



The cover image displays a word cloud generated from the transcript of the meeting we convened with 24 experts in the field of sustainable chemistry. The size of the words in the cloud corresponds to the frequency with which each word appeared in the transcript. In most cases, similar words—such as singular and plural versions of the same word—were combined into a single term. Words that were unrelated to the topic of sustainable chemistry were removed. The images around the periphery are stylized representations of chemical molecules that seek to illustrate a new conceptual framework, whereby molecules can be transformed to provide better performance; however, they are not intended to represent specific chemical compounds.

### Why GAO did this study

Chemistry contributes to virtually every aspect of modern life and the chemical industry supports more than 25 percent of the gross domestic product of the United States. While these are positive contributions, chemical production can have negative health and environmental consequences. Mitigating these potential consequences requires thoughtful design and evaluation of the life cycle effects of chemical processes and products.

GAO was asked to conduct a technology assessment to explore, among other things, the opportunities, challenges, and federal roles in sustainable chemistry. This report discusses (1) how stakeholders define and assess sustainable chemistry; (2) available or developing technologies to make chemical processes and products more sustainable; and (3) how the federal government, industry and others contribute to the development and use of such technologies.

GAO selected for assessment three technology categories—catalysts, solvents, and continuous processing; interviewed stakeholders from various fields, such as government, industry, and academia; convened a meeting of experts on sustainable chemistry technologies and approaches; and surveyed a non-generalizable sample of chemical companies. GAO is not making recommendations in this report, but is identifying strategic implications.

View [GAO-18-307](#). For more information, contact Timothy M. Persons at (202) 512-6412, [personst@gao.gov](mailto:personst@gao.gov) or John Neumann at (202) 512-3841, [neumannj@gao.gov](mailto:neumannj@gao.gov).

# Chemical Innovation

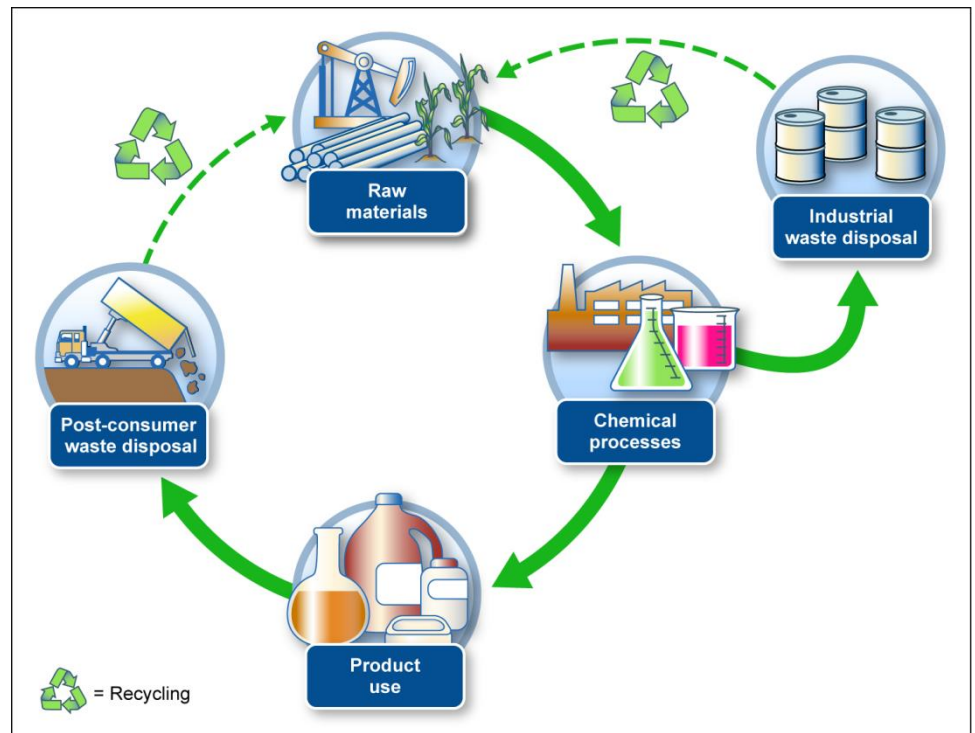
## Technologies to Make Processes and Products More Sustainable

### What GAO found

Stakeholders lack agreement on how to define sustainable chemistry and how to measure or assess the sustainability of chemical processes and products; these differences hinder the development and adoption of more sustainable chemistry technologies. However, based on a review of the literature and stakeholder interviews, GAO identified several common themes underlying what sustainable chemistry strives to achieve, including:

- improve the efficiency with which natural resources—including energy, water, and materials—are used to meet human needs for chemical products while avoiding environmental harm;
- reduce or eliminate the use or generation of hazardous substances in the design, manufacture, and use of chemical products;
- protect and benefit the economy, people, and the environment using innovative chemical transformations;
- consider all life cycle stages including manufacture, use, and disposal (see figure) when evaluating the environmental impact of a product; and
- minimize the use of non-renewable resources.

Life cycle of chemical processes and products



Source: GAO. | GAO-18-307

GAO identified three categories of more sustainable chemistry technologies—catalysts, solvents, and continuous processing—that demonstrate both progress and potential.

- Catalysts reduce the energy input required for a chemical process and allow for more efficient use of materials. Stakeholders suggested future research be directed at developing less toxic or renewable catalysts, including those that are metal-free or those from earth-abundant metals such as iron.
- Solvents are used in many chemical processes but can create waste issues and be toxic. Alternatives include solvents from renewable, non-petroleum raw materials and solvents such as water that are less hazardous to human health and the environment, among other qualities.
- An alternative to traditional batch processing is continuous processing, in which materials react as they flow along a system of channels, pipes, or tubes. Compared to batch processing, continuous processing uses materials more efficiently, generates less waste, and has a smaller physical footprint.

The federal government and other stakeholders play several roles, sometimes in collaboration, to advance the development and use of more sustainable chemistry technologies. The federal government has supported research, provided technical assistance, and offered certification programs, while stakeholders have integrated sustainable chemistry principles into educational programs and addressed chemicals of concern in consumer products. While switching to more sustainable options entails challenges, this field has the potential to inspire new products and processes, create jobs, and enhance benefits to human health and the environment. Stakeholders identified strategic implications of sustainable chemistry and offered a range of potential options to address challenges and realize the full potential of these technologies, including the following:

- Breakthrough technologies in sustainable chemistry could transform how the industry thinks about performance, function, and synthesis. Sustainable chemistry creates opportunities to use a different conceptual framework that allows industry to create molecules with better performance.
- The establishment of an organized constituency, with the involvement of both industry and government, could help make sustainable chemistry a priority. An industry consortium, working in partnership with a key supporter at the federal level, could lead to an effective national initiative or strategy.
- A national initiative that considers sustainable chemistry in a systematic manner could be useful. Such an effort could encourage collaborations among industry, academia and the government, similar to other national technology Initiatives.
- There are opportunities for the federal government to address industry-wide challenges. Federal attention that facilitates development of standard tools for assessment and a robust definition could help clarify relevant participants in the field and improve information available for decision-makers at all levels.

According to stakeholders, transitioning toward the use of more sustainable chemistry technologies will require national leadership and industry, government, and other stakeholders to work together.

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## Abbreviations

ACS	American Chemical Society
AMO	Advanced Manufacturing Office
ARS	Agricultural Research Service
BEES	Building for Environmental and Economic Sustainability
CSS	Chemical Safety for Sustainability
DOD	Department of Defense
DOE	Department of Energy
DTSC	Department of Toxic Substances Control
<i>E factor</i>	environmental factor
EPA	Environmental Protection Agency
ESTCP	Environmental Security Technology Certification Program
FDA	Food and Drug Administration
GCI	Green Chemistry Institute
GC3	Green Chemistry and Commerce Council
HHS	Department of Health and Human Services
LCA	life cycle assessment
NASA	National Aeronautics and Space Administration
NGO	nongovernmental organization
NIEHS	National Institute of Environmental Health Sciences
NIFA	National Institute of Food and Agriculture
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NREL	National Renewable Energy Laboratory
NRMRL	National Risk Management Research Laboratory
NSF	National Science Foundation
NTP	National Toxicology Program
PGM	platinum group metals
PMI	process mass intensity
PNNL	Pacific Northwest National Laboratory
R&D	research and development
RAPID	Rapid Advancement in Process Intensification Deployment
SERDP	Strategic Environmental Research and Development Program



SBIR	Small Business and Innovation Research
SNAP	Significant New Alternatives Policy
STAR	Science to Achieve Results
STTR	Small Business Technology Transfer
SusChEM	Sustainable Chemistry, Engineering, and Materials
ToxCast	Toxicity Forecaster
Tox21	Toxicology in the 21 <sup>st</sup> Century
TSCA	Toxic Substances Control Act
USDA	U.S. Department of Agriculture
VOC	volatile organic compound



441 G St. N.W.  
Washington, DC 20548

February 8, 2018

The Honorable Christopher Coons  
Ranking Member  
Subcommittee on Financial Services and General Government  
Committee on Appropriations  
United States Senate

The Honorable Susan M. Collins  
United States Senate

The Honorable Edward J. Markey  
United States Senate

Chemistry contributes to virtually every aspect of modern life, from the production of food and clean drinking water to medicines, cleaners, personal care products, and a host of other products. According to one recent report, the chemical industry supports more than 25 percent of the gross domestic product of the United States and, in 2016, accounted for \$174 billion (14 percent) of U.S. goods exported.<sup>1</sup> In addition, the Bureau of Labor Statistics reports that the chemical industry employed more than 821,000 people in October 2017 and the Department of Commerce estimates that the sector generates an additional 2.7 million indirect jobs via industry suppliers.<sup>2</sup>

Despite these positive contributions to quality of life and other social and economic goals, chemical production can result in negative health and environmental consequences. Mitigating these potential consequences requires thoughtful design and evaluation of the life cycle effects of chemical processes and products—that is, a thorough assessment of effects resulting from stages of the life cycle such as sourcing the raw materials, processing raw materials into products, handling and disposal of byproducts and industrial waste, product use, and end-of-life disposal or recycling. In addition, the United States faces a number of environmental challenges, including water scarcity, reliance on nonrenewable resources including scarce metals and fossil fuels, and difficulty obtaining adequate information on chemical toxicity and exposure levels. Many in the chemical industry are working to address these issues through improving the environmental sustainability of their own chemical processes and providing more sustainable products and technologies to others.

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<sup>1</sup>American Chemistry Council, *2017 Elements of the Business of Chemistry* (Washington, D.C.: 2017).

<sup>2</sup>International Trade Administration, Department of Commerce, *Chemical Spotlight: The Chemical Industry in the United States*, accessed October 5, 2017, <https://www.selectusa.gov/chemical-industry-united-states>.

In view of the potential benefits and nascent nature of the field of sustainable chemistry, you asked us to conduct a technology assessment to explore, among other things, the opportunities, challenges, and federal roles in this field. In response to that request, this report discusses (1) how stakeholders define sustainable chemistry and assess the sustainability of chemical processes and products; (2) technologies that are available or in development to make chemical processes and products more sustainable; and (3) how the federal government, industry, and others contribute to the development and use of such technologies.

To address these objectives, we reviewed key reports and scientific literature to establish background, identify appropriate technologies and their advantages and disadvantages, identify stakeholders, and inform survey questions. We also interviewed approximately 80 stakeholders including federal and state officials, chemical companies, industry and professional organizations, nongovernmental organizations (NGO), academics and educational institutions, and others; conducted site visits to federal laboratories; and attended two technical conferences.

In addition, we collaborated with the National Academies to convene a two-day meeting of 24 experts on sustainable chemistry technologies and approaches. We selected participants from the chemical industry, academia, federal agencies including a national laboratory, professional organizations, and others with expertise covering most significant areas of our review.<sup>3</sup> During this meeting, we moderated discussion sessions on several topics, including examples of technologies to make chemical processes and products more sustainable; applications in industry; economic and business aspects of developing and implementing the technologies; approaches to assessing the sustainability of chemical processes and products; the role of standards, regulations, and related programs; and additional stakeholder perspectives. We continued to draw on the expertise of these individuals throughout our study and, consistent with our quality assurance framework, we provided them with a draft of our report and solicited their feedback, which we incorporated as appropriate.

We also surveyed a non-generalizable sample of 27 chemical companies to gather data on four primary topics: (1) approaches these companies use to assess the sustainability of their chemical processes and products; (2) the extent and perceived value of their interactions with other stakeholders, including federal agencies, customers, suppliers, academics, and NGOs; (3) challenges or gaps in stakeholder interactions; and (4) challenges or barriers to the development and use of more sustainable chemistry technologies.

We limited the scope of our review to selected technologies in three main categories: catalysts, solvent use, and alternatives to batch processing (i.e., continuous processing and continuous

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<sup>3</sup>After the expert meeting we changed one of our three target industry sectors from textiles/apparel to formulators (i.e., makers of personal care and cleaning products). We did not have a formulator represented at the meeting; however, we interviewed and surveyed representatives from several formulator companies during the course of our study.

flow microreactors). We did not assess all available or developing technologies in these three categories, nor did we assess technologies in other phases of the chemical product life cycle. For example, we did not assess technologies for recycling industrial waste into new feedstocks or for post-consumer recycling of chemical products. See appendix I for additional details on our scope and methodology, appendix II for a list of the experts who participated in our expert meeting, appendix III for a list of the chemical companies we interviewed and surveyed, and appendix IV for the questions in the survey instrument and the quantitative results (i.e., response counts) from the survey.

We conducted our work from October 2015 to February 2018 in accordance with all sections of GAO's Quality Assurance Framework that are relevant to technology assessments. The framework requires that we plan and perform the engagement to obtain sufficient and appropriate evidence to meet our stated objectives and to discuss any limitations to our work. We believe that the information and data obtained, and the analysis conducted, provide a reasonable basis for the findings and conclusions in this product.

# 1 Background

## 1.1 Sustainability and the chemical industry

The chemical industry relies on the use of natural resources as inputs to make chemical products, and the industry's outputs, in turn, can have an impact on the environment.<sup>4</sup> The International Trade Administration of the Department of Commerce identifies the chemical industry as one of the largest manufacturing industries in the United States, with more than 10,000 firms producing more than 70,000 products.<sup>5</sup> It is comprised of several industry subsectors including formulators (makers of cleaning and personal care products), chemical manufacturers (makers of basic and specialty chemicals), and pharmaceutical companies.<sup>6</sup> Since the beginning of the 20<sup>th</sup> century, the chemical industry has depended on fossil fuels as both an energy source and a primary feedstock for manufacturing chemicals. The chemical industry is the second largest user of energy among manufacturing sectors, and more than

<sup>4</sup>For purposes of this report, the term 'chemical product' includes a wide variety of products manufactured by chemical companies, including single chemicals (e.g., methanol, ammonia) and other products made with chemicals or mixtures of chemicals (e.g., pharmaceuticals, cleaning products, cosmetics).

<sup>5</sup>International Trade Association, U.S. Department of Commerce, *Chemical Spotlight: The Chemical Industry in the United States*, accessed October 5, 2017, <https://www.selectusa.gov/chemical-industry-united-states>.

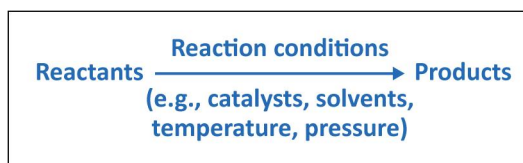
<sup>6</sup>Cleaning and personal care products include soaps, detergents, cleaners, toiletries, and cosmetics. Basic chemicals include organic and inorganic chemicals, plastic resins, dyes, and pigments. Specialty chemicals include adhesives and sealants, water treatment chemicals, plastic additives, catalysts, and coatings. Pharmaceuticals include diagnostics, prescription drugs, vaccines, vitamins, and over-the-counter drugs for human and veterinary applications.

98 percent of organic, or carbon-based, chemicals are derived from petroleum or natural gas (i.e., petrochemicals). Inorganic chemicals do not contain carbon as a principal element and the chemical industry generally derives these from metals and non-metallic minerals, some of which face supply limitations. The growth of the chemical industry in the 20<sup>th</sup> century also resulted in the production of large quantities of waste, including hazardous waste.

Chemicals, including basic and specialty chemicals and pharmaceuticals, are manufactured through chemical synthesis—a process involving one or more chemical reactions.<sup>7</sup> Chemical reactions generally follow a common pattern that chemists describe using a chemical equation as shown in figure 1.

**Figure 1: A standard chemical equation**

Although not shown in the figure, additional reactants may also be included above or below the arrow.



Source: GAO. | GAO-18-307

The left side of the equation shows one or more reactants—chemical substances that enter into and are chemically changed by the reaction. The arrow represents the reaction itself; additional information is often provided

<sup>7</sup>Formulators generally make their cleaning and personal care products by mixing chemicals together rather than through chemical reactions.

above and below the arrow to describe reaction conditions—other factors that allow the reaction to occur optimally—which can include components that are not chemically changed during the reaction, such as catalysts, solvents, or other conditions such as a specific temperature or pressure. The right side of the equation shows one or more products—chemical substances that result from the reaction. In some cases, the goal is to produce only certain of these products; the others are often called ‘byproducts’ and may be commercially useful or considered waste.

Within the chemical industry, the product of one company may be the raw material for another. For example, bulk chemicals—a kind of basic chemical—are the building blocks for many chemical products. Other companies or industries can purchase bulk chemicals and incorporate them into other chemical products (e.g., chemical intermediates, pharmaceuticals) or manufactured products (e.g., textiles, automobiles), or use them in processing (e.g., pulp and paper, oil refining). For example, one chemical company may produce adipic acid, a bulk chemical used in the manufacture of one kind of nylon. Another chemical company may then buy the adipic acid as a raw material to produce nylon fiber, selling that product to textile companies that then incorporate it into other products such as apparel. In some cases, multiple steps

may be required to produce a chemical intermediate or other product from a bulk chemical. Specialty chemicals, including fine chemicals, are often more technologically advanced and manufactured in lower volumes than basic chemicals. Specialty chemicals are used for a specific purpose and can also be incorporated into a range of other products.

The term ‘sustainability’ can have many interpretations depending on the context in which it is used. The 1987 Brundtland report stated that sustainable development ‘meets the needs of the present without compromising the ability of future generations to meet their own needs.’<sup>8</sup> Sustainability may refer to economic, environmental, or social sustainability. Achieving all three—a concept known as the ‘triple bottom line’—has become a goal of some businesses, including many in the chemical industry. Sustainable development is relevant to the chemical industry as it concerns both the responsible use of natural resources—using natural resources at rates such that supplies remain available over the long term—as well as the minimization of pollution. Several organizations have attempted to define sustainability as it applies to chemicals and the chemical industry (see table 1).

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<sup>8</sup>World Commission on Environment and Development, *Our Common Future*, (Oxford University Press, 1987).

**Table 1: Example definitions of sustainable (or green) chemistry**

Organization	Definition
<b>Organisation for Economic Co-operation and Development</b>	Sustainable chemistry is a scientific concept that seeks to improve the efficiency with which natural resources are used to meet human needs for chemical products and services. Sustainable chemistry encompasses the design, manufacture and use of efficient, effective, safe and more environmentally benign chemical products and processes, accessed January 4, 2018 ( <a href="http://www.oecd.org/chemicalsafety/risk-management/sustainablechemistry.htm">http://www.oecd.org/chemicalsafety/risk-management/sustainablechemistry.htm</a> ).
<b>U.S. Environmental Protection Agency</b>	Green chemistry is the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Green chemistry applies across the life cycle of a chemical product, including its design, manufacture, use, and ultimate disposal. Green chemistry is also known as sustainable chemistry, accessed June 19, 2017 ( <a href="https://www.epa.gov/greenchemistry/basics-green-chemistry">https://www.epa.gov/greenchemistry/basics-green-chemistry</a> ).
<b>American Chemical Society</b>	Sustainable and green chemistry [is] a different way of thinking about how chemistry and chemical engineering can be done. Over the years different principles have been proposed that can be used when thinking about the design, development and implementation of chemical products and processes. These principles enable scientists and engineers to protect and benefit the economy, people and the planet by finding creative and innovative ways to reduce waste, conserve energy, and discover replacements for hazardous substances. [T]he scope of these green chemistry and engineering principles go beyond concerns over hazards from chemical toxicity and include energy conservation, waste reduction, and life cycle considerations such as the use of more sustainable or renewable feedstocks and designing for end of life or the final disposition of the product, accessed January 4, 2018 ( <a href="https://www.acs.org/content/acs/en/greenchemistry/what-is-green-chemistry/definition.html">https://www.acs.org/content/acs/en/greenchemistry/what-is-green-chemistry/definition.html</a> ).

Source: GAO analysis of agency and other stakeholder documents. | GAO-18-307

As noted in table 1, green chemistry is another term that some associate with sustainability efforts in the chemical industry. Green chemistry reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and application of chemical products using the 12 Principles of Green Chemistry (the 12 Principles).<sup>9</sup> See appendix V for the full list of the 12 Principles. According to the definitions of both the U.S. Environmental Protection Agency (EPA) and the American Chemical Society (ACS) shown in the table, the concepts of green chemistry

and sustainable chemistry are synonymous. Green chemistry is rooted in the Pollution Prevention Act of 1990, which marked a shift in regulatory policy from pollution control to pollution prevention.<sup>10</sup> Staff in EPA’s Office of Pollution Prevention and Toxics first used the term green chemistry in the early 1990s. The Green Chemistry Institute (GCI)—an independent nonprofit organization dedicated to advancing green chemistry—was founded in 1997 and eventually became part of the ACS.

<sup>9</sup>Paul T. Anastas and John C. Warner, *Green Chemistry: Theory and Practice* (New York: Oxford University Press, 1998).

<sup>10</sup>Public Law 101-508 (Nov. 5, 1990).

Life cycle assessment (LCA) is one tool for evaluating the relative sustainability of a process or product. While reducing or eliminating the use of hazardous substances (i.e., doing 'green chemistry') may offer one viable path for improving sustainability in the chemical industry, following these principles alone does not guarantee improved sustainability from a life cycle perspective. LCA is a method for systematically evaluating the environmental impact of a product through all the stages of its life cycle.<sup>11</sup> As shown in figure 2, life cycle stages for chemical processes and products can include raw materials extraction and processing,

chemical processing, product use, and post-consumer or industrial disposal or recycling.<sup>12</sup> By attempting to improve one stage of the life cycle without considering the others, chemists run the risk of moving sustainability problems around rather than solving them. Analyzing the full life cycle of a process or product can reveal benefits as well as tradeoffs or unintended consequences of different choices along the way. Practitioners use LCA to compare the environmental performance of processes and products under different conditions.

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<sup>11</sup>The Coca Cola Company together with the Midwest Research Institute developed the original concept of analyzing a product life cycle in the 1960's while trying to quantify the energy, material, and environmental impacts of different beverage containers. In the 1990's, the Society of Environmental Toxicology and Chemistry coined the term LCA and coordinated the harmonization of terminology and methodology. The 14040 series of the International Organization for Standardization contains standards and technical reports for LCA.

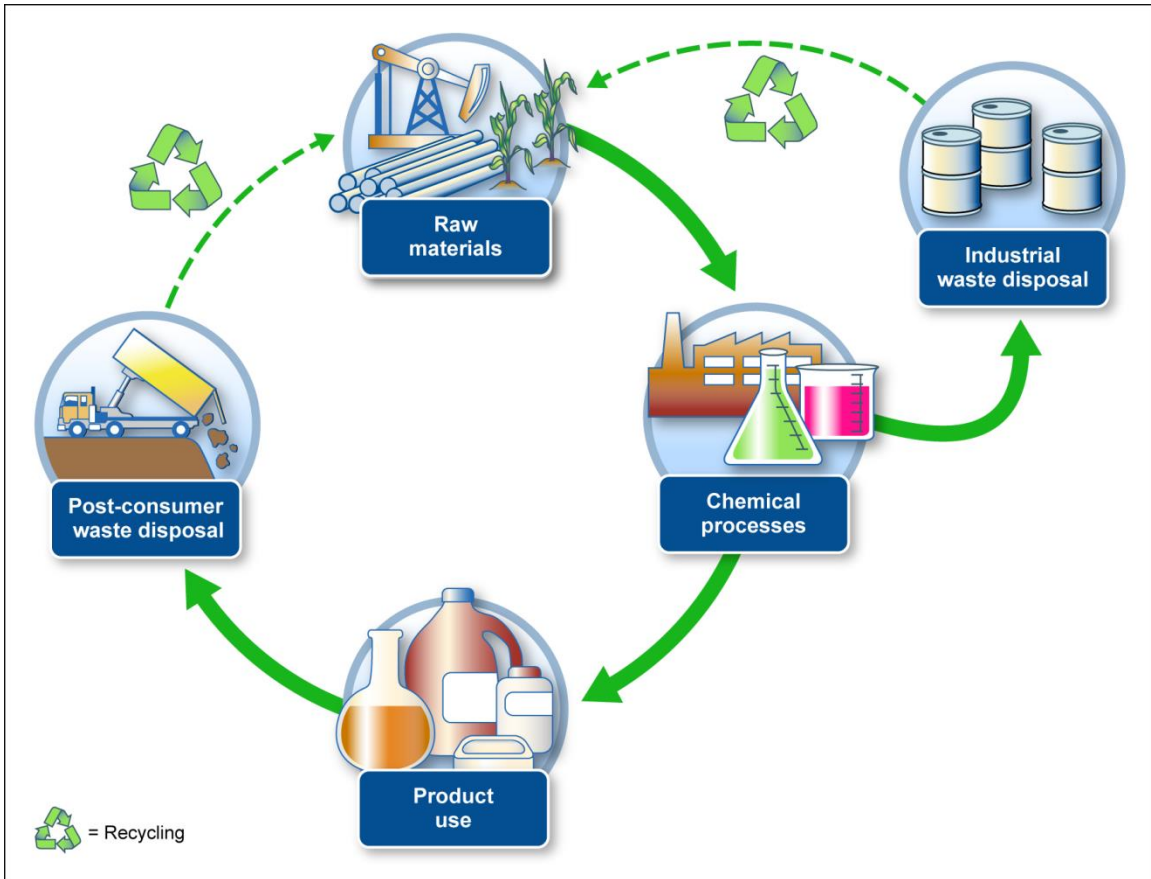
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<sup>12</sup>Although sustainable chemistry technologies exist in each stage of the life cycle, we were not able to cover all life cycle stages in this report.



**Figure 2: Life cycle of chemical processes and products**

Transportation and distribution of materials and products, represented by the green arrows between stages, can also be considered a life cycle stage.



Source: GAO. | GAO-18-307

LCA practitioners can tailor the parameters of the assessment to meet their needs; however, the use of this assessment in the chemical industry still faces challenges. Generally, LCA practitioners select system boundaries depending on the goals of the assessment. Example boundaries are ‘cradle-to-grave’—covering the entire supply chain from raw materials extraction to disposal, ‘cradle-to-gate’—covering raw materials extractions and processing, and ‘gate-to-gate’—covering manufacturing or processing only. A number of quantifiable environmental indicators can contribute to the assessment

including energy use, global warming, ozone depletion, human and environmental toxicity, and waste. The practitioner can also vary the relative importance of these indicators based on the needs of the assessment. The results of an LCA can depend on the amount and quality of data available as well as what the practitioner chooses to include. Therefore, different assessments of the same product or process can yield different results. A lack of data can be a challenge for the application of LCA to the manufacture of some chemical products. Additionally, there is not a coherent framework for characterizing the toxicological

impacts of chemicals. LCA can also be costly. As a tool, LCA can be more useful for products or processes that are at a high technology readiness level or already commercially available than those earlier in development, for which simpler metrics may be more appropriate.

## 1.2 Federal government agencies and other stakeholders

The federal government and other stakeholders play a number of roles, sometimes in collaboration, to advance the development and use of more sustainable chemical processes and products. Federal programs support research on the impacts of chemicals on human and environmental health. Federal programs also support the development of more sustainable chemical processes and their commercialization. Additionally, federal programs aid the expansion of markets for products manufactured with more sustainable chemicals and processes. Other stakeholders play similar roles and some additional roles that contribute to the development and use of more sustainable chemical processes and products.

Federal programs conduct and fund basic research on the characteristics and biological effects of chemicals that underpins the development and use of more sustainable chemistry products and processes. Decision makers must have a scientific understanding of the potential harmful impacts of exposure to chemicals for multiple reasons. For example, federal regulators need information to effectively minimize the harmful effects of chemicals through regulations and other means and to assess the regulated community's compliance with them. Industry

needs this information to make informed decisions about the selection, design, and use of more sustainable chemicals in their products and processes, including their impact on workers.

Federal programs also seek to support the development of new, more sustainable chemistry processes and facilitate the commercialization of these processes. The federal government conducts and funds both basic and applied research in the development of more sustainable processes. In addition, federal programs seek to facilitate the transition of new technologies from the research and development phase to commercialization, a transition that can be expensive and challenging for researchers as well as small and medium companies, according to experts. To support the transition to commercialization, federal programs provide loan guarantees, grants, and technical assistance to researchers and companies and recognize innovative technologies through an award program, among other activities.

Federal programs also aid market growth for products made with sustainable chemicals and processes by informing consumers about these products and by facilitating their purchase by federal offices. While growing numbers of consumers are seeking out "greener" or more sustainably manufactured products, it can be challenging for consumers to identify such products or verify company claims about their products. Companies seeking to manufacture more sustainable products strive to ensure that their products are differentiated from less sustainable products in order to reach these consumers. Federal sustainability certifications and evaluations are publically available to connect

interested consumers and purchasers with more sustainable products. Additionally, the Federal Acquisitions Regulation and Executive Order 13693—Planning for Federal Sustainability in the Next Decade—requires that federal agencies purchase selected products manufactured with more sustainable chemicals, creating a market for those products.<sup>13</sup>

Various agency programs play a role in the development and use of more sustainable chemistry processes and products. Some federal agencies have programs with goals that support the development and use of more sustainable chemistry and others have programs that do so consistent with broader goals. As part of its mission to protect human health and the environment, EPA has programs that conduct and fund research to evaluate the impacts of chemicals on human health and the environment. Additional programs support the development of products and processes that are more sustainable by awarding innovators of sustainable chemistry technologies and by evaluating and certifying those products and making the results available publically. Similarly, the Department of Health and Human Services (HHS) conducts and funds research on the impacts of chemicals as part of its mission to enhance and protect the health and well-being of Americans. The National Science Foundation’s (NSF) mission includes promoting the progress of science and advancing the national health, prosperity, and welfare. In terms of sustainable chemistry, NSF carries out this mission by funding research on the impacts of chemicals

on human and environmental health and on developing sustainable chemistry technologies. Part of the U.S. Department of Agriculture’s (USDA) mission is to provide leadership on agriculture and rural development in order to provide economic opportunity, help rural America, and promote agriculture production. As part of that mission, USDA programs support the development and use of technologies that can convert agricultural and forestry biomass into fuels and other products such as chemicals, and thereby create markets for agricultural products. The biobased chemicals produced using these renewable resources rather than traditional non-renewable sources such as fossil fuels, may be more sustainable. A number of programs at the Department of Energy (DOE), which works to ensure America’s security and prosperity by addressing its energy, environmental, and nuclear challenges through science and technology, seek to reduce the energy used in manufacturing, including energy used by chemical technologies. The Department of Commerce’s National Institute of Standards and Technology (NIST) advances measurement science, standards, and technology, including those needed to measure sustainability. As part of its mission, the Department of Defense (DOD) protects readiness, people, and the environment by: (1) identifying and researching risks associated with chemicals; (2) developing, evaluating, and demonstrating sustainable solutions to meet DOD’s environmental and performance challenges, including more sustainable chemical products and processes; and (3) ensuring DOD meets the requirements of applicable federal green procurement preference programs.

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<sup>13</sup>See Exec. Order No. 13963, *Planning for Federal Sustainability in the Next Decade*, 80 Fed. Reg. 15871 (March 25, 2015); 48 CFR 1.102.

Other stakeholders, such as industry, companies and retailers, states, academic institutions, and NGOs also seek to influence the development and use of more sustainable chemistry processes and products through activities such as supporting workforce development and developing tools and resources for industry. These organizations may work collaboratively to share expertise and resources or to identify areas of common interest in order to promote mutual goals related to sustainable chemistry. By focusing on a wide range of approaches to supporting sustainable chemistry, from transforming education to developing industry-specific standards, together these groups may facilitate the transition of the chemical industry to a new, more sustainable framework for chemical technologies.

### 1.3 Legal framework

Consistent with the goals of sustainable chemistry that include making chemicals in a purposefully more environmentally benign way, several federal requirements and directives address chemical and other risks to public health and the environment. For example, EPA's ability to effectively implement its mission of protecting public health and the environment is critically dependent on credible and timely assessments of the risks posed by chemicals. Such assessments are the cornerstone of scientifically sound environmental decisions, policies, and regulations under a variety of statutes, such as the Toxic Substances Control Act (TSCA),<sup>14</sup> which provides EPA with

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<sup>14</sup> 15 U.S.C. § 2601 et. seq. After many years of congressional committees considering legislation aimed at reforming TSCA, in June 2016, Congress passed and the President signed the Frank R. Lautenberg Chemical Safety for the 21st Century Act, which

authority to obtain information on chemicals and to regulate those that it determines pose unreasonable risks; the Safe Drinking Water Act (SDWA),<sup>15</sup> which authorizes EPA to regulate contaminants in public drinking water systems; the Clean Air Act,<sup>16</sup> which regulates air pollution from stationary and mobile sources; and the Clean Water Act, which aims to restore and maintain the chemical, physical and biological integrity of the nation's waters.<sup>17</sup> The Food and Drug Administration (FDA) oversees the safety of food, drugs and medical devices, and cosmetics under the Federal Food, Drug and Cosmetic Act.<sup>18</sup> The Department of Defense, the General Services Administration, and the National Aeronautics and Space Administration jointly issue the Federal Acquisition Regulation<sup>19</sup> for use by executive agencies for acquiring goods and services, and Executive Order 13693 encourages federal agencies, among other things, to acquire Safer Choice labeled products (chemically intensive products that contain safer ingredients).<sup>20</sup>

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gave EPA greater authority to improve its processes for assessing and controlling toxic chemicals. Pub. L. No. 114-182, 130 Stat. 448.

<sup>15</sup> 42 U.S.C. § 300f et. seq.

<sup>16</sup> 42 U.S.C. § 7401 et. seq.

<sup>17</sup> The Federal Water Pollution Control Act Amendments of 1972, Pub. L. No. 92-500, § 2, 86 Stat. 816, codified as amended at 33 U.S.C. §§ 1251-1387 (2013) (commonly referred to as the Clean Water Act). See <https://www.gao.gov/products/GAO-14-80>.

<sup>18</sup> 21 U.S.C. § 301 et. seq.

<sup>19</sup> Title 48, Code of Federal Regulations.

<sup>20</sup> Exec. Order No. 13963, *Planning for Federal Sustainability in the Next Decade*, 80 Fed. Reg. 15871 (March 25, 2015), <https://www.gpo.gov/fdsys/pkg/FR-2015-03-25/pdf/2015-07016.pdf>.

## 1.4 Supply, demand, and economics

Various economic factors influence the development of sustainable products. Stakeholders described how interactions between the demand for and supply of sustainable products can influence the extent and pace of growth. For example, the supply of any product is strongly influenced by the costs of production, as well as costs of getting that product to market. Whether that cost is worth the undertaking depends on what consumers are willing to pay for the product and the overall consumer demand.

Consumer demand can be influenced by a range of factors such as changes in mindset, an increased willingness to pay, and price sensitivity. Consumers are increasingly seeking products that help them reduce their own environmental footprint and the footprint of their supply chain. Hence, chemical companies are innovating to develop products made with safer chemicals and are also increasing the use of recycled, biobased, and renewable materials. When consumers are willing to pay a premium for such products, increasing demand, firms are incentivized to start producing more of them in order to preserve their market share, maintain their reputation, or even increase profits. According to a 2015 online survey of 30,000 consumers in 60 countries by Nielsen, 66 percent of consumers say they are willing to pay more for sustainable brands—up from 55 percent in 2014 and 50 percent in 2013.<sup>21</sup> Similarly, some large retailers such as Walmart and Target are also experiencing

increased demand for more sustainable products. Target’s sales in natural and organic products are growing at a rate of about 15 to 20 percent per year. This growth resulted in Target launching “Made to Matter” in 2014, an initiative showcasing a selection of the company’s “handpicked natural, organic, and sustainable” products. Walmart created a “Sustainability Leaders” website for consumers that rates suppliers on environmental and social criteria.

The supply of such products can be influenced by the costs of production, competitive advantage and reputational effects. For example, if some technology or process offers a clear benefit to a firm in terms of lower costs of production, with no effect on quality, firms will have a natural incentive to adopt it. Similarly, if a more sustainable product or use of technology helps a firm differentiate from another firm and creates a competitive advantage that consumers recognize and value, it will encourage firms to create more sustainable products. The creation of more sustainable products may have a good reputational effect for a firm in the minds of consumers, which may even extend to other products made by that firm, regardless of whether those products are also more sustainable. As a result, consumers may start regarding the products of these firms to have a greater quality or additional benefits and show a willingness to pay a premium for them. According to a Nielsen study, commitment to social and environmental responsibility is becoming more important than other traditional influences on consumer loyalty and brand performance.<sup>22</sup> Firms may also invest in sustainable chemistry to align

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<sup>21</sup>The Nielsen Company, *The Sustainability Imperative, New Insights on Consumer Expectations, Global Sustainability Report* (October 2015), 2.

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<sup>22</sup>Nielsen, *The Sustainability Imperative*, 3.

with internal goals of corporate social responsibility.

There are a number of inherent challenges in the market for sustainable products in the industry, such as the upfront costs in the face of uncertain demand. For any new industry, the substantial upfront costs in the face of uncertainty and risk associated with consumer demand would be a substantial barrier or challenge. If the benefits are obvious, firms may be able to increase prices to consumers to recoup these costs without harming demand; however, if the benefits are not easily understood and measureable (e.g., long-term health benefits), or are external to consumers (e.g., broad environmental impacts), then consumers may not be willing to pay higher prices. Thus, the upfront costs required to create new products or use new technology can be a big challenge, especially when faced with uncertain demand.

In addition to market incentives that encourage firms to produce more sustainable products, government can offer subsidies, tax credits, and other incentives. For example, an Organisation for Economic Co-operation and Development report on sustainable chemistry patent data identifies positive and negative tools that aim to stimulate sustainable chemistry.<sup>23</sup> Positive tools include such things as incentives for the adoption of green chemistry products, training, and award programs, while negative tools include such things as limits, bans, and taxes that discourage use of chemicals of concern. A report on the economic benefits of green

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<sup>23</sup>Organisation for Economic Co-operation and Development, Environment Directorate, *Sustainable Chemistry: Evidence on Innovation from Patent Data*, No. 25 (Paris, France: Feb. 2011), 43-45.

chemistry published by the University of Massachusetts found that appropriately designed regulations support innovation, productivity, and employment despite the frequent argument that imposing new standards on the chemical industry will damage competitiveness and cost the U.S. economy jobs.<sup>24</sup> They argue that just as the federal government has supported innovative developments in agriculture, biotechnology, computers, and the Internet, similar support is needed to build a green chemical industry. The report also makes a case for dissemination of environmental and health-related information to help guide the choices of consumers, workers, downstream users, and investors. For new markets and investments to be realized, sufficient information is needed on the environmental damage and health hazards associated with chemicals and the possibilities that exist to develop alternatives that overcome these challenges.

Improving resource performance is also key to industry growth, according to a McKinsey report on the circular economy.<sup>25</sup> A linear model of production and consumption in which goods are manufactured from raw materials, sold, used, and then discarded or incinerated as waste is reaching its limits, according to the report. In the face of ongoing resource depletion, McKinsey makes the case for a substantial improvement in resource

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<sup>24</sup>James Heintz and Robert Pollin, Political Economy Research Institute, University of Massachusetts, Amherst. Blue Green Alliance, *The Economic Benefits of a Green Chemical Industry in the United States*, (2011), 6-7.

<sup>25</sup>A circular economy is an industrial model that decouples revenues from material input. World Economic Forum, *Towards the Circular Economy: Accelerating the Scale-Up Across Global Supply Chains*,” Ellen MacArthur Foundation and McKinsey & Company, (Geneva, Switzerland, 2014), 13.

performance, urging firms to explore ways to reuse products or their components. Strategies to co-produce other products to make the main product more economically viable are also worth considering, according to the report, and may be another way to become more cost-competitive.

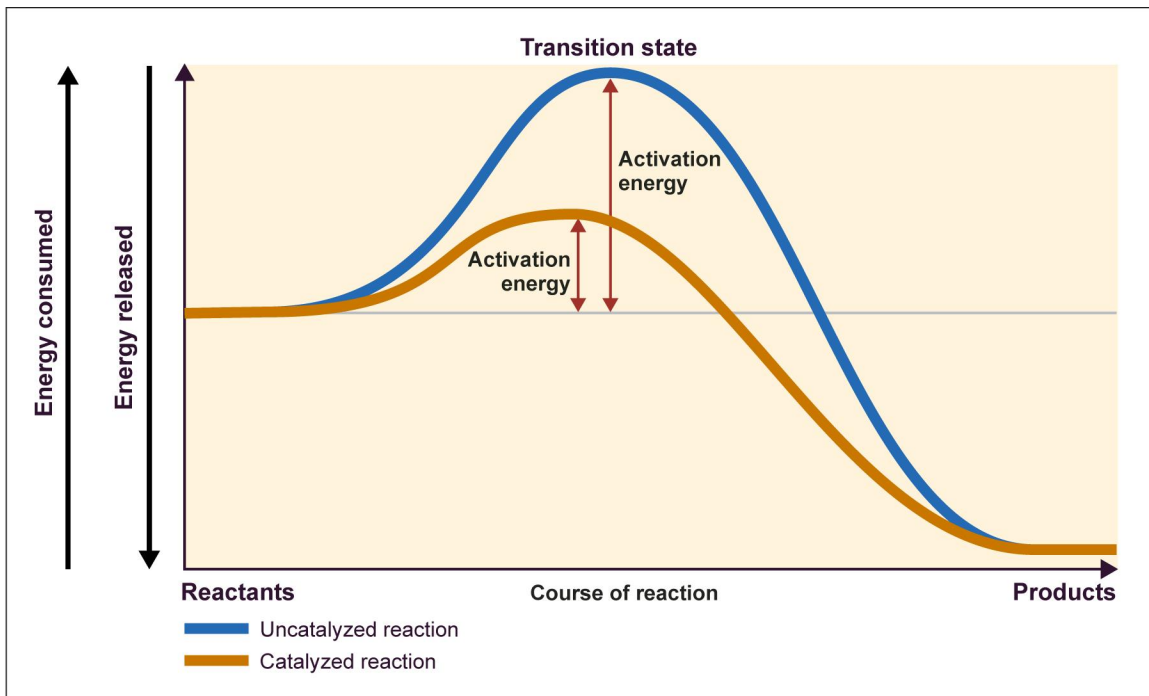
### 1.5 The sustainability of catalysts

A catalyst is a substance that increases the rate of a chemical reaction without being

substantially consumed in the process. Many chemical reactions require energy input (known as the activation energy) to get the reaction started by ‘pushing’ the reactants over an initial energy barrier. A catalyst increases reaction rates by providing the reactants with an alternative reaction pathway that has lower activation energy than the uncatalyzed reaction thereby reducing the energy input required for a process (see fig. 3). This is one of the main sustainability advantages provided by catalysts.

**Figure 3: Examples of catalyzed and uncatalyzed reaction energy paths**

The activation energy for a catalyzed reaction is lower than the activation energy for an uncatalyzed reaction. Lower activation energy results in a faster reaction.



Source: GAO. | GAO-18-307

In addition to reducing the energy input required for a process, catalysts allow for more efficient use of materials, thus reducing

waste. For example, most catalysts can be recovered after the reaction and used again.<sup>26</sup>

<sup>26</sup>A 2013 study by Bravo-Suárez and colleagues reported that, among all the catalytic processes used in the industry,

In addition, catalysts are generally only required in small quantities. They also help to minimize waste by creating a more targeted and selective reaction pathway that forms fewer byproducts. This property, called selectivity, is among the most important sustainability feature of catalysts.

One scientific paper reported that catalysts are a necessary and critical tool for achieving social and economic objectives as described in the 12 Principles, such as the economical use of materials, use of simple and safe processes, avoidance of toxic chemicals, and reducing or avoiding waste formation.<sup>27</sup> (See app. V for a full list of the 12 Principles.) Today, catalysts play a critical role in promoting the feasibility, sustainability, and economics of over 90 percent of chemical processes.<sup>28</sup> Specifically in the pharmaceutical industry, advances in catalysis have enabled the synthesis of highly complex active pharmaceutical ingredients (i.e., drugs) in fewer steps, with increased efficiency in material use, and often with high product

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heterogeneous catalysts (where the catalyst and the reactants are in different phases; e.g., solid catalyst and gaseous reactants) were the most widely used and constituted 80 percent of the market share. Homogeneous catalysts (where the catalyst and reactants are in the same phase) constituted 17 percent of the market share, with enzymatic catalysts making up the remaining 3 percent. J. J. Bravo-Suárez, R. V. Chaudhari, and B. Subramaniam, *Design of Heterogeneous Catalysts for Fuels and Chemicals Processing: An Overview* (ACS Symposium Series, American Chemical Society: (Washington, D.C., 2013). According to one of our experts, heterogeneous catalysts are recyclable while homogeneous catalysts generally are not.

<sup>27</sup>G. Centi and S. Perathoner, "Catalysis and Sustainable (Green) Chemistry," *Catalysis Today*, vol. 77 (2003).

