of concern in environmental systems; and toxic to ecosystems and humans, particularly a concern for chemical workers. Just as we are aspiring to design safer chemical products, the same effort and attention should applied to the design of safer solvents or solvent-free processes.[62] This can be accomplished by reducing inherent hazard as well as minimizing exposure potential.[63,64]

7.1 25, aqueous and biobased solvents (Aq)

Water is the original solvent: the solvent of life. And yet, the long history of the chemical enterprise largely eschewed water as a solvent. As petrochemical processes came to be dominant, it was considered to be logical that organic solvents would be most compatible with hydrocarbon-based transformations. Research launched in the 20th Century but accelerating in the 21st has shown that water can be not only a possible but also desirable solvent for many chemical processes where it was once thought not possible.[65] Water has been shown in cases to accelerate reaction rates, enhance selectivity, and bring benefits of non-toxicity, non-flammability, low cost, and ready availability in most instances. While there may be circumstances where water has environmental drawbacks, for example in energy requirements for recyclability, separation of products, or waste treatment, overall water can be a preferable solvent for many chemical processes.

Similarly, biomass shows increasing promise for replacing fossil resources in the production of solvents. Recently, biobased derivatives have been either used directly as green solvents or as key precursors to innovative solvents that are potentially less toxic and more bio-compatible.[66]

7.2 43, ionic liquids/non-volatile solvents (Il)

When salts can be designed to perturb their crystal structure adequately such that they are a liquid at room temperature, they are known as room temperature ionic liquids (RT-IL). These liquids have been demonstrated to be effective solvents in a wide range of applications all while having negligible vapor pressure.[67] This is important as lack of vapor pressure avoids one of the most concerning routes of exposure for most volatile solvents, that of respiration. Another major concern with traditional solvents is their direct impact on the atmosphere, for example *via* photochemical processes. With RT-IL, this would be virtually impossible, however it should be recognized that indirect impacts from RT-IL raw materials or manufacturing processes could still be significant.[68]

While the lack of vapor pressure is an elegant attribute for this class of solvents, it is also critical that these solvents are designed for reduced toxicity as well.[69]

7.3 61, sub- and super-critical fluids (Sc)

There are compressible gases that at a certain temperature and under a certain pressure, collectively their critical point, become fluids that are neither gas nor liquid but rather a "supercritical fluid". These fluids have been known for centuries but ongoing research is creating new opportunities for their application as solvents.[70] Carbon dioxide is the most highly studied of these and has been demonstrated at large scale to be a useful solvent for everything from synthesis to extraction, cleaning, and analysis.[71,72]

The green advantages of these supercritical fluids are numerous including lack of toxicity for water and carbon dioxide, lack of flammability, tunability, and the possibility of 'infinite recyclability' by cycling pressure. (Note: The use of carbon dioxide as a solvent does not require the generation of new CO_2 and therefore does not contribute to greenhouse gas emissions.)

7.4 79, "smart" solvents (obedient, tunable) (S)

The ability to make a solvent respond to stimuli and change its properties under new conditions can be extremely consequential. Historically, solvents were energy consuming because solubility was controlled almost exclusively through heating and cooling. With next generation solvents that have been demonstrated and developed, solvents can be controlled by factors such as pressure or pH.

These new so-called obedient solvents open up possibilities for niche and industrial uses that change the energy profiles for many chemical processes.[73]

8. Energy

The chemical sector consumes approximately 20% of total industrial energy consumption in the U.S., and contributes in similar proportions to U.S. greenhouse gas emissions.[74] Given the reliance on fossil fuel resources and the associated greenhouse gas emissions, there is a clear indication that, at a minimum, the chemical enterprise should strive to be as energy efficient as possible, normalizing to chemical function rather than mass in the assessment.[75] Gain in efficiency can be realized by considering both the quantity and quality of energy inputs as well as waste energy utilization. Of course, the chemical sector has a significant role to play in changing the nature of our energy feedstocks towards ones that are renewable, and developing materials that can enhance energy generation, storage, and transmission to enable the use of these renewable energy sources.[76]

8.1 26, energy and material efficient synthesis and processing (Ee)

Synthesizing, transforming, and manufacturing of raw materials into the desired chemical products requires the input of energy to drive the reaction. The form of this energy, in addition to the amount, has a significant impact of the environmental cost of carrying out the reaction. There have been recent advances to reduce the overall energy demand, and subsequent environmental and economic impacts, of chemical production by exploring different means of energy delivery including mechano-,[77] electro-,[78] photo-,[79] and electromagnetic[62] chemical driven transformations.

The synthesis, transformation and manufacture of chemical products almost always involves separations in the form of removal of contaminants (purification), retrieving the desired molecules (isolation), removal of extraneous/undesirable materials (cleaning), or breaking a complex mixture into its components, including the removal of water (separations). While these operations have historically been extraordinarily material and energy intensive,[42] new approaches and new methods for the wide range of separations need to be developed and utilized to make these necessary processes more effective, efficient, and sustainable.

8.2 44, renewable/carbon-free energy inputs (R)

As long as the chemical enterprise is among the largest energy consumers of the economy, there is an imperative to ensure that the energy consumed is renewable and minimal-carbon. In the past this was often limited to fortuitous alignment of economic incentives with local resources, *e.g.* siting operations to take advantage of hydropower or geothermal energy. Now the options are becoming less geographically limited with solar and wind energy more plentiful and increasingly integrated with energy grids. There remain challenges in meeting the unique demands of chemical manufacturing processes. Renewable energy systems must be further improved to deliver the scale and quality needed for chemical processing, refining, and distillation.[80]

8.3 62, energy storage and transmission materials (Es)

Even the most sustainable and renewable sources of energy risk going to waste when not utilized immediately if there is not adequate ability to store or transport this energy. Physical, mechanical, chemical and other methods of energy storage and transmission will require the underlying materials to be benign and Earth abundant. Battery technologies, hydrogen storage, *etc.*, will only be as sustainable as the materials are throughout their life-cycles.[81]

8.4 80, waste energy utilization and valorization (V)

While much attention is often paid to the amount of waste materials that fill up landfills around the world or that make their way to become ocean contaminants, there is less attention to waste energy generation. Energy waste in the form of heat, light, vibration, noise, *etc.*, has a cost due to the impacts of energy generation for which there is no return as well as the impacts of the waste energy on the systems around it (*e.g.*, warming, wear and tear, mechanical erosion). The ability to capture this waste energy and find value-added uses is an important part of any design strategies for a sustainable product process, or system.[82]

9. Renewable feedstocks

Fossil fuel is the basis of the chemical, material and energy foundation of the global economy. Fossil fuel feedstocks are used to generate electricity, to produce transportation fuels, and to produce a wide range of consumer goods, such as plastics, healthcare and drug products, and agrichemicals. These reserves are finite and pose additional challenges related to geopolitics and physical accessibility.

Given this context, there has been emerging and important efforts to increase the use of biobased feedstocks for energy, chemicals, and materials production. Using renewable feedstocks from agricultural, forestry and aquatic resources, particularly nonfood, residues, and waste streams from processing these materials, will be essential to developing changing the material and energy basis of our economy and society.[83] However, this must be implemented in a context of competition with food, land and water use, as well as benign and efficient downstream processing for recovery of the full value of the feedstock. This will require advances in our synthetic transformation portfolio and changes to our current chemical production infrastructure (*e.g.*, solvent selection, separation processes) while unlocking new functionality and performance from these feedstocks that is not available in petroleum-based inputs. Moving to renewable feedstocks is an imperative for the advancement of a more sustainable future.

9.1 27, integrated biorefinery (Ib)

While matter is neither created nor destroyed, the molecular conversion of natural resources through industrialized processes has the ability transform these resources from benefits into burdens. The conversion of energy dense hydrocarbons to heat-trapping greenhouse gasses is the most known example but the concept extends to water resources, mineral resources, biodiversity resources, water resources, soil resources, *etc.* In the absence of the ability to fully renew and restore, there can be no license for our chemical enterprise to access and transform the parts of the geosphere and biosphere that cannot be replaced.

Perhaps the most materially efficient technological process in history is the refinery. The modern petrochemical refinery has lessons for the bio-based chemical economy that has not reached the same level of efficiency. Being able to retrieve value from all extractable fractions from high volume low value to low volume high value in an integrated biorefinery will be an important piece of realizing the goal of a bio-based economy.[84] This effort requires not only advances in extraction through green solvents but the ability to tune the quality (*e.g.*, purity) of the extract, be it from lignocellulose,[85] agricultural or other waste streams,[37] algae biomass,[86] or other renewable sources.

