1
Green Chemistry Metrics

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1.1
Introduction and General Considerations

Green chemistry has recently been recognized as having achieved its twenty-fifth anniversary [1,2]. Across this span of time there has been a steady growth in green chemistry-related research and a deepening understanding of what green chemistry is and what it is not, although it is fair to say that it is still consistently debated. Since the earliest discussions about green chemistry, it is also fair to say that the field of chemistry has not embraced green chemistry nor seen the pursuit of green chemistry for the good science and innovation opportunities that are inherent to it. Green chemistry is fundamentally how one thinks about chemistry and how one performs or practices chemistry. Interestingly and perhaps unfortunately, green chemistry has been seen by many chemists as something akin to a social movement similar to other environmental movements [3]. A consequence of this perception is that green chemistry is sometimes seen as not being worthy of serious scientific consideration, in spite of the fact that the major proponents of green chemistry have always pointed to the fact that it is intended to spur innovation and promote the very best science while seeking to avoid or prevent human health and environmental problems. Green chemistry is not about environmental chemistry; to do the best green chemistry, one must however, understand environmental chemistry. It is also not about end-of-pipe environmental improvement, although this is often an important area to pursue.

Part of the problem for this mistaken perception of green chemistry, especially when the term was beginning to be used, was a lack of precision or rigor in providing evidence when making claims about chemistry and labeling a new innovation as “environment-friendly” or “eco-friendly” or “green” or “greener.” The good news is that over the past 15 or so years, there has been considerable work on the part of many in the green chemistry and engineering community to develop methodologies and approaches to systematically and rigorously assess whether or not something is green or sustainable [4–23] (Curzons, A.D., Constable, D.J.C., and Cunningham, V.L. (2002) *Bond Economy: An Alternative*

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Approach to Synthetic Efficiency, Unpublished, GlaxoSmithKline.). Ironically, perhaps, despite all the work to develop metrics, there are still a large number of researchers and practitioners in chemistry publishing research in the top green chemistry and engineering journals who either ignore the use of metrics, claim that it is impossible to assess whether or not something is truly green or sustainable, or use a single metric to justify calling their chemistry innovation "green." This is truly unfortunate because much of what is published in the green chemistry and engineering literature, if viewed from a multivariate metrics perspective, is decidedly lacking in sufficient justification for a chemistry innovation to be called "green," "greener," sustainable, or more sustainable.

It is worth taking a moment to discuss some general ideas about metrics before getting into the details of green chemistry and engineering metrics. Generally speaking, it is commonly accepted that metrics must be clearly defined, simple to interpret and use, measurable, rely on objective determinations rather than subjective approaches, and should ultimately drive some kind of desired behavior or practice. The best way to use metrics is in a comparative sense; it is generally not very productive to engage in assessments from an absolute or absolutist frame of mind, particularly when focusing on sustainability. Rather, one should choose a frame or point of reference against which to apply a metric or make a comparison. In this way, one is able to say with some confidence that one particular outcome or impact is better or worse, greener or more sustainable than the alternatives. Absolutes tend to get in the way of people moving forward and making progress, and the lack of knowing something absolutely is frequently the reason given as to why nothing can or should be done. For example, "there are many possible approaches to metrics and who knows which ones are the best" is frequently offered as a reason for not applying metrics of any kind. This is a spurious argument at best.

Another thing to consider is that one's approach to metrics should be from a multivariate perspective. That is to say that the assessment of "green" or "sustainable" should be from multiple discreetly different kinds of measurements and adapted for a given context. Stated slightly differently, a single metric is insufficient to characterize a chemical, a type of chemistry, a process, or a product as being green, greener, or more sustainable. For example, just because a chemical transformation is done with a catalyst does not mean that it is as green as may be presumed. If, for example, that catalytic transformation is carried out using a platinum group element, and the catalyst is a homogeneous one (as opposed to a heterogeneous one), it is not green or sustainable from multiple perspectives. First, platinum group metals currently favored by many chemists, for example, iridium or platinum, are extremely rare, with relatively low abundance in the Earth's crust. Second, the mining and subsequent extraction of these metals from ore, followed by the refining of those metals to separate the various elements that commonly occur in the ore is a highly mass and energy intensive process and results in significant environmental impacts from waste ore, spent extraction liquors, and so on. Finally, running a catalytic reaction homogeneously where the metal is not extracted from the spent mother liquors, it is likely for that metal to end up as a trace contaminant of incinerator slag, unlikely to be recycled, and most likely disposed of as hazardous waste.