<sup>28</sup>F. Cavani, G. Centi, S. Perathoner, and F. Trifirò, *Sustainable Industrial Chemistry: Principles Tools and Industrial Examples*, Wiley-VCH (2009) 1-72.

yields.<sup>29</sup> Without catalysts, many of the items we use each day such as medicines, fine chemicals, polymers, fibers, fuels, paints, lubricants, much of the food we eat, and a myriad of other products could not be produced in sufficient quantities to meet demand. For all of these reasons, catalysts improve the sustainability of chemical processes.

Despite their many benefits, the use of catalysts also raises sustainability concerns. In particular, most catalysts in use today are platinum group metals (PGM), which are scarce, nonrenewable, and potentially toxic.

Platinum group metals (PGM): PGMs are a group of six very similar chemical elements: platinum, palladium, ruthenium, rhodium, iridium, and osmium. Their leading role as catalysts stems from their unique characteristics and distinct advantages over other options, including chemical stability, selectivity, and predictable and well understood reaction mechanisms. PGMs are also resistant to the loss of catalytic activity known as catalytic poisoning.<sup>30</sup> They have higher melting points than base metals—more earth-abundant metals such as lead or copper— so they are very stable at high temperatures. As a result, they can retain their catalytic activity for a longer period than other materials when exposed to harsh conditions such as automotive exhaust. PGMs

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<sup>29</sup>An active pharmaceutical ingredient is any component that is intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. In this report, we refer to active pharmaceutical ingredients as "drugs."

<sup>30</sup>Catalytic poisoning results from the capture of chemicals (often impurities) on sites that would otherwise be available for catalysis. Over time this results in the loss of catalytic activity.



are also recyclable, which means they can be re-used many times, thus minimizing their impact on the environment.

Despite their prevalence as catalysts, the scientific community has raised sustainability concerns about the continued use of PGMs by industry. For example, PGMs are scarce, generally nonrenewable, and susceptible to supply and price fluctuations. Their presence in the earth's crust is orders of magnitude lower than that of earth-abundant metals. PGMs were included in the European Union's Report on Critical Raw Materials because, by the year 2020, they are expected to have insufficient supply to meet demand. Furthermore, the limited availability of PGMs is exacerbated by the growing demand for these materials in other applications, such as newer organic light emitting diode displays in smart phones and televisions, and renewable energy systems, such as fuel cells, wind energy, and photovoltaics. Additionally, PGMs—mainly platinum and palladium—have proven to be indispensable in the automotive industry for catalytic converters, which has driven recent demand.<sup>31</sup> Automotive emissions regulations in the United States and Europe and the burgeoning auto markets in China and India are expected to further strain the supply of these metals in the coming years.

In addition, exposure to PGMs may be harmful to human health and the environment. As pollutants, PGMs are generally airborne particles; they are a health risk due to their small size and ability to react with many compounds in our body to form

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<sup>31</sup>A catalytic converter is a device incorporated in the exhaust system of a motor vehicle, with a catalyst for converting pollutant gases into harmless products.

more toxic compounds. Wiseman et al. reported that exposure to PGMs can lead to oxidative stress, pulmonary inflammation, and increased risk of pneumonia and other respiratory diseases.<sup>32</sup> There is also some evidence that PGMs can cause autoimmune diseases. The risks are especially high for children and the elderly. Bioaccumulation of these metals in the food chain is another concern even when the environmental levels are not high.

For all of these reasons, the scientific community is actively researching options for the replacement of PGMs in catalysis. Potential alternative catalysts include earth-abundant metals (iron, manganese, nickel, and cobalt) and metal-free catalysts such as organocatalysts and biocatalysts.<sup>33</sup>

We discuss sustainable alternatives to PGMs in chapter 3.

## 1.6 The sustainability of solvents

Rethinking solvent use in a number of different applications is another approach to increase sustainability in the chemical industry. A solvent is a substance capable of dissolving other substances in order to form a homogenous mixture, known as a solution

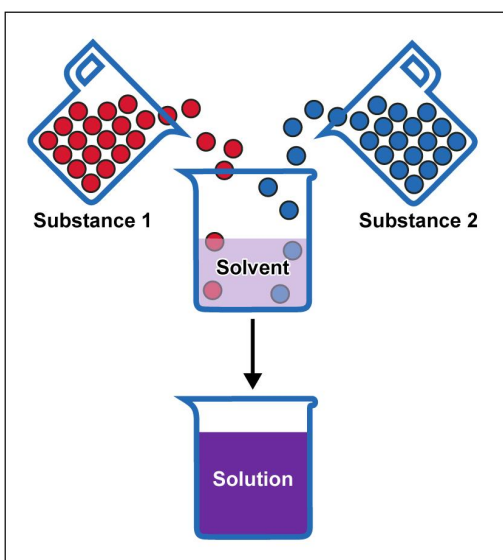
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<sup>32</sup>C. L. S. Wiseman and F. Zereini, "Airborne Particulate Matter, Platinum Group Elements and Human Health: A Review of Recent Evidence," *Science of the Total Environment*, vol. 407 (2009). The authors of this paper did an assessment of the risk related to environmental exposures to PGMs, particularly in airborne particulate matter and highlighted the need to monitor environmental levels of PGMs and continue research on their associated toxicity to better assess their potential to elicit health effects in humans.

<sup>33</sup>Organocatalysts are organic (non-metallic, carbon-based) compounds that can serve as catalysts. Biocatalysts are enzymes (proteins originating from living cells) that are used in chemical processes to perform reactions.

(see fig. 4).<sup>34</sup> The chemical industry uses solvents for several different purposes, including (a) as media for chemical reactions, (b) in the separation and purification of chemicals, and (c) for cleaning the equipment used in chemical processes. Solvents may also be included as a primary component or ingredient in formulated products such as paints, inks, or cleaning and personal care products. These uses can be interrelated; for example, the choice of reaction medium can facilitate the separation and purification of products.

**Figure 4: Substances dissolve in a solvent to form a homogenous mixture known as a solution**



Source: GAO. | GAO-18-307

Given the variety and nature of their applications, solvents are used by a variety of industries and constitute a large portion of the total volume of chemicals used in industrial chemical processes. Benchmarking studies of the pharmaceutical industry by the

<sup>34</sup>A solution can be gaseous, solid, or liquid.

ACS GCI Pharmaceutical Roundtable in 2007 and 2008 showed that organic solvents constitute more than half of the materials by mass that are used to manufacture an active pharmaceutical ingredient. According to one analysis of papers published in 2010 in the journal *Green Chemistry*, much of the research on more sustainable solvents has focused on reaction media for chemical synthesis.<sup>35</sup> However, this is not the only solvent use for which alternatives could be used. In the pharmaceutical industry, for example, the purification of chemicals can be the largest contributor to solvent waste. Reducing overall solvent use, therefore, can impact the environmental performance, cost, and safety and health issues associated with a process. Additionally, many industries use solvents, including industries not related to chemical synthesis. For example, in addition to the chemical industry several other industries use solvents for cleaning equipment and other items, including the automotive, electronics, textiles, and paper industries.

Many conventional solvents are considered hazardous to both the environment and human health. Many conventional solvents are volatile organic compounds (VOC)—organic compounds whose composition allows them to evaporate at normal temperatures and pressures.<sup>36</sup> A low boiling

<sup>35</sup>P. G. Jessop, "Searching for green solvents," *Green Chemistry*, vol. 13 (2011).

<sup>36</sup>There are multiple definitions of VOCs. EPA regulations define VOCs as any compound of carbon, with a few exclusions including carbon dioxide, which participates in atmospheric photochemical reactions, except those designated by EPA as having negligible photochemical activity (40 C.F.R. § 51.100). However, the more general definition used in this report aligns with the scientific literature and is also used by EPA in certain contexts.

point is advantageous because it facilitates removal of the solvent when it is no longer needed; however, this solvent property is associated with environmental health and safety concerns such as flammability and worker exposure. In addition, conventional solvents are often toxic to both humans and the ecosystem and can be air pollutants. For the above reasons among others, both legislation and voluntary control measures regarding solvents have been introduced.

There is not a single universal green or sustainable solvent; chemical processes or other solvent applications will have different specifications, and require alternative solvent options that still meet performance characteristics. Solvents can serve multiple purposes when used as reaction media for chemical processes. For example, the solvent can improve contact between the reactants. Depending on its properties, a solvent can affect the outcome or increase the speed of a reaction. For example, a particular reaction may result in different products depending on the choice of solvent. It can also stabilize the transition state of the reaction—a higher energy species temporarily formed by reactants before forming the final product—thus increasing the speed of the reaction. Solvents can also aid in heat transfer. For reactions that generate heat, for example, a solvent can absorb excess heat thereby preventing runaway, or uncontrollable, reactions.

Solvents can be a primary component or ingredient in formulated products, and a 2015 perspective article from the ACS GCI Formulator’s Roundtable highlighted the need for more sustainable solvent alternatives in

formulations.<sup>37</sup> Solvents serve a number of purposes in formulated products including dissolving raw materials or essential oils to form the product; or dissolving unwanted materials, for example grease or ink, for cleaning. The authors of the perspective article stated that suitable alternatives must continue to meet key performance characteristics for these products, including cleaning benefits such as grease removal, stabilizing the formulation by keeping other ingredients in solution, and modifying particular physical properties in the final formulation. They also stated that alternative solvents should:<sup>38</sup>

- be sourced from renewable, non-petroleum feedstocks;
- undergo a life cycle assessment that includes the impact of solvent manufacture in addition to solvent use;
- show no reproductive toxicity and have low toxicity, in general, to humans;
- be non-sensitizing and non-irritating; and
- have minimal odor or color.

We discuss more sustainable solvent use in chapter 4.

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<sup>37</sup>P. G. Jessop, F. Ahmadpour, M. A. Buczynski, T. J. Burns, N. B. Green II, R. Korwin, D. Long, S. K. Massad, J. B. Manley, N. Omidbakhsh, R. Pearl, S. Pereira, R. A. Predale, P. G. Sliva, H. VanderBilt, S. Weller, and M. H. Wolf, “Opportunities for Greener Alternatives in Chemical Formulations,” *Green Chemistry*, vol. 17 (2015).

<sup>38</sup>The authors also mentioned that alternative solvents should meet the EPA Design for the Environment criteria for acceptable formulation ingredients. The Safer Choice Label replaced the Design for the Environment label in 2015. For more on the EPA Safer Choice program see chapter 6.

## 1.7 The sustainability of batch processing

Historically, industrial chemicals have been produced mainly using an approach known as batch processing. Batch processing is a discontinuous process. That is, finite quantities of raw materials (the reactants) and any other necessary components such as catalysts or solvents are combined in a closed vessel or vat—also called a batch reactor—under appropriate conditions of temperature and pressure. The reaction takes place as the contents of the vessel are stirred and allowed to react together. When the reaction has proceeded as far as desired, the resulting mixture is transferred to the next vat or reactor for the next stage of processing, the first vat is cleaned, and the process is repeated with the next batch. Batch processing is typically suitable for higher value, small-scale production, and when a range of different products such as pigments, dyes, and polymers are all produced using the same equipment. It is also well suited for reactions with long reaction times. Batch processing is currently used in the chemical, pharmaceutical, and food process industries.

Batch processing can occur at small scales—for example, a chemical synthesis could be done in a test tube or a flask—but in most of the chemical industry, it is typically a large-scale approach. Therefore, batch reactors typically have a large physical footprint (i.e., require significant space). Batch processing raises other sustainability concerns as well. For example, cleaning the vats between batches can use significant amounts of cleaning solvents and energy. Researchers have reported that the large-scale operations often associated with batch processing may also pose a safety risk under some circumstances, such as when high pressures

are required to complete a reaction or when a hazardous intermediate is produced during the course of a reaction.<sup>39</sup> Other considerations include potentially long wait times while a batch is processing and high capital expenses.

Continuous processing (also known as continuous flow) is an alternative that allows chemical reactions to occur as the reaction mixture is pumped through a continuous processing line composed of pipes or tubes where reactions take place continuously. Reactants can be introduced and byproducts removed at appropriate points along the line; finished product materials are continuously removed at the end of the line.

Microreactors are a specific technology that allows continuous processing to be conducted in relatively small volumes.<sup>40</sup> Continuous processing microreactors have enabled new paradigms in sustainable chemistry such as alternative reaction pathways, less hazardous and energy-efficient syntheses, and low-solvent or solvent-free reactions, among others.

See chapter 5 for our discussion on the sustainability of continuous processing and microreactors.

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<sup>39</sup>B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, and D. T. McQuade, "Greener Approaches to Organic Synthesis Using Microreactor Technology," *Chemical Reviews*, vol. 107, no. 6 (2007).

<sup>40</sup>A microreactor can be defined as a technology that couples the miniaturization of chemical reactors with continuous flow. This approach can provide optimal reaction conditions and eliminate typical scale-up problems. In this technology assessment we focus on applications of microreactors in the pharmaceutical industry. In addition to microreactors there are other types of reactors reported in the literature for more sustainable chemical processing and synthesis, including spinning disk reactors, cavitation reactors, and membrane bioreactors, among others. We have chosen to not include these additional reactor types in this technology assessment.

## 2 Stakeholders vary in how they define and assess the sustainability of chemical processes and products

Stakeholders define sustainable chemistry in a variety of ways. In addition, they use many different approaches for assessing the sustainability of chemical processes and products. For example, some chemical companies have designed their own in-house tools for assessing the sustainability of their own processes and products, while others use common methods considered appropriate by their industry sector. Stakeholders such as federal agencies, professional associations, and non-governmental organizations have developed a variety of third-party certification and measurement programs to assess the sustainability of products and companies. However, these programs vary in the criteria they use and the factors they consider important to assess, making comparisons between them difficult. Similarly, chemical companies that responded to our survey vary widely on the environmental and health factors they consider most important to include when assessing sustainability. Nonetheless, most responding companies agreed that a standardized set of such factors for assessing sustainability across their industry sector and across the entire chemical industry would be somewhat or very useful.

### 2.1 Stakeholder definitions of sustainable chemistry vary

Stakeholders do not agree on a single definition of sustainable chemistry, but there are some common understandings of what this term means. In total, we asked 71 representatives of stakeholder organizations

how they or their organization define sustainable chemistry.<sup>41</sup> The most common response we received, with 28 respondents agreeing, was that sustainable chemistry includes minimizing the use of non-renewable resources such as feedstocks. The second most common response (27) was that sustainable chemistry is similar, synonymous, or interchangeable with green chemistry. However, 17 stakeholders described sustainable chemistry as broader than green chemistry. Stakeholders mentioned various ways in which sustainable chemistry may go beyond green chemistry, for example by considering the entire life cycle of a process or product, or by incorporating economic considerations.

Other concepts that stakeholders commonly associated with sustainable chemistry included:

- minimizing the negative impact of chemicals, products, or processes on the environment (24) as well as human health and safety (17);
- considering various factors in each phase of the life cycle, including potential tradeoffs (23);
- minimizing the use of toxic or hazardous chemicals (22) and increasing the use of environmentally benign chemicals in products and processes (7);

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<sup>41</sup>Stakeholders we interviewed included federal and state officials, chemical companies, industry and professional organizations, academics and educational institutions, NGOs, and others.

- minimizing energy (22) and water use (14);
- conserving or using resources and materials efficiently (21);
- minimizing waste and pollution, particularly hazardous waste (20);
- including economic considerations such as cost (12);
- minimizing the impact of product end of life, for example by increasing biodegradability or recyclability (9); and
- encouraging innovation and the creation of new processes (9).

For the purposes of this report, we refer to a chemical process, product, or technology as ‘more sustainable’ compared to a conventional alternative if it better aligns with one or more of the goals above or with one or more of the 12 Principles.

## 2.2 Stakeholders vary in the approaches they use for assessing the sustainability of chemical processes and products

Stakeholders such as chemical companies, federal agencies, and others use many different approaches for assessing the sustainability of chemical processes and products. For example, some chemical companies have designed their own systems for assessing sustainability, while others use a common approach considered appropriate by their industry sector. While the varying approaches provide flexibility to meet the priorities of the user, the lack of a standardized approach makes it very difficult for customers, decision makers, and others to

compare the sustainability of various products to make informed decisions.

### 2.2.1 Company-designed approaches

Some companies and organizations design their own approaches for assessing chemical sustainability and use those approaches to make internal decisions on product design and processing. For example, the pharmaceutical and healthcare company GlaxoSmithKline has created the GSK Solvent Sustainability Guide, which combines multiple health, environment, safety, and waste categories to reach a single composite score and color assignment for each of the 154 solvents included in the 2016 version of the guide.<sup>42</sup>

Dow Chemical uses an internally developed metric called the Dow Chemical Sustainability Footprint Tool that asks 23 questions across six dimensions: economic, social, greenhouse gas emissions, water use, nonrenewable resource requirement, and a company dimension.<sup>43</sup> Many of the questions involve comparisons of a project or new idea with an incumbent project (the base case) that delivers an equivalent service to the end user. For example, one question asks the end user to assess whether the toxicity profile of the new product “is expected to: [considerably improve / slightly improve / remain the

<sup>42</sup>For additional details, see C.M. Alder, J.D. Hayler, R.K. Henderson, A.M. Redman, L. Shukla, L.E. Shuster, and H.F. Sneddon, “Updating and Further Expanding GSK’s Solvent Sustainability Guide,” *Green Chemistry*, vol. 18, no. 13 (2016).

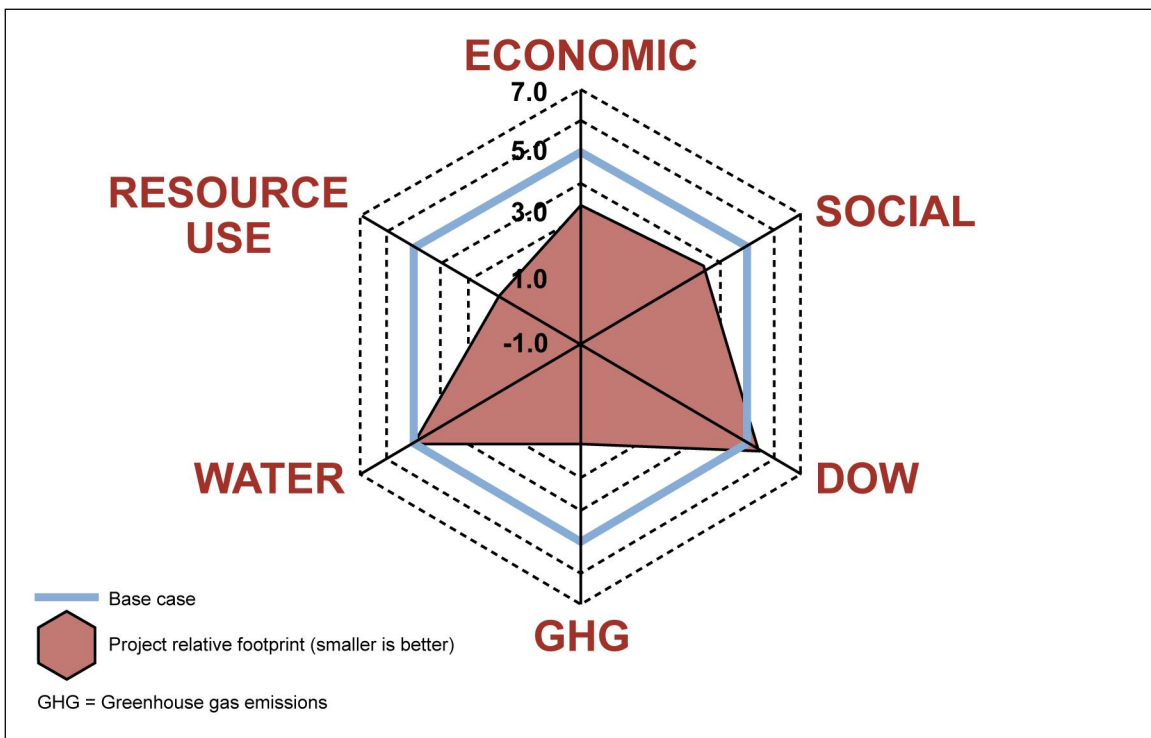
<sup>43</sup>For additional details, see D. A. M. Russell and D. L. Shiang, “Thinking about More Sustainable Products: Using an Efficient Tool for Sustainability Education, Innovation, and Project Management to Encourage Sustainability Thinking in a Multinational Corporation,” *ACS Sustainable Chemistry & Engineering*, vol. 1, no. 1 (2013).

same / get worse] compared to the current product-service provided to the end user.”

The questions allow Dow to rate each project on a 7-point scale for each of the six dimensions, where a higher number is a less desirable (i.e., less sustainable) result. Dow then combines the scores for each of the six dimensions into a diagram that visually

presents the sustainability footprint for the project (see fig. 5). The goal is to achieve a smaller footprint inside the web, indicating improved sustainability. For an entirely new project that has no incumbent project for comparison, Dow assigns the base case score of 5.0 to encourage future sustainability improvements.

**Figure 5: A hypothetical result for the Dow Chemical Sustainability Footprint Tool**



Source: Dow Chemical. | GAO-18-307

Dow can use this tool to assess an entirely new project or to compare a newly developed approach (represented in this hypothetical example by the colored polygon) to an existing approach (represented by the blue hexagonal line at the 5.0 mark).

### 2.2.2 Common approaches used to assess sustainability

Some stakeholders assess the sustainability of chemical processes and products using a common approach that others also accept as appropriate. These include metrics, chemical selection guides, and third-party certifications.

## Metrics

Companies in the chemical industry use several established metrics to measure their efficiency in using materials to generate products; each metric accounts for one or more factors related to the efficiency of chemical processes. For example, the scientific literature reports a variety of metrics including atom economy, carbon efficiency, mass intensity, process mass efficiency, solvent intensity, and wastewater intensity, among others.<sup>44</sup> Each of these metrics is calculated using a different set of underlying factors, such as the amount of waste produced, the yield of the desired product, solvent use, and water use. The variety of metrics used—and variation in the underlying factors included in their calculation—hinders the ability of companies and others to compare the sustainability of chemical processes or products.

Although a full discussion of these metrics and others is beyond the scope of this report, mass-based metrics—that is, metrics that assess a chemical process based on the total mass of materials used or the mass of waste produced—are common. According to scientific literature, the Environmental factor (*E* factor) and process mass intensity (PMI) are two examples of commonly used mass-based metrics.

***E* factor:** R.A. Sheldon published the first paper describing the *E* factor in 1992, based on discoveries about the enormity of the waste problem resulting from methods in use

at that time across different segments of the chemical industry.<sup>45</sup> He and his coworkers conducted an inventory of the amounts of waste generated in the production of fine chemicals, pharmaceutical intermediates, and some bulk chemicals. They calculated the results using a new quantitative metric:

$$E \text{ factor} = \frac{\text{mass of waste (kg)}}{\text{mass of product (kg)}}$$

In the original 1992 paper, Sheldon defined waste as “everything but the desired product,” including solvent losses but excluding water. An ideal process would have an *E* factor of zero (no waste produced), and higher *E* factors indicate more waste and thus (presumably) greater negative environmental impact. Sheldon’s inventory indicated that the production of bulk chemicals had *E* factors ranging from less than 1 to 5—that is, up to 5 kg of waste produced per kg of product. *E* factors for fine chemicals were higher, ranging from 5 to 50, and for pharmaceuticals the *E* factors ranged from 25 to greater than 100 kg of waste produced per kg of product.

According to Sheldon, lower *E* factors correlate well with reduced manufacturing costs for drug ingredients, which reflects lower materials input and reduced hazardous waste disposal, among other factors. This provides an economic incentive for companies to reduce waste in their chemical processes. However, simply reducing the amount of waste, even to a significant degree compared to the original process, does not

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<sup>44</sup>See F. Roschangar, R. A. Sheldon, and C.H. Senanayake, “Overcoming Barriers to Green Chemistry in the Pharmaceutical Industry – the Green Aspiration Level Concept,” *Green Chemistry*, vol. 17, no. 2 (2015).

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<sup>45</sup>R. A. Sheldon, “Organic Synthesis – Past, Present, and Future,” *Chemistry and Industry*, vol. 23 (1992).



indicate an optimized process.<sup>46</sup> The process may still be inefficient and have unnecessarily adverse environmental impacts. Specifically, two issues with the use of *E* factors affect the interpretation of results. First, the final *E* factor depends on the boundaries used for the calculation. Sheldon’s original formula set gate-to-gate boundaries—that is, the starting point was the material entering the factory gate and the end was the product leaving it. However, in a later paper Sheldon noted that this gate-to-gate approach could lead to inconsistencies in the application of *E* factors, given that purchasing an intermediate rather than producing it in-house can allow a company to claim a dramatically lower *E* factor.<sup>47</sup> He suggests that one possibility to avoid this inconsistency is to define the starting point as a commodity-type, commercially available raw material. As an example, he describes a process for the manufacture of the drug ingredient sildenafil citrate in which using the original formula (including an estimate of 10 percent of solvents going to waste and excluding water) gives an *E* factor of 6.4 kg waste per kg product for the production process. However, one of the primary raw materials does not meet the definition of a commodity-type chemical; including the intrinsic *E* factor resulting from the production of that raw material more than doubles the *E* factor to 13.8 kg waste per kg product. A second issue is that the *E* factor does not differentiate between wastes that are relatively benign and

those that are highly toxic and environmentally persistent. Therefore, one process with a low *E* factor (based on producing a relatively small amount of highly toxic waste) may actually be much more environmentally harmful than another process with a higher *E* factor where the waste, although produced in larger quantities, is environmentally benign.

Process Mass Intensity (PMI): The ACS GCI Pharmaceutical Roundtable has identified PMI as the key mass-based metric for the pharmaceutical industry. In a 2011 publication discussing the rationale for this selection, the authors noted the routine use of PMI to benchmark the greenness of processes and to drive greater efficiency and innovation in the pharmaceutical and fine chemical industries.<sup>48</sup>

PMI is a measure of the total mass of materials used per mass of product:

$$\text{PMI} = \frac{\text{total mass of materials used (kg)}}{\text{mass of product (kg)}}$$

The calculation includes the mass of reactants, reagents, catalysts, and solvents, including water, used for the reaction or for purification. In an ideal situation, no waste is produced and all materials are incorporated into the product, resulting in PMI = 1. Benchmarking analyses conducted by the Pharmaceutical Roundtable in 2008 indicated that solvents make up the majority (56

<sup>46</sup>F. Roschangar, R. A. Sheldon, and C.H. Senanayake, “Overcoming Barriers to Green Chemistry in the Pharmaceutical Industry – the Green Aspiration Level Concept,” *Green Chemistry*, vol. 17, no. 2 (2015).

<sup>47</sup>R.A. Sheldon, “The *E* Factor 25 Years On: The Rise of Green Chemistry and Sustainability,” *Green Chemistry*, vol. 19, no. 1 (2017).

<sup>48</sup>C. Jimenez-Gonzalez, C.S. Ponder, Q.B. Broxterman, and J.B. Manley, “Using the Right Green Yardstick: Why Process Mass Intensity Is Used in the Pharmaceutical Industry To Drive More Sustainable Processes,” *Organic Process Research & Development*, vol. 15, no. 4 (2011).

percent) of the total mass of materials used to manufacture drug ingredients, with water (32 percent) making up much of the remaining mass.<sup>49</sup> The Roundtable uses PMI to compare data from each company on an equivalent basis, starting from commonly available materials. This approach accounts for all steps in the synthesis of a drug ingredient regardless of whether a company performs all steps in-house or outsources some of them.

Although PMI does not account for many possible factors that a full LCA would include, the Pharmaceutical Roundtable reported that PMI correlates well with the life cycle global warming potential and life cycle water use of a portfolio of pharmaceutical chemical processes, and thus can be a convenient surrogate for a more time-consuming and complicated LCA.<sup>50</sup> Further, they report that PMI is a better surrogate for assessing cumulative environmental effects than the *E* factor.

### Chemical selection guides

In addition to common metrics, some sectors have developed guides that companies and others can use to compare the sustainability of materials used in chemical processes. These include solvent selection guides and reagent guides.

Solvent selection guides: Several pharmaceutical companies as well as industry consortia, including the Pharmaceutical Roundtable, have developed or made publicly available solvent selection guides to help chemists make informed solvent choices for use in chemical processes.<sup>51</sup> These guides assess both conventional and newer solvents based on a variety of sustainability criteria, such as life cycle analysis; environmental, health, and safety impacts; recyclability; and regulatory concerns, among others. Several pharmaceutical companies have published multiple iterations of their guides, expanding and updating them as new data and solvents become available. Some guides rank solvents by preference, while others do not give an overall recommendation but rather provide users with additional information to consider in conjunction with relevant process specifications. Many of the published guides attempt to present the data in a simplified manner, for example, by color coding solvents from the most (green) to least (red) sustainable, while still providing access to more detailed assessments in recognition that simple systems may mask the complexity of solvent selection (see fig. 6).

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<sup>49</sup>Jimenez-Gonzalez, Ponder, Broxterman, and Manley, "Using the Right Green Yardstick," 913.

<sup>50</sup>Jimenez-Gonzalez, Ponder, Broxterman, and Manley, "Using the Right Green Yardstick," 915.

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<sup>51</sup>More information about solvents, including access to their solvent selection guide, is available from the Pharmaceutical Roundtable at <https://www.acs.org/content/acs/en/greenchemistry/research-innovation/research-topics/solvents.html> (accessed September 12, 2017).

**Figure 6:** Excerpt from the ACS GCI Pharmaceutical Roundtable solvent selection guide

Substance Information			Scoring Information				
Solvent Class	Solvent Name	CAS Number	Safety	Health	Env (Air)	Env (Water)	Env (Waste)
Acid	ACETIC ACID	64-19-7	3	6	6	3	6
Acid	ACETIC ANHYDRIDE	108-24-7	3	6	6	2	7
Acid	FORMIC ACID	64-18-6	2	6	5	4	7
Acid	METHANE SULPHONIC ACID	75-75-2			6	6	10
Acid	PROPIONIC ACID	79-09-4	2	5	6	4	6
Alcohol	1-BUTANOL	71-36-3	3	5	5	5	3
Alcohol	1-PROPANOL	71-23-8	4	4	6	2	6
Alcohol	2-BUTANOL	78-92-2	4	5	6	3	5
Alcohol	2-METHOXYETHANOL	109-86-4	4	9	5	3	7
Alcohol	BENZYL ALCOHOL	100-51-6	4	3	4	2	4
Alcohol	ETHANOL	64-17-5	4	3	5	1	6
Alcohol	ETHYLENE GLYCOL	107-21-1	3	3	5	1	7
Alcohol	ISOAMYL ALCOHOL	123-51-3	3	4	5	3	4
Alcohol	ISOBUTANOL	78-83-1	3	5	4	3	3
Alcohol	ISOPROPYL ALCOHOL (IPA)	67-63-0	5	5	6	2	6
Alcohol	METHANOL	67-56-1	3	5	6	3	6
Alcohol	T-BUTANOL	75-65-0	3	5	7	2	6

Source: American Chemical Society (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable. | GAO-18-307

The creators of these guides have stated a variety of goals for their development in addition to improving process sustainability. One pharmaceutical company reported that one aim of their guide is to highlight the use of more sustainable solvents including those of limited availability, thereby incentivizing manufacturers to increase supply. The increasing regulation of certain potentially hazardous solvents has also encouraged the development of selection guides. For example, another objective of some guides is to reduce the use of chlorinated solvents, which pharmaceutical companies widely use early in the drug development process. These solvents pose environmental health and safety issues and face a growing legislative burden in some cases. One pharmaceutical company reported a 50 percent decrease in the use of chlorinated solvents after the introduction of a solvent selection guide.

**Reagent guides:** The Pharmaceutical Roundtable and pharmaceutical companies have also released reagent guides with a similar aim of helping scientists to make informed decisions regarding reagent

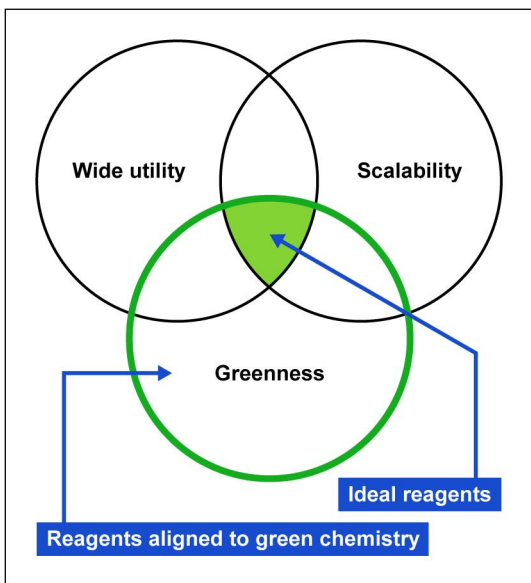
sustainability.<sup>52</sup> The Pharmaceutical Roundtable organizes their guides by selected chemical transformations (e.g., oxidation of an alcohol functional group) and has assembled them together in an interactive online tool.<sup>53</sup> Users can select a transformation to read an overview of various known methods, a list of reagents from which to choose, and a Venn diagram comparing the reagents (see fig. 7). Although the Pharmaceutical Roundtable designed the guides to promote green chemistry, they also included reagents not considered ‘green’ with the aim of creating a more exhaustive reference. The Venn diagram provides a visual depiction of which reagents meet the three criteria of wide utility, scalability, and greenness of the various reagents. In the ethos of the guides, the Pharmaceutical Roundtable encourages scientists to use the guides a part of a holistic approach—to

<sup>52</sup>In this case, a reagent refers to a substance that is added to a mixture to cause a reaction, which we generally refer to as a reactant in this report.

<sup>53</sup>The reagent guides are available at <https://www.reagentguides.com/> (accessed October 20, 2017). The guides are available for use following registration.

consider how reagent selection affects sustainability of the overall process and not just reagent ‘greenness.’

**Figure 7: Example Venn diagram from the ACS GCI Pharmaceutical Roundtable reagent guide**



Source: American Chemical Society (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable. | GAO-18-307

### Third-party certifications and assessment tools

NGOs, federal agencies, and professional associations are also developing methods for measuring and assessing the relative

sustainability of products and processes, including product certification programs and assessment tools. One approach to measure sustainability is the use of third-party certifications. Companies that we surveyed told us that they use third-party certifications to provide independent verification of sustainability that may be attractive to customers. Certification programs examine a range of different sustainability factors for products and processes. Each program sets minimum criteria that products must meet to be certified, including, for example, biodegradability, toxicity, performance, or water and energy usage. Certifying bodies make databases of certified products available online for public access and allow manufacturers to affix certification labels or logos to their products. Certifications are available from federal offices, such as EPA’s Safer Choice or USDA’s BioPreferred programs, from non-profit organizations, such as the Cradle to Cradle Products Innovation Institute and Green Seal, or from private companies, such as UL’s EcoLogo program. See table 2 for examples of certification programs and a summary of the criteria each uses to measure sustainability. For additional information on certification programs, see chapter 6.

**Table 2: Illustrative examples of product certification programs with criteria related to sustainable chemistry**

Certification logo	Certification program and awarding organization	Selected examples of types of products certified	Criteria or standards for certification	Approximate number of products certified
	<b>BioPreferred</b> Department of Agriculture	Lubricants, inks, fertilizers, disposable cutlery, air fresheners, wood stains, and others	Products must meet or exceed a minimum percentage of biobased content based on their product category.	3000
	<b>Cradle to Cradle</b> Cradle to Cradle Products Innovation Institute	Building materials, interior design products, paper and packaging, personal care products, textiles, and others	Products must meet minimum criteria in the use of safer chemicals, reuse of materials, renewable energy use, water stewardship, and social responsibility.	490
 <small>for illustrative purposes only</small>	<b>EcoLogo</b> UL (Underwriters Laboratories)	Building materials, chemicals, plastics, cleaning products, personal care products, office products, electronics, and others	Products must meet minimum criteria on raw materials, energy, manufacturing and operations, health and environment, product performance and use, and product stewardship and innovation. Criteria include prohibiting or restricting harmful chemical ingredients.	6800
	<b>Green Seal</b> Green Seal	Cleaning products, lighting, paper products, personal care products, paints, vehicle maintenance products, and others	Products must meet category-specific environmental and health requirements in processing, ingredients, and packaging as well as performance standards. Standards include prohibiting or restricting harmful chemical ingredients.	6000
	<b>Safer Choice</b> Environmental Protection Agency	Cleaners, paints, odor removers, laundry products, pet care products, and others	Each chemical ingredient in a product must pose the least concern for human and environmental health among chemicals that perform the same function. The product must also meet minimum performance and packaging standards.	2350

Source: GAO analysis of agency and organization documents; United States Department of Agriculture; Cradle to Cradle Products Innovation Institute; UL LLC; GreenSeal; Environmental Protection Agency. | GAO-18-307

Note: USDA defines biobased products as those derived from plants and other renewable agricultural, marine, and forestry materials; 'Cradle to Cradle Certified'™ is a certification mark licensed by the Cradle to Cradle Products Innovation Institute.

Furthermore, manufacturers and formulators can also make use of tools designed to facilitate internal or business-to-business assessments and benchmarking to measure sustainability. For example, Clean Production Action Network, Lowell Center for Sustainable Production, and Pure Strategies developed the Chemical Footprint Project, an assessment tool for companies to measure their progress toward the use of safer chemicals. The tool measures company performance on a 100 point scale based on the company’s chemical management strategy and policies, chemical inventory and data collection practices, measures and goal-setting on sustainability, and public disclosure and verification practices. Another example of an assessment tool is the Higg Index. The index, an industry framework for measuring and evaluating sustainability at the brand, facility, or product level, was developed by the apparel and footwear industry, retailers, brands, suppliers, and other stakeholders working through the Sustainable Apparel Coalition. An internal tool that assesses sustainability across a product life cycle, the index measures a number of factors including energy use, greenhouse gas emissions, waste, water, chemical management, and social impacts, among others. A company can share its index performance score with other companies in its product supply chain. Project staff also aggregate and anonymize the scores so that companies can benchmark their progress against others in the industry and identify areas for improvement. For examples of questions used in the Chemical Footprint Project and Higg Index assessments, see table 3.

**Table 3: Selected questions from the Chemical Footprint Project and Higg Index assessment tools related to sustainable chemistry**

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**Chemical Footprint Project**

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- Does your company have a chemicals policy that aims to avoid chemicals of high concern?
- What chemical information does your company collect from suppliers?
- How does your company assure conformance with your chemicals policy?
- How does your company assess the hazards of chemicals in its products beyond regulatory requirements?
- What information does your company disclose about the chemical ingredients in its products?

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**Higg Index – Facilities Module**

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- Does this facility systematically monitor applicable chemical use regulations on a regular basis to ensure compliance and to identify new or changing compliance requirements?
- Does this facility have a documented inventory of chemicals used to make your products, and the respective supplier for each chemical?
- Does this facility collaborate with brands and chemical suppliers to prioritize and select chemical alternatives assessment for substances of concern and/or restricted substance lists?
- Does this facility restrict chemicals used in manufacturing processes and/or residing in final product that goes beyond a list of regulated chemicals and RSLs?

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Source: Chemical Footprint Project, Higg Index. | GAO-18-307

Note: The Higg Index has separate modules to assess the sustainability of brands, facilities, and products.

### **2.3 Companies vary in which environmental and health factors they consider most important to optimize**

Companies weight various environmental and health factors differently when assessing sustainability. In order to examine these differences in detail, we surveyed 27 chemical companies and asked respondents to indicate the relative importance their company gives

to each of 13 environmental and health factors. Specifically, we presented the factors in pairs (e.g., factor A with factor B) and asked respondents to select the factor in each pair for which they considered it most important to maximize the sustainability benefit, even if that benefit came at the expense of the other factor in the pair. For example, a company might compare 'energy use' with 'water use' and determine that it was more important to their company to maximize the sustainability benefit relative to the 'energy use' of a process even if it resulted in less sustainable use of water. (See app. IV (question 6) for a complete list of response counts for each pair of factors.)

The 13 environmental and health factors we examined in the survey were:

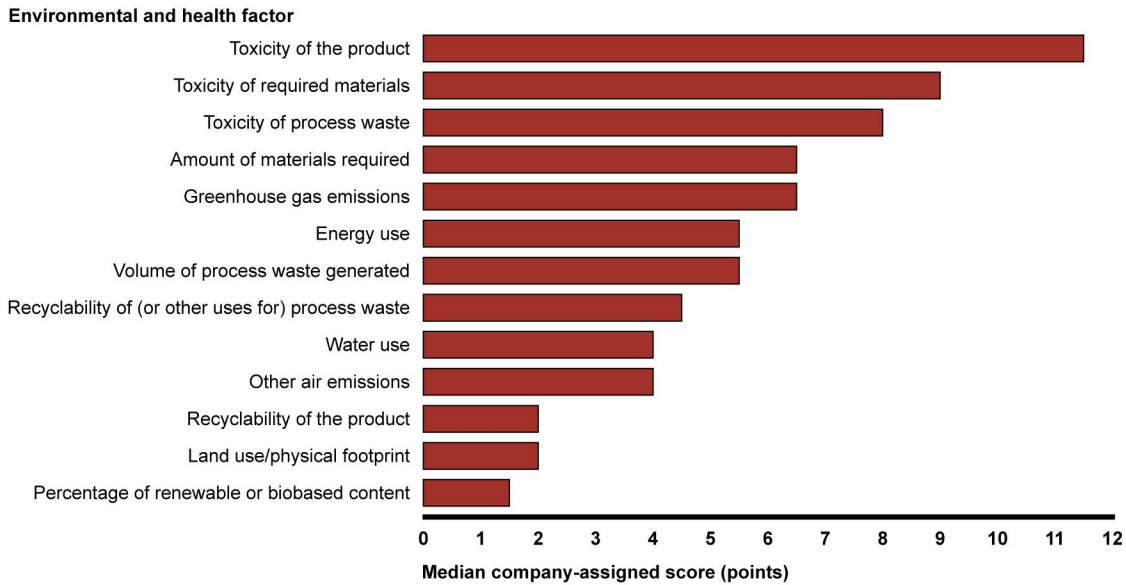
- Percentage of renewable or biobased content
- Amount of materials required
- Toxicity of required materials
- Energy use
- Water use
- Land use/physical footprint

- Greenhouse gas emissions
- Other air emissions
- Volume of process waste generated
- Toxicity of process waste
- Recyclability of (or other uses for) process waste
- Toxicity of the product
- Recyclability of the product

We analyzed the results by assigning 1 point for a factor each time a company chose that factor as more important than another factor and ½ point each time a company chose that factor as equal to another factor. Figure 8 provides median of the company-assigned scores for each factor, with the 13 factors arranged from top to bottom in order based on the median score each factor earned. 'Toxicity of the product' earned the highest median score of 11.5 points (i.e., most important factor) and 'percentage of renewable or biobased content' earned the lowest median score of 1.5 points (i.e., least important factor).

**Figure 8: The median score assigned to each factor by the companies that responded to our survey**

A low score for a given factor indicates that a company considered it more important to maximize the sustainability benefits of other environmental or health factors rather than the given factor. A higher score indicates that a company considered it important to maximize the sustainability benefits of the given factor rather than other factors.



Source: GAO analysis of survey data. | GAO-18-307

In addition to the median scores, we also examined the full range of scores assigned to each factor by the companies that responded to our survey. A narrow range of responses indicates general agreement among the 15 responding companies regarding the importance of that factor compared to the other 12 factors. Such factors include:

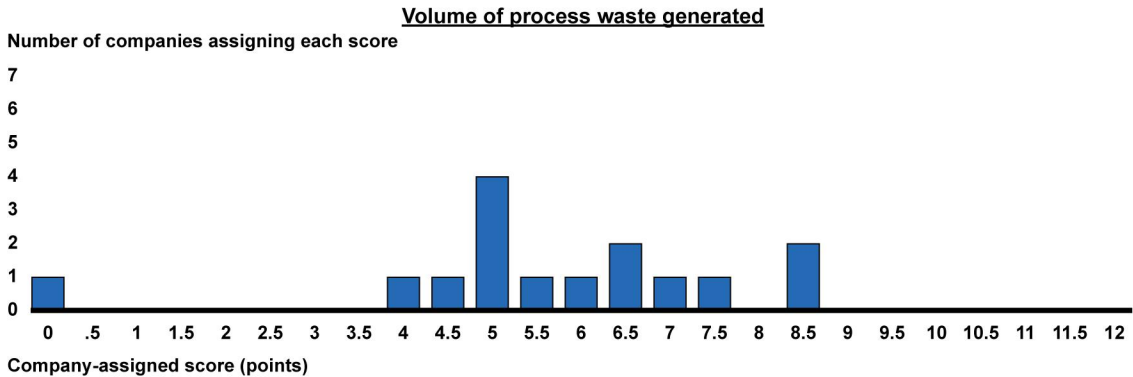
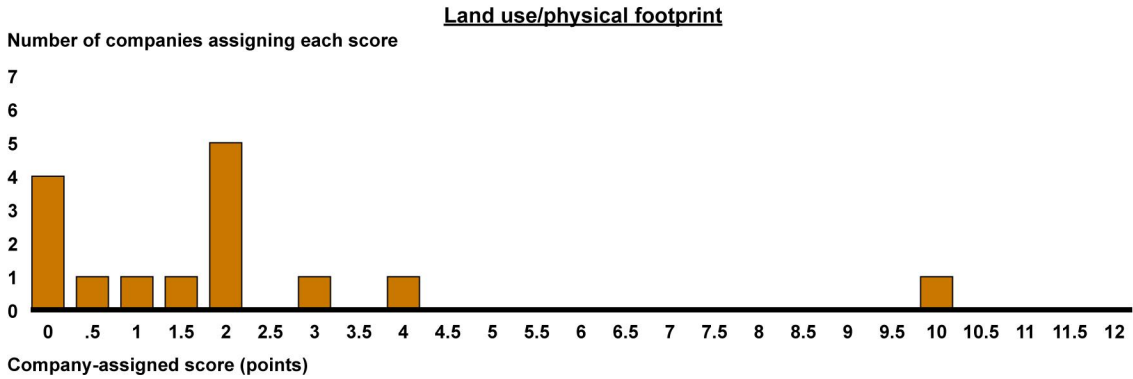
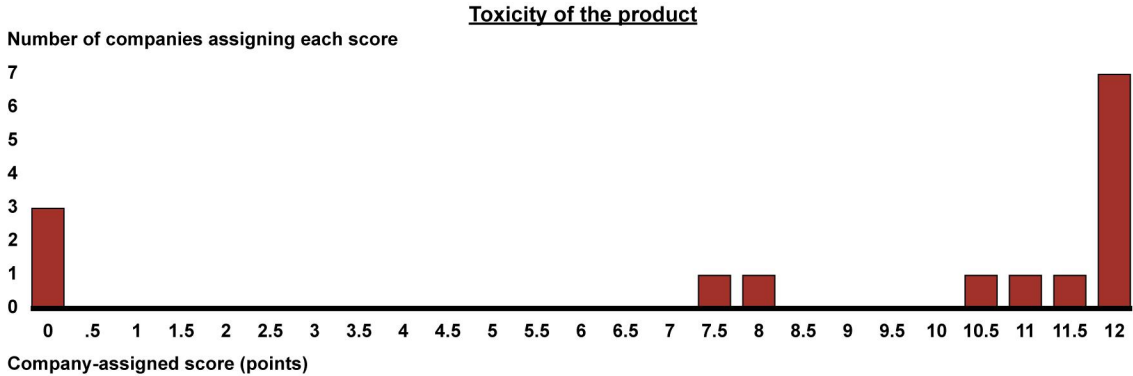
- toxicity of the product,
- volume of process waste generated, and
- land use/physical footprint.