9.2 45, carbon dioxide and other C1 feedstocks (C)

Carbon has been lusted over in its diamond form. Carbon has driven economies in its coal form. Carbon has emerged as a 21st Century energy source in its methane form. Carbon is essential to the biosphere and threatens climate stability in its carbon dioxide form. Carbon is deadly in its carbon monoxide form. The emergence of C1 chemistry is the essential manipulation of one-carbon building blocks to transform them from recalcitrant to useful, from destructive to value-adding, from challenge to an opportunity.[87]

Learning to sustainably access the promise of carbon dioxide and other C1 molecules as a feedstock is one of the great tasks of green and sustainable chemistry.[88–90]

9.3 63, synthetic biology (Sb)

New genomes are no longer science fiction. The ability to design and control biological organisms and processes is well on its way and has the potential to become one of the most powerful tools to benefit the move toward a sustainable world. It also has the potential to cause almost unimaginable harm. Thoughtful development, use and implementation of synthetic biology processes must proceed within a sustainability construct.[91] Long-term implication of use and misuse much be considered and built in prior to implementation. The impact of synthetic biology will be felt by this world in the coming decades and it is essential that these impacts be positive and not follow the errors of previous technological advances of realizing a specific utility coupled with myriad unintended consequences.

9.4 81, biologically-enabled transformation (Bt)

Nature is the original chemist carrying out an inconceivable numbers chemical transformations each second with a volume that dwarfs the combined output of every chemical company and an elegance that puts the occupants of the best chemistry departments to shame. Capturing and harnessing the power of biological processes to carry out chemical transformations can be a powerful strategy for a sustainable economy.[92] Oriented toward renewable, bio-based feedstocks, these processes (*e.g.*, fermentation) can be utilized for production of materials in a manner that is supportive of and conducive to life.

10. Catalysis

There are few areas of chemistry that exemplify sustainability better than catalysis. Catalysis allows for increasing the rate of a transformation, increased efficiency, use of less feedstock, enhanced product quality, lower waste and lower emissions while at the same time increasing the profitability of a process/product.[93] Virtually every major petrochemical, specialty chemical, or pharmaceutical company would not be economically viable without the use of catalysis. The blend of environmental benefit and economic returns *via* catalysis makes it amongst the most obvious and powerful tools to advance sustainability through chemistry.

10.1 28, enzymes (E)

Enzymes are often viewed the pinnacle of what catalysis strives to be. They carry out conversion of chemicals with an elegance and selectivity that most chemists would only dream of. Yet the limitations of enzymatic catalysis are something that needs to be understood; useful technologies require tolerance of a wide range of temperature, pressure, pH and concentration levels. The development of manufacturing methods that exploit the advantages of enzymes will be an important contribution to green and sustainable chemistry manufacturing.[94]

10.2 46, earth abundant metal catalysis (Ac)

The recent history of metal catalysis is that often some of the most toxic and/or precious metals were developed and used as catalysts and targeted for research and study. These include osmium, mercury, chromium, platinum, palladium, gold, iridium and others. The cost and sustainability impacts of this approach are significant. While it must be noted that there exist excellent recovery schemes, each of these have costs and risks that should be minimized.

The exploitation of Earth-abundant metals (*e.g.*, iron, copper) that are neither scarce nor depleting is an active area of development that will be important to achieve the necessary advantages of metal catalysis without the same associated historic impacts.[95]

10.3 64, heterogeneous catalysis (Ht)

Heterogeneous implies that something is not uniform in nature and contains a few or many different components, or substances that make up one whole or mixture. In chemistry, it can also mean something is comprised of the same substance only in different phases (gas, liquid, solid). For example, ice water is heterogeneous because it is comprised of liquid water and solid water. In sustainability, heterogeneity can confer some desirable properties. In consideration of a catalyst, heterogeneous catalysts confer many advantages compared to homogeneous catalysts including better stability, ease of handling, separation, and simplified recycling of the catalyst.[96]

10.4 82, homogeneous catalysis (Hm)

When something is the same throughout and consists of all the same parts it is homogeneous. In chemistry, this means that it is a pure element, or a compound or mixture that contains the same composition throughout and in the same state of matter (solid, liquid, and gas). Homogeneous catalysts are important to green and sustainable chemistry due to ease in characterizing how they function; they are typically straightforward to modify for optimized performance or lower environmental impacts.[97] Homogeneous catalysts are amenable to interesting strategies such as controlled phase transfer or changes in solubility aiding recovery and reuse. The boundary between homogeneous and heterogenous catalysis can be blurred by immobilization or compartmentalization techniques. In any case, the technologies are a powerful tool for aligning performance, economic, and sustainability aims for a chemical process.[93]

11. Degradation

Persistent substances may remain in the natural and manmade environments for an indefinite time. These compounds may accumulate to reach levels that are harmful to health, environment and natural resources.[98] Such contamination may be poorly reversible or even irreversible, and could render natural resources such as soil and water unusable far into the future.[99] As such, there is a need to design chemicals and materials, particularly those that are intentionally or unintentionally distributed in the environment, that are stable during their useful life, and then completely degrade once they are no longer functionally necessary. Designing for degradation is necessary but not sufficient to realize the goals of green and sustainable chemistry; the subsequent degradation products should, themselves, be non-persistent and benign to human health and the environment.[100]

11.1 29, benign metabolites (Bm)

Metabolites are small molecules that are by-products of metabolism or degradation of larger molecules in a living organism. Metabolites can be formed during physiological metabolism in humans, during plant metabolism, or in other living organisms. Many of these metabolites have specific functions within the organism that help to regulate various processes.[101] However, some can cause adverse health effects and are toxic to the environment. Benign metabolites refer to the metabolites that are non-toxic to an organism or the environment. This thinking is important in sustainability practices as design must account for product breakdown and not just the product itself in order to mitigate toxicity in humans and ecotoxicity. Benign parent compounds can break down into very harmful metabolites. This may be especially relevant to biologically active chemicals such as pharmaceutical[102] and herbicides/pesticides[103] that could be better designed to ensure degradation in the environment would produce benign metabolites.

11.2 47, molecular degradation triggers (Md)

Molecular degradation triggers are events that help to promote degradation and break down of chemicals and molecules.[20] These could include molecule modification, UV light triggers, or any number of different triggering events. Today there are many stable compounds that persist in the environment for lengthy periods of time. Triggers could help to mitigate the presence of these harmful, persistent molecules and could be key in sustainability efforts. Molecular degradation triggers can help to form benign by-products following the end of life of chemicals and products.

11.3 65, degradable polymers and other materials (Dp)

Polymers should not be (effectively) immortal. Yet, many approach that level of persistence when compared to the human time-scale. This has resulted in well-known concerns for plastics in landfills and in the oceans.[104] It also is of concern for lesser-known issues such as the potential impacts of all of the micro- and/or water soluble synthetic plastics that due to their persistence are being integrated into ecosystems and the biosphere. Polymers can be designed such that their entire lifetime is approximately the same as their useful lifetime.[105] Enduring and persisting beyond intended use serves little purpose and has been the cause of serious problems.

11.4 83, prediction and design tools (Pd)

Designing next generation chemicals and materials will require next generation prediction and design tools.[106] Analytical understanding and computational models continue to be more powerful allowing increased insights to go beyond simply predicting potential adverse impacts towards informing design. This is critical because predicting that something may be harmful without a mechanistic basis for that model outcome does not provide sufficient and necessary guidance to a chemist on how to redesign the molecule to preserve function while minimizing or eliminating the hazards.[107]

12. Measurement and awareness

In order to know whether an action or invention is positive or negative for the world, there needs to be some kind of feedback from the system.[108] In the absence of this feedback, there is little more than insufficient guesses and suppositions. However, the way that we choose to measure the performance and impact of our products, processes, and systems will often have a profound impact on the understanding that we take away from these measurements. If we are operating in multidimensional systems like those involved with sustainability, we will need measurement systems that are as multi-dimensional if we wish to gain insight from them. Traditional, limited measurements such as efficiency measures will be insufficient for this complex system. Additionally, our measurement systems have often been retrospective tools that would give us reports on what happened in the past sometimes with long enough lag times that the information itself is irrelevant. We now have tools and computational abilities that can provide real-time insights and awareness that allow for relevant action.