The last example about platinum group metals is also a good example of thinking about chemistry from a systems perspective, and/or using life cycle thinking to make a more realistic assessment of whether or not something is “green” or sustainable. Systems thinking is something that is more common in the biological sciences, where dependencies and connections between and among living systems are seen in the context of their ecological niche, the ecosystem an organism inhabits, and the broader environment containing that ecosystem. In other words, life is seen to exist as a complex web of interactions and interdependencies where perturbations to that system are felt in multiple parts of the system, although they may not be immediately noticeable. Systems thinking is also more common in chemical engineering, where one is forced to see a particular unit operation in the context of the overall process, or one is thinking about mass and energy integration across a plant. In the latter instance, mapping the mass and energy inputs and outputs of every unit operation and thinking about how these might be better utilized to increase the overall mass and energy efficiency of the plant is now quite common and a well-developed practice.

Among many chemists, however, research is focused on the immediate environment of two reactants in a round-bottom flask, along with some additional reagents, solvents, and catalysts. The idea that the choice of reactants, reagents, or solvents made in a laboratory for a given experiment has an impact on a broader system, the environment, or humans seems to be largely irrelevant to what may appear as the much more interesting consideration of whether or not two chemicals may react in a novel way. The previous discussion about platinum group metals is a great example of systems thinking and how few chemists are equipped to employ it. If they were, they might think twice about using an element like iridium as a homogeneous catalyst in a biomass conversion process. While its immediate benefit for catalytically converting lignin to a useful framework molecule, for example, may illustrate interesting chemistry that has not been previously done, using an extremely rare element that is dispersed as waste and effectively lost is a dubious application at best, and the approach is unlikely to be ever commercially applied.

A familiarity with life cycle thinking and the even more desirable life cycle inventory/assessment methodology would help chemists in systems thinking, the idea of boundary conditions, and human or environmental impacts trading. Life cycle inventory/assessment in the context of green chemistry is covered in great detail in Chapter 4 as well as elsewhere [24–37]. The idea of the boundary in which an assessment is carried out that is associated with life cycle impact/assessment is very important if one wants to perform a sustainability or green assessment. Where one draws the boundary for the assessment will likely make considerable differences in the outcome of the assessment. For example, just performing an environment, health and safety, or a life cycle impact category assessment (i.e., the ozone depleting potential, greenhouse gas equivalent, eutrophication potential, etc.) of materials used in a particular reaction (boundary is limited) may be a good starting point, but it neglects the cumulative impacts associated with the materials throughout their life cycle.

If one does actually do a fully burdened cradle-to-gate or cradle-to-cradle impact assessment, one will invariably be faced with many difficult questions. For example, which is more important – the cumulative greenhouse gas impact or the ozone-depleting impact, or the nonrenewable resource impact?

Another aspect of metrics that is worth keeping in mind is that metrics should not be collected just for the sake of keeping metrics. Good metrics should be systematically analyzed, promote strategic analysis of trends, outcome, and impacts, and promote continuous improvement. In some instances once metrics are established, these are not revisited on a regular basis and assessed as to whether or not they are successfully changing behavior. This is unfortunate, because metrics should change behavior in the desired direction.

Virtually every discipline of chemistry can and should be seeking to develop and apply metrics to evaluate whether or not the chemistry they are practicing is being done in a green, greener, or more sustainable fashion than existing methods. Chemists seem to understand and accept that the chemistry innovation they report in the literature needs to be superior in some fashion to an existing method or approach; indeed, part of demonstrating the novelty of an approach is in reviewing precedent and comparing with what has been done previously. This same mind set is recommended to be carried over and the green or sustainability aspects of the innovation should be equally proven. A variety of tools created from applying metrics have been created over many years that enable chemists to evaluate the chemicals, solvents, reagents, and so on that are routinely used in chemistry of all kinds [38–48],1),2),3) and these tools can now be used routinely.

It is worth pointing to several chemistry disciplines where metrics are being applied as success stories of the value of using green chemistry metrics. None of these approaches are perfect, but they are certainly a step in the right direction and illustrate the breadth of what is possible. The first discipline to be discussed is synthetic organic chemistry, where metrics approaches have a long history and have been reported for assessing individual reactions, synthesis routes, and design approaches [49–82]. This is one area of chemistry that now has very complete and well-articulated precedent for applying metrics. A second area that serves as a good example is analytical chemistry, where metrics have been developed for analytical instrumental techniques, such as chromatography and spectroscopy, but have also been applied to sample preparation and waste [83–94]. Finally, it is worth noting that green chemistry metrics approaches are being successfully integrated into chemistry education [95–103]. This is an extremely significant development given the importance of educating the next generation of chemists who will not only see that it is eminently

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1) www.reagentguides.com/(accessed January 14, 2017).

2) https://www.acs.org/content/acs/en/greenchemistry/research-innovation/tools-for-green-chemistry.html (accessed January 14, 2017).