For example, 7 of the responding companies gave ‘toxicity of the product’ a score of 12 points (see fig. 9, top graph), indicating that these companies judged it most important to maximize the sustainability of this factor over any other factor. In fact, 10 of the 15 respondents gave ‘toxicity of the product’ a score of at least 10.5 points. Interestingly, 3 companies gave this factor a score of 0 points, meaning that they never judged it more important (or equally important) to maximize the sustainability of this factor compared to the other factors.



**Figure 9: Company-assigned scores for three environmental or health factors**

A low score for a given factor indicates that a company considered it more important to maximize the sustainability benefits of other environmental or health factors rather than the given factor. A higher score indicates that a company considered it important to maximize the sustainability benefits of the given factor rather than other factors.



Source: GAO analysis of survey data. | GAO-18-307

As shown in figure 9 (middle graph), scores for 'land use/physical footprint' were clustered from 0 to 4 points with the exception of a single score of 10 points. In fact, 12 of the 15 respondents gave 'land use/physical footprint' a score from 0 to 2 points. That clustering of scores at the low end indicates that the responding companies generally agreed that this was a less important factor compared to the other factors, although one company had a very different view of this factor. Similarly, scores for 'volume of process waste generated' (fig. 9, bottom graph) were generally clustered in the middle of the range (from 4 to 8.5 points),

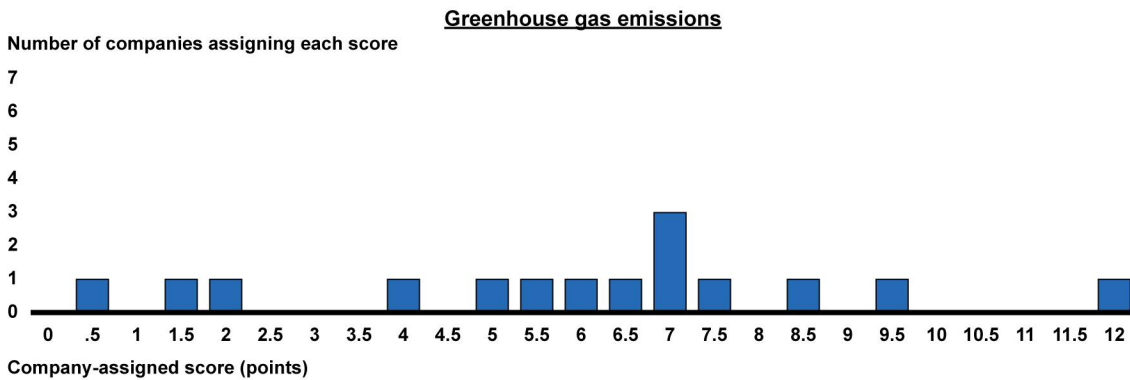
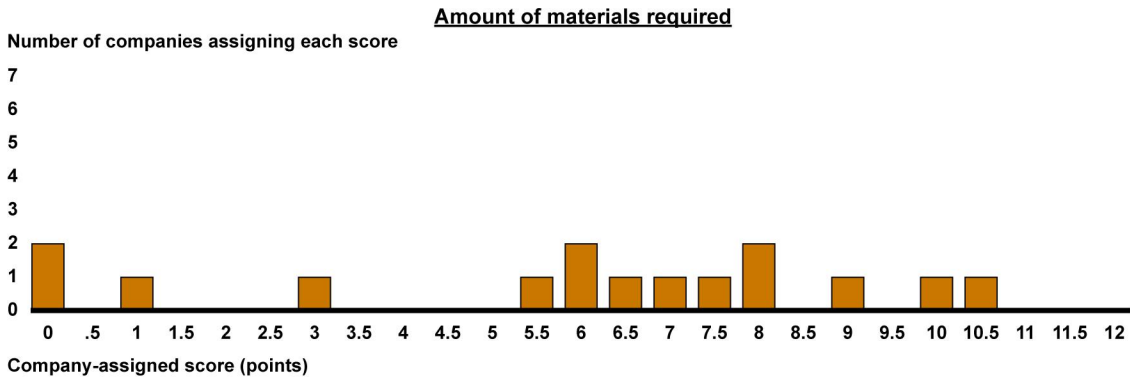
indicating agreement among most respondents that this factor is moderately important to maximize for sustainability compared to the other factors.

In contrast, figure 10 shows two factors that earned an exceptionally wide range of scores, indicating considerable lack of agreement among responding companies regarding their importance:

- amount of materials required and
- greenhouse gas emissions.

**Figure 10: Company-assigned scores for two environmental factors**

A low score for a given factor indicates that a company considered it more important to maximize the sustainability benefits of other environmental or health factors rather than the given factor. A higher score indicates that a company considered it important to maximize the sustainability benefits of the given factor rather than other factors.



Source: GAO analysis of survey data. | GAO-18-307

As shown in figure 10 (top graph), scores for ‘amount of materials required’ ranged from 0 to 10.5 points, with no single score having agreement from more than 2 respondents. The scores for ‘greenhouse gas emissions’ (fig. 10, bottom graph) exhibited an even wider range, from 0.5 to 12 points. From these data, it is clear that the responding companies had a wide range of views regarding the importance of maximizing the sustainability benefits of these two factors.

In addition to determining the individual company scores for each factor, we also added the points across all 15 responding companies to produce a total score for each factor, with a maximum possible score of 180 points.<sup>54</sup> We interpreted factors with higher overall scores to be relatively more important to our survey respondents as a group compared to factors with lower overall scores (see fig. 11).

**Figure 11: The total scores for each factor across all 15 responding companies**



Note: Partial scores (e.g., 84.5) were rounded up to the next whole number.

Our survey respondents represented companies in three industry sectors: chemical manufacturing, pharmaceuticals, and formulators (i.e., makers of personal care and cleaning products). There were some noteworthy differences among sectors in their views on the importance of these 13 factors (see table 4).

<sup>54</sup>Fifteen companies responded to this question on our survey and each company could give a maximum score of 12 to a single factor, so the maximum possible score each factor could earn was 180 points (i.e., 12 points from a given company multiplied by 15 companies).

**Table 4: Sector-specific differences in the importance of various environmental and health factors**

Ranking of importance (out of 13 factors) by each sector based on the total of all company-assigned scores

Factor	Chemical manufacturing sector	Pharmaceutical sector <sup>a</sup>	Formulator sector
Toxicity of the product	1	5	1
Greenhouse gas emissions	3	7	3
Volume of process waste generated	7	4	7/8 (tie)
Recyclability of the product	12	13	6

Source: GAO analysis of survey data. | GAO-18-307

Note: Companies could self-identify with more than one sector.

<sup>a</sup>Responding companies in the pharmaceutical sector ranked “toxicity of required materials” as the most important factor.

## 2.4 Stakeholders cite the importance of a standard definition and metrics for sustainability

The scientific literature and our analysis of the interviews and survey we conducted reveal significant variation in how stakeholders define sustainable chemistry and assess the sustainability of their chemical processes and products. For example, stakeholders in the sustainable chemistry community have reported in the literature that the lack of a clear definition and agreed upon standards for assessing the sustainability of chemical processes and products inhibits the advancement of the goals of sustainable chemistry. According to the Green Chemistry and Commerce Council (GC3), the lack of a clear definition and metrics for measuring green chemistry can lead to confusion in the marketplace. Such misunderstandings occur where innovations that are not truly “green” are mislabeled as such.<sup>55</sup> Moreover, academic

literature on green chemistry in the pharmaceutical industry has described the current green chemistry community as one that is dealing with a plethora of similar metrics without standardized definitions or agreed upon process starting points, inhibiting industry-wide green chemistry integration.<sup>56</sup> It is difficult for consumers, purchasers, policymakers, and even manufacturers to compare the sustainability of one process or product with another when such processes and products are assessed using different metrics that incorporate different factors.

The stakeholders we interviewed also had varying definitions of sustainable chemistry and disagreed about whether it was the same as green chemistry. In addition, the companies that responded to our survey varied significantly with regard to which environmental and health factors they

<sup>55</sup>GC3 is a cross-sectoral business-to-business network of firms working collaboratively to accelerate green chemistry. See J.A. Tickner and M. Becker, “Mainstreaming Green Chemistry: The

Need for Metrics,” *Current Opinion in Green and Sustainable Chemistry*, vol. 1 (2016).

<sup>56</sup>Roschangar, Sheldon, and Senanayake, “Overcoming Barriers to Green Chemistry,” 2015.

considered most important to prioritize when optimizing the sustainability of a chemical process or product, as discussed in section 2.3. Despite this variation of opinion on the importance of different factors, most companies responding to our survey agreed that it would be somewhat or very useful to have a standardized set of factors for assessing sustainability across their industry sector and (to a lesser degree) across the

entire industry. Specifically, most respondents indicated that it would be useful for all companies in their sector to use a common set of factors for assessing sustainability (see table 5). Respondents also indicated that it would be useful for all companies across the entire chemical industry to use common factors, but the responses to that question were not as strong.

**Table 5: Company responses when asked how useful it would be for all companies to use a standard set of factors when assessing sustainability**

	How useful would it be for all companies in your sector to use a standardized set of factors for assessing sustainability?	How useful would it be for all companies across the entire chemical industry to use a standardized set of factors for assessing sustainability?
Very useful	9	5
Somewhat useful	6	7
Slightly useful	1	3
Not useful	0	0
Do not know/cannot judge	1	1

Source: GAO analysis of survey data. | GAO-18-307

In summary, the literature and the results of our interviews and survey indicate that the lack of a standard definition for sustainable chemistry, combined with the lack of

standard ways of measuring or assessing sustainability, hinder the development and adoption of sustainable chemistry technologies.

### 3 Technologies to make catalysts more sustainable

According to one of our experts, catalysts have long been known to provide economic and environmental benefits. For example, most chemical companies conduct significant research and development in catalysis (action of a catalyst), according to this expert. Platinum group metals (PGMs) are the most frequently used catalysts for a variety of industrial applications. However, PGMs are expensive, scarce, generally non-renewable, and susceptible to supply and price fluctuations. Their continued use has raised sustainability concerns among the scientific community. Current research efforts are

directed at finding alternatives to PGMs, such as earth-abundant metals. Metal-free catalysts such as organocatalysts and biocatalysts (catalysts having a biological origin) are other emerging options that are gaining popularity with the pharmaceutical and fine chemicals industries. Due to their potential advantages, the industry has begun to research and implement these options as alternatives to PGMs in some chemical processes. See table 6 for our assessment of alternative catalyst technologies; we provide additional details in the remainder of the chapter.

**Table 6: Summary of assessment of selected catalyst technologies as alternatives to platinum group metals (PGM)**

Technology	Advantages	Disadvantages
<b>Earth-abundant metals</b>	<p>Relatively less costly with fewer supply fluctuations than precious metals.</p> <p>Abundance and relatively low toxicity relaxes the recycling and separation burden, resulting in lowering of operational costs.</p>	<p>Inherent reactivity (tendency to react with other elements) causes issues with its chemical stability, and selectivity, impeding its progress.</p> <p>Limited scope of reaction—compatible with fewer functional groups.</p> <p>Toxicity concerns with some earth-abundant metals remain.</p>
<b>Organocatalysts</b>	<p>Metal-free and low-cost alternative to metal catalysts.</p> <p>Ease of availability and ease of handling (inert towards water and air).</p> <p>Sustainability benefits from the ability to use environmentally friendly solvents such as water or solvent-free conditions.</p> <p>Potential to reduce energy consumption.</p>	<p>May need large amounts for an appreciable increase in reaction rate, especially for industrial use.</p> <p>Difficulties in separation and reuse may limit their industrial applicability.</p> <p>Difficult to recycle.</p>

Technology	Advantages	Disadvantages
<b>Biocatalysts</b>	<p>Some reactions can be performed with higher selectivities, at ambient conditions, and with fewer steps, therefore producing less waste as byproducts and improving sustainability.</p> <p>Biodegradable and derived from renewable resources.</p> <p>Enzymatic polymerization can be used to synthesize commodity plastics, and new environmentally friendly polymers that may not have a traditional chemical route of production.</p> <p>Biocatalytic or enzymatic routes have realized significant improvements in productivity in the development of many life-saving pharmaceutical drugs.</p>	<p>The use of water as a solvent can result in a large amounts of water as a waste product that would typically need treatment leading to additional economic and energy costs.</p> <p>Performing reactions in water instead of organic solvents can reduce the solubility of some reactants.</p> <p>Majority of biocatalysts are unstable, and difficult to recycle and reuse. However, immobilization techniques can help mitigate this problem and make their utilization in biotechnological processes more favorable.</p>

Source: GAO. | GAO-18-307

### 3.1 Earth-abundant metal catalysts

One option for improving the sustainability of catalysts is to replace PGMs with more earth-abundant metals such as nickel, iron, cobalt, titanium, copper, and others. According to a company scientist we interviewed, these metals are not only more abundant in nature but are generally less toxic than PGMs. Nickel is one of the most commonly used earth-abundant metals. It has chemical properties similar to palladium and platinum and is capable of performing many of the same reactions. Iron is the second most abundant metal in earth’s upper crust and is an essential element for human life. For example, the iron complex in hemoglobin (a protein contained in red blood cells) acts like a catalyst that binds to oxygen and helps transport it to the tissues of the body. Cobalt is also an essential metal for humans. It is present in vitamin B12 (cobalamin) and its radioactive form is widely used for medical applications. However, it is gaining traction as a catalyst as well.

Catalysts derived from these metals offer several advantages over PGMs but also have trade-offs that should be considered. These metals are used as catalysts in some key industrial processes and researchers are continuing to seek additional applications. However, despite the recent advances in this field, the industry has generally been slow to replace PGMs for several reasons, including risk aversion and an incomplete understanding of the newer catalytic mechanisms, according to an ACS article.

#### Advantages and disadvantages of earth-abundant metal catalysts

Earth-abundant metal catalysts offer several advantages that could make chemical processes and products more sustainable, including generally lower toxicity, a range of applications, and reduced costs.

Relatively less toxic: Some earth-abundant metal catalysts are relatively nontoxic and environmentally friendly. For example, iron is relatively nontoxic compared to palladium and nickel. Titanium is also considered

nontoxic, and is biocompatible—attractive features for handling and disposal—and thus potentially a sustainable catalyst. Their low toxicity can mitigate the need for the often energy-intensive separation and recycling processes. That is, unlike PGMs, it is often acceptable if a trace amount of an earth-abundant metal such as iron ends up in a final product; this might eliminate costly and time-consuming purification processes.

Range of potential applications: Because earth-abundant metals such as nickel and iron have a wide range of available oxidation states, they are more versatile as catalysts.<sup>57</sup> For example, depending on its oxidation state, iron can be used to either donate or accept electrons in a chemical reaction. Thus, iron catalysts can facilitate a broad range of synthetic transformations. In addition, nickel is reported to be enantioselective for many different reactions, offering the potential for reducing waste by avoiding unwanted byproducts.<sup>58</sup>

Reduced costs: Using earth-abundant metal catalysts such as iron and nickel in place of PGMs can help reduce costs. For example, various iron salts and iron complexes are commercially available on a large scale or are easy to synthesize, thus they are a low cost

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<sup>57</sup>Oxidation state, also called oxidation number, is a number assigned to a particular atom in a molecular entity that represents the relative charge on that atom. For metals, it indicates the total number of electrons that the atom either gains or loses in order to form a chemical bond with another atom.

<sup>58</sup>An enantiomer is one of a pair of molecules which are non-superimposable mirror images of each other. Because enantiomers can have different properties, often one form is preferred over the other. Enantioselectivity is the preferential formation of one enantiomer over another in a chemical reaction, which reduces waste by reducing the amount of the unwanted enantiomer that forms.

alternative to PGMs. Similarly, nickel costs significantly less than PGMs—about 2,000 times less than palladium and 10,000 times less than platinum, according to a published 2014 review by academic researchers.<sup>59</sup> In addition, earth-abundant metals tend to have fewer supply fluctuations than PGMs. Furthermore, because these metals are less expensive and more abundant, it is not as crucial that they be completely recovered for reuse, which may also lift an economic burden.

However, earth-abundant metal catalysts also have trade-offs that must be considered.

Instability and tendency to react with other elements: Earth-abundant metals have not been extensively studied as replacements for PGMs, and only recently have become a significant area of research. Furthermore, progress in earth-abundant metal catalysts has lagged due to challenges associated with their inherent reactivity (tendency to react with other elements), which causes instability as well as difficulties with selectivity and scope. That is, their selectivity is lower relative to PGMs and the scope of the reactions is limited.

Lack of “drop-in” substitutability: Another consideration is that earth-abundant metals cannot simply be interchanged in place of PGMs. New and more expensive ligands, mechanisms, and reaction conditions may be necessary in order to successfully use earth-abundant metals as industrial catalysts.<sup>60</sup> In

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<sup>59</sup>S. Z. Tasker, E. A. Standley, and T. F. Jamison, “Recent Advances in Homogeneous Nickel Catalysis,” *Nature*, vol. 509 (2014).

<sup>60</sup>A ligand is an ion or molecule that binds to a central metal atom to form a complex.



addition, earth-abundant catalysts are compatible with fewer functional groups compared with PGMs.<sup>61</sup>

Toxicity concerns: Some earth-abundant metal catalysts still raise toxicity concerns. For example, despite nickel's presence in natural biological enzyme complexes and metabolic pathways, it may be carcinogenic. Therefore, despite its sustainability advantages over palladium and platinum, it can have significant drawbacks when used to catalyze pharmaceutical reactions. A recent study has reported that the concept of toxic heavy metals and safe nontoxic alternatives based on lighter metals should be re-evaluated.<sup>62</sup> According to the authors of this study, a comparison of the toxicological data indicates that palladium and platinum compounds may be less toxic than previously thought, whereas complexes of nickel and copper, typically assumed to be sustainable alternatives, may possess significant toxicities due to their solubility in water and biological fluids. In addition, a pharmaceutical company official we interviewed told us that earth-abundant metals can be just as toxic as rarer metals.

### Applications of earth-abundant metal catalysts

Earth-abundant metals are used in some key industrial processes such as the Haber-Bosch process, a well-known but highly unsustainable reaction that uses iron as a

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<sup>61</sup>A functional group is a group of atoms that helps define chemical properties of a molecule.

<sup>62</sup>K. S. Egorova and V. P. Ananikov, "Which Metals are Green for Catalysis? Comparison of the Toxicities of Ni, Cu, Fe, Pd, Pt, Rh, and Au Salts," *Angewandte Chemie International Edition*, vol. 55 (2016).

catalyst for ammonia synthesis. More recently, some researchers are exploring iron-catalyzed reduction of carbon dioxide to methane to supplement fossil-fuel sources and reduce greenhouse gas emissions.

Other examples of the use of earth-abundant catalysts include steam reforming, which uses nickel for the production of syngas; the Fischer-Tropsch synthesis, which uses cobalt, iron, and syngas for the production of hydrocarbon chains; and the water-gas shift reaction, which uses iron, chromium, copper, and zinc to convert carbon monoxide to carbon dioxide and hydrogen.<sup>63</sup> More recently, applications of nickel catalysts instead of palladium-based catalysts in the Suzuki-Miyaura cross-coupling demonstrate a more sustainable alternative catalytic route.<sup>64</sup>

Cobalt is very promising in the activation and functionalization of bonds.<sup>65</sup> Specifically, researchers have reported many functionalization strategies that use cobalt to form carbon-hydrogen bonds. These are viable replacements for current PGM catalytic approaches. Activation of the carbon-hydrogen bond can improve the efficiency of a reaction by eliminating certain synthesis

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<sup>63</sup>Syngas (or synthesis gas) is a mixture of hydrogen and carbon monoxide.

<sup>64</sup>Cross-coupling refers to one of the most fundamental reactions in organic synthesis for carbon-carbon bond formation. Cross-coupling reactions combine two molecular fragments and lead to the formation of new bonds. In 2010 the Nobel Prize in chemistry was awarded to Akira Suzuki and two other scientists for the development of palladium-catalyzed cross-coupling reactions. The committee recognized the remarkable impact of this class of reactions on academic research and the development of new drugs and materials.

<sup>65</sup>Carbon-hydrogen bond functionalization is a type of reaction in which a carbon-hydrogen bond is cleaved and replaced with a carbon-X bond where X is usually a carbon-, oxygen-, or nitrogen-containing group such as OH or NH<sub>2</sub>.

steps. It may also be useful in converting renewable feedstocks into high-value chemicals. Cobalt is also used in many other types of chemical reactions.

Titanium complexes are used to catalyze a broad range of transformations including polymerizations.<sup>66</sup> For example, titanium dioxide has become an important photocatalyst in environmental biodecontamination for a large variety of organics, bacteria, viruses, and fungi.<sup>67</sup> Titanium-based catalysts are commercially used on a large scale for the selective catalytic reduction of nitrogen compounds in air pollution control. Researchers have shown that titanium-based catalysts can transform the toxic pollutants of automobile exhaust emissions under ultraviolet irradiation. This property is used to develop a titanium-based photocatalytic converter for automobiles, thereby avoiding the use of PGMs and reducing costs. Recently, Dow Chemical and BASF jointly developed an innovative sustainable hydrogen peroxide-to-propylene-oxide alternate route that uses a titanium-doped catalyst for industrial manufacturing of propylene oxide (among the largest-volume industrial chemicals in the world and used in a vast array of products).<sup>68</sup> This route eliminates most of the organic waste and byproducts and greatly reduces water and energy use.

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<sup>66</sup>Polymerization is the process of connecting monomers (small molecules) into a polymer (a longer chain of repeating units).

<sup>67</sup>A photocatalyst accelerates a photochemical reaction—that is, a chemical reaction caused by light or ultraviolet radiation.

<sup>68</sup>The Dow Chemical Company and BASF jointly won a Presidential Green Chemistry Challenge Award in 2010 for this innovative, environmentally benign production of propylene oxide.

## 3.2 Organocatalysts

Organocatalysts are metal-free small organic molecules that can catalyze many different reactions. Consequently, considerable effort has recently been directed toward the development of these metal-free catalysts. For example, Lelais and MacMillan reported on several significant organic chemical transformations that can be conducted with organocatalysts, providing a valuable complement to other routes.<sup>69</sup> In many cases, organocatalysts are complementary to metal and biocatalysts. That is, they can be used in place of PGMs, earth-abundant metal catalysts, and biocatalysts in some reactions. They are composed of nonmetallic elements such as carbon, hydrogen, nitrogen, oxygen, sulfur, and phosphorous. Among the most common examples are amino acids.<sup>70</sup>

### Advantages and disadvantages of organocatalysts

Organocatalysts offer several sustainability advantages including greater availability, ease of handling, the ability to use a more sustainable approach to solvents, and reduced energy consumption.

#### Ease of availability and handling:

Organocatalysts offer ease of availability, an advantage compared to metals. Another advantage is easy handling; organocatalysts tend to be stable and unreactive in water and air. Thus the demanding reaction conditions

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<sup>69</sup>G. Lelais and D. W. C. MacMillan, "Modern Strategies in Organic Catalysis: The Advent and Development of Iminium Activation," *Aldrichimica ACTA*, vol. 39, no. 3 (2006).

<sup>70</sup>The amino acid known as proline was one of the earliest organocatalysts used.

typically required of metal-catalyzed reactions—such as an inert atmosphere and low temperature—are usually not required with organocatalysts.

Elimination of metal contamination risk:

Organocatalysts eliminate the risk of metal contamination in the final product, which is especially valuable to the pharmaceutical industry.

Compatible with more sustainable solvent

use: Many organocatalysts have been found to work better (e.g., to be more selective or more rapid) in water than in organic solvents. For example, a study by Breslow showed that certain organocatalyzed reactions were accelerated in water.<sup>71</sup> Other researchers have also reported on efforts to develop organocatalyzed reactions with enhanced yield and enantioselectivity. Additionally, some reactions have been successfully demonstrated with organocatalysts under solvent-free conditions. For example, a recent review of advances in sustainable organocatalysis by Branco et al. reported two new catalysts for conducting organocatalytic reactions under neat (solvent-free) conditions.<sup>72</sup> However, these often require a large amount of other substances involved in the reaction, which can present a waste problem similar to organic solvents. (See chapter 4 for more details on alternative solvents.)

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<sup>71</sup>R. Breslow, “Hydrophobic Effects on Simple Organic Reactions in water,” *Accounts of Chemical Research*, vol. 24, no. 6 (1991).

<sup>72</sup>L. C. Branco, A. M. F. Phillips, M. M. Marques, S. Gago, and P. S. Branco, “Recent Advances in Sustainable Organocatalysis,” *INTECH* (2016).

Reduced energy consumption: The use of organocatalysts can reduce energy consumption, which is consistent with one of the 12 Principles—namely, number 6: design for energy efficiency (see app. V).<sup>73</sup>

However, as with all catalysts, organocatalysts also have some disadvantages that must be evaluated against their advantages when choosing the best options for a particular reaction.

Need for large quantities: One disadvantage of organocatalysts is that a large amount may be needed for appreciable increases in reaction rates, especially for industrial use. However, organocatalysts are much cheaper than PGMs so the use of more catalyst may not necessarily translate to higher cost. This can depend on the cost of purification processes, but this tradeoff depends largely on the specifics of each process. Also, research has shown that while decreasing the amount of catalyst may decrease the reaction rate, it can increase stereoselectivity.<sup>74</sup> That is, a slower reaction rate can produce a more uniform product, resulting in less waste.

Difficulties with recycling: Organocatalysts can be challenging to recycle. Because many standard organocatalysts are dissolved in a reaction medium that is typically in the same phase as the reactants, they are difficult to separate and reuse, which can limit their industrial use. However, immobilization

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<sup>73</sup>Branco, Phillips, Marques, Gago, and Branco, “Recent Advances in Sustainable Organocatalysis,” 141.

<sup>74</sup>Stereoselectivity is the preferential formation in a chemical reaction of one stereoisomer over another—stereoisomers are isomers that have the same chemical formula and functional groups but differ in the arrangement of their functional groups in space. Enantiomers are one example of stereoisomers.

techniques are being studied to allow for easier recovery and reuse of organocatalysts.<sup>75</sup> For example, Corma and Garcia have reported silica-bound organocatalysts as recoverable, recyclable catalysts in several organic transformations.<sup>76</sup> Other immobilization methods involve electrostatically attaching the organocatalysts to solid supports; for example, relying on ion pairs to form between the solid support and the catalyst. Another technique involves the use of zeolite supports; this is somewhat analogous to immobilizing the catalyst in a cage.

Unknown toxicity: Organocatalysts are now widely used in polymer synthesis as an alternative to traditional metal-based catalysts, in some cases because of concerns about metal toxicity. However, little is known about the toxicity of most organocatalysts. For example, a recent scientific study attempts to assess whether well-established organocatalysts may present a certain level of cytotoxicity when used to produce FDA-approved polyesters for use in food packaging.<sup>77</sup>

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<sup>75</sup>Immobilization means to restrict mobility in a fixed space. This technique is used for easy separation of the catalyst from the reaction mixture and minimizes the loss of catalyst in the product.

<sup>76</sup>A. Corma and H. Garcia, "Silica-Bound Homogenous Catalysts as Recoverable and Reusable Catalysts in Organic Synthesis," *Advanced Synthesis and Catalysis*, vol. 348, no. 12 (2006).

<sup>77</sup>A. Nachtergaele, O. Coulembier, P. Dubois, M. Helvenstein, P. Duez, B. Blankert, and L. Mespouille, "Organocatalysis Paradigm Revisited: Are Metal-Free Catalysts Really Harmless?" *Biomacromolecules*, vol. 16, no. 2 (2015). Cytotoxic means poisonous to living cells.

### 3.3 Biocatalysts

Biocatalysts, as might be expected from the name, have a biological origin. Typically these compounds are enzymes (natural compounds originating from living cells) or engineered enzymatic complexes (i.e., one part of the enzyme engineered to work somewhat differently than it would in a living organism) that catalyze biochemical reactions in organic substances.<sup>78</sup> While these comprise only 3 percent of the catalyst market (as of 2013), they are the most efficient and sustainable catalysts found in nature. Because biocatalysts come from natural sources, they are biodegradable and renewable.<sup>79</sup>

Biocatalysts have been used for thousands of years—for example, to catalyze fermentation for brewing and baking.<sup>80</sup> They are increasingly being used to improve the sustainability, efficiency, and cost of chemical production. In the past, biocatalysts were used in drug discovery and production. Today they are also being used to make non-medicinal bulk chemicals such as biofuels, surfactants, and plastics. Molecular biology has expanded knowledge of enzymes and pathways and this has led to an increased use

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<sup>78</sup>Enzymes are proteins that speed up a biochemical reaction. That is, they catalyze nearly all of the chemical reactions that occur in biological systems (chemical reactions that take place inside the cells of living things).

<sup>79</sup>In addition to organocatalysts and biocatalysts there are other categories of catalysts such as, nanocatalysts, solid acid catalysts, photocatalysts, and electrocatalysts that are also in use or being researched. However, we did not assess these technologies or their sustainability in this report.

<sup>80</sup>Fermentation is a biochemical process by which organic substances are decomposed by the action of enzymes to provide chemical energy, as in the production of alcohol.

of biocatalyzed chemical processes. Recent research has led to the engineering of both reaction pathways and enzymes to make customizable biocatalysts starting from a natural process. Researchers have used such reaction pathways and biocatalyzed processes to develop or improve the production of many life-saving drugs.

Representatives we interviewed from the pharmaceutical industry told us that biocatalysts are a major area of development and investment for their industry. For example, researchers are exploring ways to replace metals, including PGMs, with enzymatic processes. Industry representatives noted that they have used biocatalysts to perform syntheses that reduce waste and the use of solvents, thus improving the sustainability of their processes.

### Types of biocatalysts

Biocatalysts can take two forms: fermentation and free enzymes.

Fermentation: The earliest form of an industrial biocatalyst was fermentation. Brewing and baking employ this type of biocatalyst, usually in the form of yeast cells. At the outset of industrial fermentation, only natural products—substances that are naturally produced by living organisms—could be produced using biocatalysts, but today scientists are able to engineer cells to allow the production of compounds not traditionally made by an organism. For example, research efforts are underway to develop fermentation pathways to produce vitamins, steroids, solvents, valuable drugs, and polymer precursors.

Free enzymes: Enzymes (proteins) are natural substances that catalyze almost all of the chemical reactions in living organisms. Without enzymes, these reactions would take place at a rate far too slow to sustain life. Several enzymatic reaction pathways have been researched and developed recently for the synthesis of chemical and pharmaceutical products. For example, enzymatic polymerization reactions can be used to synthesize commodity plastics, as well as new environmentally friendly polymers that may not have a traditional chemical synthesis route. For example, lipases (a class of enzymes) have shown industrial potential in polyester synthesis. Polyesters are an abundant organic material in living systems and many compounds in this class have commercial applications, especially in the biomedical field, so a lipase-based polymerization process can help make the chemical industry more sustainable. In addition, Patel and Kharat report that the application of enzyme engineering to the pharmaceutical industry is growing rapidly.<sup>81</sup>

### Advantages and disadvantages of biocatalysts

Biocatalysts offer several advantages compared with PGMs, including easier handling, higher selectivities, and reduced waste and energy use that can make them more cost-effective relative to traditional catalysts.

Easier handling: Unlike many industrial processes using traditional catalysts,

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<sup>81</sup>H. H. Patel and A. R. Kharat, "Comparative Study of Free Enzyme & Immobilized Enzyme on BSA Digestion," *International Journal of Pharmaceutical Sciences and Research*, vol. 3, no. 12 (2012).

biocatalysts can generally be used at or near ambient temperature and pressure. Enzymes can also be used in water, unlike many industrial catalysts, which predominantly require organic solvents.

Higher selectivities: Both forms of biocatalysts—fermentation and enzymes—have higher selectivity than traditional catalysts. This includes high substrate specificity (meaning they only catalyze a specific chemical reaction) as well as stereoselectivity. Both features are important because they make enzymes promising as catalysts. Furthermore, high selectivity yields high purity products.

Reduced waste and energy use: Biocatalysts are also inherently more efficient than other catalysts because they tend to catalyze in one step without need for functional group protection, activation, or deprotection steps that generate more waste and use more energy. Furthermore, they can operate under moderate reaction conditions at near ambient temperature and pressure, thus resulting in reduced energy consumption. As a result, biocatalysts are often more cost effective than synthetic catalysts.

Biodegradable and renewable: Because biocatalysts come from natural sources, they are biodegradable and renewable. Furthermore, new methods and techniques have emerged that can use biocatalyzed processes in the production of a variety of compounds from renewable feedstocks such as biomass.

As with other technologies designed to make chemical processes and products more sustainable, biocatalysts have tradeoffs from both a sustainability and a feasibility

perspective. These include the potential for generating significant quantities of wastewater, limitations with use, and instability, among others.

Potential for large quantities of wastewater: The use of water as a solvent, while it provides some sustainability advantages over the use of organic solvents, can generate large amounts of wastewater. Unless this can be easily recycled, wastewater treatment typically involves additional economic and energy costs. Performing reactions in water instead of organic solvents can also reduce the solubility of some reactants. However, there are methods available to expand the utility of water as a reaction medium under these circumstances. (See chapter 4 for details). In addition, water-based solutions may need a large volume of solvents for product isolation, which minimizes the solvent-related gains of doing the reaction in water.

Limitations with use: Enzymes' high substrate specificity, while generally an advantage as discussed above, can complicate the process of finding a well-suited enzyme to catalyze a particular chemical process. Furthermore, many enzymes are subject to product inhibition—the decrease in rate of reaction brought about by the addition of a substance. Researchers have attempted to solve this problem by forming molecular complexes with the product molecules, so these molecules are not able to inhibit the enzyme.

Instability and difficulties with recovery: Most enzymes are fairly unstable. In addition, they are often hard to recover from the reaction mixture. Thus, industrial applications of enzymes are often constrained by a lack of long-term stability and the challenges

involved in their recovery and reuse. Enzymes are often immobilized to help mitigate these issues and make their use more favorable. Immobilization makes the enzyme easier to handle and easier to separate from the reaction mixture, which lowers the total production cost of enzyme-mediated reactions.

### Applications of biocatalysts

Manufacturing of penicillin: The main starting block for the synthetic production of penicillin is a compound called 6-aminopenicillanic acid. Until the mid-1980s, the conventional chemistry used to produce this compound included environmentally unattractive features such as chlorinated reagents and a reaction temperature of  $-40$  degrees Celsius ( $^{\circ}\text{C}$ ). In contrast, the newer enzymatic process for producing 6-aminopenicillanic acid uses penicillin amidase (an enzyme) in water at  $37^{\circ}\text{C}$ , without the use of chlorinated reagents. Currently the majority of this compound produced on a world-wide basis (more than 10,000 metric tons annually) uses the enzymatic route. A key sustainability advantage of the enzymatic process for the manufacture of 6-aminopenicillanic acid is the avoidance of protecting groups because such steps require additional reagents, use more energy, and generate waste.<sup>82</sup> This also aligns with Principle 8 of the 12 Principles, which calls for minimization or avoidance of such steps (see app. V).

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<sup>82</sup>A protecting group refers to a temporary functional group added during organic synthesis to prevent a portion of a molecule from reacting. While protecting groups play an important role in multistep organic syntheses, they are usually considered undesirable because it adds additional steps to the length of the overall synthesis. They can also have sustainability issues including the use of additional materials and production of additional waste.

Production of adipic acid: Production of adipic acid through an enzymatic route has been demonstrated in the scientific literature.<sup>83</sup> This process can replace conventional synthesis routes that may have sustainability issues. Currently, the large scale manufacture of adipic acid, a commercially important compound used for nylon production, involves a multistep synthesis with several unsustainable features. For example, it requires the use of cyclohexane, which in turn is made from benzene. Benzene is flammable, highly toxic, and carcinogenic material. Furthermore, the production process involves high temperature oxidation steps, and the use of corrosive reagents such as nitric acid. This is subsequently followed by an energy-intensive distillation to recover and recycle the unreacted raw material. In contrast, producing adipic acid via fermentation could significantly improve the sustainability of this process. Researchers Draths and Frost received a Presidential Green Chemistry Challenge Award in 1998 for their development of an alternative synthesis of adipic acid from glucose using fermentation. In this process, glucose is first converted to muconic acid using a single, genetically engineered microbe via a novel biosynthetic pathway that does not exist in nature. Muconic acid is subsequently hydrogenated in a fermentation broth using a platinum catalyst in a pressurized atmosphere of hydrogen at ambient temperature to yield adipic acid. Although the resulting process

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<sup>83</sup>L. C. Webster, P. T. Anastas, and T. C. Williamson, "Environmentally Benign Production of Commodity Chemicals Through Biotechnology: Recent Progress and Future Potential," ACS Symposium Series; American Chemical Society: Washington, DC (1996).

used a PGM catalyst, other sustainability gains were significant.<sup>84</sup>

Production of the drug sitagliptin: Enzymatic processes have been researched in recent years in the pharmaceutical industry as a sustainable and efficient biocatalytic manufacturing route to make certain drugs such as sitagliptin (the active ingredient in Januvia<sup>®</sup>, a type 2 diabetes drug). The multistep manufacturing route used several complex reagents and solvents, high pressure hydrogenation reaction requiring expensive specialized equipment and a rhodium-based catalyst, and a yield-reducing crystallization

step (see fig. 12).<sup>85</sup> In 2010, Merck and Codexis received a Presidential Green Chemistry Challenge Award for developing a more sustainable biocatalytic manufacturing process for sitagliptin using a transaminase enzyme.<sup>86</sup> This approach eliminates several unsustainable reaction steps to provide high purity sitagliptin directly, followed by a phosphate salt formation step to provide sitagliptin phosphate. The reported benefits of this process include a significant improvement in productivity by 56 percent with the existing equipment, a 10–13 percent increase in percentage yield, and a 19 percent reduction in overall waste.

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<sup>84</sup>According to one of our experts, Draths and Frost's fermentation process is not used commercially, mainly because significant amounts of petroleum-derived adipic acid are produced overseas.

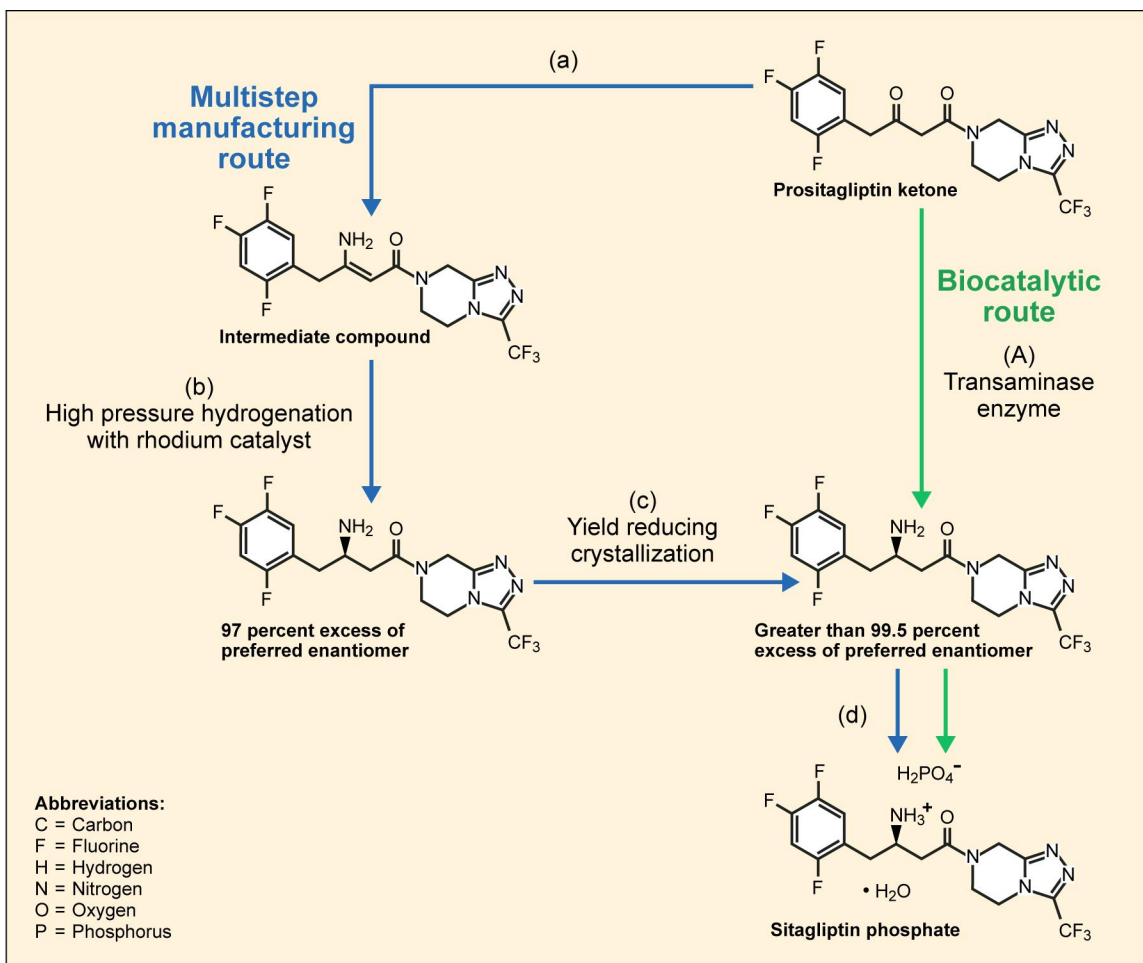
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<sup>85</sup>Hydrogenation is a chemical reaction in which hydrogen atoms add to carbon-carbon multiple bonds. In order for the reaction to proceed at a practical rate, a catalyst is almost always needed.

<sup>86</sup>Merck & Co., Inc. and Codexis, Inc. jointly won a Presidential Green Chemistry Challenge Award in 2010 for the greener manufacturing of sitagliptin enabled by a transaminase enzyme.



**Figure 12:** Conventional and biocatalytic routes for manufacturing sitagliptin (the active ingredient in Januvia®, a type 2 diabetes drug)



Source: GAO. | GAO-18-307

## 4 Technologies to make solvent use more sustainable

There is not a single universal green or sustainable solvent; chemical processes or other solvent applications have different specifications and therefore may require different alternative solvent options. Solvents constitute a large portion of the total volume of chemicals used in industrial processes and thus have an influence on the overall environmental impact of those processes. Chemists consider a number of key properties when selecting a solvent for a particular application or seeking alternative solvent technologies. An overall assessment of the environmental impact of a solvent can include factors from both an environmental health

and safety perspective and a life cycle perspective. Several commonly used solvents are problematic from a sustainability or regulatory perspective but have been particularly challenging to replace. However, there are more sustainable solvent technologies available to replace some conventional solvents, including a variety of biobased solvents; non-VOC solvents such as water, supercritical carbon dioxide, and ionic liquids; and solvent-free or reduced-solvent technologies. Table 7 summarizes our assessment of these technologies; we provide additional details in the remainder of the chapter.