12.1 30, sensors (Sn)

Chemical sensors and chemo-electronic sensors can provide a level of detection and real-time awareness that will be critical to a sustainable society.[109] With applications ranging from air and water quality to health indicators to environmental ecosystems shift, the development of ubiquitous, integrated sensors can provide data that inform insights into planetary and human health. These same sensors can inform and empower more efficient use of materials and energy in manufacturing and consumer use. Sensor technology can provide a consciousness about factors and dynamics that were once thought unknowable.

12.2 48, in-process control and optimization (Co)

In manufacturing processes and operations, the way to verify smooth operation was through periodic analysis that require extractive testing and analysis of the product. This required time and labor and resulted in waste of materials and energy. Often, product that did not meet specifications (so-called off-spec) would need to be discarded as waste, frequently in large quantities. It is now possible and important that future processes and even operations beyond manufacturing utilize in-process control and optimization through the use of real-time sensors and analysis.[110] In this way, there is the ability to sense off-spec material before it is formed in significant quantities and to make the appropriate corrections *in situ*. This becomes especially vital when pursuing the goal of process integration.

12.3 66, exposome (Ex)

The exposome refers to everything an individual is exposed to starting from the time before they are born through end of life.[111] Each of these exposures can accumulate, compound, and interact with each other and effect one's health. Exposures include anything from one's environment, diet, work place, and lifestyle and can affect health in a number of facets and ways. One component of the exposome is an individual's unique physiological characteristics and genetics, which can play a major role in how an individual will react to an exposure. In terms of sustainability it becomes important to consider the potential exposures in designing any product or chemical.[112] By better understanding the exposome we can design more sustainable and safer products and many of the harmful exposures to human health can be minimized.

12.4 84, green analytical chemistry (Ga)

Analysis of the air, water, and land to detect pollution was historically conducted with field sampling protocols that require extensive effort to be brought to a laboratory where extensive work-up generated large volumes of solvents and waste. The processes of measurement and analysis of an environmental problem often contributed to other environmental problems. With the use of real-time, in-field analysis the necessary measurements can be taken without the wasted time, material and energy. This "green analytical chemistry" has been extended to a wide-range of analytical techniques beyond environment analysis reducing the quantity of materials needed and waste generated.[113]

13. Enabling systems conditions – conceptual frameworks

Conceptual frameworks provide a basis for considering the role of the chemical enterprise in advancing sustainability and the associated complexities. Such frameworks provide a means to understand the relevant concepts as well as their relationships to one another. Frameworks of this nature help to inform the overarching design of the role of chemicals and chemistry in contributing to the goals of a sustainable future.

13.1 5, biomimicry (B)

Nature has a 3.5 billion-year head start on designing products, processes, and systems and it shows. Nature is indescribably brilliant in its ability to produce the widest range of chemicals and materials using locally available starting materials, usually at ambient temperatures and pressures, completely eliminating the concept of waste, and doing it in a way that is conducive to life. In the face of this ingenuity, the only wise and sustainable strategy is to take Nature as a mentor and a guide in designing human made products and systems.[114] The lessons to be learned are limitless and the benefits to be had, essential.

13.2 13, circular economy (Ce)

Circular economy refers to closing the material loop. This means working to keep resources in use for as long as possible and requires both the producer and consumer to be aware of how they are utilizing resources.[115] It can help to ensure waste and resources, at any point from production to end of life of a final product are reused, repaired, or recycled in some capacity. This helps to decrease waste and becomes especially important in sustainability efforts, helping companies to reduce waste, save money, and work to ensure there is not depletion of finite resources. The concept of circular economy should be considered in all phases of the product life cycle and can not only help to save resources, but also decrease the amount of toxic waste output.

13.3 31, benign by design (Bd)

"Performance" of a product, process, or system, has been a concept that has been narrowly defined in terms of how well something achieves a very specific goal. Perhaps it's a dye being a particular shade of blue or a lubricant being able to reduce friction. While performance has been focused on the desirable qualities, this has often come with undesirable or adverse unintended consequences.

Benign-by-design builds all factors into the definition of performance such that inherent safety is also included along with function.[7]

13.4 49, industrial ecology (Ie)

Industrial ecology aspires to manage material and energy flows in the same way that an ecosystem performs, with the aims of ultimately decreasing environmental stress and improving resource efficiency.[116] Considering industrial processes as a closed loop as much as possible creates the opportunity to decrease inputs through the reuse of outputs either within a facility or between different organization. By viewing waste as a resource – by closing these material and energy loops – waste and resource depletion caused by industry can be minimized. Industrial ecology helps to find solutions to environmental problems by identifying problem areas in business and industry and can aid in improved sustainability practices.

13.5 67, trans-generational design (Tg)

It has been shown that exposure to a chemical by one generation can have deleterious effects on the future generations, even without direct exposure themselves.[117] This is especially relevant to chemicals that interfere with the body's hormonal systems leading to a variety of adverse health effects including reductions in sperm counts as well as tumors, birth defects, and other developmental disorders.[118] In this way, the chemistry we practice and the chemicals we produce today can have lasting and debilitating effects on future generations. This emerging knowledge carries an enormous burden of responsibility to be accountable not only to today's population but to those not yet born.

13.6 85, bio-based economy (Be)

Bio-based economy refers to the innovation in utilization of biomass to sustainably make bio-based products such as chemicals, materials, fuel and energy. It is an attempt to move away from reliance on depleting resources and rely on renewable, bio-based feedstocks. Traditionally, chemicals have been made from petroleum feedstocks.[119] Although chemical production only accounts for 5%–7% of petroleum consumption,[120] petroleum sources represent over 98% of chemical feedstocks.[121] The advantages for moving to renewable feedstocks include an opportunity for innovation and a chance to take advantage of nature's ability to perform exquisitely selective chemistry. Petrochemical feedstocks provide very simple hydrocarbons, which chemists have learned to make more complex. Natural feedstocks are inherently different. They are complex molecules, and chemists are still developing elegant ways to efficiently transform them into useful products.

14. Enabling systems conditions – economics and market forces

While the current global economic systems and market forces tend to drive perverse incentives that have resulted in the design and evolution of our existing chemical infrastructure, these same powerful drivers can be harnessed to encourage behavior that is aligned with the goals of a sustainable future. As profit is the almighty motivator, it is imperative that we move to a system whereby externalities are internalized through costs and whereby benefits beyond financial gains can be systematically and rigorously factored into decision making. We must align environmental, social, and economic goals if we want to design a future that does not continue on our current unsustainable path.

14.1 6, life cycle cost-benefit analysis (Cb)

Cost-benefit analysis is a decision-making process that helps to identify, and quantify, the costs and benefits associated with all potential scenarios or options. It is a systematic approach to estimating the strengths and weaknesses of alternatives used to make decisions between alternatives. Opportunity cost, the benefit missed by choosing one option over the other, is often also factored into the analysis. It can be used to compare intangible items, such as ecosystems services or the benefit of choosing an option that confers less environmental and negative health impact over a more detrimental option.[122] In sustainability practices cost-benefit analysis can help to identify options that may confer more favorable environmental conditions, while also minimizing costs over the entire life cycle. It is important to consider the full life cycle in this type of analysis as costs may be higher upfront for greater benefits later on.

14.2 14, full cost accounting (Fc)

Full cost accounting allows for the implementation of environmental, health, and social assets to be considered in the economic costs and benefits of decision making.[123] It allows for complete end-to-end cost analysis of producing products or services. The goal is not necessarily to monetize their value, but rather to better understand their impact on an ecosystem and society, and potential ability to create value. Full cost accounting can help in sustainability by identifying areas where reducing environment impact could create value and confer monetary and non-monetary benefits that can be translated into economic terms.[123] It allows for better management of the natural and social resources in our world today and a way to achieve more sustainable outcomes.

14.3 32, harm charge/carbon tax (Hc)

Carbon tax is a tax placed on the burning of fossil fuels, or carbon-based fuels, and corresponds to greenhouse gas emissions.[124] The fee is either placed on the producers or passed along to the consumers for the carbon emissions produced from burning of fuel. It can be implemented in a number of different facets such as through costs associated with home heating, flights, and shipping capacities. A harm charge is a similar concept only less specific. It places a charge on any practice harmful to the environment or human health such as a chemical spill, using non-sustainable products, or water pollution. The charges or taxes are utilized in order to serve as a disincentive to practices harmful to the climate, the environment, and human health, helping to shift thinking towards more sustainable practices. Further, the revenue generated from these charges can be used to invest in sustainability practices elsewhere in the system.