3) http://learning.chem21.eu/methods-of-facilitating-change/ (accessed January 14, 2017).

possible to integrate green chemistry metrics into their professional careers, but that these metrics can be used to intelligently and confidently move the world toward more sustainable practices.

1.2
Feedstocks

As it currently exists, most of the global chemistry enterprise is deeply rooted in the use of petroleum and a variety of key inorganic elements and compounds to make the products society uses every day. From a sustainable and green chemistry perspective, most of what is used by chemists is currently obtained in ways that are completely unsustainable. For example, while one may debate how much petroleum there is to be extracted and how long it will last, eventually it will run out, and long before that, extracting it from the ground will come at an increasingly greater economic, social, and environmental cost. From the perspective of chemistry, this is important because the majority of the basic organic framework molecules that chemists use come from petroleum, and it has been recently shown that about 120 of these molecules are used in most organic syntheses [104]. There is over a 100-year tradition of chemistry being performed on petroleum-based molecules that are in a highly reduced state and very unreactive. Comparing molecules obtained from petroleum to those found above ground from bio-based sources, bio-based molecules are generally highly oxidized and/or functionalized and generally not yet available at comparable volumes as would be required, for example, to supply high-volume plastics manufacturing. Moreover, the types of chemistries one would use to convert bio-based framework molecules to products of interest are not very efficient at this point. However, there has been increasing interest and development of bio-based and renewable feedstocks. There are basically two different strategies here. The first is to make use of molecules as they are from Nature and selectively remove some of the functional groups or convert them to functionalized analogues of chemicals that are currently in widespread use. The second is to completely convert them to chemicals, such as benzene/toluene/xylene (BTX) or aniline, or any of the type of molecules you obtain from a petrochemical supply chain. One could propose variations of metrics around either of these approaches, or just stick with the kinds of metrics that will be described later. Regardless, it could be argued that converting highly functionalized molecules to a reduced molecule like BTX is not desirable based on the inherent environmental, health, and safety hazards associated with BTX.

Another approach to assessing feedstocks from renewable and bio-based sources is to use mass-based metrics to calculate the amount or proportion of the biomass put into a process to make a chemical or product. This approach has been discussed elsewhere, as a resource efficiency metric analogous to mass intensity but it is by no means the only approach [105–112]. Another extensive treatment of biomass utilization may be found in work reported by Iffland *et. al*, where a biomass utilization efficiency metric is described for application to bio-based chemicals, polymers, and fuels [113].

Regardless of the approach used, it is important to keep in mind the supply chain associated with a renewable, bio-based chemical or product, just as with one made from a petrochemical source. One should not lose sight of the complexity associated with sourcing a renewable and bio-based chemical or product, and this should necessarily bring one to assess renewability from a life cycle perspective. Growing, harvesting, transporting the biomass, processing the bulk biomass to remove the desired fraction of interest, purifying, and finally isolating the final product requires a significant amount of mass and energy.

One example of sourcing a renewable and bio-based chemical might be furfural, which can be used to produce furan or THF. The supply chain required to produce furan includes sulfuric acid, methanol, or carbon monoxide that are often derived from fossil feedstocks, and process-related energy that is likely to be sourced from a mix of renewable and nonrenewable primary energy sources.

If one is interested in a broader sustainability assessment, the production of furan from renewable and bio-based sources must account for land use and the consequential impacts on the environment, but also the potential for competition with the primary production of food. Metrics for renewable and bio-based chemicals is a complex area of continuing development where there is ongoing national and international debate and where there are no easy answers.

1.3
Chemicals

1.3.1
Hazard and Risk

Any discussion of green chemistry and engineering metrics needs to include a discussion of hazard and risk. Unfortunately, despite clear definitions for each, there is a great tendency for people to use these terms interchangeably. Chemical hazards are associated with an inherent physical or physicochemical property or an effect that a chemical has on a living organism. Examples of inherent hazards are things like acidity or basicity, acute or chronic toxicity, reactivity to air or water, and so on. There has been an enormous amount of study of chemical hazards to better understand the potential impact of chemicals on the environment, to ensure worker safety, and to avoid acute and chronic human health impacts. There is now a considerable body of good information available for many of the most used, high-volume commodity chemicals. These data have been developed to better understand and avoid chemical hazards and the development of hazard information has been a key aspect of chemicals legislation since the 1970s when laws like the US Toxic Substances Control Act (TSCA), recently reauthorized as the Frank Lautenberg Chemical Safety Act of 2016, were introduced, or in the EU, with the REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) legislation, and with many other countries throughout the world adopting legislation similar to REACH. This legislation requires manufacturers to determine environmental, safety, and human health hazards associated with chemicals before giving approval to chemical manufacture, and these data are important parts of any risk assessment. Table 1.1 contains an illustrative but not comprehensive list of common ecotoxicity hazard data that might be collected to assess chemicals. It should be understood that one would also collect analogous human toxicity data (acute and chronic toxicity, dermal, sensitization, etc.) and worker safety data (e.g., flammability, explosivity, flash point, etc.) as part of a routine chemical hazard or risk assessment. If one tries to gather data like these for most any chemical, they will rapidly find that there may be a lot of data, very little data, or some data with many gaps in the data set. When there is a significant amount of data, the most common observation is that chemicals have a large number of hazards associated with them, so trying to decide what to do about this presents a challenge. When there are data gaps, the tendency is to say it is okay to use the chemical, especially if there are no hazards identified in the existing data. Historically, when data is missing, many chemists assumed the chemical must be safe because there is no data available; if there was a problem, it is assumed that someone would have identified any problems. This is an unfortunate and poor assumption to make and certainly not recommended.