**Table 7: Summary of assessment of selected alternative solvent technologies**

Technology		Advantages	Disadvantages
<b>Biobased solvents (volatile organic compounds (VOC) or non-VOC)</b>		<ul style="list-style-type: none"> <li>Sourced from renewable raw materials</li> <li>Can be biodegradable</li> <li>Can be safer or less toxic than petroleum-derived solvents</li> <li>Some can directly replace conventional solvents</li> </ul>	<ul style="list-style-type: none"> <li>Some pose the same inherent risks as other VOCs such as atmospheric pollution, flammability, and user exposure</li> <li>Can be more expensive than other materials</li> <li>Can have variability in supply and quality control of feedstocks</li> <li>Challenges associated with building new processes at commercial scale</li> </ul>
<b>Non- VOC solvents</b>	<b>Water</b>	<ul style="list-style-type: none"> <li>Environmentally benign, nontoxic, and nonflammable</li> <li>Abundant and inexpensive</li> <li>Some reactions proceed faster in water</li> </ul>	<ul style="list-style-type: none"> <li>Many chemicals are not soluble in water</li> <li>Reaction with water can compete with the desired reaction</li> <li>Conventional solvents may be required to separate reaction products from water</li> <li>Removing unwanted byproducts from water for recycling can be energy-intensive</li> </ul>

Technology	Advantages	Disadvantages
<b>Supercritical carbon dioxide</b>	<ul style="list-style-type: none"> <li>Environmentally benign, nontoxic and nonflammable</li> <li>Inexpensive</li> <li>Supercritical temperature and pressure are relatively mild compared to some other substances</li> <li>Tunable (adjustable) solvent properties</li> <li>Ease of separation from the reaction product</li> </ul>	<ul style="list-style-type: none"> <li>Requires elevated pressure</li> <li>Requires specialized equipment and additional safety precautions</li> <li>May not be a suitable solvent for reactions involving polar or high molecular weight chemicals</li> </ul>
<b>Ionic liquids</b>	<ul style="list-style-type: none"> <li>Low volatility</li> <li>Tunable solvent properties</li> </ul>	<ul style="list-style-type: none"> <li>Concerns over toxicity and environmental persistence and footprint</li> <li>Can be complicated or costly to make</li> </ul>
<b>Solvent-free or reduced-solvent</b>	<ul style="list-style-type: none"> <li>Reduces solvent use and waste</li> <li>Decreases the need to recycle or dispose of used solvents</li> </ul>	<ul style="list-style-type: none"> <li>Solvents may still be required for product purification</li> <li>Technical challenges to achieving solvent-free reactions on an industrial scale</li> </ul>

Source: GAO. | GAO-18-307

## 4.1 Key properties of solvents

There are a number of properties that influence which solvent to select for a particular use. For example, the polarity of a solvent—that is, the distribution of electrical charges within the solvent molecules—significantly affects how that solvent behaves. Depending on its chemical structure, a solvent can be classified as polar or nonpolar.<sup>87</sup> Electrons are not symmetrically distributed in molecules of polar compounds, resulting in partially positively and negatively charged regions.<sup>88</sup> In contrast, molecules of nonpolar

compounds have a relatively symmetrical distribution of electrons. Compounds can also be ionic—consisting of positively and negatively charged component(s), or ions, held together by electrostatic forces.<sup>89</sup> The concept of “like dissolves like” is a simplified rule for understanding solvents and solubility. For example, polar solvents tend to dissolve other polar compounds or ionic compounds (e.g., salts), while nonpolar solvents tend to dissolve other nonpolar molecules (e.g., fats and oils).<sup>90</sup> The term miscible describes two liquids that are completely soluble in each other. For example ethanol and water, which are both polar, are miscible, whereas

<sup>87</sup> Although polarity is a property often used to predict the solubility of compounds, it can be difficult to quantify. Classifying solvents as polar or nonpolar is a simplification of the concept.

<sup>88</sup> Electrons are subatomic particles that have a negative electric charge.

<sup>89</sup> Table salt, for example, is an ionic compound called sodium chloride, consisting of positively charged sodium ions and a negatively charged chloride ions.

<sup>90</sup> Hydrocarbons are compounds made up of only hydrogen and carbon atoms.

hydrocarbons and water are not. Solvents and other compounds can also be classified as hydrophilic (having affinity for water, e.g., miscible with or soluble in water); hydrophobic (lacking affinity for water, e.g., not miscible with or soluble in water); or amphiphilic (molecules that contain both hydrophobic and hydrophilic regions, such as surfactants).

Solvents can also be either protic or aprotic. Protic solvents contain hydrogen atoms bound to an electron-attracting atom such as an oxygen or nitrogen atom. These hydrogen atoms allow the solvent and solute molecules to form hydrogen bonds—a strong interaction between or within molecules. Although aprotic solvents can also contain hydrogen atoms, those atoms are not bound to electron-attracting atoms such as oxygen or nitrogen and therefore do not participate in hydrogen bonding. Solvents that are both quite polar and aprotic are called dipolar aprotic.

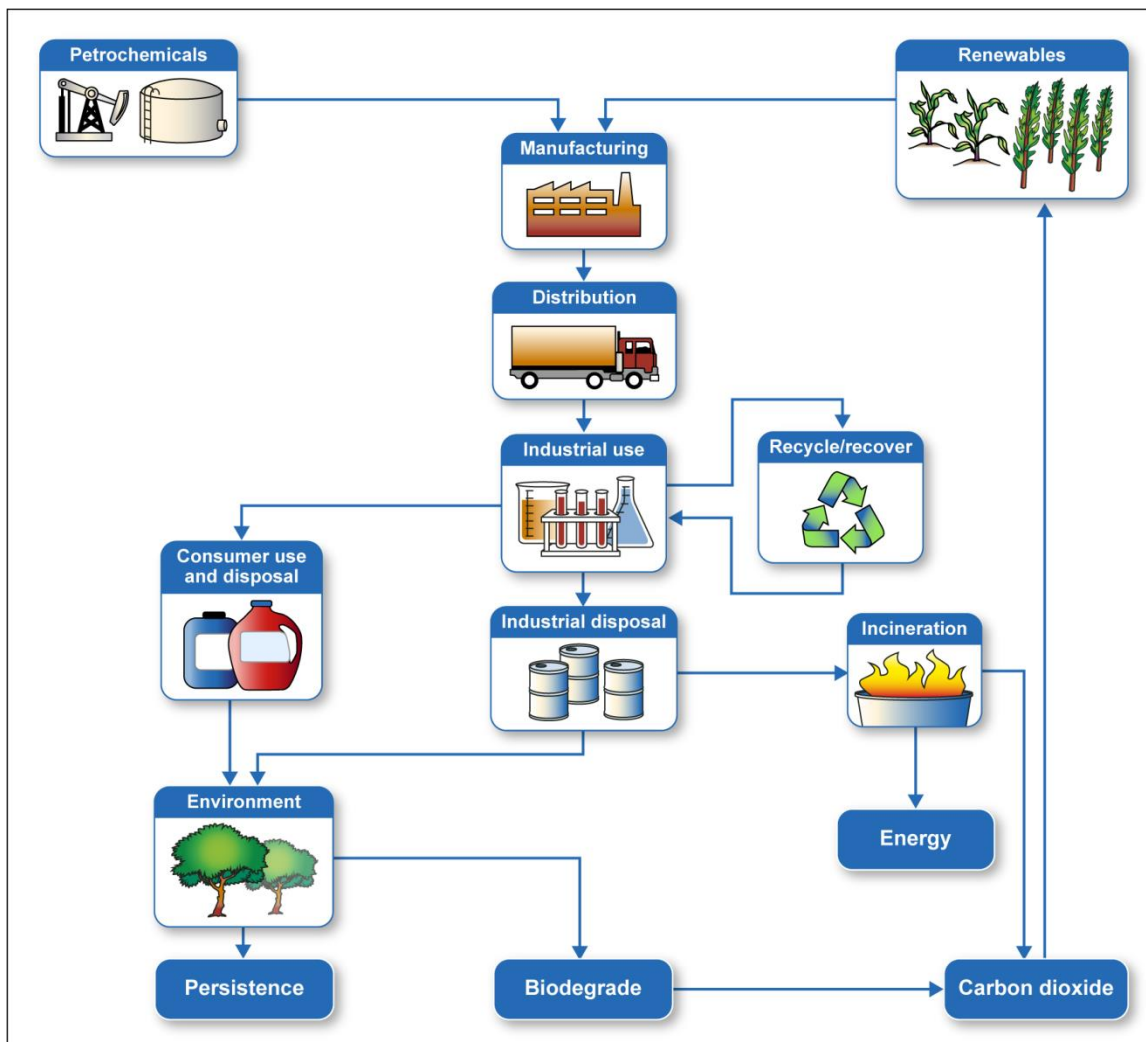
## 4.2 Sustainability challenges of solvents

The environmental impact of a solvent can be assessed using an environmental health and safety method or a life cycle method, the results of which can be combined into an overall assessment. The goal of the environmental health and safety assessment method is to identify potential hazards of solvents. An environmental health and safety assessment considers factors such as the flammability, toxicity, and environmental persistence of the solvent. The LCA method evaluates the environmental impact of the solvent through all the stages of its life cycle, including production, use, and potential recycling or disposal (see chapter 1 for a more detailed discussion of LCA). An LCA considers factors such as nonrenewable resource depletion, emissions associated with the incineration of solvent waste, and the energy required for solvent recovery and recycling (see fig. 13).<sup>91</sup> The combination of both assessments can help chemists to select solvents with the least environmental impact. These assessments can also be applied to new solvent technologies, some of which are discussed later in this chapter.

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<sup>91</sup>Although we do not discuss it in depth in this report, solvent recycling can make an important contribution to the life cycle assessment of a process.

**Figure 13: The solvent life cycle**



Source: Adapted with permission from Clark and Tavener. | GAO-18-307

Note: Adapted with permission from J. H. Clark and S. J. Tavener, "Alternative Solvents: Shades of Green," *Organic Process Research & Development*, vol. 11 (2007). Copyright 2007 American Chemical Society.

There are several classes of solvents that are problematic from a sustainability or regulatory perspective but that are particularly challenging to replace. For example, halogenated compounds such as chlorinated solvents and dipolar aprotic solvents, among others lack sufficient

replacement options.<sup>92</sup> In December 2016, EPA released the list of the first 10 chemicals for assessment under the amended TSCA regulations; the list includes dipolar aprotic and halogenated solvents (see text box below).<sup>93</sup>

<sup>92</sup>Halogenated compounds contain one or more atoms from the halogen group such as fluorine, chlorine, or bromine.

<sup>93</sup>81 Fed. Reg. 91,927 (December 19, 2016).

### Several regulations in the United States are relevant to solvent use in the chemical industry

In the United States, the Toxic Substances Control Act (TSCA) and the Clean Air Act both have implications for solvent use, as do FDA regulations and guidance. The Clean Air Act requires EPA to regulate hazardous air pollutants—chemicals known or suspected to cause cancer or other serious health effects, such as reproductive effects or birth defects, or adverse environmental effects—from various industrial facilities. EPA is working with state, local, and tribal governments to reduce air emissions of 187 hazardous air pollutants, including some commonly used solvents. The Clean Air Act also requires EPA to manage ozone-depleting substances, which also includes some solvents. FDA has regulations and guidance regarding solvents. FDA regulates additives in food and beverage, including some residual solvents, as well as the use of certain solvents as ingredients in cosmetics. FDA also provides guidance to industry on residual solvents in pharmaceuticals.

TSCA as amended by the Frank R. Lautenberg Chemical Safety for the 21<sup>st</sup> Century act requires that EPA now systematically prioritize and assess existing chemical substances and manage identified risks. In December 2016, EPA published an initial list of 10 chemical substances that will be subject to assessment. Seven out of those 10 chemical substances could be classified as solvents; 1,4-dioxane, 1-bromopropane, carbon tetrachloride, dichloromethane, N-methylpyrrolidone, trichloroethylene, and tetrachloroethylene. TSCA requires that EPA choose the first 10 chemical substances from the list of 90 chemical substances on the 2014 update of the TSCA Work Plan for Chemical Assessments. TSCA Work Plan chemicals were selected based on their hazard and potential exposure, as well as other considerations such as persistence and bioaccumulation.

Source: GAO analysis of scientific literature and agency documents. | GAO-18-307

Chlorinated solvents, such as dichloromethane and chloroform, are toxic to humans and pose risks to the environment. While these solvents are widely used, some in the industry are making efforts to reduce their use. A recent study reported the atmospheric concentration of dichloromethane—an ozone-depleting substance—is increasing rapidly, and that continued growth of dichloromethane could delay recovery of the ozone layer.<sup>94</sup> The authors note that it is probable that demand for dichloromethane for a number of applications is relatively high in developing countries such as India. Disposal of these solvents can also be challenging or costly. For example, the low flammability of

dichloromethane hinders incineration. Due to these issues, reducing the use of dichloromethane is a goal of many green chemistry programs within the pharmaceutical industry. Two pharmaceutical companies told us that they track use of chlorinated solvents as a percentage of total solvent use as a sustainability metric. One of those companies reported that dichloromethane has decreased from 35 percent to 10 percent of total solvent use since they started tracking in 2012.

Chemists commonly use several dipolar aprotic solvents, however there are concerns regarding the associated toxicity and potential negative environmental impact of these solvents. Commonly used dipolar aprotic solvents include dimethylformamide, dimethylacetamide, and N-methylpyrrolidone. However, these solvents are designated as reproductive toxins and

<sup>94</sup>R. Hossaini, M. P. Chipperfield, S. A. Montzka, A. A. Leeson, S. S. Dhomse, and J. A. Pyle, "The Increasing Threat to Stratospheric Ozone from Dichloromethane," *Nature Communications*, vol. 8 (2017).

included on the European Union's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) substances of very high concern candidate list.<sup>95</sup> Dipolar aprotic solvents are difficult to remove from a reaction mixture by distillation and therefore are usually extracted into water instead. Separation from water is also difficult and can be energy-intensive or costly. Release of wastewater contaminated with these solvents presents environmental challenges.

Finding more sustainable replacements for dipolar aprotic solvents has been a challenge; however, researchers have reported the use of several alternatives. Dipolar aprotic solvents are particularly useful for certain reactions. For example, nucleophilic substitution reactions—a common type of reaction used in the pharmaceutical industry—can be up to 100,000 times faster in dipolar aprotic solvents as opposed to protic solvents. According to one study, a survey of solvent usage in papers published in the journal *Organic Processes Research and Development* from the years 1997-2012 found that close to 50 percent of the usage of dimethylformamide, dimethylacetamide, *N*-methylpyrrolidone, and dimethyl sulfoxide was in nucleophilic substitution reactions.<sup>96</sup> One expert told us that currently there are not good replacements for these solvents. However, the study that conducted the

survey cited successful examples of this type of reaction in more sustainable solvents, including ethanol and 2-methyltetrahydrofuran (we discuss these solvents in more detail later in this chapter). Researchers have also recently demonstrated this type of reaction in water under mild conditions through the use of micellar catalysis, which we discuss later in this chapter.<sup>97</sup> Other potential alternatives for dipolar aprotic solvents include organic carbonates and biobased cyrene. However, one expert told us that neither of these substitutes is currently widely employed.

### 4.3 More sustainable solvent technologies

We assessed three general classes of more sustainable solvent technologies: (1) biobased solvents (VOC or non-VOC)—that is, solvents produced from renewable rather than petrochemical resources, (2) non-VOC solvents, and (3) solvent-free or reduced-solvent strategies to decrease the volume of solvents required for a process.<sup>98</sup>

#### 4.3.1 Biobased solvents

The benefits and challenges of biobased solvents—which can provide alternatives to petroleum-derived solvents as either a direct replacement or a substitute—vary based on

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<sup>95</sup>The substances of very high concern candidate list aims to ensure that the included hazardous chemicals are progressively replaced by less dangerous substances or technologies where technically and economically feasible alternatives are available.

<sup>96</sup>C. P. Ashcroft, P. J. Dunn, J. D. Hayler, and A. S. Wells, "Survey of Solvent Usage in Papers Published in *Organic Process Research & Development* 1997-2012," *Organic Process Research & Development*, vol. 19 (2015).

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<sup>97</sup>N. A. Isley, R. T. H. Linstadt, S. M. Kelly, F. Gallou, and B. H. Lipshutz, "Nucleophilic Aromatic Substitution Reactions in Water Enabled by Micellar Catalysis," *Organic Letters*, vol. 17 (2015).

<sup>98</sup>We identified several other more sustainable solvent technologies that are in use or under investigation, including eutectic mixtures, fluorosolvents, liquid polymers, and switchable solvent systems. However, we did not assess these technologies in this report.

the nature of each solvent. Biobased solvents (whether VOC or non-VOC) are sourced from renewable raw materials such as forestry or agricultural materials. According to a 2013 report by the International Energy Agency and others, use of biobased feedstocks for chemical production is a potential game changer in terms of reducing greenhouse gas emissions.<sup>99</sup> The three main benefits are: (1) reduced dependency on fossil fuels, (2) absorption of carbon dioxide while the feedstock source is growing, and (3) the feedstock source is renewable and therefore may not experience the same price volatility in the future as fossil fuels. However, any reduction in greenhouse gas emissions must be weighed against the energy requirements for biobased production, according to the report. According to one expert, studies have shown that the manufacture of many, but not all, organic solvents from biomass may be more environmentally damaging or energy intensive than their manufacture from petroleum.

Certain biobased solvents may be biodegradable or may be safer or less toxic than petroleum-derived solvents. However, many biobased solvents are VOCs and therefore maintain the inherent risks of VOCs including atmospheric pollution, flammability, and user exposure. Some are toxic or have other negative environmental health and safety properties. Some biobased solvents can serve as a direct replacement for conventional solvents without having to alter the equipment or process. Other biobased

solvents are not direct replacements but may lead to opportunities for new technologies. One company told us that new biobased materials are frequently more expensive than other materials, which presents a challenge to their use. There is ongoing research in academia and industry examining chemical processes that may be suitable for these new solvents.

We identified several examples of biobased solvents and the associated benefits and challenges they may face in industrial applications. Although a variety of solvents and solvent classes can be renewably sourced, current technology does not offer direct replacements for all conventional solvents. Because biobased raw materials, such as cellulose and starch, contain oxygen atoms, most biobased solvents are oxygen-containing compounds such as alcohols, esters, and ethers. Other solvents, such as certain hydrocarbons, can potentially be produced from cellulose and lignocellulose materials. Chlorinated solvents cannot currently be produced from biobased raw materials. However, as previously discussed, many in the industry are already working to reduce the use of this class of highly regulated solvents in part due to their environmental and health hazards. We discuss several biobased solvents below.

### Ethanol

Ethanol is a conventional solvent that can be renewably sourced for use in several industrial applications. Ethanol is an inexpensive product of fermentation of starch crops or can be produced from cellulose from waste materials. Ethanol is biodegradable, less toxic than some other solvents, and miscible with both water and many organic

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<sup>99</sup>International Energy Agency (IEA), International Council of Chemical Associations, and Dechema Gesellschaft für Chemische Technik und Biotechnologie e. V., *Technology Roadmap: Energy and GHG Reductions in the Chemical Industry via Catalytic Processes*, (Paris, France: IEA Publications, 2013).



solvents. However, ethanol is a volatile solvent and has a relatively low flash point, which can present hazards to users.<sup>100</sup> A manufacturer of cellulosic ethanol cited several advantages, including that it is sourced from a non-food feedstock and its production uses less water compared to the conventional production of ethanol. They also told us that production of cellulosic ethanol as a replacement solvent faces challenges, including building a supply chain, variability in the supply and quality of agricultural feedstocks, scalability, public awareness, and public policy uncertainty. Ethanol is commonly used in products such as scents, flavors, and medicines. It is also conventionally used as a solvent in chemical processes including both reaction and separation applications. Ethanol can also serve as a solvent in formulated products. For example, DuPont and Procter & Gamble announced a partnership in 2014 to use ethanol derived from cellulose in Tide® Cold Water laundry detergent.

### 1,3-Propanediol

1,3-Propanediol is another biobased solvent used in formulated products. A joint team from DuPont and Genencor International, Inc. won a Presidential Green Chemistry Challenge Award in 2003 for the microbial production of 1,3-propanediol from glucose sourced from renewable cornstarch (see text box below).<sup>101</sup>

<sup>100</sup>The flash point is the lowest temperature at which sufficient vapor of a volatile liquid has collected in order to form an ignitable mixture with air.

<sup>101</sup>For a full list of Presidential Green Chemistry Challenge Awards from 1996-2016, see [https://www.epa.gov/sites/production/files/2016-10/documents/award\\_recipients\\_1996\\_2016.pdf](https://www.epa.gov/sites/production/files/2016-10/documents/award_recipients_1996_2016.pdf), accessed August 1, 2016.

Representatives from a chemical manufacturer told us that in addition to being sustainably and renewably sourced, 1,3-propanediol is nontoxic and safe for food. They also mentioned that it is a USDA Certified Biobased Product and that there is customer and consumer value in biobased alternatives. However, they also mentioned that building new processes at commercial scale can be expensive and high-risk. 1,3-Propanediol can be used as a solvent in personal care products as well as household cleaning products such as liquid laundry or hand detergents, dish detergent, hard surface cleaners, glass cleaners, and carpet and rug cleaners.

#### **Presidential Green Chemistry Challenge Award for the Microbial Production of 1,3-Propanediol**

In addition to its use as a biobased solvent, 1,3-propanediol is a building block for other chemical products. According to the Presidential Green Chemistry Challenge Award summary for this technology, for more than 50 years, scientists recognized the performance benefits of polyesters produced with 1,3-propanediol; however, the high cost of manufacturing the ingredient using petroleum feedstock and traditional chemistry kept it from the marketplace. The microbial process is both less expensive and more productive than the traditional chemical process. In terms of sustainability, the microbial process allowed replacement of a petroleum feedstock and increased both the energy efficiency and safety of the manufacturing process. Polymers containing 1,3-propanediol are used in a variety of applications including apparel and upholstery. (For more information on the Presidential Green Chemistry Challenge Awards, see chapter 6.)

Source: GAO analysis of EPA documents. | GAO-18-307

## Glycerol

Biobased glycerol, produced from vegetable oils or as a byproduct of the biodiesel industry, and its derivatives can be used as solvents in biocatalysis, among other applications.<sup>102</sup> Glycerol is inexpensive, renewable, nontoxic, and nonflammable. Glycerol is available in a variety of grades based on the level of purity. Crude glycerol is both the least expensive and the most environmentally-friendly grade because it requires the least amount of purification to produce. Glycerol is a polar solvent and has been shown to increase the rate of some organic reactions. However, it is not a good solvent for hydrophobic compounds or for certain gases including hydrogen, oxygen, and carbon dioxide. Glycerol is also highly viscous, which can be a drawback for certain chemical processes.<sup>103</sup> The price of biobased glycerol is tied to fluctuations in the biodiesel market, which could affect its adoption as a solvent by the chemical industry. Researchers have demonstrated the use of biobased glycerol as a medium for a variety of reactions, including as a substitute for dipolar aprotic solvents. Glycerol and several derivatives show promise as a reaction medium for biocatalysis among a variety of other applications. Glycerol carbonate, for example, is an ingredient in personal care products. However, the synthesis required to make glycerol derivatives remains an issue from a sustainability perspective.

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<sup>102</sup>A derivative of a chemical is another chemical that is structurally similar to or made from it. See chapter 3 for more details on biocatalysis.

<sup>103</sup>A viscous liquid is resistant to flow, meaning it has a thick consistency. Molasses is a classic example of viscous liquid.

## Methyl soyate

Methyl soyate is a type of biodiesel used industrially as a cleaning and degreasing solvent. Methyl soyate is produced from methanol and soybean oil—the predominant seed oil crop in the United States. Methyl soyate is nontoxic, nonhazardous, and biodegradable. Methyl soyate evaporates slowly and is not considered a hazardous air pollutant or an ozone-depleting substance; however if used alone it can leave behind a residue which is a drawback in certain applications. In cleaning formulations, use of a more volatile co-solvent such as ethyl lactate can mitigate this drawback. Methyl soyate and ethyl lactate blends can replace chlorinated and other petroleum-derived solvents in applications such as paint strippers, printing ink cleaners, and graffiti removers. Other potential solvent applications of methyl soyate include household and industrial cleaners, paints, and oil spill cleanup. For extraction applications, the distribution behavior of various substances in methyl soyate in liquid-liquid extraction processes with water has been shown to be comparable to that of conventional solvent-water systems.<sup>104</sup>

## Ethyl lactate

Lactate esters such as ethyl lactate are another class of biobased solvents with a variety of applications. The parent compound for this class, lactic acid, is produced via fermentation of a variety of carbohydrates, such as corn starch, sugar beets, sugarcane,

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<sup>104</sup>Liquid-liquid extraction is a technique to transfer a dissolved substance from one liquid phase to another (immiscible or partially miscible) liquid phase in contact with it and in which it is more soluble.

or wheat. Ethyl lactate is produced through the reaction of ethanol and lactic acid in a low-cost process with water as the only byproduct. Lactate esters are generally biodegradable or recyclable and not corrosive, carcinogenic, or ozone-depleting. In addition to the environmental advantages associated with lactate esters, as a solvent ethyl lactate is compatible with water, miscible with organic compounds, and has a relatively high boiling point (154 °C). Ethyl lactate is a possible substitute for halogenated solvents. Industrially, ethyl lactate is used for several applications including as a solvent in the coatings and inks industry and as a biodegradable cleaning fluid. It has also been used as a reaction medium, although to a lesser extent than some other biobased solvents.

### 2-Methyltetrahydrofuran

2-Methyltetrahydrofuran is a biobased solvent with growing use in industry. It can be produced from renewable raw materials including agricultural waste such as corncobs. This solvent has a number of properties in common with some conventional solvents such as tetrahydrofuran. However, 2-methyltetrahydrofuran is less miscible with water than tetrahydrofuran, thus facilitating separation from water and reducing waste in some cases. 2-Methyltetrahydrofuran suffers from some of the same drawbacks as related solvents. For example, 2-methyltetrahydrofuran is susceptible to the formation of peroxides when exposed to air if no stabilizer is present which can be explosive under certain circumstances. In preliminary toxicological studies, 2-methyltetrahydrofuran was not associated

with genotoxicity.<sup>105</sup> The use of 2-methyltetrahydrofuran in industry is growing. For example, in 2011, the pharmaceutical company GlaxoSmithKline reported 16 percent of the chemical processes in their pilot plants used 2-methyltetrahydrofuran in 2007-2009, up from 3.5 percent in 2005-2006.<sup>106</sup> A study from 2015 proposed 2-methyltetrahydrofuran as an industrial alternative to *n*-hexane in the extraction of vegetable oils from their source plants.<sup>107</sup> It is also considered a viable substitute for chlorinated solvents in both extraction and reaction medium applications.

### d-Limonene

Terpenes such as d-limonene are biobased hydrocarbons used in a number of applications. Terpenes are sourced from essential oils of plants, including citrus and conifers. d-Limonene, which is extracted from citrus peel waste, has the most widespread use as a solvent. In addition to being biobased, d-limonene is less volatile than conventional solvents and therefore poses a lower risk of exposure to humans and the environment. FDA regulations list d-limonene as a generally safe for use as a flavoring

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<sup>105</sup> Genotoxic substances are a type of carcinogen, specifically those capable of causing genetic mutation and of contributing to the development of tumors. This includes certain chemical compounds, metals, and certain types of radiation.

<sup>106</sup> R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, and A. D. Curzons. "Expanding GSK's Solvent Selection Guide – Embedding Sustainability into Solvent Selection Starting at Medicinal Chemistry," *Green Chemistry*, vol. 13 (2011).

<sup>107</sup> A.-G. Sicaire, M. Vian, F. Fine, F. Joffre, P. Carré, S. Tostain, and F. Chemat. "Alternative Bio-Based Solvents for Extraction of Fat and Oils: Solubility Prediction, Global Yield, Extraction Kinetics, Chemical Composition and Cost of Manufacturing," *International Journal of Molecular Sciences*, vol. 16 (2015).

substance.<sup>108</sup> However, the regionality and seasonality of the supply of the citrus feedstock can present a challenge to the production of d-limonene. d-Limonene has been used in a variety of products, including as an ingredient in household and personal care products due to its fragrance properties, and has promise as a cleaning or degreasing solvent. One formulator told us that d-limonene is one of the top 10 raw materials they use and it has been found to be ozone-friendly. Due to its low polarity, d-limonene offers a replacement for petroleum-derived hydrocarbons, such as *n*-hexane, which are commonly used in the extraction of fats and oils from natural sources. One drawback of this approach is that separating d-limonene from the desired fats and oils after extraction may be more energy intensive than the removal of *n*-hexane given its higher boiling point. Although the use of d-limonene as a solvent for organic reactions has not been studied as extensively, researchers have reported examples of d-limonene as a reaction medium in catalytic reactions, including biocatalysis. d-Limonene has also found use as a solvent in the hydraulic fracturing industry (see text box).

#### Citrus terpenes and hydraulic fracturing

A representative from Florida Chemical, a company that produces terpene products, told us that the hydraulic fracturing industry is using d-limonene and other citrus terpenes as green solvents. The chemicals, as part of the fracking fluid mixture, are injected into a wellbore to break apart shale or sand and allow natural gas and crude oil products to escape. According to the representative, d-limonene is a better solvent for asphaltene and wax than the traditionally used fossil fuel products, and the hydraulic fracturing industry is concerned about contamination of source and groundwater and therefore values the low toxicity of citrus terpenes.

Source: GAO analysis of industry interview. | GAO 18-307

### 4.3.2 Non-volatile organic compound (non-VOC) solvents

#### Water

Although water is in some ways considered an ideal sustainable solvent, it also faces certain challenges and tradeoffs. In addition to being environmentally benign, nontoxic, and nonflammable, water is also abundant and inexpensive. Water is sometimes referred to as ‘nature’s solvent’ as many biochemical reactions occur in water. However, many chemicals (e.g., nonpolar hydrocarbons) are not soluble in water. Other chemicals may react with water instead of undergoing the desired reaction. Many catalysts are moisture-sensitive and become inactive in the presence of water. Modern organic chemistry processes have been developed for the most part in conventional organic solvents. However, there are several methods available to expand the utility of water as a reaction medium when working with hydrophobic chemicals including aqueous-organic biphasic systems and micelles.

<sup>108</sup>21 C.F.R. §182.60.

The use of water as a reaction medium can sometimes affect the outcome of a reaction in advantageous ways. For example, some reactions have been shown to proceed faster in water than in conventional organic solvents even though the components may not fully dissolve. The hydrophobic effect—a phenomenon believed to contribute to this observation—describes the fact that nonpolar molecules tend to aggregate in water to minimize interactions with water molecules. Water can provide additional benefits as a reaction medium even in cases where it does not accelerate the rate of reaction—for example, through improved temperature control and easier product separation.

Despite its advantages, water is not always the most sustainable reaction medium, often due to issues associated with recovery of products or removal of byproducts. In some cases, large amounts of organic solvents are necessary to separate the desired product from the aqueous (water-based) reaction medium, which could counteract sustainability gains. The resulting aqueous solution could also be contaminated by organic compounds. In the case of reactions that generate salts as byproducts, such as certain metal-catalyzed cross-coupling reactions, removing the salt in order to recycle the water can be energy-intensive. In contrast, when using a VOC solvent, unwanted salt byproducts can often be removed by filtration and the low-boiling solvent can easily be recovered by distillation.

Chemistry in natural systems predominantly occurs in water as the solvent, making it a good solvent for related processes and chemicals. Water is used in many biocatalytic reactions. It is also a good solvent for many inorganic chemicals and certain organic

chemicals such as sugars, proteins, and some acids. Chemists have also studied water as a reaction medium for transformations of biobased raw materials. For example, cellulose can be broken down in water to yield glucose under relatively mild reaction conditions. Water is also used in steam distillation, a process for isolating heat-sensitive chemicals, such as essential oils.

Aqueous-organic biphasic systems are an effective method for using water as a solvent when working with hydrophobic chemicals, which can facilitate additional sustainability benefits such as catalyst recycling. In a biphasic system, hydrophobic substances are dissolved in the organic phase while hydrophilic substances are dissolved in the water phase. Aqueous-organic biphasic systems can be especially useful for catalyst recycling. The catalyst can be selected to preferentially dissolve in the water phase, facilitating recovery and recycling from the rest of the reaction mixture, which remains in the organic phase. Vigorous stirring can be used to increase contact between the hydrophilic catalyst and hydrophobic reactants at the aqueous-organic interface. In another technique, a phase-transfer catalyst is added to the reaction, which facilitates the transport of reactants between phases thereby increasing the rate of reaction. Water can also form biphasic systems with other non-VOC solvents such as supercritical carbon dioxide and others, further reducing the use of VOCs in a process.

Micelles are another method for using water as a reaction medium with hydrophobic chemicals. A micelle is a sphere (or bubble) with a wall composed of a single layer of molecules. In water, micelles are formed by surfactants whose hydrophobic portions point

toward the center of the micelle to form the interior 'lining' of the bubble while the hydrophilic portions interact with water on the exterior of the micelle.<sup>109</sup> Hydrophobic molecules will aggregate inside the hydrophobic center of these micelles and reactions can occur between the molecules gathered there. (See fig. 14.) One estimate is

that micelles are used to produce ten million tons of polymer each year, primarily for use in environmentally friendly coatings.<sup>110</sup> Micellar catalysis allows for catalysis of hydrophobic reactants or the use of hydrophobic catalysts in water. Micelles can be used with metal catalysts, nanoparticle catalysts, and organocatalysts.<sup>111</sup>

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<sup>109</sup>Commercial surfactants are typically derived from petroleum, but there are efforts underway to make from biobased feedstocks new surfactants that could be biodegradable or biocompatible.

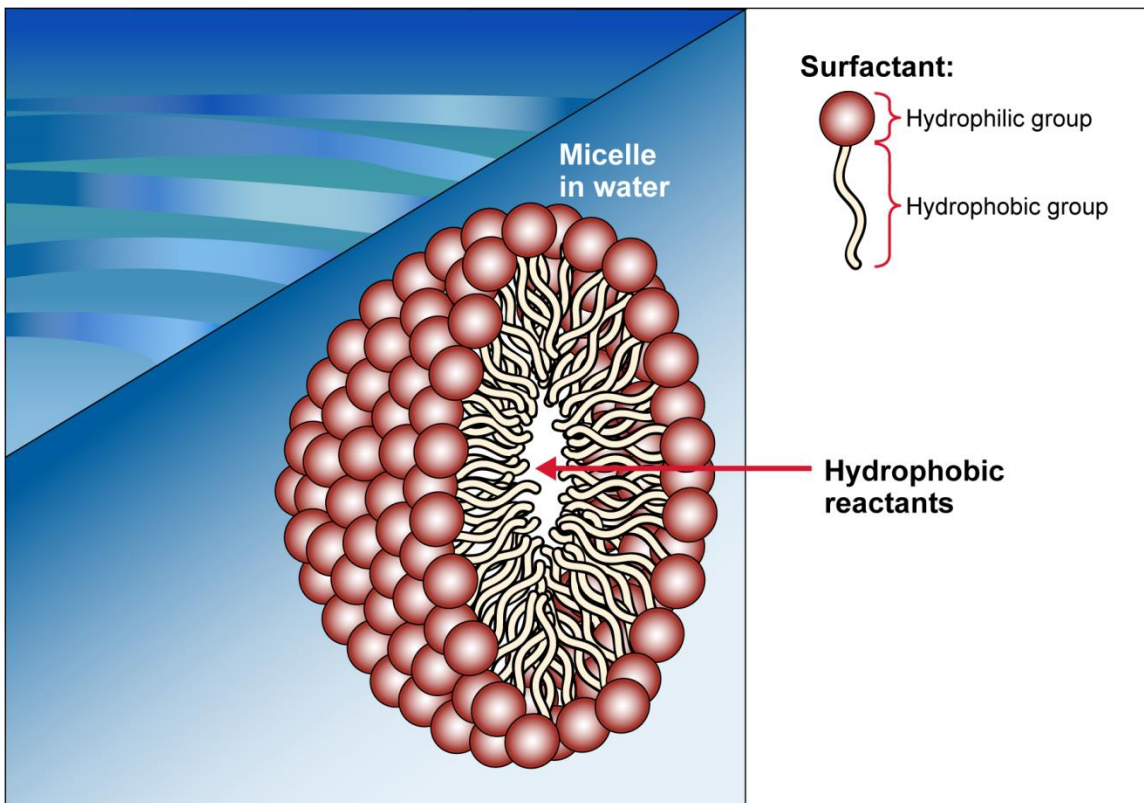
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<sup>110</sup>F. M. Kerton and R. Marriott, *Alternative Solvents for Green Chemistry*, 2<sup>nd</sup> ed. (Cambridge, U.K.: The Royal Society of Chemistry, 2013), 102.

<sup>111</sup>For more on different types of catalysts see chapter 3.

**Figure 14: Reactions between hydrophobic reactants can occur inside micelles in water**

This figure depicts a cross-section of a spherical micelle.



Source: GAO. | GAO-18-307

There are several benefits to using micelles for catalytic purposes; however, there may be a limitation to using this method on a large scale. In addition to allowing reactions to occur in water, micellar catalysis offers other sustainability benefits such as facilitating production extraction. Similar to biphasic systems, an organic solvent that does not mix with water can be used to extract hydrophobic products from the mixture, leaving the micelles and catalysts in the water phase, which facilitates catalyst recycling. In cases where the product is completely insoluble in water, it can be collected by filtration and product extraction with an organic solvent is not necessary. A potential limitation is that the amount of reactants

inside the micelles may be lower than in conventional solvents. However, according to one of our experts, the limited volume inside the micelle can be an advantage, as the higher concentrations of reactants found there can allow some reactions that require the addition of heat when run in conventional solvents to proceed at ambient temperature instead.

One study by a pharmaceutical company found that use of surfactant technology in water in the synthesis of an active pharmaceutical ingredient provided both environmental and economic benefits as

compared to the conventional route.<sup>112</sup> The study compared two possible synthetic routes to an active pharmaceutical ingredient: conventional catalysis using organic solvents, and catalysis using surfactant technology in water. The authors used the metric PMI to assess the environmental performance of the two routes.<sup>113</sup> Using surfactant technology, the authors carried out the entire multi-step synthesis in water and reduced the overall PMI by over 30 percent as compared to the conventional route. The overall yield increased by five percent as well. Therefore, the authors reported both an environmental improvement and better process performance. In particular, the reduction in solvent use—approximately 50 percent—provided most of the environmental benefits. The surfactant technology process produced a similar amount of water waste as the conventional process and the nature of the contamination did not vary, which the authors reported as a benefit. For the purposes of this study the authors did not attempt to recycle the catalyst system. The authors propose that the reported process could also result in economic benefits due to increased yield and decreased costs of raw materials, among other reasons.

### Supercritical carbon dioxide

Supercritical carbon dioxide is an environmentally benign solvent with a

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<sup>112</sup>F. Gallou, N. A. Isley, A. Ganic, U. Onken, and M. Parmentier, "Surfactant Technology Applied Toward an Active Pharmaceutical Ingredient: More than a Simple Green Chemistry Advance," *Green Chemistry*, vol. 18 (2016). The authors reported that the process may involve a micellar-assisted mechanism, although another mechanism is possible and further elucidation was still needed.

<sup>113</sup>See chapter 2 for a more detailed discussion of PMI.

number of interesting solvent properties; however, there are limitations to its use for certain applications.<sup>114</sup> It is inexpensive, nontoxic, nonflammable, and the temperature and pressure at which it becomes a supercritical fluid are relatively mild compared to some other substances. However, the use of supercritical fluids also violates the green chemistry principle that synthetic methods should be carried out at ambient temperature and pressure. Chemists can adjust, or tune, the solubility of other substances in supercritical carbon dioxide by changing the pressure of the system. It can serve as an inert reaction medium or in reactions where carbon dioxide is consumed as one of the reactants. After a reaction, supercritical carbon dioxide can be separated from the product by depressurization, reducing energy consumption as compared to a process in which organic solvents must be removed. Many gases are soluble in supercritical carbon dioxide, which is not the case for most conventional solvents. However, it is nonpolar and may not be a suitable solvent for reactions involving polar or high molecular weight chemicals. Several techniques have been developed to mitigate this limitation including the use of cosolvents such as alcohols, or the introduction of agents such as surfactants to enhance solubility.

There are several types of reactions for which supercritical carbon dioxide is potentially a suitable solvent; however, there are still some barriers to implementation on a commercial scale. Supercritical carbon dioxide may be a

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<sup>114</sup>Supercritical fluids are substances that have properties in between those of a gas and a liquid at or above a given temperature and pressure, known as the critical point. Several other supercritical fluids are used by industry as solvents; however supercritical carbon dioxide is particularly relevant to sustainability efforts.



particularly suitable solvent for reactions that: (1) run in nonpolar solvents, (2) are solvent-sensitive and thus likely to be 'pressure-tunable', (3) use gaseous reactants, and (4) have products of high enough value to offset the capital investment required to implement this technology. In some cases, the use of supercritical fluids in industrial processes is not commercially viable, most often due to the perceived high energy and equipment costs of pressurizing and working with the fluids. Special reactors and additional safety precautions are usually required for conducting reactions at elevated pressure. However, a 2015 study found that pressurizing carbon dioxide only accounted for a small portion of the total energy consumed in a pilot plant process, and therefore concluded that the perception that working at higher pressures means higher operating costs may not necessarily be true.<sup>115</sup> A process for the production of fluoropolymers such as Teflon™ in supercritical carbon dioxide was commercialized; however, this process is no longer in use by that company.<sup>116</sup> Use of supercritical carbon dioxide improves several environmental health and safety issues associated with the aqueous process for certain fluoropolymers, such as eliminating the use and disposal of large quantities of acid, including the hazardous chemical perfluorooctanoic acid (PFOA).

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<sup>115</sup>L. Martin, C. Skinner, and R. J. Marriott, "Supercritical Extraction of Oil Seed Rape: Energetic Evaluation of Process Scale," *The Journal of Supercritical Fluids*, vol. 105 (2015).

<sup>116</sup>According to an article written by one of the academic inventors of this technology and others, the licensing company did not scale the technology up beyond the initial investment, not due to problems with the technology but rather based on internal economic and other decisions. J. M. DeSimone, S. J. Mecham, and C. L. Farrell, "Organic Polymer Chemistry in the Context of Novel Processes," *ACS Central Science*, vol. 2 (2016).

Supercritical carbon dioxide has been demonstrated as a solvent in a variety of other applications. For example, supercritical carbon dioxide can replace ultrapure water in the manufacture of circuits and eliminate the need to use an alcohol solvent as a drying agent, or replace hazardous dry-cleaning chemicals. It can also be used to separate or purify substances in a process called supercritical fluid chromatography, providing an alternative to conventional liquid chromatography techniques that contribute significantly to organic solvent waste. One company representative we talked to told us that the use of this technology in the pharmaceutical industry has grown in the past 5 to 10 years. However, the representative cited the upfront costs of instrumentation and infrastructure, the high pressures required to run the process, and the solubility limitations of supercritical carbon dioxide due to its nonpolar nature as some of the challenges to implementation. Supercritical carbon dioxide is also a good extraction solvent because it is nontoxic; does not have a color, odor, or taste; and is easy to remove from the extracted materials, among other reasons. It is a potential replacement for *n*-hexane due to its nonpolar nature. The beverage, food, flavor, and cosmetic industries have used supercritical carbon dioxide extraction to process various products, for example coffee decaffeination. Instrumentation for supercritical chromatography and extraction are commercially available for both large and small scale processes.

### Ionic liquids

The use of ionic liquids as sustainable solvents is a popular topic in research; however, there is some debate as to sustainability benefits of

this class of compounds. Ionic liquids are salts, usually composed of a positively charged organic ion and a negatively charged organic or inorganic ion, that are liquid at or below 100°C—the boiling point of water. Ionic liquids generally have low volatility, which is the primary potential sustainability gain they offer over conventional solvents. However, there are concerns about the toxicity as well as environmental persistence and footprint of ionic liquids. One of our experts told us that many ionic liquids have been shown to be acutely toxic. However, whether an ionic liquid is toxic or nontoxic depends on the compound, and according to scientific literature and one of our experts, more research and data are needed to fully understand the toxicity of these compounds. The complex synthesis required to make some ionic liquids may also reduce their sustainability or increase costs. Recent research efforts have attempted to address these challenges by reducing the toxicity and increasing the biodegradability of ionic liquids. According to one of our experts, a major disadvantage of ionic liquids is that often another solvent is required for product separation and purification, in which case recycling the ionic liquid is usually not possible or not economically viable.

Many ionic liquids are available and many more combinations of ions are possible, making it difficult to describe general properties of this class of solvents. Depending on their design, ionic liquids may be characterized by low volatility, overall robustness, and high heat capacity, among other properties.<sup>117</sup> The solvent properties of

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<sup>117</sup>The heat capacity of a substance describes the amount of heat required to increase the temperature of a particular quantity of the substance by one degree Celsius.

ionic liquids can be tuned by varying the positively and negatively charged components of the compound (see text box below for an example of federal efforts to support the development of ionic liquids). Research has demonstrated the use of ionic liquids in a wide range of applications, including extraction of renewable raw materials, catalysis, and degreasing. According to one of our experts, industry is commercializing applications of ionic liquids, but at a slow rate.

**Example federal government program to support the development of ionic liquids**

The National Institute of Standards and Technology (NIST) hosts an Ionic Liquids Database, ILThermo (<http://ilthermo.boulder.nist.gov/>). The database, which was created in 2006 in cooperation with the International Union of Pure & Applied Chemistry (IUPAC), is a free, web-based research tool that allows users worldwide to access current data on various properties of both pure ionic liquids and mixtures. In creating the database, NIST and IUPAC recognized the need for organized, reliable data on the properties of ionic liquids, which are critical when designing industrial processes.