14.4 50, depletion charge (Dc)

Similar to harm charge, depletion charge presents an opportunity to internalize an externality. In this case, the externality is the consumption of finite resources. Depletion charge presents an opportunity to incrementally increase the economic cost associated with the use of a finite resource by factoring in scarcity.[125] That is, using the next amount of a finite resource would be increasingly expensive to disincentivize its ongoing use. This incremental charge does not need to be linear, and could itself increase with ongoing use of the finite resource rapidly leading to a price that is cost prohibitive rendering that finite resource economically infeasible.

14.5 68, sustained research funding (Rf)

Scientific investigations, studies, and breakthroughs will be necessary to move away from the unsustainable trajectory that we are on. These investigations, in many cases, may require sustained efforts either due to the difficulty of the challenge or the inherent nature of longitudinal insights.[126] These research efforts are particularly fragile to disruptions caused by the unpredictable modalities of research funding schemes whether in the public or private sector. The imperative of sustained, predictable funding support will be an essential element of achieving the kinds of insights and inventions necessary for sustainable prosperity.

14.6 86, capital investment (Ci)

The chemicals and material manufacturing infrastructure that makes everything from building materials to wind turbines is very capital intensive. Current schemes for capital investment, (*e.g.*, venture, private equity) have the common goal of getting targeted returns while minimizing risk. This model significantly favors incrementalism which is far easier to understand and analyze what the risk profile might be for technological investments. It also favors low capital-intensive projects such as software and "app" projects and disfavors projects such as large-scale infrastructure and manufacturing. Achieving sustainability goals necessitates transformative technologies and dramatically reconstituted sustainable infrastructure at unprecedented scale requiring wise, patient capital at a significantly increased level.

15. Enabling systems conditions – metrics

For metrics to be useful in sustainability, they must have attributes that reflect sustainability itself. They must be both quantitative and qualitative.[127] They must be relevant across time scales and able

$$\mathrm{F} = \text{Function/kg of chemical}$$

to combine both reductionism and integrative systems thinking. Too often traditional metrics that have determined the cost or benefit of our product or processes have looked at only one aspect of the overall system.[108] These reductionist metrics are flawed in terms of limiting our purview, our design space, and our innovation. Further, they have been inadvertently enabling of unsustainable technologies and policies. Broad thinking is developing on how to enhance the old metrics with new systems indicators that are a reflection of the magnitude and directionality needed for sustainable design and decision-making. These multi-dimensional 'vector metrics' will be essential in setting the course for sustainability in the future.

15.1 7, atom economy (Ae)

Measuring the efficiency of chemical reactions is necessary to compare alternative synthetic routes to products in terms of environmental and economic costs. Percentage yield has historically served this function, as it compares the (predicted) theoretical and actual product quantity. However, a high yield is not sufficient to identify environmentally-preferable synthetic routes because there can be significant waste generated in a reaction that produces close the predicted amount of product. As such, we need an additional metric, atom economy, to measure how much of the reactant atoms actually form the final product[128] whereby:

$$\%\text{Atom economy} = \text{molar mass of product/molar mass of all reactants} \times 100\%$$

This is effectively guiding a chemist to pursue pollution prevention at the molecular scale. In principle, the higher the atom economy, the lower the amount of waste product formed, so considering both the yield and the atom economy can help in designing a green chemical process. In practice, other components of a reaction that do not appear in the balanced chemical equation, such as solvents or separations, may have a larger impact on waste generation. The metrics discussed below can provide additional guidance.

15.2 15, *E*-factor (Ef)

The amount of waste produced in the manufacture of a chemical product or a product of any kind should be minimized. While one would intuit that this measure was always part of manufacturing efficiency, it was not. The introduction of the calculation of the *E*-factor[51] took the original form of:

$$E \text{ factor} = \text{kg waste/kg product}$$

and can be adjusted to include a variety of aspects of the manufacturing process. *E*-Factor provides information that was historically neglected but is critical to moving towards more efficient and effective chemical production.

15.3 33, *F*-factor (Ff)

Virtually, no one ever bought a chemical. They bought function or performance. They wanted the service the chemical provided. With that realization, a metric, *F* factor, has been developed to recognize and quantify the desire to get maximum function with the minimal amount of chemical used.[75]

This approach has been expanded in the discussions of the chemical equivalent of Moore's Law.[129]

The desire is for the value of *F* to be as large as possible by increasing the functional performance and/or decreasing the amount used to achieve some functional performance. This drives the system towards ideality where you get all of the function of a chemical or product without the existence a chemical or a product; the chemical analogy of getting the function of the telephone without the need for telephone wires on every street.

15.4 51, qualitative metrics (Ql)

While most of traditional assessment is based around quantitative metrics, qualitative metrics may be equally necessary in providing understanding related to sustainability,[130] especially in the early design phases. The nature and the character of aspects of green and sustainable chemistry are not always reductionist exercises.[131] The renewability of a feedstock, the toxicity of a molecule, the environmental justice implications of a factory siting, market acceptance of an energy technology *etc.*, may all have qualitative aspects that are critically important. While qualitative metrics may be less rigorous and involve integrative systems thinking that is outside traditional analytical frameworks, it is possible that they are more closely linked to the interconnected nature of sustainability systems and goals as outlined in the sustainable development goals.[3]

15.5 69, quantitative metrics (Qn)

One of the most active areas in analytical tools related to green chemistry and engineering is that is quantifiable metrics.[132] There are important measures of (process) mass intensity ((P) MI),[133] reaction mass efficiency (RME),[134] carbon efficiency (CE), innovative green aspiration level (iGAL)[135] and others. These quantifiable metrics can be useful and informative in answering specific questions of efficiency and informing potential downstream environmental impact (through tools such as life cycle assessment, section 17.3) when a reductionist analysis is necessary to inform improvement. It is as important to know what data or information the quantifiable metrics are providing as it is to understand what questions they aren't addressing. The strengths of quantifiable metrics are essential and their weaknesses must be equally respected.

15.6 87, chemical body burden (Bb)

Chemical body burden refers to the measurement or load of chemicals in the body.[136] This load can be detected through blood, urine, breast milk sampling or any number of biomonitoring activities. Chemicals in the body could have numerous harmful effects and could weaken the immune system making the body more susceptible to disease.[137] The burden may be due to bioaccumulation through various mechanisms of exposure. Understanding the amount and types of chemicals in the body can help to better inform what chemicals are in the environment. Chemical body burden is important to sustainability because it can make known the chemicals with the greatest bioaccumulation in nature and greatest exposures to humans, helping to inform future design of chemicals and products that avoid these unintentional impacts.

16. Enabling systems conditions – policies and regulations

The landscape of technologies in the chemical enterprise is not merely shaped by scientific and engineering solutions alone but rather in combination with the environment of regulation, policies, and laws that construct the social context in which they operate.[138,139] Policies and regulations can accelerate or retard sustainability solutions and they can protect or help displace entrenched unsustainable technologies. The development of regulations and policy that will empower and enable green chemistry and green engineering to succeed in society will be necessary to remove the obstacles and inertia that keep the *status quo* in place.[60,140]

16.1 8, extended producer responsibility (Pr)

Extended producer responsibility refers to the responsibility a producer holds to design their product in a way that reduces negative environmental and health impact.[141] It also places end-of-life management on the producer and not the consumer.[142] This is especially important to sustainability. If the producers, who are responsible for what the environment and the population is exposed to are not held responsible for ensuring their products are healthy and environmentally friendly, it becomes a problem of remedy rather than stopping it at the source. Extended producer responsibility helps to manage and mitigate end-of-life waste and all pollution generated from products at all stages of its life cycle.

16.2 16, property-based regulation (Pb)

The history of chemical regulation is to construct lists of chemicals that are considered too hazardous or too risky and impose some types of controls on them. Chemical-by-chemical regulation is slow, costly, inefficient, and inadequate.[143] The nature of the concern for a chemical is not based on its chemical name but rather on it combination of properties. Some combinations of properties may lead a chemical to be bioavailable, others to be persistent, still others to be reactive or explosive.[58,144] Since it is the combination of these properties that cause the concern, it is the properties that should be the basis of regulation. In this way, the chemicals of concern can be addressed proactively while providing certainty to the regulated community and critical guidance to the molecular designers of future products.