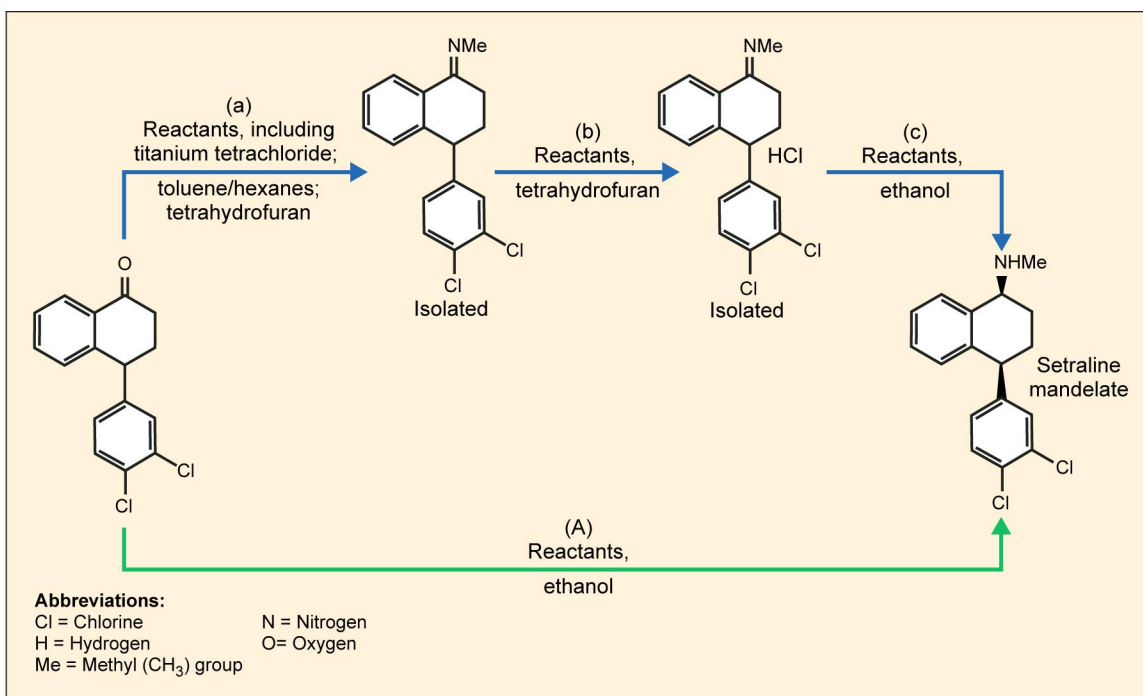
Source: GAO analysis of agency announcement. | GAO-18-307

In one industrial example, employing ionic liquid technology resulted in several benefits, including increased productivity and recycling of materials. This process, known as the BASIL™ process (Biphasic Acid Scavenging utilizing Ionic Liquids), was established in 2002 by BASF. This process replaces the conventional approach for making a raw material used in coating and ink technologies. In both the conventional and BASIL™ approaches, hydrogen chloride forms as a byproduct of the process and significantly decreases the yield if not removed. In the conventional process, triethylamine was

added to scavenge hydrogen chloride. However, the resulting triethylammonium chloride formed a thick mixture that reduced the efficiency of the reaction. In the BASIL™ process, 1-methylimidazole is added to the reaction mixture instead; it reacts with the hydrogen chloride to form an ionic liquid (1-methylimidazolium chloride) which melts at around 75°C. These conditions reportedly increased the reaction rate and increased the

yield from 50 to 98 percent. In addition, the pure product can be easily separated from the 1-methylimidazolium chloride, and the latter can be recycled back to 1-methylimidazole and reused. The new process also allowed BASF to replace the use of batch processing in large reaction vessels with new reactor technologies, greatly increasing productivity. (For more on the disadvantages of batch processing, see chapter 5).

**Figure 15: The redesign of the sertraline manufacturing process**



Source: Adapted with permission from Taber, *et al.* | GAO-18-307

Note: Adapted with permission from G. P. Taber, D. M. Pfisterer, and J. C. Colberg, "A New and Simplified Process for Preparing *N*-[4-(3,4-Dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenyldene]methanamine and a Telescoped Process for the Synthesis of (1*S*-*cis*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine Mandelate: Key Intermediates in the Synthesis of Sertraline Hydrochloride," *Organic Process Research & Development*, vol. 8 (2004). Copyright 2004 American Chemical Society. For simplicity we have omitted some details of the reaction conditions, such as catalysts or some reactants.

### 4.3.3 Solvent-free or reduced-solvent technologies

#### Reduction in reaction steps

The amount of solvent used in a chemical process can also be reduced by simplifying a multistep reaction scheme, thereby decreasing the volume and number of different solvents used. Many conventional chemical processes include multiple chemical reactions occurring in a stepwise manner. Often the desired intermediate compound produced in one step is isolated—separated from the rest of the reaction mixture—and purified before proceeding to the next step. The process of separation and purification can be solvent-intensive, leading to large quantities of solvent waste. Additionally, a multistep chemical process may use multiple solvents, and cross-contamination of solvents can make recycling a challenge.

Examples of this strategy come from the pharmaceutical industry, where complex multistep processes are commonly used in the synthesis of active pharmaceutical ingredients. Pfizer redesigned the synthetic process for sildenafil citrate (brand name Viagra®) in transitioning from the medicinal chemistry route used in the early stages of drug development to the commercial route of production.<sup>118</sup> Pfizer developed a more efficient synthetic process, while also moving steps involving toxic chemicals to the beginning of the process and the cleaner steps closer to the final product. The new process reduced the number of purification

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<sup>118</sup>P. J. Dunn, S. Galvin, and K. Hettenbach, "The Development of an Environmentally Benign Synthesis of Sildenafil Citrate (Viagra™) and Its Assessment by Green Chemistry Metrics," *Green Chemistry*, vol. 6 (2004).

steps and consequently the volume of solvent used. The process change together with the introduction of a solvent recovery system reduced the volume of organic waste generated in the production of one kilogram of product from 1,300 liters to 7 liters. They also eliminated the use of chlorinated solvents and several other VOCs. In another example, Pfizer won a Presidential Green Chemistry Challenge Award in 2002 for redesigning the synthesis of sertraline, the active ingredient in the antidepressant marketed as Zoloft®.<sup>119</sup> In redesigning the process, Pfizer streamlined a three-step sequence into a single step (see fig. 15).<sup>120</sup> They also optimized the process by eliminating the need to use, distill, and recover four conventional VOC solvents—dichloromethane, tetrahydrofuran, toluene, and hexane—by using the more benign solvent ethanol. The use of ethanol as a solvent also reduced the need for large quantities of a problematic chemical (titanium tetrachloride). The final process used two different solvents rather than five and reduced the total volume of solvent by 76 percent.

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<sup>119</sup>For a full list of Presidential Green Chemistry Challenge Awards from 1996-2016, see [https://www.epa.gov/sites/production/files/2016-10/documents/award\\_recipients\\_1996\\_2016.pdf](https://www.epa.gov/sites/production/files/2016-10/documents/award_recipients_1996_2016.pdf), accessed September 10, 2017.

<sup>120</sup>G. P. Taber, D. M. Pfisterer, and J. C. Colberg, "A New and Simplified Process for Preparing *N*-[4-(3,4-Dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]methanamine and a Telescoped Process for the Synthesis of (1*S*-*cis*)-4-(3,4-Dichlorophenol)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine Mandelate: Key Intermediates in the Synthesis of Sertraline Hydrochloride," *Organic Process Research & Development*, vol. 8 (2004).

## Solvent-free or neat reactions

Chemical processes that do not use any solvents at all may offer the most sustainable option in terms of reducing waste. Solvent-free reactions can occur between chemicals in the liquid, gas, or solid states. For liquid phase reactions with no added solvent, often one of the reactants may be used in excess, essentially forming a solution.<sup>121</sup> With solvent-free processes there is no reaction medium to remove, recycle, or dispose of as waste. This can lead to cost savings in addition to potential sustainability gains. Solvent-free reactions can also be very rapid and high yielding. For example, researchers reported incorporating a solvent-free step into the synthesis of a potential antituberculosis drug, which had a higher yield than the same transformation conducted in ethanol.<sup>122</sup> Introduction of a solvent-free reaction also facilitated the integration of multiple steps, thereby decreasing the number of energy-intensive separation and purification steps and further reducing solvent consumption. The optimized process including the solvent-free step allowed the authors to achieve almost three times the yield while using one-third as much solvent as compared to the original synthetic approach.

Although solvent-free reactions are common in some sectors of the chemical industry, there are technical challenges to achieving new solvent-free chemical processes,

especially on an industrial scale. Solvent-free reactions are well established in some sectors of the chemical industry. For example, gas phase chemical processes are common in the manufacture of bulk chemicals such as polyethylene. One drawback to solvent-free reactions is that without a reaction medium, it can be difficult for heat generated during the reaction to dissipate evenly throughout the mixture. This can lead to ‘hot spots’ and unwanted side reactions. Further, some chemical reactions may become explosive when conducted in the solid or neat liquid state, something which solvent use generally prevents. Additionally, these reactions can lead to highly viscous or solid products, making industrial development a challenge. As VOCs are used for separation and purification in many solvent-free approaches, a reaction may be solvent-free while the chemical process as a whole is not.

There are techniques with the potential to overcome the challenges associated with solvent-free reactions at the industrial scale. In an approach called mechanochemistry, grinding is used to initiate chemical reactions in the solid state. One variant of this approach is the use of a ball mill—a vessel containing the reacting chemicals and ball bearings which is shaken at high speed. However, solid state reactions do not yet have widespread application in industry. In another approach, microwave reactors have been reported for use in solvent-free reactions that could be relevant to the pharmaceutical industry.<sup>123</sup> (See text box below for some examples of low- and no-VOCs in formulations).

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<sup>121</sup>Such cases may be more appropriately referred as neat reactions rather than solvent-free.

<sup>122</sup>A. Orita, K. Miwa, G. Uehara, and J. Otera “Integration of Solventless Reaction in a Multi-Step Process: Application to an Efficient Synthesis of PA-824,” *Advanced Synthesis & Catalysis*, vol. 349 (2007).

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<sup>123</sup>A. Kulkarni and B. Török, “Microwave-Assisted Multicomponent Domino Cyclization-Aromatization: An Efficient Approach for the Synthesis of Substituted Quinolines,” *Green Chemistry*, vol. 12 (2010).

### Low- or no-VOC formulations in coating technologies

Industry has developed a variety of new coating technologies in response to regulations and environmental concerns regarding volatile organic compounds (VOCs). Many industry sectors are currently using coatings, such as paints or printing inks, containing low or no VOCs or hazardous air pollutants (HAPs) in the formulation. Examples of these coatings include waterborne, biobased solventborne, and powder coatings, among others. Several new technologies for low-VOC coatings have received Presidential Green Chemistry Challenge Awards. For example, in 2011, Sherwin-Williams developed low-VOC waterborne paints made from recycled soda bottle plastic, acrylics, and soybean oil. They manufactured enough of these new paints in 2010 to eliminate over 800,000 pounds of VOCs. In 2009, Procter & Gamble and Cook Composites and Polymers developed paint formulations using biobased Sefose<sup>®</sup> oils to replace petroleum-derived solvents. Sefose<sup>®</sup> oils, made from sugar and vegetable oil, enabled the production of paints with less than half the solvent. (For more information on the Presidential Green Chemistry Challenge Awards, see chapter 6.)

Powder coatings are applied to a surface as a dry powder and do not require any solvent. The powder is sprayed electrostatically and then heated to allow the coating to fuse. Powder coatings improve product durability as they can protect the product from scratches, corrosion, and other damage. In the 2015, the DOD's Strategic Environmental Research and Development Program (SERDP) awarded its project-of-the-year award to the development of powder coating technology for Chemical Agent Resistant Coatings (CARC). (For more information on SERDP, see chapter 6.) According to a SERDP press release, at the time of the project the use of conventional CARC topcoats contributed 2.3 million pounds of VOCs and hazardous air pollutants to the environment each year. The key challenges to developing powder coatings suitable for this application were chemical warfare agent resistance, extremely low gloss, and high durability. A collaborative team from industry, academia, and the military successfully developed a CARC powder coating technology. These powder coatings emit nearly zero VOCs, can be recycled, and are compatible with existing CARC systems. Initial testing also indicates the powder coatings have better exterior durability than liquid CARC systems, which is important for corrosion prevention and mitigation.

Source: GAO analysis of scientific literature, agency documents, and an agency press release. | GAO-18-307

## 5 Technologies as more sustainable alternatives to batch processing

The historical approach to chemical processing for centuries was batch processing, in which a chemical process was conducted in a closed vessel (batch reactor), the resulting mixture was transferred to a second vessel for the next step in the process, and so on, with the vats cleaned between batches so the process could be repeated. This approach, which is still widely used in some sectors of the chemical industry, raises a number of sustainability concerns—especially when conducted on a large scale. These include the significant physical footprint required for the equipment; high energy and solvent use; and safety concerns under certain conditions, such as when high pressures are required or when a hazardous intermediate is produced in significant

quantities. Furthermore, processing in batch reactors can be labor-intensive and require a lot of manual coordination to execute the process flow, according to one industry representative we interviewed. Therefore, the industry is researching and developing alternative technologies to improve efficiencies in manufacturing while also realizing significant gains in sustainability and environmental benefits. We assessed two such technologies—continuous processing and continuous flow microreactors—that can help chemical companies address some of these sustainability concerns. Table 8 summarizes some of the advantages and disadvantages of these two technologies; we provide additional details in the remainder of the chapter.

**Table 8: Summary of assessment of selected technologies as alternatives to batch processing**

Technology	Advantages	Disadvantages
<b>Continuous processing</b>	<ul style="list-style-type: none"> <li>Reduced physical footprint of a plant.</li> <li>Savings in capital and operational expenditure; lower inventory costs.</li> <li>Potential for improved product yield and quality.</li> <li>Improved product safety; reduced product exposure to the environment, and to operators.</li> <li>Process automation.</li> <li>In-line analytics result in improved product consistency, high product quality, and more controllable and repeatable processes.</li> </ul>	<ul style="list-style-type: none"> <li>Global regulatory uncertainty—need to satisfy regulatory requirements in multiple countries.</li> <li>Risk aversion (reluctance to change an already validated process).</li> <li>Economic aspects: cost involved in developing new infrastructure for continuous manufacturing.</li> </ul>

Technology	Advantages	Disadvantages
<b>Continuous flow microreactor</b>	<p>Process safety: smaller reaction volume, reduced worker exposure to chemicals, and safe completion of hazardous reactions involving unstable or potentially explosive intermediates.</p> <p>Smaller scale: results in shorter reaction times, lower energy consumption, and improved efficiency.</p> <p>Potential for improved product quality.</p> <p>Hazard minimization: enhanced reaction control, superior heat dissipation, and smaller reactor volume allows high temperature and high pressure reactions to be conducted safely.</p> <p>Prevention of waste through reduced need for solvents.</p> <p>Ease of scale-up.</p> <p>Process automation, faster screening of reagents, and reduced research and development cycle time.</p> <p>In-line analytics capability results in improved product consistency, high product quality, and more controllable and repeatable processes.</p> <p>Economic aspects: savings in capital and operational expenditure.</p>	<p>Global regulatory uncertainty—need to satisfy regulatory requirements in multiple countries.</p> <p>Risk aversion (reluctance to change an already validated process).</p> <p>Difficulties with reactions involving solids may limit the applicability of microreactors.</p> <p>Highly specialized reactions or complex processing conditions can make the adoption of continuous manufacturing challenging for pharmaceutical and fine chemical industries.</p> <p>Economic aspects: cost involved in developing new infrastructure for continuous manufacturing.</p> <p>Workforce challenges: may need specialized personnel to design, develop, validate and operate a continuous flow process.</p>

Source: GAO. | GAO-18-307

## 5.1 Continuous processing

In contrast to batch processing, in continuous processing the reaction mixture is continuously pumped through a reactor consisting of pipes or tube where reactions take place in a continuous mode. Reactants can be introduced and byproducts removed at appropriate points along the line, while finished product materials are continuously removed at the end. For reactions consisting of multiple steps using different conditions or components, vessels with different purposes can be linked and reaction components can flow from one stage to the next. In 2007, the ACS GCI Pharmaceutical Roundtable highlighted continuous processing as a key area where research was required to facilitate

the development of sustainable manufacturing.<sup>124</sup>

Continuous manufacturing is not new. It has been widely used by many sectors of the chemical industry for decades. Industries as diverse as oil, gas, chemicals, polymers, and food currently operate in continuous processing mode. One of our experts told us that his company uses continuous processing

<sup>124</sup>In 2005, the ACS GCI and global pharmaceutical corporations developed the ACS GCI Pharmaceutical Roundtable to encourage innovation while catalyzing the integration of green chemistry and green engineering in the pharmaceutical industry. The activities of the Roundtable reflect its member's shared belief that the pursuit of green chemistry and engineering is imperative for business and environmental sustainability.



in most—estimated to be over 95 percent—of their production and generally at large scales.

In contrast, the pharmaceutical industry has traditionally been dominated by batch processing and only recently has there been a drive towards continuous processing. The current adoption rate is approximately 5 percent in the pharmaceutical sector, despite one report noting that up to 50 percent of reactions could benefit from a continuous process.<sup>125</sup> In recent years, the pharmaceutical industry has started to research continuous processing as a manufacturing strategy to realize operational efficiencies and drive down cost. Continuous flow systems have become popular for the preparation of fine chemicals such as natural products and drugs, especially in academic research. For example, a collaborative effort between Massachusetts Institute of Technology (MIT) and the pharmaceutical industry at the Novartis-MIT Center for Continuous Manufacturing seeks to develop new technologies to replace the pharmaceutical industry's conventional batch processing with continuous processing.

### Advantages of continuous processing

One of the key benefits of continuous processing is eliminating a fixed batch size, thus allowing operational flexibility. Because of operational efficiencies achieved with continuous flow, the processing time can be reduced from months to days. Continuous processing product lead times (i.e., the time

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<sup>125</sup>T. S. Harrington, L. Alinaghian, and J. S. Srail, "Making the Business Case for Continuous Manufacturing in the Pharmaceutical Industry" (paper presented at the 25th Annual Production and Operations Management Society Conference, Atlanta, GA, May 2014).

from raw materials procurement to distribution of finished product) are typically significantly less than for batch, which can substantially reduce inventory carrying costs. According to a university research presentation, product yield and quality can be better in continuous processing compared to batch processes.<sup>126</sup> Furthermore, continuous processing supports many of the key aspects of sustainable chemistry that are beneficial to workers and the environment, such as lower energy consumption, less waste production, less consumption of solvents, safer processes, and less exposure to chemicals. This technology can meet 10 out of the 12 Principles as outlined by Anastas et al., according to authors of a recent scientific publication.<sup>127</sup>

According to one researcher, continuous processing is usually preferred for large-scale production and is particularly well-suited for cases involving considerable heat transfer and when high pressures and high or low temperatures occur.<sup>128</sup> For example, the Haber-Bosch process for production of ammonia—a gas phase reaction run under very high pressure—is a good candidate for

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<sup>126</sup>J. Srail, "Exploring Alternative Product-Process Supply Network Models in Pharma," Engineering and Physical Sciences Research Council, Center for Innovative Manufacturing in Continuous Manufacturing and Crystallization, University of Cambridge, 2012, accessed December 20, 2017, [https://www.cmac.ac.uk/files/media/Jag\\_Srail.pdf](https://www.cmac.ac.uk/files/media/Jag_Srail.pdf).

<sup>127</sup>C. Wiles and P. Watts, "Continuous Flow Reactors: A Perspective," *Green Chemistry*, vol. 14, no. 38 (2012).

<sup>128</sup>S. Nanda, "Pharmaceutical Engineering: Reactors and Fundamentals of Reactors Design for Chemical Reaction," Department of Pharmaceutical Sciences, Maharshi Dayanand University, 2008, accessed November 14, 2017, <https://pdfs.semanticscholar.org/e5c1/60655207fd7c0ba00e9a02f0482a753704f7.pdf>.

continuous processing.<sup>129</sup> Continuous processing is generally used for gaseous reactions, but is also suitable for some liquid-phase reactions. It can reduce the physical footprint of a chemical process as well as labor costs through automation. This can reduce capital and maintenance costs, according to a company official we interviewed. The official noted that they recently converted from batch processing to continuous processing for their polystyrene-to-styrene conversion process. The operational efficiency realized through continuous processing was critical to making the economics workable for them. A leading pharmaceutical company told us that they have installed an integrated continuous processing system at one of their manufacturing sites for making tablets from drug powders.<sup>130</sup> This approach resulted in lower upfront investment costs compared to traditional facilities, a reduced environmental footprint, and savings of up to 35 percent in energy and resource use compared to batch processing. Estimates from an experimental study of process equipment showed approximately 10 times less material usage and 10 times faster processing than conventional batch equipment.

According to a company's technical product literature and a conference paper, the

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<sup>129</sup>The Haber-Bosch process is used to synthesize ammonia from gaseous nitrogen and hydrogen under high pressure and temperature in the presence of a catalyst.

<sup>130</sup>One pharmaceutical company has adopted a hybrid manufacturing approach that incorporates the best of batch and continuous manufacturing. That is, only certain segments of their operation are run in a continuous mode while the rest of the line is still run in a batch mode. Company representatives told us that they have used this approach to produce drug powders using a batch processing mode and then make tablets from the drug powders in a continuous mode.

introduction of high levels of automation and reduced manual intervention, together with integrating inline analytical tools, provides significant benefits in terms of improved product consistency, high product quality, and a more controllable and repeatable process. Other benefits include faster time-to-market for new drugs by saving time at the development stage and in the move from development to production. Furthermore, a continuous processing system also improves overall safety and reduces risk. Interconnected unit operations typical of continuous processing systems can mean less product exposure to the environment and to operators, leading to increased product safety.

Pharmaceutical company representatives we interviewed told us that some of the challenges they face in implementing continuous processing are: global regulatory uncertainty—that is, the need to satisfy regulatory requirements in multiple countries; risk aversion—a reluctance to change an already validated process, including the need to have changes in manufacturing approved by the Food and Drug Administration (FDA); and economic uncertainties related to costs involved in developing new infrastructure for continuous manufacturing.

## 5.2 Continuous flow microreactors for pharmaceuticals and fine chemicals

Innovations in continuous processing have led to the development of new reactor designs and support apparatus that allow substantially smaller, cleaner, safer, more energy-efficient, and more scalable methods for the production of pharmaceutical and fine (specialty) chemical products. One such

reactor design that is gaining acceptance in pharmaceutical and fine chemicals industry is the continuous flow microreactor.

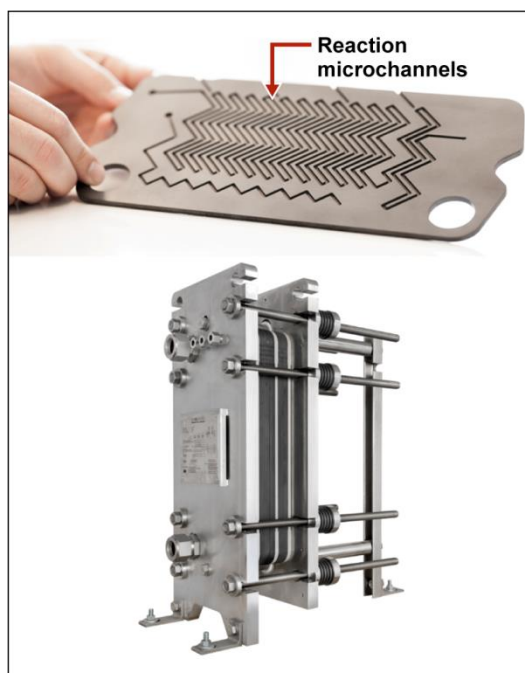
As the name indicates, these reactors have very small dimensions and use continuous flow for chemical processing. Microreactors can potentially improve chemical processes and routes. However, their integration into chemical production processes depends on many factors such as technical advancements, costs, and production logistics, among others.

Microreactors have various designs, but one design consists of channels of small dimensions that are etched in glass, silicon-glass, ceramic, polymers, or stainless steel that have volumes typically ranging from 50 microliters to 100 milliliters and channel diameters from 50 to 1000 micrometers. The chemical reactions take place in a series of microchannels forming the core of the reactor (see fig. 16). Microreactors can include additional elements to precisely control the reaction parameters and improve energy efficiency.

Microreactor technology has been adopted by companies in the pharmaceutical, flavor and fragrance, fine chemical, and agricultural chemical industries, among others. New generations of pharmaceutical drugs have been developed through research using microreactors. This technology enables cost-effective synthesis and screening of novel chemicals with enhanced speed.

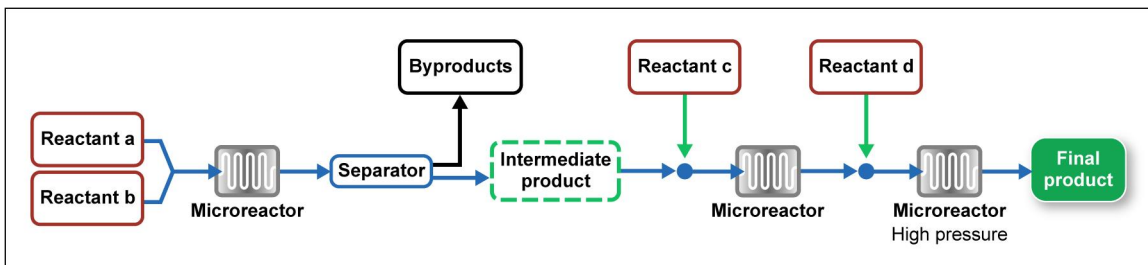
Miniaturization of chemical reactors offers many fundamental and practical advantages to the pharmaceutical industry. Figure 17 illustrates a generic multi-step synthesis that uses continuous flow microreactors to produce a drug or other chemical.

**Figure 16: Pictures of the channels of a microreactor and a production scale continuous flow microreactor**



Source: Chemtrix® | GAO-18-307

**Figure 17:** A generic multi-step synthesis that uses continuous flow microreactors to produce a drug or other chemical



Source: GAO. | GAO-18-307

Recent publications report on the growing interest of pharmaceutical companies in the use of microreactor technology for the safe and efficient production of drugs. Figure 18 shows continuous flow microreactors used in a pharmaceutical production plant.

**Figure 18:** Continuous flow microreactors in a pharmaceutical production plant



Source: Chemtrix®. | GAO-18-307

According to many pharmaceutical company representatives we interviewed, their companies are researching continuous flow processes because this technology offers several benefits, including a smaller manufacturing footprint, higher throughput compared to a batch process, and safety, among others.

### Advantages of microreactor technology

Innovations in the developing field of microreactors have delivered more sustainable chemical processes and technologies resulting in higher productivity and commercially viable high-purity products. The advantages inherent to microreactors—enhanced reaction control, improved safety, reduced material inputs, and reduced levels of hazardous waste, among others—provide a more sustainable option for the chemical industry.

Enhanced reaction control: According to some researchers, the key advantage of microreactors in organic synthesis is the ability to achieve a high degree of control over reaction parameters such as temperature, pressure, and residence time (i.e., the amount of time the reactants spend inside the system). The high surface-to-volume ratio of microreactors—potentially over 1000 times higher than a batch reactor—and the reactor design allow for rapid and efficient mixing to achieve homogeneity, precise control of stoichiometry, high reaction speed, and improved heat transfer leading to enhanced temperature control compared to a batch reactor. According to pharmaceutical company representatives we interviewed, for

reactions requiring mixing, continuous processing achieves a higher degree of mixing than can be achieved in batch processing. Furthermore, at this scale the reactants do not mix by turbulent flow, as when a batch reactor is stirred, but rather diffuse together as they move along the channel, allowing for a highly controllable and repeatable process.

Microreactors are also much easier to pressurize, allowing for high pressure and high temperature operations that can be advantageous for some reactions. This offers additional flexibility for process chemistry. For example, solvents such as dichloromethane can be used at 70°C, or acetonitrile at 140°C, much above their respective boiling points.<sup>131</sup> Additionally, the smaller reactor volume makes it relatively easier to scale-up exothermic reactions without the need for special equipment or additional precautions.<sup>132</sup>

Safe completion of hazardous reactions involving unstable or potentially explosive intermediates: According to pharmaceutical company representatives we interviewed, a continuous flow microreactor provides an opportunity to safely handle hazardous materials—including potentially explosive intermediates such as azides that may form during a reaction—because such intermediates move right into subsequent

reactions as soon as they are produced.<sup>133</sup> For example, a review article by Mason and colleagues reported a well-controlled and direct fluorination reaction (a carbon–fluorine bond-forming reaction that introduces fluorine into a compound) in microreactors.<sup>134</sup> These reactions typically cannot be run on a large scale because of their exothermicity, potential for explosion, and lack of selectivity. According to one of our experts, while the use of inherently hazardous substances does not meet the goals of sustainable chemistry, a microreactor can make their use in a process possible.

Furthermore, some exothermic reactions require extremely low temperatures to control—as low as –80°C, which can be very challenging to achieve, requiring costly cryogenic systems—and may not be practical on a large scale. For these processes, a continuous flow microreactor can be considered as an alternative to low temperature reactions, because at very small volumes, managing temperature becomes less important, according to pharmaceutical company representatives we interviewed. The unique heat transfer characteristics of a continuous flow microreactor allow highly exothermic reactions to be conducted in a controlled manner at significantly higher temperatures than in batch processing, thus decreasing the overall process energy demands.

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<sup>131</sup>These solvents have boiling points of 40°C and 82°C respectively at normal atmospheric pressure. Thus, higher pressure operation elevates their boiling points so they can remain in liquid phase even at temperatures above their boiling points. Putting the solvent in a super-heated state above its normal boiling point speeds up the reaction.

<sup>132</sup>An exothermic reaction releases heat into its surroundings.

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<sup>133</sup>Azides are any class of chemical compounds containing three nitrogen atoms as a group, represented as (–N<sub>3</sub>). Most azides are unstable substances that are highly sensitive to shock and have explosive characteristics.

<sup>134</sup>B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, and D. T. McQuade, “Greener Approaches to Organic Synthesis Using Microreactor Technology,” *Chemical Reviews*, vol. 107, no. 6 (2007). Fluorinated molecules are valuable as pharmaceuticals and agricultural chemicals, among other uses.

In another example, tetrazoles are not suited for large-scale synthesis since explosive reagents, toxic metal-containing compounds, or an excess of azide are required.<sup>135</sup> The hazard with azide use is the generation of hydrazoic acid, which is a volatile and explosive liquid. Palde and Jamison reported a safe and efficient synthesis of tetrazole products from nitrile compounds and sodium azide performed in a flow microreactor that minimized safety risks while allowing a shorter reaction time due to the flexibility of operating at elevated temperature and pressure.<sup>136</sup> The authors concluded that the most important attributes of this process—high yield, near-equal nitrile:azide ratio, minimal hydrazoic acid generation, and short reaction time—are collectively possible only because the reactions can be conducted at elevated temperature (190°C). This critical reaction feature is feasible only in the continuous flow format, wherein there is no headspace in which hydrazoic acid could accumulate to an explosive level. In contrast, a closed-system batch process at 190°C would be far too hazardous, and without elevation of the reaction temperature, the reaction rate would be well below a usable level. Thus, the continuous flow microreactor made it possible to safely produce tetrazoles on a commercial scale.

Shorter reaction time: Continuous flow microreactors generally increase the

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<sup>135</sup>Tetrazoles are an important class of cyclic compounds which are used in a wide range of applications such as organocatalysis and transition metal catalysis, as propellants and explosives, and perhaps most commonly in medicinal chemistry. Their wide utility has prompted significant efforts towards their safer synthesis.

<sup>136</sup>P. B. Palde and T. F. Jamison, "Safe and Efficient Tetrazole Synthesis in a Continuous-Flow Microreactor," *Angewandte Chemie International Edition*, vol. 50, issue 15 (2011).

efficiency of a process, which is reflected in a decrease in total reaction time. This is possible through better temperature control compared to batch processing. Shorter reaction times allow for lower energy use, especially in high or low temperature reactions or for reactions requiring very precise temperature control. The improved efficiency also leads to more selective chemistry, which reduces waste. Therefore, a short reaction time generally correlates to lower waste, less energy consumption, and a more efficient reaction overall. For example, scientists from Eli Lilly reported on a multi-step flow synthesis of the drug fluoxetine, the active ingredient in Prozac<sup>®</sup>, in 2011. The flow reactor afforded a shorter reaction time and the safe handling of hazardous intermediates. In general, the hazard potential of strongly exothermic or explosive reactions can be significantly reduced because of ease of control of process parameters—including pressure, temperature, residence time, and flow rates—in reactions that take place in small volumes.

Prevention of waste through optimization of solvents: According to authors of a recent scientific publication, reaction solvents contribute greatly towards waste generation in synthetic processes. Performing reactions under solvent-free conditions is still a desirable approach.<sup>137</sup> However, in batch reactions, there is often poor thermal management and solvents are needed to keep solutions dilute and prevent an uncontrolled reaction. Thus, batch processes can be wasteful.<sup>138</sup> In contrast, continuous

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<sup>137</sup>Wiles and Watts, "Continuous Flow Reactors," 38.

<sup>138</sup>For example, Gerogiorgis and Jolliffe reported that the E-factor (waste-to-product ratio) of a batch procedure could be as high as 25-100 for drugs, indicating that 25-100 kg of waste

flow microreactors have much better thermal management. Therefore, it is possible to manage such reactions in a safe and efficient manner in the absence of a diluting solvent. Thus, continuous flow microreactors help to prevent waste as they are more amenable to low-solvent or no-solvent reaction conditions. In this regard, Jamison and co-workers developed a continuous flow process using a microreactor for the synthesis of diphenhydramine hydrochloride, which is an active ingredient in several widely used medications (e.g., Benadryl<sup>®</sup>, Tylenol<sup>®</sup> PM) and has a worldwide demand higher than 100 tons/year.<sup>139</sup> By using a microreactor at 175°C with a residence time of 16 minutes, their process minimized waste and reduced purification steps and production time with respect to existing batch synthetic routes. The reaction rate was also enhanced by running the reaction at a higher temperature (above the boiling point of the reactant) under solvent-free conditions. Similarly, Merck and Lonza devised a simpler and safer continuous flow synthesis of efavirenz (an essential drug for the treatment of human immunodeficiency virus (HIV)) without the use of toxic solvents that led to its shortest manufacturing route. Continuous flow reactions also align with atom economy (a measure of the percentage of the mass of reactants that are incorporated into the product), another metric to assess waste. Because continuous flow allows for enhanced control over the reaction conditions, high-

purity products can be produced. This reduces waste that may otherwise be produced from subsequent purification processes.

#### Automated process optimization and analysis:

According to a company's microreactor technology review, much of the effort of organic chemists is consumed in searching for optimal reaction conditions to achieve a particular transformation resulting in a specific molecular target. For example, many organic transformations depend on multiple factors that determine the outcome of the reaction. Thus, process optimization frequently requires an investment of time and large quantities of valuable starting materials. Additionally, in traditional batch processing, reactions may take days to optimize because processing takes place in a series of discrete steps, with hold times between steps so samples can be tested offline for quality. In contrast, in a flow process, a sequence of reactions can be run continuously through the system. High levels of automation and rapid screening of reaction conditions reduces processing time. That is, process monitoring is automated in continuous processing and is carried out more frequently than in batch processing. Reaction parameters such as reaction time, stoichiometry, temperature, and the timing for adding reactants can be varied in any combination. Each experiment consumes very little of the starting material—as little as 100 microliters—according to one company's product literature. This means that many experimental points can be generated in a short time, allowing the chemist to quickly identify the optimum conditions. This greatly reduces drug development time. A company's product literature reported that continuous flow microreactors have the ability to accelerate the research and development phase in organic chemistry and

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are generated for every 1 kg of drug produced. D. I. Gerogiorgis and H. G. Jolliffe, "Continuous Pharmaceutical Process Engineering and Economics," *Chimica Oggi - Chemistry Today*, vol. 33, no. 6 (2015).

<sup>139</sup>D. R. Snead and T. F. Jamison, "End-to-End Continuous Flow Synthesis and Purification of Diphenhydramine Hydrochloride Featuring Atom Economy, In-line Separation, and Flow of Molten Ammonium Salts," *Chemical Science*, vol. 4 (2013).

reduce development cost so that companies can benefit from much shorter time-to-market for new drugs.

Another advantage over batch processing is the tunable nature of continuous flow through the use of in-line analytics. In-line analytics are used to monitor the process in real-time and its implementation is considered key to quality control in continuous processing. The introduction of in-line analytics improves the quality, consistency, and efficiency of process steps, leading to improved product quality. For example, real-time monitoring of continuous flow processes through the use of in-line analytics enables rapid identification and resolution of issues with product quality. In-line analytical tools such as Raman spectroscopy, infrared spectroscopy, and mass spectroscopy have been coupled to microreactors. These tools allow a researcher to monitor the reaction in real time, determine reaction parameters, and characterize intermediates. These data can help improve process understanding and control which may reduce the risk of wasting product because of non-compliance with desired product quality. Real time analysis also assists with the optimization of key reaction parameters such as residence time, temperature, reaction time, pressure, feed rate of contents, and concentration of reactants, leading to improved product quality and consistency.

Ease of scale-up: One of the benefits of microreactor technology is its ease of scalability compared to conventional batch reactors.<sup>140</sup> For example, continuous flow

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<sup>140</sup>Scale-up in this case refers to increasing product output by adding more microreactors to the production line, rather than

processes allow reactions to be conducted with fewer steps and fewer formal protecting groups. This eliminates the need for extra purification steps and allows for more efficient use of time and materials. Overall, this enables a safer scale-up process, which is among the primary reasons companies consider using continuous flow microreactors, according to a review by Wiles and Watts.<sup>141</sup> Additionally, continuous manufacturing can potentially allow increased production volume without the bottlenecks related to scale-up, providing more response capacity. Eliminating such bottlenecks may facilitate rapid clinical development of breakthrough drugs. For example, the authors of a published review of drug synthesis using continuous flow chemistry reported on AstraZeneca's scale-up efforts for their gastroesophageal reflux inhibitor target drug called AZD6906, which they achieved through better control of exothermic reaction with flow chemistry.<sup>142</sup> In early development, this drug was prepared in batches. However, studies showed potential concerns regarding exothermic reaction profiles as well as product instability which needed to be addressed when moving to larger scale synthesis. They used microreactor flow chemistry to circumvent some of these issues and subsequently developed a route to

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increasing the reactor volume as is generally done during a scale-up operation.

<sup>141</sup>C. Wiles and P. Watts, "Continuous Process Technology: A Tool for Sustainable Production," *Green Chemistry*, vol.16, no. 55 (2014). According to the authors, a recent survey of 50 European Companies reported that safety was the primary reason for choosing to implement or investigate flow processing.

<sup>142</sup>M. Baumann and I. R. Baxendale, "The Synthesis of Active Pharmaceutical Ingredients (APIs) Using Continuous Flow Chemistry," *Beilstein Journal of Organic Chemistry*, vol. 11 (2015).



efficiently and reliably provide sufficient quantities of AZD6906 in continuous flow mode while addressing safety issues. The benefits of a continuous flow microreactor—superior heat dissipation and improved temperature control due to reduced reaction volume—allowed the exothermic reaction to be carried out safely. More recently, scientists at Novartis developed a semi-continuous flow process for the synthesis of the oral anti-diabetic agent vildagliptine. The flow process allowed for the instantaneous consumption of a hazardous intermediate formed during the reaction, thus allowing for a safe scale-up.

Savings in capital and operational expenditures: Pharmaceutical companies also consider using continuous processing in response to increasing research and development costs and competition from manufacturers of generic drugs. Several studies have reported that continuous manufacturing could reduce both operating expenditures and capital expenditures for the fine chemical and pharmaceutical industries.<sup>143</sup> According to the authors of these studies, capital expenditures are reduced because continuous manufacturing allows the use of smaller production facilities that also have a smaller plant footprint and fewer unit operations. Operational expenditures are lower in continuous manufacturing due to factors such as reduced

labor, greater automation of the process resulting in reduced manual intervention, increasing asset utilization (that is, operating on a 24-hour production cycle with minimal or no interruption, according to a company official we interviewed), reduced catalyst and solvent use, minimization of reaction time through better temperature control, effective scale-up of exothermic reactions without the need for special equipment, reduced inventory, less product reject due to real time monitoring, and reduced waste. According to a company scientist we interviewed, although an upfront capital investment is required to implement microreactor technology, the reactions associated with this approach are generally 5 to 10 times lower in cost. That is, the relatively smaller footprint of a continuous flow microreactor has an economic advantage compared to batch flow reactors. According to another company scientist we interviewed, continuous flow technology is a significant area of investment, justifying new development funding, because it ultimately reduces costs through lower energy usage and also reduces waste.

Potential for improved product yield: A review article by Mason and colleagues reported that a Suzuki reaction—an important type of reaction—achieved 68 percent conversion in a microreactor, a notable increase relative to the batch reaction (10 percent yield).<sup>144</sup>

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<sup>143</sup>T. Harrington, L. Alinaghian, and J. Srai, “Continuous Manufacturing and Product-Process Archetypes: Implications for Supply Network Design in Pharma” (paper presented at the 24th Annual Production and Operations Management Society Conference, Denver, CO, May 2013). I. R. Baxendale, R. D. Braatz, A. J. Florence, B. K. Hodnett, K. F. Jensen, M. D. Johnson, P. Sharratt, and J. Sherlock, “Achieving Continuous Manufacturing: Technologies and Approaches for Synthesis, Work-up and Isolation of Drug Substance,” *Journal of Pharmaceutical Science*, vol. 104, no. 3 (2015). Gerogiorgis and Jolliffe, “Continuous Pharmaceutical Process Engineering,” 29.

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<sup>144</sup>Mason, Price, Steinbacher, Bogdan, and McQuade, “Greener Approaches to Organic Synthesis,” 2300.

### 5.3 Disadvantages of and barriers to continuous manufacturing

However, despite the many advantages offered by continuous processing and microreactors for some processes, there are also trade-offs. According to representatives of a pharmaceutical company we interviewed, some of the reasons for the slow adoption of continuous manufacturing by the pharmaceutical industry include risk aversion and economic aspects—for example, the cost of building new infrastructure for flow systems. Batch manufacturing has been the process of choice for the pharma industry because of its familiarity, among other reasons. Industry scientists told us that it is challenging to change from what is proven and accepted to something new. Furthermore, pharmaceutical company officials we interviewed told us that the cost involved in developing new infrastructure for continuous processing may discourage the use of this technology.

Complex processing conditions: According to a white paper by Baxendale et al., the diversity and complexity of molecules of interest and the consequent need for diverse and complex processing conditions makes the adoption of continuous manufacturing challenging for the pharmaceutical and fine chemical industries.<sup>145</sup> Pharmaceutical molecules typically have complicated synthetic routes requiring several steps that involve highly specialized molecular transformations, such as separation and purification steps. This is a key reason why

batch processing dominates in pharmaceutical production: a small number of temperature- or pressure-controlled, agitated vessels can be used for virtually all of the necessary reaction, liquid-liquid extraction, distillation, adsorption, and crystallization steps associated with a drug's synthetic route. Integrating these steps in a continuous process is challenging because it requires carefully controlled reaction rates that are coordinated with the process flows of sequential steps. Furthermore, most routes conceived during small-scale laboratory development have historically been batch-based and were scaled-up accordingly.

Economic uncertainties: While cost savings can be expected from continuous processing in a microreactor through improved yield, automation, new reaction pathways such as solvent-free reactions, and improvements in safety, these economic gains are difficult to evaluate, according to the authors of a report.<sup>146</sup> However, representatives from one pharmaceutical company we interviewed told us that they are manufacturing tablet drug products from drug powders—previously a batch operation—in a continuous mode. According to a company's website article, tablet manufacturing is one area where pharmaceutical companies are choosing to demonstrate continuous processing in drug manufacturing. The reported benefits are increased equipment efficiency, savings in space, reduction of raw material and energy usage, reduction of scrap waste, and reduction of human interference, among others, which the company believes would

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<sup>145</sup>Baxendale, Braatz, Florence, Hodnett, Jensen, Johnson, Sharratt, and Sherlock. "Achieving Continuous Manufacturing," 781.

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<sup>146</sup>D. M. Roberge, L. Ducry, N. Bieler, P. Cretton, and B. Zimmermann, "Microreactor Technology: A Revolution for the Fine Chemical and Pharmaceutical Industries?" *Chemical Engineering & Technology*, vol. 28, no. 3 (2005).

also result in lower costs of operations and improved safety.<sup>147</sup>

Different reaction phases: While pharmaceutical companies are developing continuous processing to enhance operational efficiency and sustainability, it is not a universal solution for every reaction, according to scientists from one company we interviewed. For example, continuous processing is not well-suited to a slurry-based reaction.<sup>148</sup> An analysis by Roberge et al. of various aspects and applicability of microreactor technology reported that continuous flow microreactors handle solids very poorly.<sup>149</sup> Rather, they are suited for homogenous reactions—those occurring in a single phase—and, to some extent, gas-liquid, or liquid-liquid reactions. The authors found that solids were present as catalysts, reactants, or products in more than 60 percent of the reactions they studied. They noted that this limitation of microreactor technology is an important consideration, given that the number of potential candidates drops significantly after discounting reactions involving solids—unless technological capabilities are developed that allow microreactors to handle solids.

Workforce challenges: According to the authors of a white paper, “Achieving Continuous Manufacturing,” another

challenge with continuous manufacturing is that the skill set and capabilities required to design, develop, validate, and operate a continuous flow process are different from those required for conventional batch processing.<sup>150</sup> Furthermore, according to a policy article on promoting continuous manufacturing in the pharmaceutical sector, “designing, implementing, and adequately regulating these new approaches to manufacturing will require a highly skilled and well-trained workforce.”<sup>151</sup>

Global regulatory uncertainty: According to a policy article on continuous manufacturing and industry representatives we interviewed, the pharmaceutical sector is highly regulated, and any changes to an established manufacturing process may face regulatory delays.<sup>152</sup> Therefore, global regulatory uncertainty may be another barrier to implementing continuous manufacturing in the pharmaceutical industry. Industry representatives we interviewed told us that while FDA may support continuous manufacturing, regulatory authorities in other countries may not be as accommodating or may impose a heavier burden in terms of having to demonstrate product equivalency for any process changes, among others.

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<sup>147</sup>I. Backx, *The Key to Continuous Manufacturing*, accessed January 8, 2018, <http://www.industry.siemens.com/verticals/global/en/pharma-industries/continuous-manufacturing/Documents/Article-The-Key-to-Continuous-Manufacturing.pdf>.

<sup>148</sup>A slurry is a semi-liquid mixture with fine particles suspended in water.

<sup>149</sup>Roberge, Ducry, Bieler, Cretton, and Zimmermann, “Microreactor Technology,” 318.

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<sup>150</sup>Baxendale, Braatz, Florence, Hodnett, Jensen, Johnson, Sharratt, and Sherlock. “Achieving Continuous Manufacturing,” 781.

<sup>151</sup>Center for Health Policy at Brookings, Promoting Continuous Manufacturing in the Pharmaceutical Sector, Discussion guide, October 19, 2015, accessed November 17, 2017, <https://www.brookings.edu/wp-content/uploads/2015/10/Continuous-manufacturing-discussion-guide.pdf>.

<sup>152</sup>Center for Health Policy at Brookings, Promoting Continuous Manufacturing, 2015.

## 6 Roles of the federal government and other stakeholders in supporting the development and use of more sustainable chemical processes and products

The federal government and other stakeholders play a number of roles, sometimes in collaboration, to advance the development and use of more sustainable chemical processes and products. First, federal programs and offices support research on the impacts of chemicals on human and environmental health. Second, federal programs and offices support the development of more sustainable chemical processes and their commercialization. Third, federal programs and offices aid in the expansion of markets for products manufactured with more sustainable chemicals and processes. In addition, other stakeholders play similar roles and some additional roles that contribute to the development and use of more sustainable chemical processes and products.

### 6.1 Federal programs support research on the impacts of chemicals on human and environmental health

A number of federal programs and offices support basic research on the characteristics and biological effects of chemicals that underpins the development and use of more sustainable chemistry products and processes. Federal programs fund and study the impacts of chemicals on human health and the environment, develop new methodologies for testing and predicting these effects, award grants for research on chemicals and new methodologies, identify more sustainable chemical alternatives, and evaluate the risks of chemicals. See table 9 for selected examples of federal programs and

offices that support research on the impacts of chemicals on human health and environment health. (For more information how these programs and offices were selected, see app. 1.)

#### 6.1.1 The National Toxicology Program (NTP) conducts studies on chemical substances that inform regulatory agencies

NTP, headquartered at the National Institute of Environmental Health Sciences (NIEHS), conducts and coordinates HHS toxicology research on the potential human health effects of chemicals, develops improved methods and approaches for testing these effects, and shares information about hazardous chemicals with decision makers. According to NTP's 2016 Annual Report, the program's budget was \$131 million in fiscal year 2016.<sup>153</sup>

Since its inception in 1978, NTP has studied the health effects of more than 2,500 chemical substances, including dietary supplements, industrial chemicals, consumer products, and complex mixtures. NTP selects which chemicals to study based on recommendations from a range of stakeholders, including academic institutions, advocacy groups, federal, state, and local

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<sup>153</sup>U.S. Department of Health and Human Services, National Toxicology Program Office of Liaison, Policy, and Review, *Annual Report for Fiscal Year 2016* (Research Triangle Park, N.C.: 2017).

agencies, industry, and programs within NTP. NTP’s current research portfolio focuses on testing synthetic industrial chemicals, pesticides, drugs, metals, and food additives. For example, NTP has investigated such things as the health effects of a flame retardant used in furniture materials, an artificial flavoring used in food and beverages, and a perfume

ingredient used in soaps and shampoos. In 2014, when about 10,000 gallons of coal-processing chemicals spilled into the Elk River in West Virginia, the water source for the city of Charleston, West Virginia, NTP evaluated the potential toxicity of the chemicals to inform the public and federal and local decision makers.

**Table 9: Selected federal programs and offices support research on the impacts of chemicals on human and environmental health**

Federal program or office	Selected activities related to sustainable chemistry
National Toxicology Program (NTP) - Department of Health and Human Services	Conducts toxicology research on the potential health effects of chemicals.
Toxicology in the 21st Century (Tox21) program - Department of Health and Human Services / Environmental Protection Agency	Seeks to improve how scientists predict the safety of chemicals by developing new testing methodologies.
Chemical Safety for Sustainability (CSS) program - Environmental Protection Agency	Conducts research on the properties of chemicals and generates hazard, exposure, and risk assessment data.
Science to Achieve Results (STAR) grant program - Environmental Protection Agency	Funds academic research on new methodologies for testing and understanding chemicals and the effects of exposure.
Networks for Characterizing Chemical Life Cycles grant Environmental Protection Agency and the National Science Foundation	Funded research to build the scientific basis and evaluation tools required to understand and predict potential for manufactured chemicals and materials to impact human health and the environment.
National Institute for Environmental Health Sciences (NIEHS) Department of Health and Human Services	Funds research on the impacts of chemicals on human health.
Energy Frontier Research Centers Department of Energy	Centers seek to address long-term fundamental challenges in chemical research.
Significant New Alternatives Policy (SNAP) program Environmental Protection Agency	Evaluates alternatives for ozone-depleting substances to help industry identify acceptable alternatives in order to comply with Clean Air Act regulations.
Chemical and Material Risk Management Program Department of Defense	Identifies and seeks to manage the risks associated with hazardous chemicals and materials.

Source: GAO analysis of agency documentation. | GAO-18-307

NTP also develops new and improved testing methodologies to evaluate the human health effects of chemicals. While NTP generally conducts toxicological testing using rodent models, the program also seeks to develop faster and predictive tests for toxicological

research that reduce or replace animal testing. NTP also participates in programs that support alternative testing methods including the Toxicology in the 21<sup>st</sup> Century (Tox21) program (described in more detail below) and the Transform Tox Testing Challenge:

Innovating for Metabolism.<sup>154</sup> NTP is also working to ensure that new tests are accepted for regulatory decision making. NTP manages the Interagency Coordinating Committee on the Validation of Alternative Methods, which includes representatives from 16 federal regulatory and research agencies and offices that use, generate, or disseminate toxicological and safety testing information, including the National Cancer Institute and Occupational Safety and Health Administration.<sup>155</sup>

NTP makes its research available to federal agencies, states, scientists, the medical community, and the public and provides guidance and interpretation of the scientific data and its appropriate use. NTP information is available through technical, toxicity, and research reports, federal register notices, journal publications, press releases, and online databases. Agencies use NTP's research for decision making when developing guidelines and regulations to protect public health. For example, NTP findings are used by the EPA in its Integrated Risk Information System (IRIS), which identifies and characterizes the health hazards of chemicals found in the environment and by the Human Health Risk

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<sup>154</sup>In 2016, EPA, NIH's National Center for Advancing Translational Sciences, NIH's NIEHS, and NTP announced the Transform Tox Testing Challenge: Innovating for Metabolism, which plans to award up to \$1 million for improvements in the relevance and predictivity of data generated from automated chemical screening technology used for toxicity testing.

<sup>155</sup>The 16 agencies and offices include: Agency for Toxic Substances and Disease Registry, Consumer Product Safety Commission, DOD, DOE, Department of Interior, Department of Transportation, EPA, FDA, NIEHS, NIH, USDA, National Cancer Institute, National Institute for Occupational Safety and Health, National Institute of Standards and Technology, National Library of Medicine, and Occupational Safety and Health Administration.

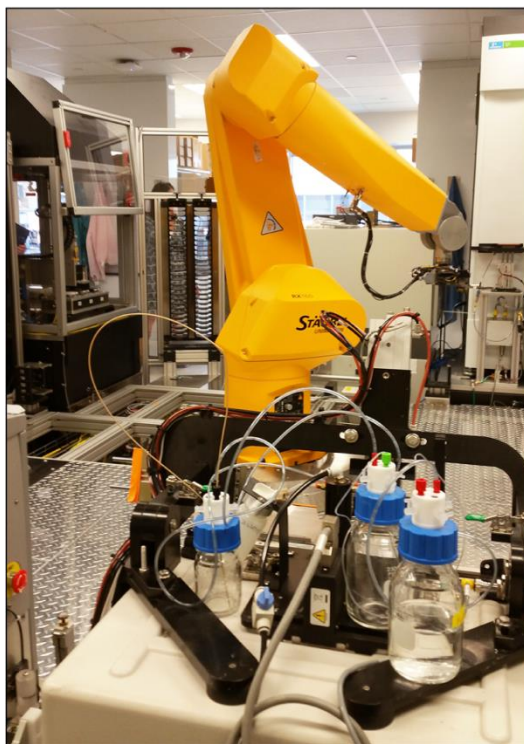
Assessment program, which supports environmental decision making by assessing the human and environmental health risks posed by chemicals. Based on NTP's study findings that hexavalent chromium in drinking water can cause cancer, California adopted drinking water standards for the chemical in 2014. In 2016, citing NTP's Report on carcinogens and others that found that the chemical trichloroethylene can lead to a cancer, the Department of Veterans Affairs amended its regulations regarding veteran's service-connected disability benefits for service members exposed to the chemical in the water supply at U.S Marine Corps Base Camp Lejeune. NTP also interprets relevant scientific results for the public's benefit through factsheets and podcasts. For example, NTP has compiled a factsheet and produced a podcast for the general public on the potential health hazards of bisphenol A (BPA), a chemical found in many plastic products such as water bottles.

### 6.1.2 HHS and EPA screen chemicals through the Tox21 program

Tox21 seeks to improve how scientists predict the safety of chemicals by developing and applying new testing methods to accurately and quickly predict whether chemicals have the potential to affect human health. Tox21 combines funding, expertise, data, and tools from NIH, including NTP at NIEHS and the National Center for Advancing Translational Sciences, and EPA and FDA. The Tox21 testing methods allow officials to prioritize chemicals for further, more costly and time-consuming toxicological evaluations and could be used to develop strategies that can be used directly by regulatory agencies to regulate chemicals). For example, high-throughput screening uses automated methods (including the robotic

arm pictured in fig. 19) to rapidly evaluate a large number of chemicals for biological responses to determine how the chemicals affect cellular functions that are linked to diseases. The partner agencies work together and solicit input from researchers, companies, and NGOs to select the chemicals and tests that will be performed as part of the Tox21 program. Since 2008, the Tox21 partner agencies have used a high-throughput screening platform to assess approximately 10,000 chemicals for their potential impacts on biological systems. The results of these tests, which are available free of charge, allow researchers to prioritize chemicals that have shown a potential to effect human health for testing and are also used by decision makers to assess health risks. For instance, the Minnesota Department of Health is using Tox21 data for assessing health risks associated with water contaminants. Tox21 relies on voluntary budget allocations and in kind contributions from its partner agencies.

**Figure 19: High throughput screening equipment at the Toxicology in the 21<sup>st</sup> Century (Tox21) robotics facility at the National Institutes of Health National Center for Advancing Health National Center for Advancing Translational Sciences**



Source: GAO. | GAO-18-307

### 6.1.3 EPA's Chemical Safety for Sustainability (CSS) program generates data and develops tools and public databases

The CSS research program develops tools and methodologies to test the properties of chemicals and generate hazard, exposure, and risk assessment data across the life cycle of thousands of chemicals. A number of EPA laboratories and centers contribute to the CSS research program, including the National Center for Computational Toxicology and the National Risk Management Research

Laboratory.<sup>156</sup> According to EPA officials, CSS's budget for fiscal year 2016 was \$89 million.

CSS develops new methodologies, tools, and models for evaluating and predicting the safety of chemicals for human health and generates data using these tools. For example, the National Center for Computational Toxicology runs the Toxicity Forecaster (ToxCast) which uses high throughput screening data to identify and prioritize chemicals used in industrial and consumer products that may present a potential risk to human health. The Center, in partnership with the National Exposure Research Laboratory, also manages an Exposure Forecaster tool that predicts the potential for human and environmental exposures to chemicals. To address a critical gap in data on the potential of chemicals to disrupt neurodevelopment, CSS is also working to develop faster and less costly methods for testing for neurodevelopmental toxicity, according to EPA officials. CSS uses these tools and others to identify the characteristics and potential human health risks of chemicals, evaluating thousands of chemicals more efficiently than is possible using traditional research methods such as animal testing. For example, over 1,800 chemicals have been evaluated by ToxCast and the Exposure Forecaster has predicted exposures for almost 8,000 chemicals.

CSS develops public databases and tools to facilitate the use of chemical data by industry in the selection, design, and use of chemicals by federal regulators. For example, CSS has

made the results of ToxCast and Tox21 testing publically available for decision makers through a ToxCast Dashboard and is developing guidance for decision makers on how to interpret and evaluate ToxCast data in several different decision contexts. CSS is also working on case studies to guide decision-making when using its data, including two with the EPA's Office of Pesticide Programs to support the prioritization of pesticide ingredients for further testing. CSS compiles and centralizes data for decision makers from a wide range of sources. One of these resources, the CompTox Chemistry Dashboard, provides users access to curated information from a wide variety of sources on the structures and properties of more than 700,000 chemicals. According to EPA officials, the data in the dashboard can be used by decision makers to inform regulations, prioritize chemicals for additional testing, or support the use of alternative chemicals.

Information generated by CSS supports decision making by federal and state actors. For example, CSS data are used to inform EPA legislative mandates and policies, including the Clean Air and Water Acts, Safe Drinking Water Act, Federal Food, Drug, and Cosmetic Act, and others. EPA's Office of Chemical Safety and Pollution Prevention is using CSS tools and approaches to support the implementation of TSCA and the Federal Insecticide, Fungicide, and Rodenticide Act, according to EPA officials. To assist EPA in fulfilling its congressional mandate to screen certain chemicals for potential endocrine disruption,<sup>157</sup> CSS used data from ToxCast, to

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<sup>156</sup>Other EPA entities that contribute to the CSS research program include the National Health and Environmental Effects Research Laboratory, National Exposure Research Laboratory, and National Center for Environmental Assessment.

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<sup>157</sup>Specifically, the Food Quality Protection Act requires EPA to develop a screening program to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, and other other endocrine effects that EPA may designate. 21 U.S.C §



create a customized tool, the Endocrine Disruption Screening Program. According to officials, the State of California uses National Center for Computational Toxicology data to support risk assessments of pesticides and companies include the data in dossiers on their products submitted to the European Chemicals Agency. CSS works closely with the offices that administer federal regulations to shape CSS's research plans to best meet their needs.

The National Risk Management Research Laboratory (NRMRL), one of the EPA offices that support CSS research, works to identify risks to human and environmental health, including those posed by chemicals, and develops tools to help manage those risks. According to EPA officials, these tools and data enable decision makers to identify and design chemicals that are more sustainable. NRMRL also develops and conducts life cycle inventories to develop a base of information for use by decision makers in conducting LCAs. For instance, NRMRL is working with DOE's National Renewable Energy Laboratory (NREL) on a life cycle model of electricity production and distribution that can be dropped into other analysis or tools that provide life cycle impact analysis for chemicals. NRMRL, along with EPA's National Exposure Research Laboratory, is also developing a Life-Cycle Human Exposure Model that will allow decision makers to rapidly evaluate chemical and product safety by bringing together life cycle assessment and chemical exposure modeling.

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346a(p)(1). The substances include pesticide chemicals and those chemicals that may have an effect that is cumulative to an effect of a pesticide chemical if the Administrator determines that a substantial population may be exposed to such substance. 21 U.S.C § 346a(p)(3).

#### 6.1.4 EPA, NSF, HHS, and DOE fund research on how chemicals impact human and environmental health

Federal programs provide funding for research on the impacts of chemicals and how to measure those impacts. EPA and NSF fund academic research in the development of new methodologies and models for testing and understanding chemical effects and exposure through several grant programs. EPA's Science to Achieve Results (STAR) grant program provides funding for research into safer, more sustainable use of chemicals in products. For instance, EPA awarded approximately \$3.8 million in funding to six universities through the STAR Systems-Based Research for Evaluating Ecological Impacts of Manufactured Chemicals grant program to develop new methods for evaluating how exposure to chemicals influences the health of ecosystems and how to predict, prevent, and mitigate these effects. EPA and NSF jointly awarded grants through the Networks for Characterizing Chemical Life Cycles program which provided approximately \$10 million over four years to two interdisciplinary research teams that explored methods and tools to characterize and predict the impacts of chemicals. HHS provides funding through NIEHS to support research on the impacts of chemicals on human health, such as how bisphenol A (BPA) acts as an endocrine disruptor and evaluating the toxic and carcinogenic potential of chemicals in dietary supplements and herbal medicines. DOE funds basic sustainable chemical research as well. For example, several of the Energy Frontier Research Centers focus on long-term fundamental challenges in chemical research including the Center for Direct Catalytic Conversion of Biomass to Biofuels and the

Integrated Mesoscale Architectures for Sustainable Catalysis.

### 6.1.5 EPA identifies substitutes for ozone-depleting substances

EPA's Office of Air and Radiation Significant New Alternatives Policy (SNAP) program evaluates alternatives for ozone-depleting substances to help industry identify acceptable alternatives in order to comply with Clean Air Act regulations restricting use of these chemicals.<sup>158</sup> According to EPA, ozone-depleting substances accelerate the destruction of the stratospheric ozone layer which protects humans and the environment from damaging ultraviolet light. SNAP evaluates manufacturer, formulator, or user-proposed substitutes for ozone-depleting substances. To do this, they use data primarily from the submitter of the substitute for review as well as data from a variety of sources such as other federal agencies on the health and environmental impacts of substitutes for ozone-depleting substance during the manufacturing, use, disposal, and recycling phases of the chemical's life cycle. SNAP evaluates substitutes based on their atmospheric impacts, (e.g., ozone depletion potential, global warming potential, and air quality), toxicity, flammability, and effect on occupational and consumer health and safety, and ecosystem effects. SNAP also evaluates potential exposure of the substitute by manufacturing facility workers, servicing

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<sup>158</sup>Title VI of the Clean Air Act required EPA to establish regulations protecting the ozone layer by phasing out the production of substances that deplete it. The Act requires EPA to publish a list of safe and unsafe substitutes for ozone-depleting substances, including chlorofluorocarbons (CFCs), halons, carbon tetrachloride, methyl chloroform, and hydrochlorofluorocarbons and to ban the use of unsafe substitutes. 42 U.S.C. §§ 7671-7671q.b.

technicians, and the general public. SNAP publishes an evolving list of acceptable and unacceptable substitutes in eight industrial sectors including, for example, refrigeration and air conditioning, cleaning solvents, and fire suppression. In addition, SNAP publishes a series of factsheets and case studies on transitioning to alternatives. Companies can use the online list to identify alternatives to ozone-depleting substances to use in their manufacturing and products.

### 6.1.6 DOD assesses chemical risks on human and environmental health

DOD's Chemical and Material Risk Management Program is designed to manage risks associated with hazardous chemicals and materials in order to minimize adverse impacts on human and environmental health and DOD mission areas, as well as to reduce life cycle costs of weapons systems, platforms, equipment, and facilities. The program identifies and assesses the risks of emerging contaminants—chemicals that lack human health standards or have an evolving science and regulatory status. The program has scanned over 500 emerging contaminants to identify their importance to DOD, conducted approximately 50 impact assessments of emerging contaminants that pose risks to DOD, and developed 60 risk management actions for high-risk emerging contaminants. For example, the program issued an alert for decision makers on the potential risks to humans and the environment of the chemicals used in a fire suppressant for liquid fires, how to identify whether the chemicals were present, when the firefighting foams could be used, and how

to dispose of them properly.<sup>159</sup> According to DOD, the budget authority for the program in fiscal year 2016 was \$818,000.

## 6.2 Federal agencies support the development and commercialization of more sustainable chemistry technologies

Multiple federal agency programs and offices support the development of new more sustainable chemistry processes and facilitate the commercialization of these processes. These programs provide support in a variety of ways including conducting and funding basic and applied research to develop more sustainable processes and products; providing loan guarantees, grants, and technical assistance to researchers and companies; and recognizing innovative technologies through an award program. The following are selected examples of federal programs and offices that support the development and commercialization of more sustainable chemistry technologies (see table 10).

### 6.2.1 NSF grant programs support research to develop more sustainable chemistry processes

NSF funds academic research on sustainable chemistry technologies through targeted grant funding from the Sustainable Chemistry, Engineering, and Materials (SusChEM) initiative as well as through its core research grant programs. In response to a 2011 law passed by Congress, NSF established the SusChEM program to support research into

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<sup>159</sup>Chemical & Material Emerging Risk Alert: Aqueous Film Forming Foam (AFFF). Risk Alert #03-11. Department of Defense, Chemical and Risk Management Directorate.

sustainable chemistry which would lead to clean, safe, and economical alternatives to traditional chemical products and practices.<sup>160</sup> NSF awarded SusChEM grants for research throughout the life cycle of chemicals, but focused on awarding grants for research on improving the processing and use of raw materials. For example, Stanford University and IBM received a SusChEM grant to develop catalytic methods to produce biodegradable polymers that could be used to manufacture a range of plastic products, including medical stents and compostable plastic ware. Another SusChEM grant funded research at Arizona State University on the use of iron oxysulfide to replace the toxic materials currently used to manufacture solar cells. When determining what research it would fund, NSF officials considered the chemical breakthroughs and research priorities identified by participants in workshops they sponsored. Workshop participants included academic researchers, federal agency officials, representatives from the American Chemical Society, and chemical manufacturers and users. SusChEM awarded 349 grants totaling about \$134 million between 2013 and 2017. While the SusChEM program ended in fiscal year 2017 as planned, according to officials, NSF will continue to fund grants related to sustainable chemistry through its core research grant programs in the conventional scientific disciplines.<sup>161</sup> The

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<sup>160</sup>America Competes Reauthorization Act of 2010, PL 111-358, Section 509.

<sup>161</sup>SusChEM is part of the NSF Science, Engineering and Education for Sustainability programs. When this program was initiated, it was envisioned as a limited-life focus, as is typical for NSF topical initiatives. SusChEM ended in fiscal year 2017 along with the Science, Engineering and Education for Sustainability program. According to NSF officials, the Divisions of Chemistry; Chemical, Bioengineering, Environmental, and Transport Systems; Materials Research; Earth Sciences; and Civil, Mechanical and Manufacturing Innovation have pledged to continue to support sustainable chemistry technologies.

results of NSF funded research are published in peer reviewed journals and freely available on the NSF website.

NSF also funds nine Centers for Chemical Innovation, research centers that include scientists from across academic institutions to focus on major chemical research challenges. According to NSF officials, five of the Centers focus on challenges related to sustainable chemistry technologies, including, for example, the Center for Enabling New Technologies through Catalysis and the Center for Sustainable Polymers. NSF funds Centers in two phases of research: Phase I Centers receive a total of \$1.75 million over three years for the formation and development of a research center and Phase II grants provide follow-on, renewable funding of \$4 million a year for five years to Centers. For example, the Center for Sustainable Polymers focuses on identifying and developing biobased, nontoxic, renewable, and functional polymer-based plastics, as opposed to traditional petroleum-based plastics. The Centers are collaborative, bringing together the expertise and perspectives of a variety of stakeholders, including scientists from different universities and industry. The Center for Selective C-H Functionalization—which explores methods for making organic molecules in a more streamlined, cost-effective, and environmentally benign way—includes collaborators from 14 universities, a research institution, international collaborators, and industry. The Centers also organize educational outreach programs for elementary, middle, and high schools, colleges and universities, and the community to increase understanding about chemicals.

The NSF and EPA Networks for Sustainable Molecular Design and Synthesis grant program funded research on the development of safe and sustainable chemicals, awarding approximately \$19 million over four years to four research groups. Each research group that received one of these awards was required to develop an innovation plan describing how the team would collaborate with industry or support technology transfer. For example, a University of Arizona research team worked with a startup company to commercialize a technology to develop a more sustainable surfactant. (For a list of all the selected grants described in this report, see table 12.)

### 6.2.2 USDA supports more sustainable biorefining technologies and biobased chemicals

USDA supports the development and commercialization of more sustainable chemistry technologies that convert renewable feedstocks into biobased products, including biobased chemicals. Biobased chemicals are chemicals that are manufactured using renewable resources such as municipal solid waste, algae, and the byproducts of other processes—such as corn oil produced in the process of producing corn ethanol. While the goals of USDA’s support of biorefining are to increase the profitability and market for agricultural feedstocks and biobased products and to support the existing biorefining industry, there is also a sustainability benefit to replacing petroleum-based chemicals with those manufactured using renewable resources. The following are examples of USDA programs that support the development of more sustainable biorefining technologies and the manufacture of biobased chemicals.

**Table 10: Selected federal programs and offices that support the development and commercialization of more sustainable chemicals and chemical processes**

Federal program or office	Selected activities related to sustainable chemistry
<b>Sustainable Chemistry, Engineering, and Materials (SusChEM)</b> - National Science Foundation	Funds research to develop clean, safe, and economical alternatives to traditional chemical products and practices.
<b>Centers for Chemical Innovation</b> - National Science Foundation	Funds research centers focused on fundamental chemical research challenges.
<b>Networks for Sustainable Molecular Design and Synthesis</b> – National Science Foundation and Environmental Protection Agency	Funded research to develop safe, sustainable chemicals as well as safe, sustainable processes and procedures.
<b>Agricultural Research Service (ARS) National Program on Biorefining</b> - Department of Agriculture	Conducts research on feedstocks and commercially-viable technologies to convert agricultural material into biochemicals and other byproducts.
<b>National Institute of Food and Agriculture (NIFA)</b> - Department of Agriculture	Funds research into the development of renewable feedstocks and biobased products.
<b>Biorefinery, Renewable Chemical and Biobased Product Manufacturing Assistance Program</b> - Department of Agriculture	Provides loan guarantees for developing, constructing, or retrofitting commercial-scale biorefineries.
<b>Advanced Manufacturing Office (AMO)</b> - Department of Energy	Supports the development of materials and technologies that reduce the energy intensity of sustainable chemistry technologies.
<b>Manufacturing USA – Rapid Advancement in Process Intensification Deployment (RAPID) Institute</b> - Department of Energy	Researches, develops, and demonstrates new chemical processes that save energy and reduce waste.
<b>National Laboratories</b> - Department of Energy	Conduct research and provide unique scientific capabilities on sustainable chemistry technologies.
<b>Department of Energy funding programs</b> - Department of Energy	Provide funding and technical assistance to build knowledge that impacts the development of sustainable chemistry technologies.
<b>Small Business and Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grant programs</b> - Multiple agencies	Fund sustainable chemistry technological innovation and increase commercialization of innovations.
<b>National Institute of Standards and Technology</b> - Department of Commerce	Develops methodologies and standards for measuring and evaluating the sustainability of chemicals and chemistry technologies.
<b>Presidential Green Chemistry Challenge Awards</b> - Environmental Protection Agency	Recognizes chemical technologies that incorporate the principles of green chemistry into chemical design, manufacture, and use.
<b>Strategic Environmental Research and Development Program (SERDP) and Environmental Security Technology Certification Program (ESTCP)</b> - Department of Defense	Funds research on contaminants of concern to the DOD and for the validation and demonstration of new, more sustainable products.

Source: GAO analysis of agency documentation. | GAO-18-307

The Agricultural Research Service (ARS) National Program on Biorefining conducts research on feedstocks and commercially-viable technologies to convert agricultural material into biochemicals and other byproducts. For example, in 2015, researchers identified an enzyme that converts citrus peel waste into an acid that can be used for the development of fine chemicals, such as adipic acid. Adipic acid is used in making nylon, which is manufactured using benzene, a carcinogenic chemical manufactured from nonrenewable fossil fuels. Furthermore, the National Program on Biorefining 2014-2019 5-Year Action Plan lists research on the use of biochemical conversion processes to create biobased chemicals, including alcohols, carboxylic acids, and biopolymers, as a way to maintain the economic viability of biorefineries in the face of the relatively low value of fuel products. The National Program on Biorefining researchers coordinate with other USDA programs working on related research as well as with industry to ensure the research will benefit industry and maximize economic impacts. According to ARS officials, the National Program on Biorefining budget in fiscal year 2016 was approximately \$15 million.

The National Institute of Food and Agriculture (NIFA) program awards grants for more sustainable chemistry technologies. For example, NIFA awards funding for research into the development of renewable feedstocks and biobased products and related analytical tools through the Biomass Research and Development Initiative, a partnership between NIFA, USDA's Institute of Bioenergy, Climate, and Environment, and DOE's Energy Efficiency and Renewable Energy Golden Field Office, Bioenergy Technologies Office. In 2012, for instance, the Biomass Research and

Development Initiative awarded a tire company approximately \$6.9 million over five years to research biorefining technologies to convert a desert shrub into biobased polymers that could be used to replace petroleum-based polymers in rubber tires. The research team, which included academic and federal partners, successfully produced and tested concept tires that will be commercialized within the next two years, according to ARS officials.

Through the Biorefinery, Renewable Chemical and Biobased Product Manufacturing Assistance Program, USDA supports the commercialization of biorefining technologies and production of biobased products by providing loan guarantees for developing, constructing, or retrofitting commercial-scale biorefineries that can convert biomass to biofuels, biobased chemicals, and other products. Eligible projects may receive loan guarantees through the program for up to \$250 million, not to exceed 80 percent of the total project costs. According to USDA officials, as of October 2017, USDA has committed to conditional loan guarantees for nine projects. The budget authority for the program in fiscal year 2016 was \$50 million, according to officials.

### 6.2.3 DOE programs seek to reduce energy use in chemical processing

DOE supports programs that seek to reduce the energy used in manufacturing, including by chemical processes and technologies. DOE funds research through cooperative agreements to reduce energy intensity in manufacturing and also supports technology transfer and the commercialization of the technologies developed through its research and grant programs. The following are

examples of DOE programs that support the reduction of energy use in chemistry technologies.

DOE's Advanced Manufacturing Office (AMO) supports the development of materials and technologies that reduce the energy intensity of manufacturing processes throughout the life cycle of a product, including through sustainable chemistry technologies. For example, in order to support the development of less energy intensive manufacturing processes, AMO awards funding to scientists, consortia, national laboratories, companies, and state and local governments, and also provides technical assistance to industry. AMO funded a team of researchers at Purdue University in partnership with several chemical companies to develop an algorithm to increase energy efficiency in chemical distillation processes, for instance. With proof-of-principle financial assistance from AMO, a company commercialized a method for recycling nylon carpeting that recovers the chemical building blocks of nylon carpeting for reuse while consuming less total energy compared with conventional production. According to DOE officials, AMO identifies challenges to using sustainable chemistry technologies by conducting its own analysis and gathering information from stakeholders including companies, universities, and trade associations, and by holding workshops with stakeholders.

DOE also supports reductions in energy consumption in chemical processes by sponsoring the Rapid Advancement in Process Intensification Deployment (RAPID) institute, one of 14 Manufacturing USA Institutes that seek to bring together industry, academia, and federal partners to create a national

manufacturing research and development infrastructure.<sup>162</sup> The mission of the RAPID institute is to research, develop, and demonstrate new chemical processes that will increase energy efficiency in a variety of chemical processes, including mixing, reaction, and separation. Launched in March 2017, the RAPID Institute is led by the American Institute of Chemical Engineers and its members include 22 academic institutions, 5 government and national laboratories, 18 companies, and 4 NGOs. In addition, more than 130 institute partners committed to cost-shares of \$70 million to match DOE's contribution of \$70 million over five years.

Using cutting-edge scientific facilities and equipment, DOE scientists, engineers, and others employed at DOE's 17 national laboratories carry out research and development on a range of topics, including research on sustainable chemistry technologies. In addition, the national labs support technology transfer and commercialization of processes and technology developed in the labs. According to officials at Pacific Northwest National Laboratory (PNNL) and Argonne National Laboratory (Argonne), technology transfer of lab-developed processes can be moved into commercial production through a range of activities including: direct interactions between scientists or engineers at a lab and a company, co-development of intellectual property, laboratory support during scale up, assistance with initial operations, and

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<sup>162</sup>The Manufacturing USA initiative, also known as the National Network for Manufacturing Innovation, was authorized by Congress in December 2014 with the passing of the Revitalize American Manufacturing and Innovation Act. The Manufacturing USA network of institutes is operated by the interagency Advanced Manufacturing National Program Office, headquartered at NIST.

licensing agreements. Examples of programs at National Labs that support the development and use of more sustainable chemistry technologies include the following.

- At NREL, scientists are researching materials and processes to efficiently convert biomass to high value, biobased chemicals. In addition, NREL develops analytical tools, methodologies, and studies to increase understanding of the potential impact and challenges of the emerging bioeconomy.
- Researchers at PNNL are developing new processes for the conversion of biomass into biobased chemicals. For example, PNNL developed an innovative catalytic process that converts plant-based feedstocks into propylene glycol, a chemical additive in liquid detergents, pharmaceuticals, and plastics typically made from petroleum. The research was supported by PNNL and cost-sharing agreements between DOE's Office of Energy Efficiency and Renewable Energy, the National Corn Growers Association, and other companies. One of the companies licensed the technology from PNNL and began operating a full-scale production facility producing the chemical from soybeans and canola in 2011.
- Argonne has a number of research initiatives that contribute to the development of more sustainable chemistry technologies. For example, Argonne is researching more sustainable catalysts for converting renewable feedstocks to biofuels and biochemicals. The lab also conducts life cycle analysis of bioproducts. Argonne conducted a life cycle analysis to identify a sustainable process for converting non-recycled

plastic into fuel, which can provide a viable waste management option for petroleum-based plastics.

To facilitate the development and commercialization of innovative technologies, DOE provides funding for research and to allow academic researchers and small businesses to take advantage of the state-of-the-art facilities and scientific expertise at national labs. Some of this funding supports the development and commercialization of sustainable chemistry technologies. For example, through cooperative agreements, the Bioenergy Technologies Office provided \$13.1 million to four research projects through the Bioproducts to Enable Biofuels Funding Opportunity to support the development of biomass conversion processes that can produce coproducts such as biobased chemicals along with biofuels. The Advanced Manufacturing Office's Cyclotron Road program at Lawrence Berkeley National Laboratory helps entrepreneurs bridge the gap between early stage technology concepts and commercialization. Through the program, DOE awards two-year fellowships to scientists who are developing innovative energy technologies, and provides funding, lab space, access to scientists at the national lab, and business mentoring. For example, the founders of a company received funding from Cyclotron Road to develop a method to recycle waste carbon dioxide back into fuels and chemicals using only water and electricity as inputs. In 2015, DOE's Office of Energy Efficiency and Renewable Energy launched the Small Business Vouchers Pilot to help small businesses overcome technology and commercialization challenges in bringing new clean technologies to market. Through the program, DOE provides businesses with



vouchers that can be used to request technical assistance from national labs for activities such as prototyping, scaling, regulatory compliance, or modeling and simulations. For example, in 2016, another company received \$300,000 to use facilities at NREL and Lawrence Berkeley National Laboratory to scale up a new technology to produce biobased malonic acid, a chemical used to produce electronics, medicine, and fragrance, through a sugar and water fermentation process rather than the current process which uses toxic chemicals. The Office of Energy Efficiency and Renewable Energy announced that 38 small businesses would participate in the voucher program in fiscal year 2017.

#### 6.2.4 Federal small business programs encourage the development and commercialization of sustainable chemistry technologies

Federal agencies also support the development and commercialization of more sustainable chemistry technologies through the congressionally-mandated SBIR and STTR programs. The SBIR program was initiated in 1982 and has four purposes: (1) to use small businesses to meet federal R&D needs, (2) to stimulate technological innovation, (3) to increase commercialization of innovations derived from federal R&D efforts, and (4) to encourage participation in technological innovation by small businesses owned by disadvantaged individuals and women. The purpose of the STTR program—initiated in 1992—is to stimulate a partnership of ideas and technologies between innovative small businesses and research institutions through federally funded R&D. Together, the agencies that participate in SBIR and STTR have awarded more than \$40 billion through the

two programs since their inception.<sup>163</sup> Some of the funding has been awarded to support the development of more sustainable chemistry technologies. Examples of two research efforts are included below.

- A company received SBIR funding from DOE and NSF to develop a catalytic process to convert lignin found in waste from paper pulping facilities and biorefineries into high value biobased chemicals.
- A company that has developed a process to capture methane and convert it into various biobased products using bacteria has received two SBIR grants through NSF to support the production of biobased, biodegradable polymers from methane gas at a wastewater treatment plant. The company also received two STTR grants from the National Aeronautics and Space Administration (NASA) to modify their technology to produce biobased polymers in space, where they could be produced on-demand.

#### 6.2.5 NIST develops methodologies and standards for evaluating the sustainability of chemical technologies

NIST develops methodologies and standards for measuring and evaluating the sustainability of materials and manufacturing processes, including chemicals and chemistry technologies. In order to improve sustainability, industry needs to accurately measure and evaluate the consumption of

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<sup>163</sup>SBIR participants include USDA, DOD, DOE, EPA, NSF, HHS, NASA and the Departments of Commerce, Education, Homeland Security, and Transportation. STTR participants include the DOD, DOE, HHS, NASA, and NSF.

energy and materials, emissions, waste, and water usage, as well as environmental impacts, at each step in the life cycle (see chapter 2). NIST does not quantify the sustainability of technologies, but provides methodologies, standards, metrics, and validated data to decision makers to assess the sustainability of their choices on a case-by-case basis. NIST works with industry stakeholders to prioritize research goals and identify areas lacking standards. According to NIST officials, the Institute has engaged largely with traditional manufacturers, but is beginning to engage more with chemical manufacturers.

For example, NIST's Sustainable Manufacturing project develops methods for characterizing the environmental aspects of manufacturing processes at the unit, factory, and network levels, which enables the evaluation of the sustainability of these processes. Additionally, according to NIST officials, NIST collaborates with standard setting organizations such as ASTM International to provide industry and federal agencies with protocols and methods for measuring the sustainability of manufacturing processes including inputs, outputs, and waste. NIST led the development of ASTM E3012-16, the Standard Guide for Characterizing Environmental Aspects of Manufacturing Processes, which enables manufacturers to virtually characterize their production processes as computer models, and then, using a standardized method, 'plug and play' the environmental data for each process step to visualize impacts and identify areas for improving overall sustainability of the system.

The Materials Science and Engineering Division, in partnership with industry, other

government agencies, and academia, develops the measurement science, technology, and research required to support the design, manufacture, and use of materials, including chemicals. One program, the Sustainable Composites project, is developing tools to measure the characteristics of sustainable polymer composites in order to enable manufacturers to develop high performance bio-based composites. According to NIST officials, other Division researchers are exploring using biomass to produce nanocellulose materials, a sustainable alternative to petroleum-based chemicals. Division officials also said they are coordinating with companies to develop methods for reducing the amount of solvents companies use and working to develop new solvents that are less toxic. The budget authority for the Materials Science and Engineering Division was approximately \$25 million in fiscal year 2016, according to NIST officials.

In addition, NIST maintains a number of tools that facilitate the selection and use of more sustainable chemicals and processes. For example, NIST maintains a database of information on the thermochemical properties of organic materials that can be used to calculate the energy content for various fuels and the energy used in chemical processes that industry decision makers can use to design more sustainable chemical and manufacturing processes and a database on chemical reactions that occur under gaseous conditions. NIST has also developed calculations that estimate the global warming potential of molecules, which allows for the screening and identification of candidate chemicals to replace hydrofluorocarbon refrigerants that cause climate change. To help industry measure their sustainability

performance, NIST's Sustainable Manufacturing Indicator Repository provides access to centralized information on a range of sustainable indicators from sources such as Dow Jones, the United Nations, and Walmart.

#### 6.2.6 EPA recognizes companies with innovative sustainable chemistry technologies

Since 1996, the EPA in partnership with the American Chemical Society Green Chemistry Institute has awarded the annual Presidential Green Chemistry Challenge Awards to academics and companies for the development of innovative, sustainable chemistry technologies. The awards are presented for new technologies that incorporate the principles of green chemistry into chemical design, manufacture, and use, including technologies that reduce toxicity, improve use of natural resources, or reduce the production of waste, among others.<sup>164</sup> Awards are presented in six categories: Greener Synthetic Pathway, Greener Reaction Conditions, Design of Greener Chemicals, Small Business, Academia, and for Specific Environmental Benefit: Climate Change, for a technology that reduces greenhouse gas emissions. For example, in 2016, Newlight Technologies won the award in the Climate Change category for developing and commercializing a biocatalyst technology that combines captured methane, a potent greenhouse gas, with air to create a material that matches the performance of petroleum-based plastics at a lower cost. Several companies are now using this material to make a range of products including packaging, cellphone cases, and furniture. In 2017, the

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<sup>164</sup>See appendix V for the 12 Principles of Green Chemistry.

companies Amgen, Inc. and Bachem won the Greener Reaction Conditions Award for their process for manufacturing the active ingredient in the drug Parsabiv<sup>TM</sup>, which uses 71 percent less chemical solvent.

#### 6.2.7 DOD funds research to develop products using more sustainable chemistry that also meet performance needs

DOD's Strategic Environmental Research and Development Program (SERDP) funds basic and applied research on contaminants of concern to DOD and DOD's Environmental Security Technology Certification Program (ESTCP) funds validation and demonstrations of new, more sustainable chemistry technologies and products, among other activities. SERDP is jointly managed by DOD, EPA, and DOE and research funding priorities for both programs are identified by these agencies, experts, and by DOD's Emerging Contaminants program. SERDP and ESTCP fund federal organization and award contracts to universities and private industry. For example, according to DOD officials, after Camp Edwards was shut down in part because hazardous chemicals from flares were leaching into the community water supply, SERDP funded research to develop new flares without the chemicals of concern. According to officials, DOD has invested in research on new paint technologies that eliminate carcinogenic hexavalent chromium in paint primers and in research into methods for reducing or eliminating solvents. ESTCP funded research at the Army Armament Research, Development and Engineering Center to validate the performance of nontoxic, biodegradable biobased cleaner, lubricant, and preservative products as potential alternatives to petroleum-based

products or other products containing chemicals that may cause eye, skin, and respiratory irritation. SERDP and ESTCP make the results of funded research, development and demonstration, and validation efforts available to the public through its websites when possible. According to DOD officials, SERDP’s budget authority for fiscal year 2016 was \$54.3 million and ESTCP’s budget authority for the same time period was \$51.4 million.

### 6.3 Federal programs aid market growth for products made with sustainable chemicals and processes

Federal programs aid the growth of markets for products developed using more sustainable chemistry by informing

consumers about these products and by facilitating their purchase by federal offices. For example, federal programs conduct evaluations of the chemical content of products, manage product certification and labeling programs, provide information to consumers and federal purchasers on the chemical content of products, and develop purchasing and sustainability plans to support agency purchase and use of more sustainable products. In addition, federal programs facilitate compliance with Executive Order 13693 and the Federal Acquisitions Regulation federal regulations that require agencies to purchase certain more sustainable products when practicable. The following are selected examples of federal programs and offices that facilitate the growth of markets for more sustainable products (see table 11).

**Table 11: Selected federal programs and offices aid market growth for products manufactured with more sustainable chemicals and processes**

Federal program or office	Selected activities related to sustainable chemistry
<b>Safer Choice</b> - Environmental Protection Agency	Certifies products that contain chemicals posing the least health and environmental risk.
<b>BioPreferred</b> - Department of Agriculture	Maintains a catalog of biobased products and certifies products with minimum biobased content.
<b>Building for Environmental and Economic Sustainability (BEES)</b> - Department of Commerce, National Institute of Standards and Technology	Evaluates the life-cycle environmental and economic performance data of building materials and products.
<b>Agency Sustainable Purchasing Plans and Sustainability Plans</b> – Multiple Agencies	Develops plans to promote the acquisition and use of products manufactured with more sustainable chemicals and processes.
<b>Chemical and Material Risk Management Program, Sustainable Product Center, Sustainable Procurement Program</b> - Department of Defense	Encourages and facilitates the purchase of more sustainable chemicals and products by DOD facilities.

Source: GAO analysis of agency documentation. | GAO-18-307

### 6.3.1 Federal programs evaluate and share information about consumer products and their chemical content

EPA's Safer Choice voluntary certification and labeling program supports the market for more sustainable products by helping consumers make informed purchasing decisions, and incentivizing manufacturers to select more sustainable chemical alternatives when developing products by providing a way to differentiate and market their more sustainable products to interested consumers. More than 2,350 products from nearly 500 formulators and manufacturers currently qualify for the Safer Choice label, including products such as odor removers, hand soap, and pet care products (see fig. 20). In order to carry the Safer Choice label, a third-party reviewer must certify that the chemical ingredients in the product comply with Safer Choice criteria on category specific attributes such as carcinogenicity, human and environmental toxicity, skin sensitization, and recyclability of packaging. Safer Choice evaluates each chemical ingredient by functional class (e.g., colorants, solvents, or preservatives), comparing the profiles of chemicals to identify those that pose the least health and environmental concerns among chemicals that serve a similar function. Safer Choice also evaluates product performance to ensure it is comparable to that of a similar conventional product. Safer Choice assessments focus on the health and environmental impacts of consumer and institutional use and disposal of chemical-based cleaning and related products and do not assess chemical manufacturing processes or technologies. In addition to meeting all the Safer Choice criteria, manufacturers seeking certification must disclose all product ingredients on the product label or on the

manufacturer's website and undertake continuous product improvement. Safer Choice has also developed the online Safer Chemical Ingredients List for manufacturers, which includes more than 800 chemicals that meet Safer Choice criteria. Safer Choice certified products are listed in the publicly available Safer Choice database, facilitating their purchase by both consumers and federal agencies. Federal agencies are required by Executive Order 13693 to purchase Safer Choice products when practicable.