16.3 34, chemical transparency (Ct)

Chemical transparency refers to the disclosure of all chemicals and ingredients in all products. This is becoming exceedingly important among consumers.[145] Consumers want to know what is in their chemical products and as part of their decision to trust the brands they use.[146] This pressure from consumers and government can help to hold manufacturers accountable and aid in the development of safer, more benign chemicals, and continually move toward developing more sustainable products.[147] Not only does this let consumers have the choice to choose safer, more environmentally friendly products, but it also allows for easier and better exchange of practices among different companies. There are significant efforts underway to standardize the reporting of chemical ingredients in a variety of products to aid in data collection and product comparison.

16.4 52, chemical leasing (Cl)

Virtually no one ever bought a chemical. They bought function. The bought performance. There is very little value to the ownership of the vast majority of chemicals unless they are used for their intended purpose. And yet, because of the traditional sell/own business model, the waste that results from over-purchasing is significant and systemic. Further, the system is constantly driving towards selling more chemical to make more profit driving towards designed obsolescence and short-term use. The chemical leasing model is one where the "sellers" supply the service or function rather than selling a chemical.[148] In this model, instead of selling as much chemical as possible (resulting in excess and waste), the motivation is to use as little of a chemical to accomplish the desired service as the same profit can be generated from delivering much less product.[148] Chemical leasing is a business model whose effectiveness has been demonstrated at large scale and has extensive potential to be expanded.[149]

16.5 70, self-enforcing regulations (Se)

The idea that regulations and laws to protect the environment and human health can be effectively enforced by government inspectors and officials has been belied by experience.[150] This historical model has demonstrated over the past half-century that most of the damage is not detected and when it is detected it is at a timeframe that is inadequate to prevent the often tragic, consequences. With the advent of sensors, real-time in-process controls, big-data analysis, and machine-learning, it is now possible to rethink models for enforcement. Instead of sampling hazardous waste sites for laboratory analysis to determine levels of contamination, there are now possibilities for integrated, networked monitoring systems. New processes can be designed such that they only can function as long as emissions are below certain levels for various contaminants. The emerging field of self-enforcing regulations can also build in predictability and reduced economic and time burden for the regulated community while ensuring enhanced effectiveness in achieving the goals of the regulation.

16.6 88, innovation ecosystem – translation from lab to commerce (I)

In order for a discovery or innovation to have an impact on the world, it virtually always needs to be enabled by an innovation ecosystem that incorporates the essential enabling elements.[151] These include support for basic research and development and that R&D needs to be commercialized through thoughtful and risk-taking investment. These roles can be filled by various actors ranging from public sector government agencies to private sector investors.[152] Appropriate and just intellectual property considerations need to be supported by governance and returns on investment need to realized through adequate financial systems. With key roles and responsibilities assured, the innovation ecosystem can be used to bring about the transformative innovations in the chemical enterprise that are needed to advance sustainability.[153]

17. Enabling systems conditions – tools

Increasing the development of tools to enable green chemistry and green engineering has expedited the adoption of more sustainable choices in the selection and innovation of products and processes. These often-quantitative resources allow chemists, engineers, and other professionals to pursue the incorporation of green chemistry into a wider range of products and processes with greater confidence in their decision-making and more credibility in building the business case for implementing these innovations.

17.1 9, epidemiological analysis and ecosystem health (Ea)

Epidemiological analysis refers to the understanding and analysis of how different populations are effected by various risk-factors, disease and other health outcomes.[154] Ecosystem health refers to the health or condition of the environment and all living organisms in that environment. That is, its susceptibility/resiliency to natural disaster and ability to sustain life defined by a number of indicators unique to the ecosystem.[155] In conjunction, these two concepts define the health of an area and all the living organisms within it. These concepts are key to sustainability because they define the success of sustainability practices. If something is being carried out in an unsustainable way it will be directly reflected in the health of the population and environment.

17.2 17, alternatives assessment (Aa)

Alternatives assessment is a technique aimed at minimizing harm by assessing all options and solutions and understanding the consequences of each.[156] They help to characterize hazard based on health and environmental information. It is often utilized in risk assessment and as a decision-making approach. One common application is a chemical alternatives assessment in order to aid in choosing the safer chemical over a more hazardous one with the aim of avoiding regrettable substitution.

17.3 35, life cycle assessment (Lc)

Life cycle assessment determines the total environmental impact of a product from beginning to end of life, or cradle-to-grave.[157] This is done through accounting for all material and energy-related inputs and outputs throughout the life of a product.[157] It helps to measure all steps of production and use, and their subsequent environmental and health implications. Life cycle assessment provides a producer information for all direct and indirect environmental impacts associated with their products and processes, illuminating areas for improved design choices or making decisions between one chemical product or process and another.[158]

17.4 53, solvent selection screens (So)

Solvents are often critical to a chemical process as a medium in which to dissolve solutes and form solutions. They are also often the deciding aspect in the cost and environmental impact of a chemical process.[159] However, when it comes to choosing the right solvent there are often many options, all which have different properties and different environmental impacts. A solvent selection tool identifies different solvent options using a variety of statistical, regression, and structure/property-based strategies, and then provides comparisons through various graphical outputs and shortlists.[160] It allows the user to apply filters that select for certain properties and pick the best possible solvent for the situation. It also can aid in sustainability through improving industrial process and aiding in the evaluation of solvents in regard to their environmental and health impact.[161]

17.5 71, chemical footprinting (Cf)

Chemical footprinting allows for comprehensive, full life cycle management of chemicals being used by companies today. It gives companies the tools and ability to better understand what chemicals are in their products and a metric to better manage the safety and environmental impact of those chemicals.[162] This benchmarking tool is important in sustainability practices because it helps to create a common standard for all to follow, while also reducing chemical risk, identifying areas for improvement, and measuring the progress being made.

17.6 89, education in toxicology and systems thinking (Et)

In most professions, the people that create something have responsibility for the implications of what they create. This is not true in the field of chemistry. All chemists need to understand the consequences to the world and its inhabitants of what they create and study. Yet, virtually no education programs for chemists include the requirement of training in molecular toxicology or systems thinking. The basic principles of chemical dose-response, bioavailability, bioaccumulation, and biomagnification need to be understood by chemists as well as the molecular level understanding of the fundamentals of acute and chronic toxicity, carcinogenicity, and endocrine disruption, among all relevant human health endpoints.[163,164]

Many of the innovations necessary to realize green and sustainable chemistry, it is necessary to consider a broad array of issues that often involve systems of systems, such as the vital role and value of ecological systems and services and the life cycle impacts and benefits of an engineered system, from its raw materials to end of life.[108] Although chemists have a long history of thinking in complex systems, there is a need to extend this type of thinking to include the regulatory environment, economic drivers, and social behavior. For example, the systems thinking within green and sustainable chemistry should also include acknowledging who have been disadvantaged through environmental justice and understanding the role of economic incentives and policy instruments to align socioeconomic behavior with environmental goals.[165] Finally, there is an urgent need to effectively communicate not only the innovation(s), but the contextualizing system in which it will be implemented.

18. Noble goals

There are some concepts that are transcendent. These considerations rise above the immediate economic or political concerns of the day. Noble elements are those they are grounded in moral imperatives that are shared across cultures and across time. These elements find their basis in values, justice and trans-generational equity. Chemistry can impact all of these issues either positively or negatively and therefore they must consciously enter into our decision-making and our designs.

18.1 2, hippocratic oath for chemistry (Ho)

First, do no harm. The products that are made and the processes that make them and the resources that they come from will do no harm to the planet, both the biosphere that occupies it and the geosphere that sustains all living things. There will be no harm to those workers obtaining the feedstocks and transforming them, to the consumers using them, to the communities and populations, human and non-human alike, that may be exposed to them.[166] There will be as much thought and care put into the consequences of chemistry as there is into the design and invention of the chemistry.

18.2 10, design for posterity (P)

We borrow this planet and everything that is in it from the future. We own nothing. We owe everything. Our debt is repaid through the care exhibited by thoughtful use and design. Perpetuating flawed unsustainable systems based on limited knowledge or short-sighted perspectives is design for the past which simply enshrines ignorance and errors.

Constant change to reflect the highest levels of awareness that can lead to a more sustainable world is the path toward being respected by the future and ensuring that there will be a future to be respected by.

18.3 18, life-compatible products & processes (Lp)

Nature is conducive to life. We are part of Nature and must assume our role as being conducive to life. The chemistry we discover and the chemicals we introduce into the world must reflect this role. The idea of legally acceptable toxicity and poisoning, socially acceptable degradation of ecosystems, and tolerable rates of species extinctions are frameworks that are flawed, illogical and incompatible with our role in Nature.

18.4 36, zero waste (Z)

Waste is a man-made concept. In Nature outside of man, there is no waste. Evolutionary brilliance ensures that the waste from one organism will be utilized at high value to another organism. Waste in our chemical and material world is simply a material or energy for which a valuable use has not be discovered or implemented. While we will never defeat thermodynamics in attaining perfect cycles and entropy will always win, the cycles and systems that can be constructed can strive for continuously moving toward the perfect goal of zero waste.

18.5 54, chemistry is equitable and fully inclusive (Fi)

The natural laws of chemistry have no predisposition to any gender, race, creed, religion, nationality, ability, nor orientation. Yet the participation within the chemical enterprise has historically been dominated by a small demographic sliver of the population. The science and application of chemistry can only benefit by a maximum breadth of perspectives, skills, experiences, cognitive approaches, and values of a diverse community with a culture of inclusion. No endeavor, scientific or otherwise, can be 100% effective it if excludes so much of its talent. It would be as absurd to limit participants of a scientific field to individuals of a certain height or weight as it would be to limit them by their gender or ethnic background.

Full inclusion of all groups in the chemical enterprise should be pursued as a pathway to genuine excellence and not merely the narrow historical definitions of excellence as posited by those who have historically dominated the field.

18.6 72, benefits distributed equitably (De)

The benefits of chemistry are immense and have revolutionized the quality and length of human life. But not for everyone. The benefits of chemistry and chemicals are not distributed equally. Large percentages of the population have borne the burdens of a chemical-intensive society where the smallest percentage of the population has received benefits with virtually no burden.

18.7 90, extraordinary chemical knowledge comes with extraordinary responsibility (K)

A diminishingly small percentage of the population has the knowledge and understanding of how to manipulate matter at the molecular level. Those possessing this knowledge came to it through a confluence of the gift of sufficient intellectual capacity and the good fortune of having access to some type of educational framework not of their making. The power of chemistry is daunting and world-changing. It impacts societies, oceans, and atmospheres.

With these two gifts comes a responsibility to use the power of molecular manipulation for good and not ill. To build and not destroy. To heal and not to harm.

19. Conclusion

To attain the full the power and potential of chemistry to improve the world, it needs to begin with the fundamental science of green chemistry and green engineering. This requires not only implementing all of the tools, frameworks and perspectives contained in the elements of sustainable chemistry, but also developing predictive tools to inform the design of more sustainable products, processes, and systems. You cannot achieve sustainable chemistry without green chemistry. Green chemistry will not be implemented at scale without the other elements of sustainable chemistry. Like all human endeavors and actions, all of these efforts in chemistry need to take place within an ethical, humanitarian, and moral framework. Just like the countless possible substances of the known universe are comprised of the known elements of the Periodic Table, there are countless possible paths to a sustainable future when employing the elements of sustainable chemistry.

Conflicts of interest

There are no conflicts to declare.

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Appendix 2: The Green ChemisTREE: 20 years after taking root with the 12 principles

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

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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.

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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, *e*xcretion; 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

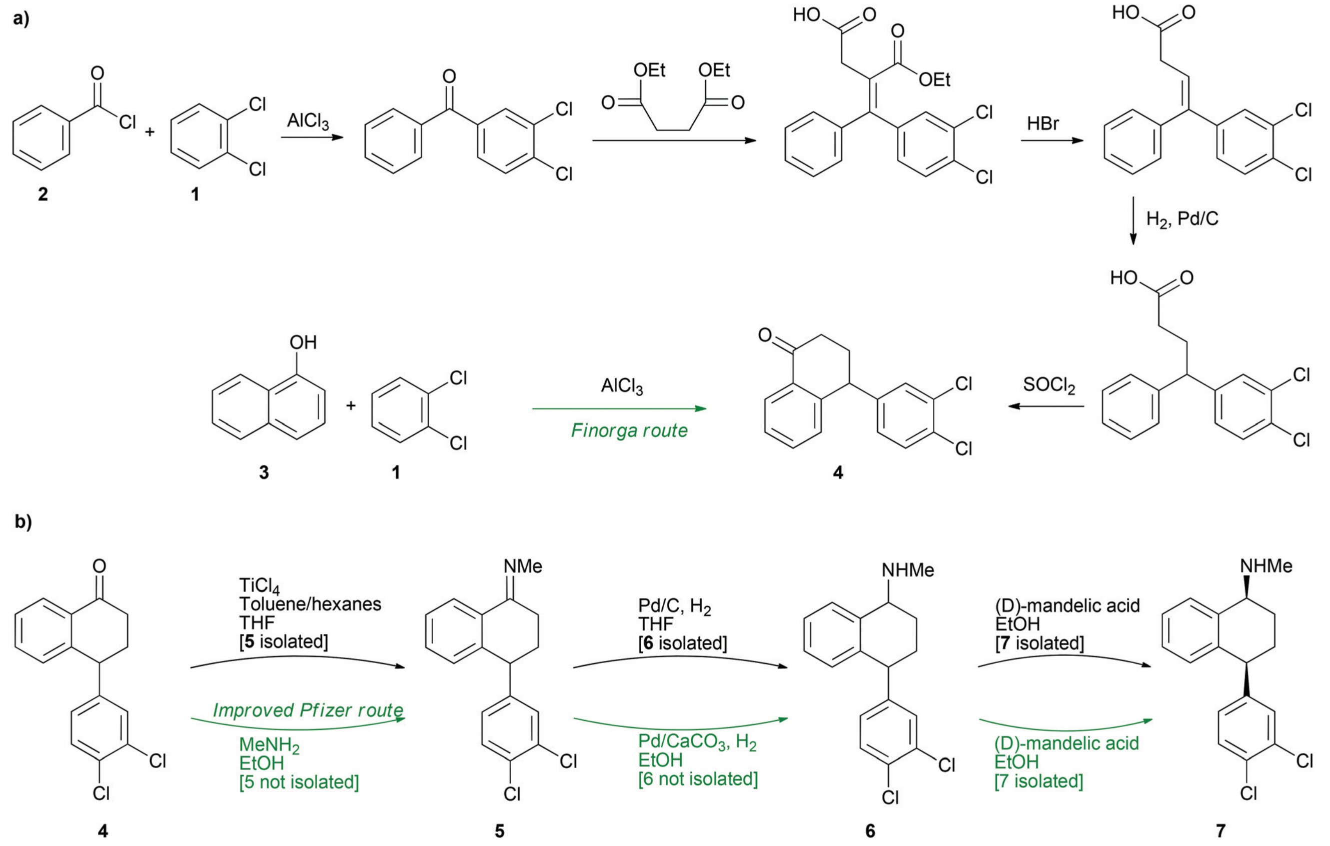
Design for degradation (10)	Real-time analysis for pollution prevention (11)	Inherently benign chemistry for accident prevention (12)
• Read across (s) • SAR/QSAR (s) • Reactivity parameters (s) • 2D/3D properties (s) • Metabolism (s) • Design guidelines (s) • Prediction tools • Biodegradation databases • 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] [$\sum$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]

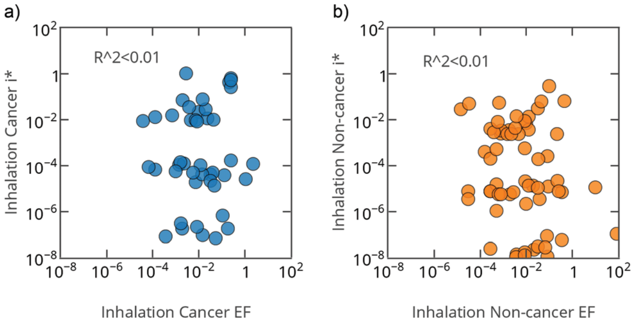


Fig. 2 Log–log scatterplots for (a) cancer and (b) non-cancer endpoints, of target chemical toxicity i (cases per kg emission) *vs.* life cycle inherent toxicity i* (cases per kg exposure) in organic chemical syntheses.[88] Reproduced with permission of the Royal Society of Chemistry.