**Figure 20: The Environmental Protection Agency's Safer Choice certification label**



Source: Environmental Protection Agency. | GAO-18-307

Safer Choice works closely with manufacturers and other stakeholders in developing program goals, logistics for certificate application, meeting standards and criteria, outreach, and selecting new product types to be included in the program. For

example, Safer Choice holds an annual summit to gather feedback from manufacturers, NGOs, and other stakeholders to improve the program and advises companies on identifying safer ingredients. Safer Choice conducts public outreach and awareness campaigns for the Safer Choice program, such as promoting the label in social media, through targeted factsheets, and through seasonal promotions. Through its “Safer Choice Partner of the Year Awards,” Safer Choice recognizes manufacturers for advancing the goal of chemical safety through participation in or promotion of Safer Choice. For example, in 2017, a supermarket chain was recognized for its use of social media to promote the Safer Choice program.

USDA’s BioPreferred program supports federal purchasing requirements and administers a voluntary labeling program to increase the purchase and use of biobased products in order to increase the use of renewable agricultural resources, minimize the use of petroleum, and reduce health and environmental impacts, according to USDA. The Farm Security and Rural Investment Act of 2002 (2002 Farm Bill) as amended in 2008 and 2014 establishes federal purchasing requirements for biobased products. The act defines a biobased product as a product that is DOE determines is composed in whole or part of biological products or renewable agricultural materials, including plant, animal, and marine materials, or forestry materials.<sup>165</sup>

The BioPreferred program maintains a catalog through which consumers and federal purchasers can identify approximately 15,000

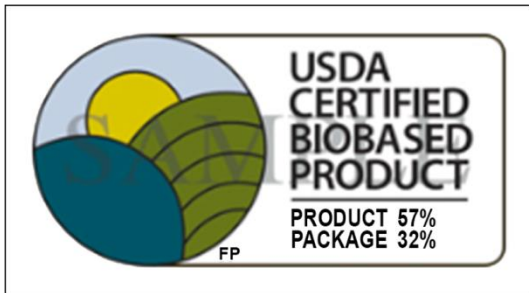
biobased products in 97 categories ranging from asphalt removers to deodorants. Product categories are added based on market research that identifies a government need as well as suggestions from stakeholders, such as industry associations or the public. To be included in the catalog, manufacturers must self-certify that a product contains the minimum required biobased content for a given product category as determined by the BioPreferred program. For example, general purpose carpet cleaners must have a minimum biobased content of 54 percent to qualify and candles must have a minimum of 88 percent. To facilitate the purchase of products listed in the catalog by federal agencies, officials also provide acquisition tools and training resources for federal agencies.

The BioPreferred program also manages a voluntary certification and labeling initiative that helps consumers identify and purchase products with a verified minimum of biobased content. Manufacturers can use USDA’s “Certified Biobased Product” label on their product after a third-party organization verifies the amount of biobased content (see fig. 21). BioPreferred has certified approximately 3,000 products, including stain removers, fertilizers, and notebooks. Certified products are also included in the BioPreferred Catalog and labeled as such. According to USDA officials, the fiscal year 2016 authorized budget for the Biopreferred program was \$3 million.

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<sup>165</sup> 7 U.S.C. § 8101(4). The term also includes intermediate ingredients and feedstocks. Id.

**Figure 21: The United States Department of Agriculture's (USDA) BioPreferred label**



Source: United States Department of Agriculture. | GAO-18-307

Note: The above figure shows a sample of the BioPreferred label, showing the percent of biobased content in a hypothetical product and packaging.

NIST's Applied Economics Office conducts life cycle analyses of building products to help decision makers, such as architects, builders, and product manufacturers, select more sustainable building materials through the online Building for Environmental and Economic Sustainability (BEES) tool. The BEES database includes life-cycle environmental and economic performance data for 256 building materials and products including wall insulation, floor coverings, interior wall finishes, and parking lot paving, based on data provided by product manufacturers. The data are made available through the interactive BEES tool that allows users to evaluate both the cost and the environmental impacts of a material throughout its life cycle, including use of raw materials, transportation to site, and disposal. For example, a decision maker could use the BEES tool to compare the economics and environmental impacts of different types of flooring, such as wool or nylon carpet tiles, including their lifetime toxicity, ozone depletion, and use of fossil fuels. NIST conducts outreach to industry associations to increase industry participation in submitting data and for growing the user

base for BEES, according to this official. In addition, according to officials, the Office is working with green building certification, standards, and codes development organizations, such as the U.S. Green Building Council, to align development of BEES with future stakeholder needs.

### 6.3.2 Agency plans encourage the purchase of products with more sustainable chemicals

To encourage the purchase of more sustainable products, including those manufactured with more sustainable chemicals and processes, federal agencies have developed sustainable purchasing and sustainability plans and developed tools to facilitate green purchasing. Executive Order 13693, "Planning for Federal Sustainability in the Next Decade," issued in 2015, directs agencies to develop plans to advance waste prevention and pollution prevention by, among other things, reducing or minimizing the quantity of toxic and hazardous chemicals and materials acquired, used, and disposed. For example, the Department of Housing and Urban Development's 2016 Strategic Sustainability Performance Plan states that the agency will implement integrated pest management and improved landscape management practices to reduce and eliminate the use of toxic and hazardous chemicals and materials. Additionally, the Department of Commerce Green Procurement Program states that the agency will provide preference to the purchase of nontoxic or less toxic product alternatives, including cleaning products that are nontoxic, non-volatile, and biodegradable. EPA enables federal purchasers and the public to identify more sustainable products by maintaining an online Sustainable Marketplace that

recommends greener products and services, standards, and ecolabels. The General Services Administration also provides a compilation of federal green purchasing resources.

DOD has several programs that encourage and facilitate the purchase of more sustainable chemicals products. DOD encourages acquisitions managers to purchase cost effective products that conform to federal sustainable procurement requirements by developing and testing products that contain more sustainable chemicals, setting purchasing policies and recommendations for these products, and providing DOD decision makers with data and demonstrations to inform purchasing decisions. DOD's Chemical and Material Risk Management Program develops policies, procedures, and guidance to integrate life cycle environment, safety, and health considerations into DOD's acquisition processes of products containing chemicals.

For example, the program developed a policy to minimize the use of hexavalent chromium DOD-wide and developed an acquisitions rule that sought to minimize the chemical in new acquisitions. According to DOD officials, this requirement provided an incentive for the industry to create products without the harmful chemical. The program has also developed a life cycle analysis process that allows decision makers to accurately compare the life cycle impacts and costs of conventional and more sustainable alternatives. In addition, DOD's Sustainable Products Center compiles information on sustainable products, evaluates the military's need for more sustainable products, hosts sustainable product demonstrations, and highlights success stories and lessons learned. DOD's Sustainable Procurement Program encourages DOD programs to procure more sustainable products and conducts life cycle assessment to evaluate how improvements in sustainability may result in cost savings.



**Table 12: Selected federal grants and awards supporting the development and use of more sustainable chemistry technologies**

Grant program	Agency	Purpose of program
Biomass Research and Development Initiative	Department of Agriculture / Department of Energy	Support the development of a biomass-based industry in the United States.
Sustainable Bioenergy and Bioproducts Challenge Area	Department of Agriculture	Advance the bioeconomy by facilitating development of regional systems for the sustainable production of bioenergy, industrial chemicals, and biobased products.
Strategic Environmental Research and Development Program (SERDP) and Environmental Security Technology Certification Program (ESTCP)	Department of Defense	Fund research on contaminants of concern and for the validation and demonstration of new, more sustainable chemistry technologies and products.
Manufacturing USA Institute - Rapid Advancement in Process Intensification Deployment (RAPID)	Department of Energy	Research, develop, and demonstrate new chemical processes that will save energy and reduce waste in a variety of chemical reactions.
Bioproducts to Enable Biofuels	Department of Energy	Develop bioconversion processes that coproduce biofuels and bioproducts, including biochemicals.
Science to Achieve Results (STAR) Safer Chemicals	Environmental Protection Agency	Support the development of safer, more sustainable use of chemicals in products.
Networks for Characterizing Chemical Life Cycles and Networks for Sustainable Molecular Design and Synthesis	Environmental Protection Agency / National Science Foundation	Funded research to characterize and predict health impacts of chemicals on humans and the environment by studying chemicals throughout their life cycle and to develop more sustainable chemicals.
Sustainable Chemistry, Engineering, and Materials (SusChEM)	National Science Foundation	Support research leading to clean, safe, and economical alternatives to traditional chemical products and practices.
Centers for Chemical Innovation	National Science Foundation	Support research centers focused on major, long-term fundamental chemical research challenges.
Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR)	Multiple agencies	Stimulate technological innovation and facilitate technology transfer.
Award program	Agency	Purpose of program
Transform Tox Testing Challenge	Department of Health and Human Services and Environmental Protection Agency	Recognize innovative technological solutions to transform chemical testing methods.
Presidential Green Chemistry Challenge Awards	Environmental Protection Agency	Recognize chemical technologies that incorporate the principles of green chemistry into chemical design, manufacture, and use.

Source: GAO analysis of agency documentation. | GAO-18-307

## 6.4 Other stakeholders including the chemical manufacturing industry, academic institutions, states, and companies also support more sustainable chemistry

Other stakeholders, including industry, academic institutions, state governments, NGOs, and companies seek to influence the development and use of sustainable chemistry through a variety of activities. For example, the chemical industry conducts and supports research into more sustainable chemistry technologies, collaborates with other stakeholders to support sustainability initiatives, and other activities. Large purchasers such as companies and retailers create demand for more sustainable products from their suppliers by setting sustainability criteria for purchases. Academic institutions conduct research on the impacts of chemicals and sustainable chemistry technologies and train the next generation of chemists and engineers. States seek to protect public health by regulating chemicals in products. NGOs also play a diverse range of roles such as supporting workforce development, facilitating collaboration between other stakeholders, and developing tools and resources for industry.

### 6.4.1 The chemical manufacturing industry collaborates with stakeholders to address common challenges and goals in using more sustainable chemistry

Interested companies in the chemical manufacturing industry collaborate with each other and other stakeholders to advance sustainable chemistry practices. These companies support the development and use of more sustainable chemistry through a

variety of activities, including conducting and funding research, setting standards, and supporting sustainable chemistry education. For example, industry collaborates through the American Chemistry Society's Green Chemistry Institute to encourage the integration of green chemistry and engineering throughout research, education, and industry. For example, the Green Chemistry Institute's Pharmaceutical Roundtable brings together pharmaceutical manufacturers to implement green chemistry in the industry through activities such as developing solvent and reagent selection guides for decision makers and awarding grants to support academic research. Industry also collaborates with other stakeholders through the Green Chemistry and Commerce Council, a project of the Lowell Center for Sustainable Production at the University of Massachusetts, Lowell that seeks to integrate green chemistry across business sectors and the supply chain. Members include manufacturers, retailers, education institutions, and state and federal government agencies. Green Chemistry and Commerce Council activities include convening working groups, supporting education and training in sustainable chemistry, and developing tools for collaboration and information sharing. In an example of a public-private partnership, NIKE, Inc. joined with NASA, the United States Agency for International Development, and the State Department to create the LAUNCH program, which funds innovative approaches to sustainability challenges, including a 2016 Chemistry Innovation Challenge and a 2014 Green Chemistry Challenge.

Among the 18 chemical companies that responded to our survey, 10 indicated that, with respect to the development and use of

sustainable chemistry technologies, they interacted a moderate or large amount with academics and 12 indicated that they interacted with scientific and professional organizations a moderate or large amount. Less than half of responding companies said they interacted a moderate or large amount with environmental advocacy groups. In terms of interactions with federal agencies related to sustainable chemistry technologies, half of the responding companies had performed collaborative research and development with a federal agency and 6 out of 18 had received federal funding for research and development. Of the responding companies, half had a large to moderate amount of interactions with EPA related to sustainable chemistry technologies, the most interactions of any of the federal agencies included in the survey. Of the companies surveyed that interacted with EPA with respect to the development and use of sustainable chemistry technologies, 9 found the interactions very or moderately valuable. For more information on the survey, see appendix IV.

#### 6.4.2 Companies develop policies to encourage suppliers and others to develop products using more sustainable chemistry

Corporations that set policies on purchasing products manufactured with more sustainable chemistry may increase the incentive for the development and use of more sustainable chemistry technologies by chemical manufacturers and formulators. Selected companies, such as Target and Kaiser Permanente, are developing policies and tools to ensure the products they purchase meet certain criteria with regard to chemical ingredients and other life cycle factors, and

are working with purchasers and suppliers to encourage the development of these products.

Target Corporation: Target, a retailer with more than 1,800 stores and sales of nearly \$70 billion in 2016, has launched two major initiatives that seek to encourage and incentivize its vendors to supply products that use more sustainable chemistry technologies. According to a Target official, these efforts are driven by consumer concern about the safety of chemicals in the products they buy, as well as to prevent regulatory fines by strengthening internal regulatory processes. In 2013, Target introduced a Sustainable Products Index, an internal tool that collects information from suppliers and assesses products based on sustainability criteria such as the presence of certain chemical ingredients, transparency about those ingredients, packaging, certifications, and sourcing information. The Index applies to the personal care, beauty, household cleaning, and baby care product categories. In 2017, Target introduced a new chemical policy and goals governing chemicals in products it sells in stores and uses operationally, as well as timelines for meeting these goals. Through the policy, Target commits to work toward full transparency of chemicals contained and used to make the products it sells, to collaborate with its business partners to managing chemicals through the supply chain, and to support initiatives seeking to identify, develop, and commercialize safer chemicals and processes. In addition, Target plans to contribute \$5 million by 2022 to support research to identify methods for effectively communicating about green chemistry, to develop an infrastructure for information sharing about product ingredients, and to create industry-wide hazard profiles for

chemicals, as well as to invest in companies developing products with less hazardous chemicals through a green chemistry venture capital fund. Target also collaborates with other stakeholders. For example, it is a member of the Retailer Leadership Council, consisting of leaders from seven retailers and five chemical manufacturers convened by GC3 that are working together to promote safer chemicals, materials, and products across retail supply chains by committing to dialog around goal setting and continuous improvement, communication about green chemistry throughout the supply chain, sharing information on chemical hazards and risks, providing information across the value chain with consumers, and supporting green chemistry education.<sup>166</sup>

Kaiser Permanente: Kaiser Permanente, which spends approximately \$5.8 billion per year on medical products and equipment, has developed goals, policies, and tools to support the purchase of products manufactured using more sustainable chemistry. According to Kaiser Permanente officials, the organization's goal is to increase the percentage of products it purchases meeting its environmental standards to 50 percent by 2025. In 2006, Kaiser Permanente created Environmentally Preferable Purchasing Principles requiring that certain criteria on chemical content and waste be considered in all major purchasing decisions. In 2017, Kaiser Permanente extended and strengthened the Principles by introducing an Environmentally Preferable Purchasing

Standard that mandates specific environmental criteria in the area of chemicals and waste to be met in purchasing decisions. For example, products must not contain toxic chemicals, bisphenol A (BPA), or flame retardants. According to Kaiser Permanente representatives, if multiple suppliers can provide a product that equally meets the organization's clinical, regulatory, and sourcing requirements, Kaiser Permanente can choose one over another based on sustainability factors. However, if Kaiser Permanente is procuring a product that does not meet the Environmentally Preferable Purchasing Standard then the organization informs the supply base that it is actively seeking alternative suppliers or negotiates contract terms that include sustainability requirements. In addition, when Kaiser Permanente has a particular sourcing requirement, they may have the purchasing power to ensure a new product is developed that meets its criteria. When the company decided it would no longer purchase exam and surgical gloves made from polyvinyl chloride, which produce toxic dioxin as a byproduct during the manufacturing process and disposal, the decision impacted the entire medical glove industry, according to organization representatives, because Kaiser Permanente purchases more than 50 million gloves each year. Kaiser Permanente relies on other organizations such as EPA, Healthcare Without Harm, and other NGOs for information on hazardous chemicals. Kaiser Permanente's Division of Research also conducts studies on the impacts of chemicals on human health, including the effect of workplace exposure to bisphenol A (BPA). Kaiser Permanente collaborates with other stakeholders such as NGOs on a number of initiatives. For example, the organization's Environmentally Preferable Purchasing

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<sup>166</sup>The Retail Leadership Council membership includes officials from retailers Wal-mart; Staples; Target; Home Depot; Best Buy; Lowe's Companies, Inc.; and CVS Health; and chemical manufacturers BASF Corporation, Chemours, Dow Chemical, AkzoNobel, and Eastman.

Standard was developed with expertise from the Center for Environmental Health, Healthcare Without Harm, Clean Production Action, and Practice Greenhealth, among others, and used benchmarks from other organizations including Green Seal, EcoLogo, Electronic Product Environmental Assessment Tool, and EPA's Design for the Environment program.

### 6.4.3 Academic institutions train the next generation of chemists

Academic institutions and the academics that work in them play a role in supporting the development and use of more sustainable chemistry technologies by training the next generation of chemists, conducting relevant research, and sharing their expertise in collaborations with other stakeholders. One barrier to the development and use of more sustainable chemistry technologies may be the conventional chemistry methods and practices taught in schools, which has led to a chemistry workforce that may not understand the principles of sustainable chemistry, according to officials GAO interviewed. One faculty member GAO interviewed said that one of the challenges to changing curriculums is a lack of incentives for professors along with the significant time and resources required to do so. However, some colleges and universities are beginning to integrate sustainable chemistry programs and classes into their chemistry curriculum. In addition, some academic institutions are collaborating with businesses, state and federal government, and NGOs to support the development and use of sustainable chemistry technologies. The University of Toledo's School of Green Chemistry and Engineering and University of California's Berkeley Center for Green Chemistry are two

examples of academic programs focusing on education and research in sustainable chemistry.

In 2011, the University of Toledo established the School of Green Chemistry and Engineering, which, together with other university departments, offers a range of classes in green chemistry and engineering to interested students (see text box below). The mission of the university is to promote the sustainable use, production, and recycling of chemical materials through research, education, and outreach. The university awards an undergraduate minor in Green Chemistry and Engineering as well as a Professional Science Master's Degree in Green Chemistry and Engineering that requires students to incorporate aspects of business and other professional skills into their M.S. degree, including courses such as "Technology Commercialization" and "Supply Chain Management." Students in the more traditional M.S. and Ph.D programs in chemistry and chemical engineering can take the sustainability-related courses.

#### Selected courses related to sustainable chemistry offered at the University Toledo by the School of Green Chemistry and Engineering and its partner departments

- Green Chemistry
- Green Engineering Principles for Chemical Processes
- Environmental Chemistry
- Green Engineering Applications in Chemical Industry
- Chemistry of Sustainable Energy Resources
- Biofuels
- Environmental Geochemistry
- Hazardous Waste Management
- Environmental Economics
- Environmental Policy

Source: University of Toledo School of Green Chemistry and Engineering. | GAO-18-307

The Berkeley Center for Green Chemistry at the University of California at Berkeley is an interdisciplinary program that integrates teaching and research on chemistry, environmental health, and public and private governance and management with the goal of bringing about a generational change in the design and use of more sustainable chemicals and materials. One of the courses offered by the Center is Greener Solutions, an interdisciplinary, project-based class in which students partner with a company to develop solutions to a particular sustainable chemistry problem. For example, students partnered with a technology firm to address emerging contaminants in e-waste, with an outdoor clothing manufacturer on the design of nontoxic mosquito repellency for polyester clothing, and with a workspace furniture company on developing safer colorants for a polypropylene chair. The Greener Solutions program has been supported by the California Department of Toxic Substances Control and a Pollution Prevention Grant from EPA Region 9.

#### 6.4.4 States protect public health by establishing requirement that can encourage the use of sustainable chemistry in products

State officials are enacting regulations to protect the human and environmental health of citizens and ecosystems by requiring the use of more sustainable chemistry in products and manufacturing processes. An NGO official that we interviewed noted that states have the advantage of being able to move faster than the federal government in making regulations, allowing states to play a leadership role in this area. State regulations range from banning specific chemicals, to requiring the disclosure of chemical

ingredients in certain types of products, to more comprehensive approaches to reducing toxic chemicals in products. State officials work together through organizations such as through the Interstate Chemicals Clearinghouse to collaborate and share information and grow state government capacity. Massachusetts' Toxics Use Reduction Act and California's Safer Consumer Products program are examples of state-level regulation that can support the use of more sustainable chemistry.

The state of Massachusetts enacted the Toxics Use Reduction Act in 1989 to reduce the use of toxic chemicals to promote industrial hygiene, worker safety, and protection of the environment and public health.<sup>167</sup> State industry, labor unions, and regulatory bodies came together to negotiate the statewide policy, which is loosely based on the federal Toxic Release Inventory program, according to state officials.<sup>168</sup> Under the act, facilities in the state that use defined amounts of approximately 1,500 specific toxic chemicals are required to annually report their chemical use and conduct toxic chemical use reduction planning biennially. Facilities that use toxic chemicals must also pay an annual fee based on the number of employees and toxic chemicals used at the facility. Two state offices and an academic institute work together to implement the act. The

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<sup>167</sup>ALM GL ch. 21I, § 1 et. seq.

<sup>168</sup>Under EPA's Toxics Release Inventory program, more than 22,000 U.S. facilities report how much of 675 toxic chemicals they released to the environment and/or managed through recycling, energy recovery and treatment. EPA compiles the information submitted by facilities into the Toxics Release Inventory in order to provide the public with information about chemicals that may pose a threat to human and environmental health.

Massachusetts Department of Environmental Protection enforces the law's mandates for annual reporting and biennial planning. The Toxics Use Reduction Institute, hosted by the University of Massachusetts Lowell, assists companies in meeting the act's requirements by conducting and funding research on safer chemicals and processes, and providing training and advice to companies. The Office of Technical Assistance provides confidential, free technical assistance to companies wishing to reduce their use of toxic chemicals, comply with regulations, or make their processes more sustainable. Officials said that resources for both the Office of Technical Assistance and the Department of Environmental Protection have been reduced, creating challenges for implementing the program, particularly given the numbers of chemicals entering commerce and pressure from companies that have the incentive and resources to fight new regulations.

State officials work with a range of stakeholders to advance the provisions of the act. For example, the Toxics Use Reduction Act Advisory Committee includes members from organized labor, large and small businesses, state agencies, and health and environmental advocacy groups. State officials also work with EPA. For example, state officials said they partner with EPA on conducting trainings and have received grants from EPA's Pollution Prevention program.

Under California's Safer Consumer Products program, established pursuant to state law, California's Department of Toxic Substance Control (DTSC) identifies and evaluates chemicals of concern and their potential alternatives, to determine how best to limit exposure or to reduce the level of hazard. According to a DTSC official, state officials

were frustrated the federal government was not taking action to update TSCA. DTSC, which oversees the Safer Consumer Products program, established a four-step iterative process to encourage the use of safer substitutes for chemicals of concern in consumer products.

1. DTSC establishes a list of Candidate Chemicals that have at least one quality that could harm human health or the environment. The initial list of Candidate Chemicals, released in October 2013, contained approximately 1,200 chemicals.
2. DTSC releases a list of Priority Products that DTSC has proposed for regulation that contain one or more of the Candidate Chemicals. A list of three products containing specific harmful chemicals was released in March 2014, which included certain children's foam-padded sleeping products, spray polyurethane foam, and paint strippers.
3. Responsible entities, including manufacturers, importers, assemblers, and retailers, must notify DTSC if they are manufacturing or selling Priority Products in California. The entities generally must perform an Alternatives Analysis for those products to identify how to reduce risks to human and environmental health by, for example, replacing the chemical or redesigning the product. Specific life cycle impacts must be evaluated as part of an Alternatives Analysis and DTSC provides guidance and training in conducting the analysis.<sup>169</sup> According to officials, DTSC is

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<sup>169</sup>Under California law, the following factors must be considered: (A) product function or performance; (B) useful life; (C) materials and resource consumption; (D) water conservation; (E) water quality impacts; (F) air emissions; (G) production, in-use, and transportation energy inputs; (H) energy efficiency; (I) greenhouse gas emissions; (J) waste and end-of-life disposal; (K) public health impacts, including

expecting the first Alternatives Analysis from responsible entities in 2018.

4. Following the Alternatives Analysis, DTSC may choose to regulate a Priority Product or an alternative that a responsible entity selected to replace it if needed to protect human health and the environment.

DTSC works closely with a range of stakeholders to implement the Safer Consumer Products legislation and on broader sustainable chemistry issues. For example, DTSC maintains an online database (CalSAFER) where information and comments related to regulatory action can be uploaded and shared by state offices and other stakeholders. An advisory board with members from academic institutions, industry, federal and state agencies, and others, provides advice to DTSC on scientific and technical matters. In addition, DTSC has a memorandum of understanding with EPA and Oregon and Washington for collaboration and information sharing to advance sustainable chemistry and, according to a DTSC official, has worked with the European Chemicals Agency and Organization for Economic Co-operation and Development on issues related to safer chemicals.

#### 6.4.5 Non-governmental organizations play a range of roles in supporting the development and use of more sustainable chemistry processes and products

Through a range of activities and initiatives, often in collaboration with other stakeholders, NGOs encourage and support

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potential impacts to sensitive subpopulations, including infants and children; (L) environmental impacts; and (M) economic impacts.

the development and use of more sustainable chemical processes and products. For instance, NGOs develop tools and resources to enable industry and consumers to choose more sustainable products and processes, support the integration of sustainable chemistry principles into educational programs, and develop standards and best practices to guide decision makers seeking to be more sustainable. The following organizations are examples of NGOs working through diverse means to support more sustainable chemistry.

Beyond Benign, founded in 2007, supports professional development of chemistry teachers and professors and the integration of green chemistry principles and practices into all levels of education. For example, the organization equips elementary, middle, and high school educators to teach green chemistry by conducting in-person and online teacher training for middle and high school teachers, and developing teaching and curriculum materials. Working with the State of New York's Department of Environmental Conservation, Beyond Benign conducted a series of 13 trainings for high school teachers across the state, according to Beyond Benign officials. Beyond Benign also works with industry to incorporate case studies on the companies' green chemistry technologies into curriculum. Through Beyond Benign's Green Chemistry Commitment program over 40 academic institutions have committed to implementing certain green chemistry learning objectives at their schools and collaborate to address common challenges.

Clean Production Action acts as an umbrella organization over three programs that support the use of inherently safer chemicals, materials, and products through convening



collaborators to work on sustainable chemistry and developing and managing tools to support the use of more sustainable chemicals.

- BizNGO is a working collaborative that brings together stakeholders to identify areas of consensus between business and environmental groups to advance the use of safer chemical alternatives in product areas such as electronics, building products, and health care, according to a Network official. For example, the group created a protocol for assessing chemical alternatives and case studies that identified less hazardous alternatives for specific chemicals (such as surfactants and flame retardants), according to a Network official.
- GreenScreen® is a chemical hazard assessment tool that can be used by industry, government, and NGOs to identify chemical hazards and safer alternatives. GreenScreen Benchmarks allow decision makers to identify and rank increasingly safer chemicals as defined by environmental persistence, bioaccumulation, human- and eco-toxicity, and other factors. GreenScreen benchmarks can also be used by companies and state and federal agencies. For example, Wal-mart used GreenScreen to identify priority chemicals for substitution in its chemicals policy, eight states recommend GreenScreen as a tool for hazard assessments, and the U.S. Green Building Council offers Leadership in Energy and Environmental Design credits for using GreenScreen.
- The Chemical Footprint Project allows manufacturers and retailers to benchmark and communicate their

progress in chemicals management performance and in reducing potentially hazardous chemicals relative to industry peers.

Green Seal awards certifications for products in over 400 product and service categories, based on a number of sustainability criteria, including those for chemical ingredients. The criteria identify ineligible chemicals by class (such as carcinogens), sets requirements chemicals must meet (such as biodegradability), limits certain compounds (such as volatile organic compounds), and sets requirements for use or disposal. Both state and federal offices have policies recommending the purchase of Green Seal certified products in specific categories; for example, EPA recommends Green Seal certified paints in its revised recommendations for federal purchasing. When developing a new standard for a product, Green Seal gathers information from a range of sources including the EPA's Integrated Risk Information System (IRIS) database, NTP, and NIH's Hazardous Substances Data Bank, and solicits information and comments from stakeholders including industry, the public, federal and state government, academic experts, NGOs, and others. In addition, Green Seal provides technical advice and assistance for companies and organizations developing policies and purchasing plans that incorporate sustainability concerns. Green Seal developed a green purchasing manual for the National Cooperative Highway Research Program, for instance, that included specifications for environmentally preferable alternatives for products containing toxic chemicals that are frequently used by state departments of transportation.

GreenBlue seeks to provide tools and resources to industry decision makers to inform choices about the use of safer chemicals and materials in their products. The organization encourages industry to conserve material resources, eliminate toxicity throughout the supply chain, and recover and reuse materials. The following programs are examples of how GreenBlue advances these goals.

- The Sustainable Package Coalition, whose membership consists of industry (including, for example, brands, packaging designers, retailers, and the recycling community), academic institutions, and government agencies, supports collaboration, research, and tool development with the purpose of improving the sustainability of packaging.
- CleanGredients is a database of chemical ingredients that have been pre-approved to meet EPA's Safer Choice certification criteria. The database also includes information on products and manufacturers to help formulators more efficiently obtain Safer Choice certification.
- The Material IQ program is developing a standardized methodology to facilitate the communication of chemical information between manufacturers without compromising proprietary information.

## 7 Strategic Implications

Sustainable chemistry is an emerging, innovative field within the chemical sciences that has the potential to inspire new products and processes, create jobs, and enhance benefits to human health and the environment. Chemical companies engaged in sustainable chemistry are working to reassess the entire chemical product life cycle from cradle-to-grave, seeking new conceptual frameworks for producing chemicals. These companies can be highly motivated and cited several drivers for their sustainable chemistry efforts, including consumer demand, reduced business costs, and company culture or mission. The three technology categories we discussed in this report—catalysts, solvents, and continuous processing—offer illustrations of the progress and potential for creating more sustainable chemistry technologies. However, as our survey and interviews with industry and other stakeholders found, there are a number of challenges to implementing more sustainable chemistry technologies.

The technologies we assessed offer a number of potential environmental and human health benefits. Earth-abundant metals and metal-free catalysts are often readily available, less expensive than current catalysts, and less toxic. In addition, they can provide greater selectivity while reducing solvent use and other waste. Alternatives to current solvent use, such as biobased solvents, water and other less toxic solvents, and solvent-free technologies, can be safer or less toxic than conventional solvents, reduce dependence on non-renewable resources such as petroleum, and limit the need for costly solvent removal and disposal. Continuous processing can offer a number of advantages over conventional batch processing, including improved safety

for workers and the environment, cost savings, and the potential for more controllable and repeatable processes. The small scale of continuous flow microreactors allows further benefits including shorter reaction times, lower energy consumption, and improved efficiency.

However, technological challenges remain. Alternative catalysts can be challenging to separate and reuse. In addition, some have a limited scope of reaction that can make them less widely useful, while others can be required in large quantities in order to provide sufficient reaction speed. Some biobased solvents pose the same inherent toxicity and volatility risks as their conventional counterparts; in addition, they can vary in supply and quality and can be expensive. The use of water and other less toxic solvents may require specialized equipment, greater energy input, or elevated pressure, and can be difficult to scale up for industrial use. Continuous processing can require significant capital investment to develop new infrastructure as well as specialized personnel for effective operation, among other challenges.

In addition to these technological barriers, companies told us they face many business challenges in their efforts to implement more sustainable chemistry technologies. These include the need to prioritize product performance; weigh sustainability tradeoffs between various technologies; risk disruptions to the supply chain when switching to a more sustainable option; address limited and expensive supplier options; consider regulatory challenges; develop a business case for sustainability investments; and address the often higher initial cost of more sustainable options. If

these challenges can be overcome, then companies can see a variety of economic benefits. For example, more sustainable products or technology uses can help firms differentiate from one another; this can create a competitive advantage that consumers recognize and value, and encourage firms to create more sustainable products. Similarly, the creation of more sustainable products can have good reputational effects that extend to other products made by that firm, regardless of whether those products are also more sustainable.

Furthermore, as our survey and interviews with industry and other stakeholders found, there are several basic, industry-wide challenges to implementing more sustainable chemistry technologies, such as the lack of a standard definition for sustainable chemistry as well as the lack of agreement on standard ways of measuring or assessing it. Without a standard definition that captures the full range of activities within sustainable chemistry, it is difficult to define the universe of relevant players. Without agreement on how to measure the sustainability of chemical processes and products, companies may be hesitant to invest in innovation they cannot effectively quantify, and end users are unable to make meaningful comparisons that allow them to select appropriate chemical products and processes.

Sector-specific challenges exist as well. For example, industry representatives from the pharmaceutical sector told us that they can incorporate more sustainable technologies early in the drug development process, but changing the manufacturing process for an already marketed drug triggers the need for revalidation, which can result in delays and

additional costs—thus discouraging innovation that could make their chemical processes more sustainable. Experts also noted the challenge of overturning proven conventional practices, and acknowledged that existing capital investments in current technologies can create barriers for new companies to enter a field full of well-established players.

The varied nature of chemical processes and the diverse range of stakeholders in the United States—ranging from private companies and government agencies to academics, states, and non-governmental organizations—also contribute to difficulties making progress within the field of sustainable chemistry. There is no mechanism for coordinating a standardized set of factors for assessing sustainability across these stakeholder groups at present, despite the motivation that specific sectors possess. Moreover, although the federal government has worked with stakeholders through its research support, technical assistance, and certification programs, among other efforts, there are still gaps in understanding. Many stakeholders told us that without such basic information as a standardized approach for assessing the sustainability of chemical processes and products, better information on product content throughout the supply chain, and more complete data on the health and environmental impacts of chemicals throughout the life cycle, they cannot make informed decisions that compare the sustainability of various products. Experts noted that much more work is needed to realize the full promise of sustainable chemistry. For example, they raised a range of concerns and potential solutions, such as:

- Sustainable chemistry creates opportunities to use a different conceptual framework that allows industry to create molecules with new functional performance. There are major innovations demonstrating that it isn't just about being less toxic or less polluting; breakthrough technologies in sustainable chemistry could transform how the industry thinks about performance, function, and synthesis.
- The establishment of an organized constituency, with the involvement of both industry and government, could help make sustainable chemistry a priority. An industry consortium, working in partnership with a key supporter at the federal level, could lead to an effective national initiative or strategy.
- A national initiative that considers sustainable chemistry in a systematic manner could be useful. Such an effort could encourage collaborations among industry, academia and the government, similar to the National Nanotechnology Initiative.<sup>170</sup>
- There are opportunities for the federal government to address industry-wide challenges. Federal attention that facilitates development of standard tools for assessment and a robust definition could help clarify relevant participants in the field and improve information available for decision makers at all levels.
- A research agenda that links research to policy is lacking. In Canada, for example, there is a coordinated technology effort that is focused on basic R&D and scale testing, addressing chemical substitution from the beginning to the end of the life cycle process.
- A focus on the bigger problems that need to be solved, such as supply chain issues, is an important priority. Federal agencies can play a role in demonstrating, piloting, and de-risking some of these technology development efforts.
- STEM-related initiatives and intellectual property tools can add value. For example, R&D tax credits for qualified research expenses could provide subsidies to encourage business investment in research.<sup>171</sup> In addition, patent term restoration, as has been applied to drug products, is designed to encourage innovation, as profits resulting from patent protection can serve as incentives for creating innovative products that benefit the public.<sup>172</sup> Furthermore, students and adults could be empowered to create, innovate, and turn their ideas into new products, through either volunteerism or public service.

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<sup>170</sup>The National Nanotechnology Initiative is a U.S. government R&D initiative involving 20 departments and independent agencies working on science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers; a nanometer is one billionth of a meter.

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<sup>171</sup>GAO, *Tax Policy: The Research Tax Credit's Design and Administration Can Be Improved*, GAO-10-136 (Washington, D.C.: Nov. 6, 2009).

<sup>172</sup>Patents issued by the Patent and Trademark Office grant patent holders the right to exclude others from making, using, or selling an invention. The granting of this exclusive right is designed to encourage innovation. The patent holder is likely to reap greater profits if protected from direct competition. These profits are intended to serve as incentives for creating innovative products that benefit the public.

- New training to upgrade the chemistry and manufacturing workforces could encourage innovation. Integrating sustainable chemistry principles into educational programs could bolster a new generation of chemists and advance student achievement in the field.

According to experts, transitioning toward the use of more sustainable chemistry technologies requires that industry, government, and other stakeholders work together. As they and others noted, there is a need for new processes that make more

efficient use of the resources that are available, reuse products or their components during manufacturing, and account for impacts across the entire life cycle of chemical processes and products.

Furthermore, they highlight the importance of disseminating environmental and health-related information to help guide the choices of consumers, chemists, workers, downstream users, and investors to facilitate further progress. They also indicated that momentum in this field will require national leadership in order to realize the full potential of sustainable chemistry technologies.

## 8 Agency and expert comments

We provided a draft of relevant excerpts from this report to the Department of Commerce (National Institute of Standards and Technology), Department of Defense, Department of Energy, Department of Health and Human Services, Environmental Protection Agency, National Science Foundation, and U.S. Department of Agriculture, with a request for technical comments. We incorporated the comments received into this report as appropriate.

We also provided a draft of the key chapters of this report to the participants in our expert meeting with a request to review it for scientific and technical accuracy. Of these, six provided technical comments that we incorporated as appropriate.

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As agreed with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from its issue date. At that time, we will send copies of this report to the appropriate congressional committees, relevant federal agencies, and other interested parties. In addition, the report will be available at no charge on the GAO website at <http://www.gao.gov>.

If you or your staff members have any questions about this report, please contact Timothy M. Persons at (202) 512-6412 or [personst@gao.gov](mailto:personst@gao.gov) or John Neumann at (202) 512-3841 or [neumannj@gao.gov](mailto:neumannj@gao.gov). Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix VII.



Timothy M. Persons, Ph.D.  
Chief Scientist



John Neumann  
Director  
Natural Resources and Environment

## Appendix I: Objectives, scope, and methodology

We describe our scope and methodology for addressing the three objectives outlined below, related to technologies for making chemical processes and products more sustainable.

### Objectives

1. Identify how stakeholders define sustainable chemistry and approaches that are used to assess the sustainability of chemical processes and products.
2. Assess selected technologies that are available or in development to make chemical processes and products more sustainable.
3. Describe the contributions of the federal government, industry, and others to the development and use of such technologies.

### Scope and methodology

To address our objectives, we reviewed key reports and scientific literature to establish background, identify appropriate technologies and their advantages and disadvantages, identify stakeholders, and inform survey questions. We also convened an expert meeting with the assistance of the National Academies; interviewed representatives of federal and state agencies, chemical companies, industry and professional organizations, academic institutions, nongovernmental organizations (NGO), and other stakeholders; conducted site visits to federal laboratories; fielded a survey of selected chemical companies; and attended two technical conferences.

### Limitations to scope

We limited the scope of our review to selected technologies in three main categories that are primarily related to the raw materials and chemical processing phases of the product life cycle: catalysis, solvent use, and alternatives to batch processing. We did not assess all available or developing technologies in these three categories, nor did we assess technologies in other phases of the chemical product life cycle. For example, we did not assess technologies for recycling industrial waste into new feedstocks or for post-consumer recycling of chemical products.

### Expert meeting

Early in our study, we collaborated with the National Academies to convene a two-day meeting of 24 experts on sustainable chemistry technologies and approaches. Specifically, we collaborated with National Academies staff to select participants from the chemical industry, academia, federal agencies including a national laboratory, professional organizations, and others, with expertise covering most significant areas of our review.<sup>1</sup> A conflict of interest was considered to be any current financial or other interest that might conflict with the service of an individual because it (1) could impair objectivity or (2) could create an unfair competitive advantage for any person or

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<sup>1</sup>After the expert meeting, we changed one of our three target industry sectors from textiles/apparel to formulators (i.e., makers of personal care and cleaning products); thus we did not have a formulator represented at the meeting. However, we interviewed and surveyed several formulator companies during the course of our study.



organization. The 24 experts were determined to be free of conflicts of interest except those that were easily addressed, and the group as a whole was judged to have no inappropriate biases. (See appendix II for a list of these experts and their affiliations.)

During this meeting, we solicited input from the experts on the design for our work. Specifically, we moderated discussion sessions on several topics, including examples of technologies to make chemical processes and products more sustainable; applications of such technologies in industry; economic and business aspects of developing and implementing the technologies; approaches to assessing the sustainability of chemical processes and products; the role of standards, regulations, and related programs; and additional stakeholder perspectives. The meeting was recorded and transcribed to ensure that we accurately captured the experts' statements. We also continued to draw on the expertise of these individuals throughout our study and, consistent with our quality assurance framework, we provided them with a draft of our report and solicited their feedback, which we incorporated as appropriate.

#### Site visits

We conducted site visits to federal laboratories to discuss technologies that are in development, including challenges to developing and commercializing such technologies. Specifically, we visited the Toxicology in the 21<sup>st</sup> Century (Tox21) Robotics Facility at the National Center for Advancing Translational Sciences, as well as the National Institute of Standards and Technology's (NIST) Materials Science and Engineering Division and Facility for Adsorbent Characterization and Testing.

#### Additional interviews

We conducted a total of 82 interviews with representatives from the following groups of stakeholders:

- Federal and state agencies including the Department of Commerce and NIST, Department of Defense, Department of Energy including three of its national laboratories, Department of Health and Human Services including the Food and Drug Administration (FDA) and National Institutes of Health (NIH), Environmental Protection Agency (EPA), National Science Foundation (NSF), Small Business Administration, U.S. Department of Agriculture (USDA), the California Department of Toxic Substances Control (DTSC) Safer Consumer Products Program, and two Massachusetts state offices.
- Chemical companies that we or other interviewees identified as involved in developing and implementing relevant technologies. (See app. III for a list of participating chemical companies.)
- Industry and professional organizations including the American Chemical Society (ACS) and ACS's Green Chemistry Institute (GCI); the American Chemistry Council (ACC); and the Society of Chemical Manufacturers and Affiliates (SOCMA).
- Academic institutions including the Berkeley Center for Green Chemistry, the University of Massachusetts – Lowell's Toxics Use Reduction Institute (TURI), and the University of Toledo.
- NGOs including Beyond Benign, the Clean Production Action, the Green Chemistry and Commerce Council (GC3), GreenSeal, GreenBlue, and the Natural Resources Defense Council.

- One institutional purchaser (Kaiser Permanente) and one retailer (Target Corporation).

### Identifying interviewees

#### Federal programs and offices

We relied on recommendations from federal agency officials to identify specific federal programs and offices that conduct work related to supporting the development and use of sustainable chemistry technologies. We then interviewed officials from those programs, gathered documentary evidence on their activities, and identified which of these programs and offices had activities directly related to sustainable chemistry technologies. Based on our analysis of the activities performed by those programs and offices, we identified three key roles federal agencies play in supporting sustainable chemistry technologies. For federal agencies, our goal was to identify all relevant federal programs that conduct activities to promote the development and use of sustainable chemistry technologies. We described selected programs and offices to illustrate each of these roles in the report.

#### Other stakeholders

Our aim was to identify stakeholders to serve as illustrative, non-generalizable examples of the roles that stakeholders play in supporting the development and use of sustainable chemistry technologies. Where appropriate, we sought diversity among the selected stakeholders with regard to their mission, sector focus, or policy orientation. Our primary method for obtaining specific names of organizations and individuals was to ask interviewees for recommendations of additional stakeholders; we supplemented this approach with other methods such as

searching relevant grant databases and other lists. We ended this selection process when we felt that the representation of interviewees within each category was sufficient.

#### Company selection

To select companies for our interviews and survey, our purpose was to first identify three industry sectors on which to focus: basic chemical manufacturing, pharmaceuticals, and formulators (i.e., makers of personal care and cleaning products such as soaps, detergents, toiletries, and cleaning compounds). These sectors were chosen based on expert recommendations of sectors which are active in implementing more sustainable chemistry technologies, as well as the size of these sectors and the proportion of the chemical industry they represent. According to the Bureau of Labor Statistics within the Department of Labor, as of July 2016 these three sectors were the three largest in the chemical industry in terms of number of employees. Specifically, basic chemical manufacturing (148,500 employees), pharmaceutical and medicine manufacturing (281,440 employees), and formulators (i.e., soap, cleaning compound, and toilet preparation manufacturing; 104,150 employees) accounted for about 65 percent of the 819,700 employees across the chemical industry.

We then used an iterative process to identify companies within these sectors, relying on each of our interviewees to refer us to other companies that could provide perspectives on the development and implementation of technologies within our scope. Specifically, we first interviewed two chemical manufacturers (Dow Chemical and Elevance) and two pharmaceutical companies (Merck and Pfizer) because representatives of these

companies participated in our expert meeting and thus had already demonstrated an interest in and knowledge of relevant technologies. As a second step, we contacted the ACS GCI to ask for a list of companies that belong to the three most relevant GCI industry roundtables: the Chemical Manufacturers Roundtable, the Pharmaceutical Roundtable, and the Formulators Roundtable. We believe that this was an appropriate approach for identifying companies because these companies, by voluntarily choosing to participate in the ACS GCI industry roundtables, have clearly demonstrated an interest in (and therefore increased likelihood of using) more sustainable chemistry technologies. Next, we asked each of our industry interviewees from these first two steps for additional suggestions of companies to interview and interviewed any within our target sectors that agreed to participate. We turned next to companies recommended by the federal agencies we interviewed and selected additional companies to contact, with a focus on small or medium-sized companies within our three target sectors because most of the companies from our first two rounds of interviews were large.