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 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]

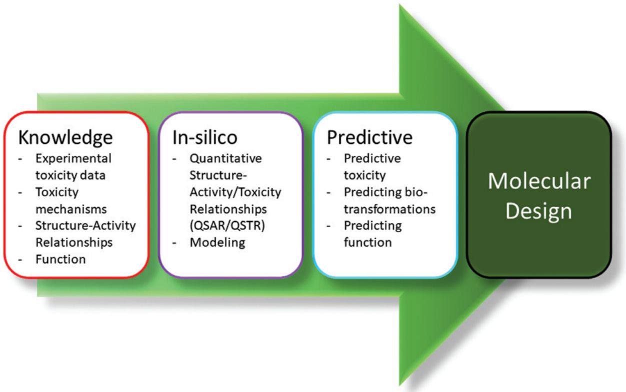


Fig. 3 A framework for molecular design leveraging knowledge from *in vivo* and *in vitro* toxicity data and mechanisms as well as molecular structure, property and function to develop *in silico* model to predict toxicity of new chemicals and inform safer molecular design.[95] Adapted with permission.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

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]

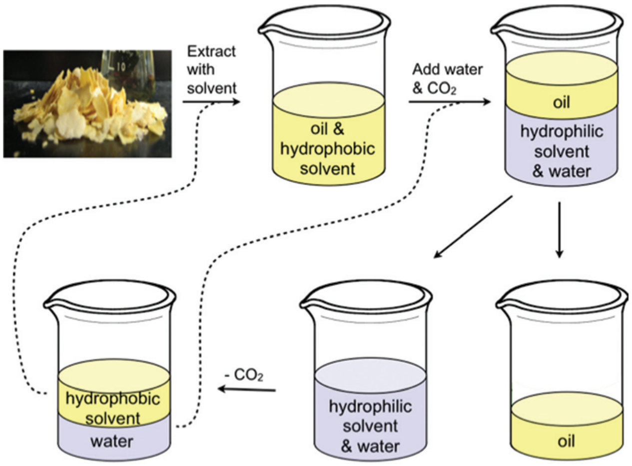


Fig. 4 The process by which a switchable-hydrophilicity solvent (SHS) can be used to extract soybean oil from soybean flakes without a distillation step. The dashed lines indicate the recycling of the solvent and the aqueous phase.[176] Reproduced with permission of the Royal Society of Chemistry.

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

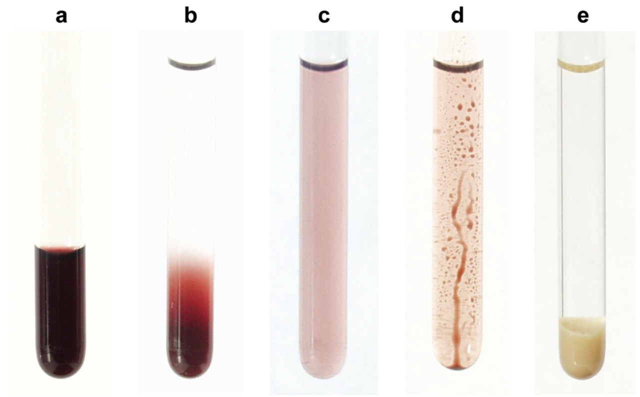


Fig. 5 Photographs of the catalytic hydrosilylation of $Et_2C{=}O$ by $[CpW(CO)_2(IMes)]^+[B(C_6F_5)_4]^-$: (a) ketone complex 4 W before adding $HSiEt_3$; (b) $HSiEt_3$ added, liquid not yet mixed; (c) mixed and homogeneous: (d) liquid clathrate formed. Reaction nearing completion; (e) end of reaction. 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]

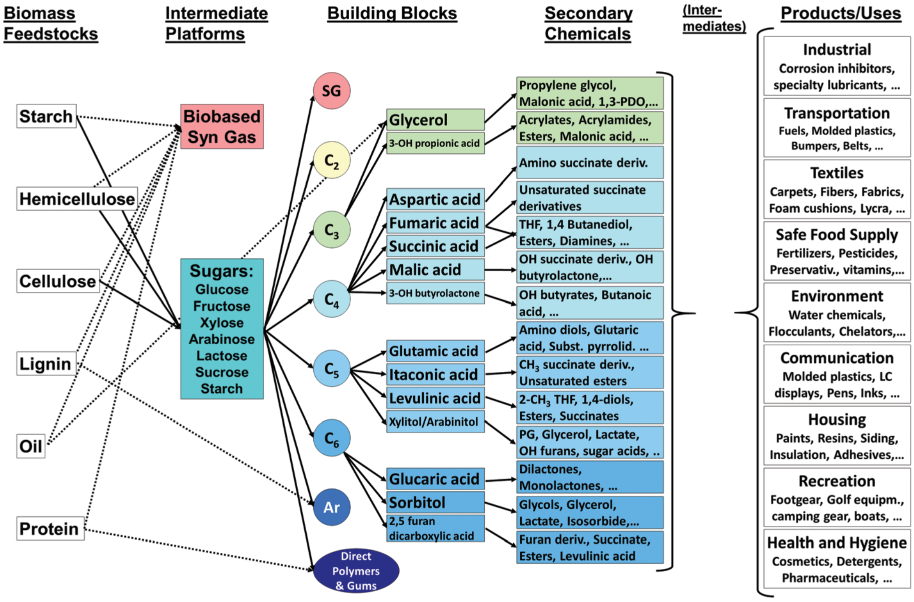


Fig. 6 An analogous model of crude oil through a petroleum refinery for products through an integrated biorefinery from renewable feedstocks. Adapted version focusing on the identified 12 top candidates for sugar-derived building blocks.[280] Courtesy of the Office of Energy Efficiency & Renewable Energy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

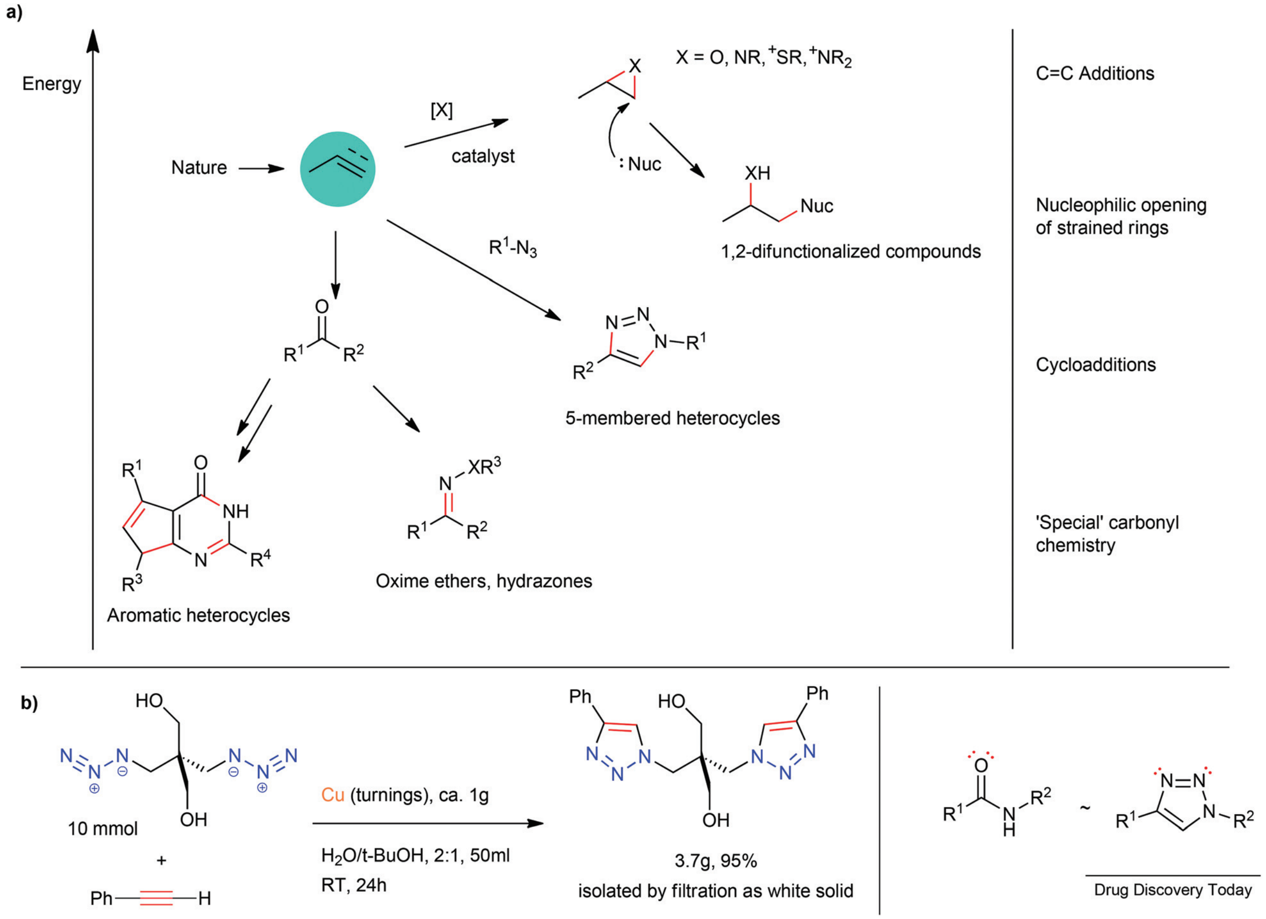
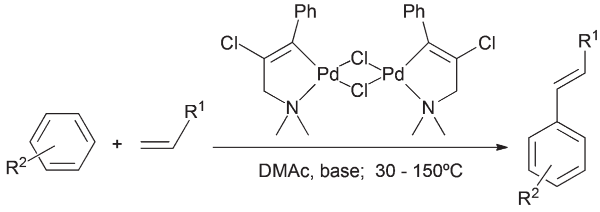