In total we interviewed representatives of 27 companies including 16 chemical manufacturers, 9 pharmaceutical companies, 6 formulators, and 1 company from another industry sector. (See app. III for a list of participating chemical companies.) Some of the 27 companies identified themselves with more than one industry sector. In addition to conducting interviews with these companies, we also sent our survey to these same companies and received responses back from 18 of the companies. Because this is a small and non-generalizable sample of the universe of U.S. chemical companies, the results of our interviews and survey are illustrative and

indicative of important issues, but not generalizable.

## Survey of selected chemical companies

We surveyed the same non-generalizable sample of 27 chemical companies we previously interviewed in order to collect data on several items that were relevant to our objectives.

### Questionnaire design

We designed a questionnaire covering four primary topics: (a) approaches the selected companies use to assess the sustainability of their chemical processes and products; (b) the extent and perceived value of their interactions with other stakeholders, including federal agencies, customers, suppliers, academics, and NGOs; (c) challenges or gaps in stakeholder interactions; and (d) challenges or barriers to the development and use of more sustainable chemistry technologies.

After drafting the questionnaire, we pretested it over the telephone with four officials from chemical companies. During these pretests we focused on making sure that (1) the questions were clear and logical, and (2) the questionnaire could be completed without undue burden on company officials. In three cases, the officials were from companies that would not receive the full survey; the final pretest was with a company that did receive the full survey. After each pretest we made revisions to clarify the questions, decrease the likelihood of inaccurate responses, and minimize response burden on company officials. The questionnaire was independently peer-reviewed by a GAO survey specialist.

Appendix IV provides the questions in the survey instrument and quantitative results (i.e., response counts) from the survey.

### Survey administration

The surveys were sent by email on January 4 – 6, 2017; in all cases they were sent to the same company officials who participated in our interviews with each company. A reminder email was sent one week after deployment and a similar reminder was sent on the original due date of January 18, 2017, to provide a one-week extension. In total, responses were received from 18 of the original 27 recipient companies, for a 67 percent response rate.

### Survey data analysis

In general, our analysis involved primarily generation of frequency counts for all of the close-ended variables in our survey. We also performed cross-tabulations of our survey data by industry sector.

There was one question in our survey that involved more advanced analytical techniques. This was the complex matrix question 6 that asked respondents to compare a set of 13 environmental and

health factors, one by one, against each other factor. For each pairing, respondents were asked: “If your company could only achieve a benefit for one of the factors in the pair at the expense of the other, for which factor would your company generally consider it more important to achieve a benefit?” To summarize the resulting data in a concise form and ascertain the relative importance of the 13 factors, we developed the following scoring approach:

- Assign one point to a factor each time a company responded that it was more important to achieve a benefit for this factor than for the other factor in the pairing.
- If the two factors were rated as equal, assign 0.5 points to both factors.
- If there was no answer provided or the company said it had no opinion, no score was assigned.
- These scores were then added for each factor across every pair of factors.

Results from these analyses are provided in chapter 2.

## Appendix II: Expert participation

We collaborated with the National Academies to convene a two-day meeting of experts to inform our work on sustainable chemistry technologies; the meeting was held on May 24-25, 2016. The experts who participated in our study are listed below. Many of these experts gave us additional assistance throughout our work, including 12 who provided additional technical assistance during our study by sending additional technical material for our review, commenting on the proposed scope of our technology chapters, or answering technical questions; 1 who pretested our survey; and 6 who reviewed our draft report for accuracy and provided technical comments.

### Dave Allen

Melvin H. Gertz Regents Chair in  
Chemical Engineering  
University of Texas at Austin

### R. Morris Bullock

Director of the Center for Molecular  
Electrocatalysis  
Pacific Northwest National Laboratory

### Joe Armstrong

Executive Director, Process Chemistry  
Merck & Co., Inc.

### Terrence Collins

Teresa Heinz Professor of Green Chemistry  
Carnegie Mellon University

### Tina Bahadori

National Program Director, Chemical Safety for  
Sustainability National Research Program  
Environmental Protection Agency

### David Constable

Director, ACS-Green Chemistry Institute  
American Chemical Society

### Eric Beckman

George M. Bevier Professor of Engineering  
Co-Director, Mascaro Center for Sustainable  
Innovation  
University of Pittsburgh

### Ian Davies

Merck & Co., Inc.

### Richard Engler

Senior Chemist  
Bergeson & Campbell PC

### Paul A. Bertin

Research Group Leader, Innovation  
Elevance Renewable Sciences

### John Frazier

Independent Consultant  
Previously Senior Director of Chemistry, NIKE

### Henry Bryndza

Global Technology Director  
DuPont Protection Solutions

### Martin Green

Materials Research Engineer  
National Institute of Standards and Technology

**Richard Helling**

Director, Sustainable Chemistry  
The Dow Chemical Company

**Philip Jessop**

Canada Research Chair in Green Chemistry  
Queen's University, Ontario, Canada

**Bruce Lipshutz**

Professor of Chemistry  
University of California, Santa Barbara

**Steve Maguire**

Professor, Strategy and Organization  
Director, Marcel Desautels Institute for  
Integrated Management  
McGill University, Quebec, Canada

**Jennifer McPartland**

Senior Scientist, Health Program  
Environmental Defense Fund

**KC Morris**

Computer Scientist  
National Institute of Standards and Technology

**Robin Rogers**

President/Owner/Founder,  
525 Solutions, Inc.  
Adjunct Professor  
McGill University, Quebec, Canada

**Kevin Swift**

Chief Economist and Managing Director,  
Economics and Statistics  
American Chemistry Council

**John Warner**

President and Chief Technology Officer  
Board of Directors  
Warner Babcock

**Todd Werpy**

Senior Vice President and Chief Technology  
Officer  
Archer Daniels Midland Company

**Julie Zimmerman**

Professor of Chemical & Environmental  
Engineering and Forestry & Environmental  
Studies  
Yale University

## Appendix III: Industry participation

We interviewed and fielded our industry survey to representatives of 27 chemical companies. One of these companies both pretested and received the survey. We also spoke with representatives of 2 additional companies; these companies assisted us by pretesting the survey.

### Chemical Companies

Agilyx Corporation	Florida Chemical
Amgen	Genetech
Amway	Glaxo Smith Kline
Asymchem	Glycosurf
BASF Corporation	Johnson & Johnson
Bimax, Inc.	Mango Materials
Boehringer-Ingelheim	Merck
Chemours	Nissan Chemical America
Connora Technologies	Novozymes
Dixie Chemical	Pfizer
Dow Chemical Company	Proctor and Gamble
Dupont	Rochester Midland
Elevance	Seventh Generation
Eli Lilly	State Industrial
Entropy Solutions	

### Industry groups or collaborations

American Chemical Society (ACS) – Green Chemistry Institute (GCI)

American Chemistry Council (ACC)

Less Energy-Intensive Alternative Separations Program (ALTSEP)

## Appendix IV: Survey of chemical companies' sustainable chemistry activities

This appendix presents the questions from our survey of chemical companies and the corresponding response counts. The survey included a limited number of open-ended questions; we have omitted the narrative responses from this appendix.

### SECTION 1: Demographics

#### 1. Which industry sectors accurately describe your company? (Check all that apply.)

Chemical manufacturing	Formulator <sup>a</sup>	Pharmaceuticals	Other	Number of respondents
11	4	7	— <sup>b</sup>	18

Notes:

<sup>a</sup>For purposes of our survey and report, formulator companies are makers of personal care and cleaning products.

<sup>b</sup>Responses of "Other" were discussed with the respondents and converted to one of the three primary sectors.

#### If you checked more than one box above, is there one that you consider to be the primary industry sector for your company?

*Narrative responses are intentionally omitted; all subsequent analyses included companies as members of any sector they checked in question 1, not just the primary sector they noted here.*

#### 2. Approximately how many employees does your company have? (Check only one box.)

Less than 100	100–499	500–999	1,000–4,999	5,000 or more	Number of respondents
3	2	0	1	12	18









**SECTION 2: Assessing the Sustainability of Chemical Processes or Products**

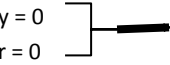
3. For each of the product development or manufacturing activities in column A, please identify which are conducted in-house as part of your company’s normal operations by checking the corresponding box in column B. (Check all that apply.)

For those activities that you checked in column B, please identify those that would typically include some type of sustainability assessment by checking the corresponding box in column C. (NOTE: For purposes of this survey, a sustainability assessment refers to some type of determination of the impact of a chemical process or product on one or more environmental or health factors such as energy use, toxicity, or volume of waste generated.)

<b>A. Product Development or Manufacturing Activity</b>	<b>B. Does your company do this activity in-house as part of your normal operations? (number checked)</b>	<b>(If applicable) C. When your company does this activity, do you also typically conduct some type of sustainability assessment? (number checked)</b>
Development of new products (including feasibility studies, R&D, and/or scale up)	18	18 of 18
Changes to the manufacturing process for an existing product	16	10 of 16
Reformulation of an existing product by changing one or more ingredients or the proportions of ingredients	15	9 of 15
Changing one or more non-formulation features of an existing product, such as the packaging or source of ingredients	14	12 of 14
<b>Number of respondents</b>	<b>18</b>	<b>18</b>

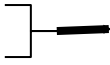
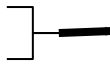
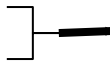
**4. Thinking across the various types of sustainability assessments your company may conduct for chemical processes or products, how often does your company include each of the following life cycle phases in those assessments? (Check one.)**

A. Life cycle phase	B. How often does your company include each phase in its sustainability assessments?	(If applicable) C. If you checked in column B that your company <u>rarely</u> or <u>never</u> includes this life cycle phase, please explain.
Supply chain	Always = 7 Usually = 6 Sometimes = 5 Rarely = 0 Never = 0  [Number of respondents = 18]	Narrative responses intentionally omitted
Starting materials	Always = 6 Usually = 9 Sometimes = 3 Rarely = 0 Never = 0  [Number of respondents = 18]	Narrative responses intentionally omitted
Chemical processes within your facility (including waste streams)	Always = 10 Usually = 5 Sometimes = 3 Rarely = 0 Never = 0  [Number of respondents = 18]	Narrative responses intentionally omitted
Product characteristics (including packaging)	Always = 3 Usually = 7 Sometimes = 7 Rarely = 1 Never = 0  [Number of respondents = 18]	Narrative responses intentionally omitted
Product use	Always = 5 Usually = 5 Sometimes = 4 Rarely = 1 Never = 3  [Number of respondents = 18]	Narrative responses intentionally omitted
Product disposal or recycling	Always = 5 Usually = 6 Sometimes = 4 Rarely = 2 Never = 1  [Number of respondents = 18]	Narrative responses intentionally omitted

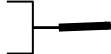
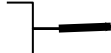
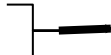
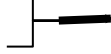
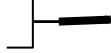
A. Life cycle phase	B. How often does your company include each phase in its sustainability assessments?	(If applicable) C. If you checked in column B that your company <u>rarely</u> or <u>never</u> includes this life cycle phase, please explain.
Other (please specify): (Narrative responses intentionally omitted)	Always = 0 Usually = 2 Sometimes = 0 Rarely = 0 Never = 0 	Narrative responses intentionally omitted
[Number of respondents = 2]		

**5. Thinking across the various types of sustainability assessments your company may conduct for chemical processes or products, how often does your company include each of the following environmental or health factors in those assessments?(Check one.)**

For any factors that you rarely or never include in your sustainability assessments, please check any appropriate reason(s) in the corresponding box in column C.

A. Environmental or health factor	B. How often does your company include each factor in its sustainability assessments? (Check one.)	(If applicable) C. If you checked in column B that your company <u>rarely</u> or <u>never</u> includes this factor, please check any appropriate reason(s). (Check all that apply.)										
Percentage of renewable or biobased content	Always = 3 Usually = 4 Sometimes = 3 Rarely = 5 Never = 3 	<table border="0"> <tr><td>Not relevant to my company</td><td>3</td></tr> <tr><td>Data not available</td><td>0</td></tr> <tr><td>Cannot be reliably measured</td><td>1</td></tr> <tr><td>Too costly to include</td><td>0</td></tr> <tr><td>Other (please specify):</td><td>3</td></tr> </table> (Narrative responses intentionally omitted)	Not relevant to my company	3	Data not available	0	Cannot be reliably measured	1	Too costly to include	0	Other (please specify):	3
Not relevant to my company	3											
Data not available	0											
Cannot be reliably measured	1											
Too costly to include	0											
Other (please specify):	3											
Amount of materials required (e.g., 'E factor' or process mass intensity)	Always = 7 Usually = 5 Sometimes = 5 Rarely = 1 Never = 0 	<table border="0"> <tr><td>Not relevant to my company</td><td>0</td></tr> <tr><td>Data not available</td><td>0</td></tr> <tr><td>Cannot be reliably measured</td><td>0</td></tr> <tr><td>Too costly to include</td><td>0</td></tr> <tr><td>Other (please specify):</td><td>1</td></tr> </table> (Narrative responses intentionally omitted)	Not relevant to my company	0	Data not available	0	Cannot be reliably measured	0	Too costly to include	0	Other (please specify):	1
Not relevant to my company	0											
Data not available	0											
Cannot be reliably measured	0											
Too costly to include	0											
Other (please specify):	1											
Toxicity of required materials	Always = 13 Usually = 3 Sometimes = 2 Rarely = 0 Never = 0 	<table border="0"> <tr><td>Not relevant to my company</td><td>n</td></tr> <tr><td>Data not available</td><td>/</td></tr> <tr><td>Cannot be reliably measured</td><td>a</td></tr> <tr><td>Too costly to include</td><td></td></tr> <tr><td>Other (please specify):</td><td></td></tr> </table> (Narrative responses intentionally omitted)	Not relevant to my company	n	Data not available	/	Cannot be reliably measured	a	Too costly to include		Other (please specify):	
Not relevant to my company	n											
Data not available	/											
Cannot be reliably measured	a											
Too costly to include												
Other (please specify):												

A. Environmental or health factor	(If applicable)		
	B. How often does your company include each factor in its sustainability assessments? (Check one.)	C. If you checked in column B that your company rarely or never includes this factor, please check any appropriate reason(s). (Check all that apply.)	
Energy use	Always = 6	Not relevant to my company	0
	Usually = 4	Data not available	1
	Sometimes = 6	Cannot be reliably measured	1
	Rarely = 2	Too costly to include	0
	Never = 0	Other (please specify):	1
	[Number of respondents = 18]	(Narrative responses intentionally omitted)	
Water use	Always = 4	Not relevant to my company	0
	Usually = 5	Data not available	2
	Sometimes = 7	Cannot be reliably measured	0
	Rarely = 2	Too costly to include	0
	Never = 0	Other (please specify):	0
	[Number of respondents = 18]	(Narrative responses intentionally omitted)	
Land use/physical footprint	Always = 1	Not relevant to my company	0
	Usually = 6	Data not available	0
	Sometimes = 7	Cannot be reliably measured	2
	Rarely = 2	Too costly to include	0
	Never = 1	Other (please specify):	0
	[Number of respondents = 17]	(Narrative responses intentionally omitted)	
Greenhouse gas emissions	Always = 5	Not relevant to my company	1
	Usually = 6	Data not available	0
	Sometimes = 4	Cannot be reliably measured	2
	Rarely = 3	Too costly to include	0
	Never = 0	Other (please specify):	0
	[Number of respondents = 18]	(Narrative responses intentionally omitted)	
Other air emissions	Always = 4	Not relevant to my company	1
	Usually = 7	Data not available	1
	Sometimes = 5	Cannot be reliably measured	0
	Rarely = 1	Too costly to include	0
	Never = 1	Other (please specify):	0
	[Number of respondents = 18]	(Narrative responses intentionally omitted)	

A. Environmental or health factor	B. How often does your company include each factor in its sustainability assessments? (Check one.)	(If applicable)	
		C. If you checked in column B that your company rarely or never includes this factor, please check any appropriate reason(s). (Check all that apply.)	
Volume of process waste generated	Always = 6 Usually = 7 Sometimes = 3 Rarely = 1 Never = 1  [Number of respondents = 18]	Not relevant to my company 0 Data not available 0 Cannot be reliably measured 1 Too costly to include 0 Other (please specify): 1 (Narrative responses intentionally omitted)	
Toxicity of process waste	Always = 9 Usually = 2 Sometimes = 4 Rarely = 3 Never = 0  [Number of respondents = 18]	Not relevant to my company 1 Data not available 0 Cannot be reliably measured 1 Too costly to include 0 Other (please specify): 1 (Narrative responses intentionally omitted)	
Recyclability of (or other uses for) process waste	Always = 2 Usually = 5 Sometimes = 7 Rarely = 4 Never = 0  [Number of respondents = 18]	Not relevant to my company 0 Data not available 0 Cannot be reliably measured 1 Too costly to include 0 Other (please specify): 1 (Narrative responses intentionally omitted)	
Other environmental or health factor (please specify): (Narrative responses intentionally omitted)	Always = 4 Usually = 0 Sometimes = 3 Rarely = 0 Never = 0  [Number of respondents = 7]	Not relevant to my company 0 Data not available 0 Cannot be reliably measured 0 Too costly to include 0 Other (please specify): 0 (Narrative responses intentionally omitted)	
Other environmental or health factor (please specify): (Narrative responses intentionally omitted)	Always = 2 Usually = 1 Sometimes = 2 Rarely = 0 Never = 0  [Number of respondents = 5]	Not relevant to my company 0 Data not available 0 Cannot be reliably measured 0 Too costly to include 0 Other (please specify): 0 (Narrative responses intentionally omitted)	

6. When making a change to a chemical process or product, it may sometimes be necessary to make sustainability tradeoffs. That is, a given change may produce a sustainability benefit for one factor at the expense of reduced sustainability for the other factor.

When comparing each pair of factors in the matrix below, if your company could only achieve a benefit for one of the factors in the pair at the expense of the other, for which factor would your company generally consider it more important to achieve a benefit?

How to fill out this table: For each cell, compare the factor listed in the row (items down the left side, in red) with the factor listed in the column (items across the top, in blue). For each pair of factors, choose your response as follows:

Row – It is generally more important to achieve a benefit for the factor in the Row

Column – It is generally more important to achieve a benefit for the factor in the Column

Equal – We give the two factors Equal emphasis

None/NA – We have No opinion or Not Applicable

*(Note: Unless otherwise noted, 15 of the 18 respondents answered this question for each cell in the matrix.)*

*(See the following pages for the matrix and results.)*

Rows are defined as follows:

- 1 – Percentage of renewable or biobased content
- 2 – Amount of materials required (e.g., ‘E factor’ or process mass intensity)
- 3 – Toxicity of required materials
- 4 – Energy use
- 5 – Water use
- 6 – Land use/physical footprint
- 7 – Greenhouse gas emissions
- 8 – Other air emissions
- 9 – Volume of process waste generated
- 10 – Toxicity of process waste
- 11 – Recyclability of (or other uses for) process waste
- 12 – Toxicity of the product

Columns are defined as follows:

- A – Amount of materials required (e.g., ‘E factor’ or process mass intensity)
- B – Toxicity of required materials
- C – Energy use
- D – Water use
- E – Land use/physical footprint
- F – Greenhouse gas emissions
- G – Other air emissions
- H – Volume of process waste generated
- I – Toxicity of process waste
- J – Recyclability of (or other uses for) process waste
- K – Toxicity of the product
- L – Recyclability of the product

	A	B	C	D	E	F	G	H	I	J	K	L
1												
2	■											
3	■	■										
4	■	■	■									
5	■	■	■	■								
6	■	■	■	■	■							
7	■	■	■	■	■	■						
8	■	■	■	■	■	■	■					
9	■	■	■	■	■	■	■	■				
10	■	■	■	■	■	■	■	■	■			
11	■	■	■	■	■	■	■	■	■	■		
12	■	■	■	■	■	■	■	■	■	■	■	

Question 6 results:

6. In each pair of factors, for which factor (row or column) would your company consider it more important to achieve a benefit?

Cell	Factors in the row and column; most frequent response(s) in bold, dark red font	Number of respondents; most frequent response(s) in bold, dark red font			None/ NA
		Row	Column	Equal	
1 A	Row: Percentage of renewable or biobased content Column: <b>Amount of materials required</b>	2	<b>10</b>	1	2
1 B	Row: Percentage of renewable or biobased content Column: <b>Toxicity of required materials</b>	0	<b>10</b>	3	2
1 C	Row: Percentage of renewable or biobased content Column: <b>Energy use</b>	0	<b>9</b>	3	3
1 D	Row: Percentage of renewable or biobased content Column: <b>Water use</b>	1	<b>6</b>	4	4
1 E	Row: Percentage of renewable or biobased content Column: <b>Land use/ physical footprint</b>	5	<b>5</b>	2	3
1 F	Row: Percentage of renewable or biobased content Column: <b>Greenhouse gas emissions</b>	1	<b>9</b>	3	2
1 G	Row: Percentage of renewable or biobased content Column: <b>Other air emissions</b>	1	<b>9</b>	2	3
1 H	Row: Percentage of renewable or biobased content Column: <b>Volume of process waste generated</b>	1	<b>10</b>	1	3
1 I	Row: Percentage of renewable or biobased content Column: <b>Toxicity of process waste</b>	1	<b>9</b>	2	3
1 J	Row: Percentage of renewable or biobased content Column: <b>Recyclability of (or other uses for) process waste</b>	1	<b>7</b>	5	2
1 K	Row: Percentage of renewable or biobased content Column: <b>Toxicity of the product</b>	1	<b>9</b>	1	4
1 L	Row: Percentage of renewable or biobased content Column: <b>Recyclability of the product</b>	3	<b>6</b>	2	4
2 B	Row: Amount of materials required Column: <b>Toxicity of required materials</b>	1	<b>11</b>	3	0
2 C <sup>a</sup>	Row: <b>Amount of materials required</b> Column: Energy use	<b>6</b>	3	4	1
2 D	Row: <b>Amount of materials required</b> Column: Water use	<b>7</b>	3	4	1
2 E	Row: <b>Amount of materials required</b> Column: Land use/physical footprint	<b>10</b>	3	1	1
2 F <sup>a</sup>	Row: <b>Amount of materials required</b> Column: Greenhouse gas emissions	<b>7</b>	4	3	0
2 G <sup>a</sup>	Row: <b>Amount of materials required</b> Column: Other air emissions	<b>6</b>	4	3	1
2 H	Row: <b>Amount of materials required</b> Column: <b>Volume of process waste generated</b>	2	3	<b>9</b>	1
2 I	Row: Amount of materials required Column: <b>Toxicity of process waste</b>	3	<b>8</b>	3	1



Cell	Factors in the row and column; most frequent response(s) in bold, dark red font	Number of respondents; most frequent response(s) in bold, dark red font			None/ NA
		Row	Column	Equal	
2 J	Row: <b>Amount of materials required</b> Column: Recyclability of (or other uses for) process waste	<b>8</b>	1	5	1
2 K	Row: Amount of materials required Column: <b>Toxicity of the product</b>	1	<b>11</b>	1	2
2 L	Row: <b>Amount of materials required</b> Column: Recyclability of the product	<b>8</b>	2	1	4
3 C <sup>a</sup>	Row: <b>Toxicity of required materials</b> Column: Energy use	<b>11</b>	1	2	0
3 D <sup>a</sup>	Row: <b>Toxicity of required materials</b> Column: Water use	<b>10</b>	1	3	0
3 E <sup>a</sup>	Row: <b>Toxicity of required materials</b> Column: Land use/physical footprint	<b>12</b>	1	1	0
3 F <sup>a</sup>	Row: <b>Toxicity of required materials</b> Column: Greenhouse gas emissions	<b>10</b>	2	2	0
3 G <sup>a</sup>	Row: <b>Toxicity of required materials</b> Column: Other air emissions	<b>8</b>	2	3	1
3 H	Row: <b>Toxicity of required materials</b> Column: Volume of process waste generated	<b>10</b>	1	3	1
3 I	Row: <b>Toxicity of required materials</b> Column: <b>Toxicity of process waste</b>	3	2	<b>9</b>	1
3 J	Row: <b>Toxicity of required materials</b> Column: Recyclability of (or other uses for) process waste	<b>11</b>	1	3	0
3 K	Row: Toxicity of required materials Column: <b>Toxicity of the product</b>	1	<b>9</b>	3	2
3 L	Row: <b>Toxicity of required materials</b> Column: Recyclability of the product	<b>9</b>	1	1	4
4 D <sup>a</sup>	Row: <b>Energy use</b> Column: Water use	<b>8</b>	2	4	0
4 E <sup>a</sup>	Row: <b>Energy use</b> Column: Land use/physical footprint	<b>10</b>	1	2	1
4 F <sup>a</sup>	Row: <b>Energy use</b> Column: <b>Greenhouse gas emissions</b>	5	3	<b>6</b>	0
4 G <sup>a</sup>	Row: <b>Energy use</b> Column: Other air emissions	<b>6</b>	2	5	1
4 H	Row: <b>Energy use</b> Column: <b>Volume of process waste generated</b>	4	3	<b>7</b>	1
4 I	Row: Energy use Column: <b>Toxicity of process waste</b>	1	<b>8</b>	5	1
4 J <sup>a</sup>	Row: <b>Energy use</b> Column: Recyclability of (or other uses for) process waste	<b>7</b>	2	3	2
4 K	Row: Energy use Column: <b>Toxicity of the product</b>	1	<b>11</b>	1	2
4 L	Row: <b>Energy use</b> Column: Recyclability of the product	<b>8</b>	2	1	4

Cell	Factors in the row and column; most frequent response(s) in bold, dark red font	Number of respondents; most frequent response(s) in bold, dark red font			
		Row	Column	Equal	None/ NA
5 E <sup>a</sup>	Row: <b>Water use</b> Column: Land use/physical footprint	<b>10</b>	1	3	0
5 F <sup>a</sup>	Row: Water use Column: <b>Greenhouse gas emissions</b>	3	<b>9</b>	2	0
5 G <sup>a</sup>	Row: <b>Water use</b> Column: <b>Other air emissions</b>	3	3	<b>7</b>	1
5 H	Row: Water use Column: <b>Volume of process waste generated</b>	4	<b>6</b>	4	1
5 I	Row: Water use Column: <b>Toxicity of process waste</b>	3	<b>9</b>	3	0
5 J <sup>a</sup>	Row: <b>Water use</b> Column: Recyclability of (or other uses for) process waste	<b>6</b>	3	4	1
5 K	Row: Water use Column: <b>Toxicity of the product</b>	1	<b>11</b>	1	2
5 L	Row: <b>Water use</b> Column: Recyclability of the product	<b>7</b>	4	0	4
6 F	Row: Land use/physical footprint Column: <b>Greenhouse gas emissions</b>	1	<b>12</b>	0	2
6 G <sup>a</sup>	Row: Land use/physical footprint Column: <b>Other air emissions</b>	4	<b>9</b>	0	1
6 H	Row: Land use/physical footprint Column: <b>Volume of process waste generated</b>	1	<b>11</b>	2	1
6 I	Row: Land use/physical footprint Column: <b>Toxicity of process waste</b>	1	<b>11</b>	2	1
6 J	Row: Land use/physical footprint Column: <b>Recyclability of (or other uses for) process waste</b>	1	<b>11</b>	1	2
6 K	Row: Land use/physical footprint Column: <b>Toxicity of the product</b>	1	<b>12</b>	0	2
6 L	Row: Land use/physical footprint Column: <b>Recyclability of the product</b>	2	<b>7</b>	2	4
7 G <sup>a</sup>	Row: <b>Greenhouse gas emissions</b> Column: Other air emissions	<b>10</b>	2	2	0
7 H	Row: <b>Greenhouse gas emissions</b> Column: <b>Volume of process waste generated</b>	<b>6</b>	<b>6</b>	3	0
7 I	Row: Greenhouse gas emissions Column: <b>Toxicity of process waste</b>	3	<b>7</b>	4	1
7 J	Row: <b>Greenhouse gas emissions</b> Column: Recyclability of (or other uses for) process waste	<b>6</b>	3	4	2
7 K	Row: Greenhouse gas emissions Column: <b>Toxicity of the product</b>	2	<b>10</b>	1	2
7 L	Row: <b>Greenhouse gas emissions</b> Column: Recyclability of the product	<b>8</b>	2	1	4
8 H	Row: Other air emissions Column: <b>Volume of process waste generated</b>	2	<b>6</b>	<b>6</b>	1

Cell	Factors in the row and column; most frequent response(s) in bold, dark red font	Number of respondents; most frequent response(s) in bold, dark red font			
		Row	Column	Equal	None/ NA
8 I <sup>a</sup>	Row: Other air emissions Column: <b>Toxicity of process waste</b>	2	<b>6</b>	5	1
8 J <sup>a</sup>	Row: <b>Other air emissions</b> Column: <b>Recyclability of (or other uses for) process waste</b>	4	3	<b>5</b>	2
8 K <sup>a</sup>	Row: Other air emissions Column: <b>Toxicity of the product</b>	1	<b>9</b>	2	2
8 L <sup>a</sup>	Row: <b>Other air emissions</b> Column: Recyclability of the product	<b>9</b>	2	0	3
9 I	Row: Volume of process waste generated Column: <b>Toxicity of process waste</b>	2	<b>10</b>	3	0
9 J	Row: <b>Volume of process waste generated</b> Column: Recyclability of (or other uses for) process waste	<b>6</b>	3	5	1
9 K	Row: Volume of process waste generated Column: <b>Toxicity of the product</b>	1	<b>12</b>	0	2
9 L	Row: <b>Volume of process waste generated</b> Column: Recyclability of the product	<b>7</b>	3	2	3
10 J	Row: <b>Toxicity of process waste</b> Column: Recyclability of (or other uses for) process waste	<b>9</b>	4	2	0
10K	Row: Toxicity of process waste Column: <b>Toxicity of the product</b>	1	<b>10</b>	2	2
10 L	Row: <b>Toxicity of process waste</b> Column: Recyclability of the product	<b>8</b>	2	2	3
11K	Row: Recyclability of (or other uses for) process waste Column: <b>Toxicity of the product</b>	1	<b>11</b>	1	2
11 L	Row: <b>Recyclability of (or other uses for) process waste</b> Column: Recyclability of the product	<b>5</b>	4	2	4
12 L	Row: <b>Toxicity of the product</b> Column: Recyclability of the product	<b>11</b>	0	0	4

<sup>a</sup>Only 14 of the 18 respondents selected an answer for these cells.

**7. Considering the sector(s) you selected for your company in Question 1, how useful would it be for all companies within your sector(s) to use a common set of factors for assessing the sustainability of chemical technologies, processes, or products?**

Very useful	Somewhat useful	Slightly useful	Not useful	Do not know/cannot judge	Number of respondents
9	6	1	0	1	<b>17</b>

**Please explain your response.**

*Narrative responses are intentionally omitted.*

8. How useful would it be for all companies across the entire chemical industry to use a common set of factors for assessing the sustainability of chemical technologies, processes, or products?

Very useful	Somewhat useful	Slightly useful	Not useful	Do not know/cannot judge	Number of respondents
5	7	3	0	1	16

Please explain your response.

*Narrative responses are intentionally omitted.*

**SECTION 3: Third-Party Certifications**

9. Which, if any, of the following third-party sustainability certifications does your company currently have, or currently seek, or did it previously have for one or more of your products? (If your company does not have and is not seeking a particular third-party sustainability certification, please choose “Do not have and not seeking.”) (Check all that apply.)

Third-party certification	Currently have	Currently seeking	Do not have now but previously had	Do not have and not seeking
Environmental Protection Agency’s (EPA) Safer Choice / Design for the Environment	4	3	1	11
EPA’s Significant New Alternatives Policy (SNAP) Program	1	0	1	15
U.S. Department of Agriculture’s (USDA) BioPreferred	8	2	0	10
EcoLogo	1	2	0	16
Green Seal	3	0	0	15
Other (please specify): <i>(Narrative responses intentionally omitted)</i>	11	6	1	9

10. If you currently have, are currently seeking, or previously had any third-party certifications, what do you consider to be the primary benefit(s) and challenges of getting those certifications?

*Narrative responses are intentionally omitted.*

**SECTION 4: Interactions with Stakeholders**

PLEASE NOTE: The term “interaction” throughout Section 4 refers to how you engage with stakeholders in developing and using sustainable chemistry technologies. Examples of interactions might include meetings, conducting joint research and development (R&D), resource and information sharing, or responding to regulations.

**11. With respect to the development and use of sustainable chemistry technologies, how much does your organization interact with the stakeholders listed below?** (Note: In answering this question, consider both the duration and frequency of your interaction with the stakeholders. Check one.)

Stakeholders	Not at all	Small/ limited amount	Moderate amount	Large amount	Number of respondents
Suppliers	0	2	10	6	18
Customers	1	3	5	9	18
Industry other than suppliers or customers (e.g., contractors, trade groups, roundtables)	0	2	12	4	18
Academics (e.g., individual researchers, research consortia)	1	7	8	2	18
Environmental advocacy groups	2	10	5	1	18
Consumer advocacy groups	5	11	1	1	18
Scientific and professional organizations	0	6	8	4	18
Department of Defense (DOD)	13	5	0	0	18
Department of Energy (DOE), including the national laboratories	11	3	3	1	18
Environmental Protection Agency (EPA)	6	3	6	3	18
Food and Drug Administration (FDA)	4	8	5	1	18
National Institute of Standards and Technology (NIST)	13	4	0	0	17
National Science Foundation (NSF)	7	8	2	1	18
U.S. Department of Agriculture (USDA)	6	7	4	1	18
Other stakeholder (please specify): (Narrative responses intentionally omitted)	3	2	1	1	—

**12. With respect to the development and use of sustainable chemistry technologies, how valuable are your interactions with the stakeholders listed below? (Please check one box per row.)**

<b>Stakeholders</b>	<b>Not applicable; no interactions</b>	<b>Not at all valuable</b>	<b>A little valuable</b>	<b>Moderately valuable</b>	<b>Very valuable</b>	<b>Number of respondents</b>
Suppliers	0	0	2	9	7	<b>18</b>
Customers	1	0	5	5	7	<b>18</b>
Industry other than suppliers or customers (e.g., other companies, trade groups, roundtables)	0	0	3	11	4	<b>18</b>
Academics (e.g., individual researchers, research consortia)	1	0	5	9	3	<b>18</b>
Environmental advocacy groups	2	0	7	5	3	<b>17</b>
Consumer advocacy groups	5	1	9	2	1	<b>18</b>
Scientific and professional organizations	0	0	3	10	5	<b>18</b>
Department of Defense (DOD)	14	1	1	2	0	<b>18</b>
Department of Energy (DOE), including the national laboratories	11	0	2	4	1	<b>18</b>
Environmental Protection Agency (EPA)	6	0	3	5	4	<b>18</b>
Food and Drug Administration (FDA)	5	1	5	6	1	<b>18</b>
National Institute of Standards and Technology (NIST)	14	1	2	1	0	<b>18</b>
National Science Foundation (NSF)	7	2	3	3	2	<b>17</b>
U.S. Department of Agriculture (USDA)	6	0	5	5	2	<b>18</b>
Other stakeholder (please specify): (Narrative responses intentionally omitted)	3	0	0	3	1	—

**13. For one or two of the most valuable interactions you identified in the previous question, please provide an example including the type of interaction and why the interaction is very valuable to your company.**

*Narrative responses are intentionally omitted.*

14. With respect to the development and use of sustainable chemistry technologies, are there gaps in or challenges to interactions among stakeholders that hinder the development and use of sustainable chemistry technologies?

Yes	No	Number of respondents
15	2	17

If yes, what are those gaps and challenges and how might they be addressed?

*Narrative responses are intentionally omitted.*

### SECTION 5: Details on Company Interactions with Federal Agencies

For this section, we identify seven federal agencies with programs designed to promote the development and use of sustainable chemistry technologies, along with the types of activities in which agencies and companies might interact.

15. Please check the relevant boxes to indicate which sustainable chemistry activities, if any, your company performed with each listed federal agency over the past three years. (Check all that apply.) (Note: There were 18 respondents for this question.)

Legend: DOD = Department of Defense; DOE/NL = Department of Energy including the national laboratories; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NIST = National Institutes of Standards and Technology; NSF = National Science Foundation; USDA = U.S. Department of Agriculture.

Sustainable chemistry activity	DOD	DOE/ NL	EPA	FDA	NIST	NSF	USDA
	(number checked)						
<b>a. Received funding for research and development (R&amp;D) from this federal agency</b>	2	6	0	0	0	2	1
<b>b. Performed collaborative research and development (R&amp;D) with this federal agency</b>	1	6	1	0	4	3	1
<b>c. Provided input to this agency's efforts to develop standards related to sustainable chemistry</b>	0	1	5	1	1	5	1
<b>d. Sold products that involve the use of sustainable chemistry to this federal agency, either in response to the Federal Acquisition Regulations or for any other reason</b>	1	1	0	0	0	0	0
<b>e. Worked on a life cycle assessment or methodology with this federal agency</b>	0	1	3	0	0	1	0
<i>Please describe one example to elaborate on your response to question 15e.</i>	<i>Narrative responses intentionally omitted</i>						
<b>f. Used sustainable chemistry technologies to respond to a regulation from this federal agency</b>	0	0	2	0	0	0	0

Sustainable chemistry activity	DOD	DOE/ NL	EPA	FDA	NIST	NSF	USDA
	(number checked)						
<i>Please describe one example to elaborate on your response to question 15f.</i>	<i>Narrative responses intentionally omitted</i>						
<b>g. Other sustainable chemistry activity (please specify)</b>	0	0	0	0	0	0	0
<i>Narrative responses intentionally omitted</i>							

**16. Please provide one or more examples of challenges or barriers, if any, that your company encountered when working with a federal agency on sustainable chemistry issues and describe how the agency might help mitigate the challenge(s) or barrier(s).**

*Narrative responses are intentionally omitted.*

**17. How, if at all, could the federal government help resolve key challenges or barriers that exist currently in developing and using sustainable chemistry technologies?**

*Narrative responses are intentionally omitted.*

**Concluding Question**

**18. Are there any additional thoughts or clarifying information you think would be helpful for us as we interpret the survey results?**

*Narrative responses are intentionally omitted.*



## Appendix V: The 12 Principles of Green Chemistry

### Principle 1<sup>1</sup>

It is better to prevent waste than to treat or clean up waste after it is formed.

### Principle 2

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

### Principle 3

Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

### Principle 4

Chemical products should be designed to preserve efficacy of function while reducing toxicity.

### Principle 5

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

### Principle 6

Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.

### Principle 7

A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable.

### Principle 8

Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.

### Principle 9

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

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<sup>1</sup> Paul T. Anastas and John C. Warner, *Green Chemistry: Theory and Practice* (New York: Oxford University Press, 1998), 30.

**Principle 10**

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

**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 12**

Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.


## Appendix VI: Roles of selected federal programs and offices in supporting the development and use of more sustainable chemistry processes and products

The following table, organized by federal agency, summarizes the roles played by the selected agency programs highlighted in chapter 6. This is not a comprehensive list of federal programs and agencies that play a role in supporting the development and use of more sustainable chemistry processes and products and represents only a selection of relevant federal activities. GAO selected the programs based on recommendations from agency officials and other experts and on GAO’s analysis of the relevancy of program activities. For more information about GAO’s methodology for selecting programs and offices, see appendix I.

**Table 13: Roles of selected federal programs and offices in supporting the development and use of more sustainable chemistry processes and products, by federal agency**

	Seek to understand the impact of chemicals on human and environmental health	Support the development and commercialization of more sustainable chemistry technologies	Aid the growth of markets for products manufactured with more sustainable chemicals and processes
<b>Department of Agriculture</b> 	Agricultural Research Service National Program on Biorefining	X	
	BioPreferred		X
	Biorefinery, Renewable Chemical and Biobased Product Manufacturing Assistance Program	X	
	National Institute of Food and Agriculture (NIFA) Biomass Research and Development Initiative	X	
<b>Department of Commerce, National Institute for Standards and Technology</b> 	Building for Environmental and Economic Sustainability (BEES) program		X
	Sustainable Manufacturing Program	X	
	Materials Science and Engineering Division	X	

		Seek to understand the impact of chemicals on human and environmental health	Support the development and commercialization of more sustainable chemistry technologies	Aid the growth of markets for products manufactured with more sustainable chemicals and processes
<b>Department of Defense</b> 	Chemical and Material Risk Management Program	X		X
	Strategic Environmental Research and Development Program (SERDP)		X	
	Environmental Security Technology Certification Program (ESTCP)		X	
	Sustainable Product Center and Sustainable Procurement Program			X
<b>Department of Energy</b> 	Advanced Manufacturing Office (AMO)		X	
	National Laboratories		X	
	Multiple funding programs		X	
	Manufacturing USA Institute - Rapid Advancement in Process Intensification Deployment (RAPID)		X	
<b>Department of Health and Human Services</b> 	National Toxicology Program (NTP)	X		
<b>Department of Health and Human Services / Environmental Protection Agency</b> 	Toxicology in the 21st Century (Tox21)	X		

		Seek to understand the impact of chemicals on human and environmental health	Support the development and commercialization of more sustainable chemistry technologies	Aid the growth of markets for products manufactured with more sustainable chemicals and processes
<b>Environmental Protection Agency</b> 	Chemical Safety for Sustainability (CSS)	X		
	Presidential Green Chemistry Challenge Awards		X	
	Safer Choice			X
	Science to Achieve Results (STAR) grant program	X		
	Significant New Alternatives Policy (SNAP) program	X		X
<b>Environmental Protection Agency / National Science Foundation</b> 	Networks for Characterizing Chemical Life Cycles / Networks for Sustainable Molecular Design and Synthesis grant programs	X	X	
<b>National Science Foundation</b> 	Centers for Chemical Innovation		X	
	Sustainable Chemistry Engineering Materials (SusChEM) grant program		X	
<b>Multiple Agencies</b>	Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grant programs		X	

Source: GAO analysis of agency documents. | GAO-18-307

## Appendix VII: GAO contacts and staff acknowledgments

### GAO contacts

**Timothy M. Persons**, Chief Scientist, at (202) 512-6412 or [personst@gao.gov](mailto:personst@gao.gov)

**John Neumann**, Director, at (202) 512-3841 or [neumannj@gao.gov](mailto:neumannj@gao.gov)

### Staff acknowledgments

In addition to the contacts named above, the following GAO staff made key contributions to this report:

#### Applied Research and Methods team

*Center for Science, Technology, and Engineering*

**Karen Howard** (Assistant Director), **Nirmal Chaudhary** (Analyst-In-Charge),  
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**Namita Bhatia-Sabharwal**

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(100398)

## Appendix VIII: Accessible Data

### Data Tables

**Data Table for Figure 8: The median score assigned to each factor by the companies that responded to our survey**

<b>Environmental and health factors</b>	<b>Median score (points)</b>
Toxicity of the product	11.5
Toxicity of required materials	9
Toxicity of process waste	8
Amount of materials required	6.5
Greenhouse gas emissions	6.5
Energy use	5.5
Volume of process waste generated	5.5
Recyclability of (or other uses for) process waste	4.5
Water use	4
Other air emissions	4
Recyclability of the product	2
Land use/physical footprint	2
Percentage of renewable or biobased content	1.5

Data Table for **Figure 9: Company-assigned scores for three environmental or health factors**

Toxicity

Company-assigned score (points)	Number of companies assigning score
0	3
.5	0
1	0
1.5	0
2	0
2.5	0
3	0
3.5	0
4	0
4.5	0
5	0
5.5	0
6	0
6.5	0
7	0
7.5	1
8	1
8.5	0
9	0
9.5	0
10	0
10.5	1
11	1
11.5	1
12	7



Middle land use

<b>Company-assigned score (points)</b>	<b>Number of companies assigning score</b>
0	4
.5	1
1	1
1.5	1
2	5
2.5	0
3	1
3.5	0
4	1
4.5	0
5	0
5.5	0
6	0
6.5	0
7	0
7.5	0
8	0
8.5	0
9	0
9.5	0
10	1
10.5	0
11	0
11.5	0
12	0

Process waste generated

<b>Company-assigned score (points)</b>	<b>Number of companies assigning score</b>
0	1
.5	0
1	0
1.5	0
2	0
2.5	0
3	0
3.5	0
4	1
4.5	1
5	4
5.5	1
6	1
6.5	2
7	1
7.5	1
8	0
8.5	2
9	0
9.5	0
10	0
10.5	0
11	0
11.5	0
12	0

Data Table for **Figure 10: Company-assigned scores for two environmental factors**

amount of materials graph:

<b>Company-assigned score (points)</b>	<b>Number of companies assigning score</b>
0	2
.5	0
1	1
1.5	0
2	0
2.5	0
3	1
3.5	0
4	0
4.5	0
5	0
5.5	1
6	2
6.5	1
7	1
7.5	1
8	2
8.5	0
9	1
9.5	0
10	1
10.5	1
11	0
11.5	0
12	0

bottom greenhouse gas

<b>Company-assigned score (points)</b>	<b>Number of companies assigning score</b>
0	0
.5	1
1	0
1.5	1
2	1
2.5	0
3	0
3.5	0
4	1
4.5	0
5	1
5.5	1
6	1
6.5	1
7	3
7.5	1
8	0
8.5	1
9	0
9.5	1
10	0
10.5	0
11	0
11.5	0
12	1

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Orice Williams Brown, Managing Director, [williamso@gao.gov](mailto:williamso@gao.gov), (202) 512-4400, U.S. Government Accountability Office, 441 G Street NW, Room 7125, Washington, DC 20548

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U.S. Government Accountability Office, 441 G Street NW, Room 7149  
Washington, DC 20548

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