Fig. 7 Click Chemistry describes reactions that are modular, wide in scope, give high yields, create only inoffensive byproducts that can be removed without chromatographical methods, are stereospecific, simple to perform, and can be conducted in easily removable or benign solvents such as those shown.[317] (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 Palladacycles: 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-

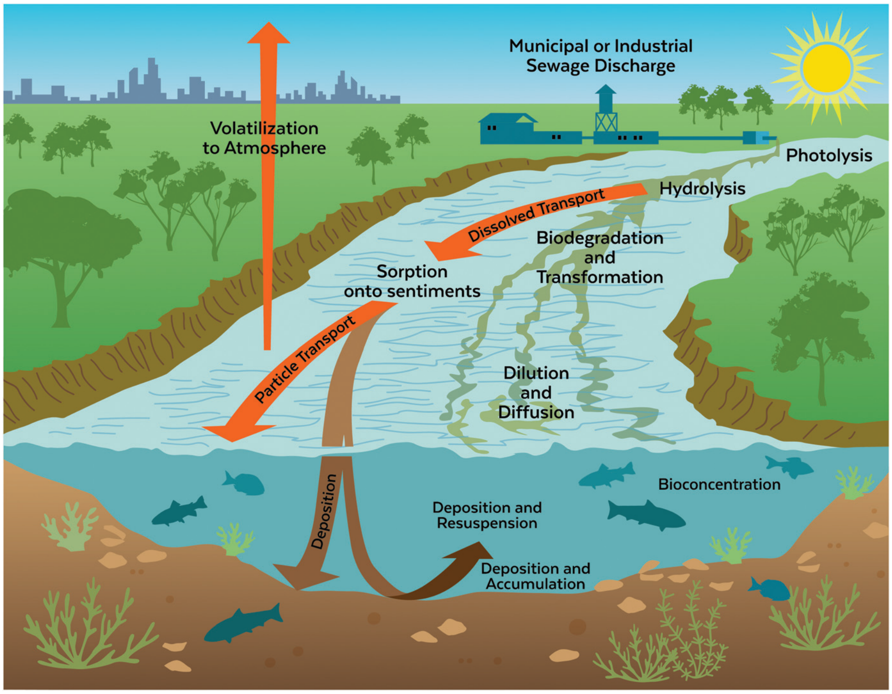


Fig. 8 Possible fate and transport of environmental contaminants.[410] Courtesy of the U.S. Geological Survey.

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 industrial 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

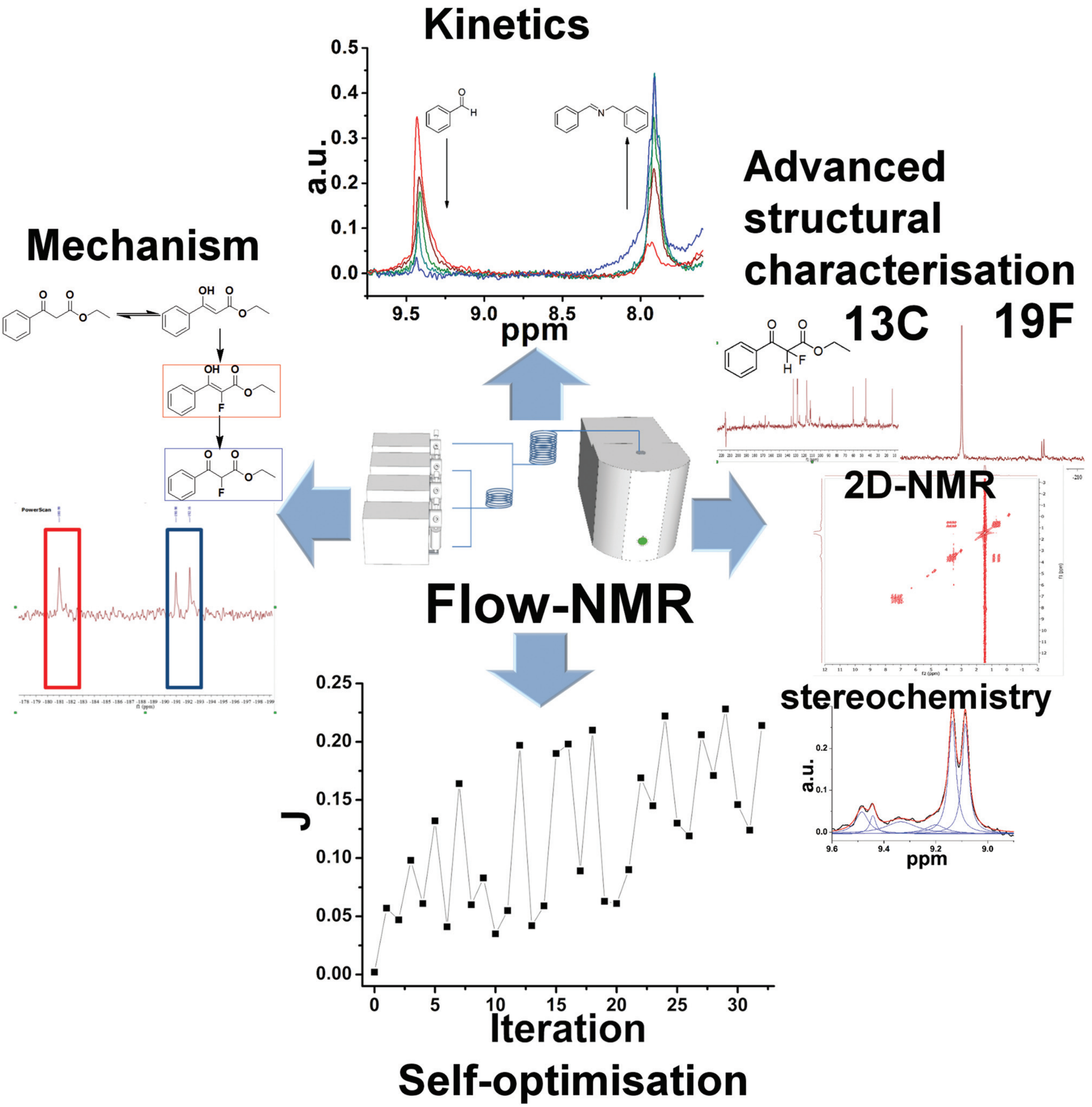


Fig. 9 An overview of real-time measurements made using an in-line NMR in a flow reactor setup to realize improved reaction yield, reduce waste, and enhance efficiency.[469] Published by the Royal Society of Chemistry.

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.

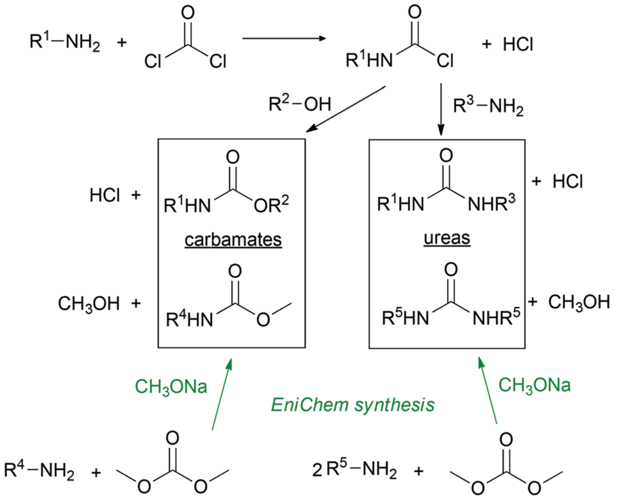
Principle 12: "Substances and the form of a substance used in chemical processes should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires"

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.

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