A variety of methods and processes have been developed to assess hazard data and on the basis of the hazard assessment, certain actions are recommended. One of the most commonly used in the last few years is GreenScreen [114–116], but other similar approaches have been developed [117]. Regardless of the approach taken, the important thing is that the assessment be transparent, that data gaps are documented, and whether or not the data used for the assessment is experimentally derived or derived from some kind of quantitative structure activity model. Another issue where the state of the art in chemical hazard assessment is not developed is in how to handle mixtures. Despite this being the case, it should not prevent one from looking at chemical hazards and taking action on the basis of the assessment. Ideally, one would choose chemicals that have comparable or superior technical performance with the least number of EHS issues associated with them.

One final way of thinking about EHS hazards of chemicals is to think about major global impacts of chemicals as is common in life cycle inventory/assessment. Table 1.2 contains a small, illustrative list of common but not in any way comprehensive impact categories that are considered to be the midpoint of the assessment. What is meant by this is that in a life cycle assessment, one can group chemicals according to broad categories such as global warming equivalents or ozone depletions equivalents, acidification equivalents, and so on, and these are considered the midpoint. An endpoint analysis means that ozone depletion can have one of many environmental or human health impacts such as increased cancer mortality, broad ecosystem impacts, and so on. Typically, it is perfectly acceptable to remain at the midpoint and assess chemicals according

Table 1.1 Illustrative ecotoxicity hazard data.

Test parameter	Results
Physical properties	
Water solubility	mg/l at 20 °C
UV/visible spectrum (photolysis)	nm (Absorption above 290 nm, photolysis may be possible)
Vapor pressure	mm Hg at 25 °C
Dissociation constant	pK1 = at 25 °C pK2 = at 25 °C
Partition coefficients	
Octanol/water partition coefficient (Log Kow)	
Distribution coefficient (Log Dow)	pH5 = X pH7 = Y pH9 = Z
Soil organic carbon distribution coefficient (Log Koc)	X to Y
Soil distribution coefficient (log K_D)	X to Y
Depletion	
Biodegradation	Aerobic – inherent Percent degradation: X%, Y days, modified Zahn-Wellens (primary, loss of parent) Aerobic – soil Percent degradation: X%, Y days
Hydrolysis rate	Half-life > X year, pH = 7, chemically stable in water (Y/N)

Ecotoxicity	Results
Activated sludge respiration	IC_{50} <, >, = X mg/l
Algal inhibition	IC_{50} = <, >, = X mg/l, 72 h, Scenedesmus subspicatus NOEC <, >, = X mg/l
Acute toxicity to daphnids	EC_{50} <, >, = X mg/l, 48 h, Daphnia pulex NOEC <, >, = X mg/l, 48 h
Chronic toxicity to daphnids	LOEC <, >, = X mg/l, 8 d, reproduction, Ceriodaphnia dubia NOEC <, >, = X mg/l, 8 d, reproduction
Acute toxicity to fish	EC_{50} <, >, = X mg/l, 96 h, juvenile Oncorhynchus mykiss (rainbow trout) NOEC <, >, = X mg/l
Earthworm toxicity	EC_{50} <, >, = X mg/kg, 28 d, Eisenia foetida (manure worm) NOEC <, >, = X mg/kg

Table 1.2 Brief list of LCI/A impact categories.

Greenhouse gasses	Acidification	Eutrophication
Photochemical ozone creation potential	Volatile organic compounds	Human toxicity
Heavy metals	Hazardous waste	Solids to landfill

to their potential impacts as a midpoint category. This will be explained in greater detail in Chapter 4 and the reader is referred elsewhere for a more comprehensive treatment of this subject.

Risk is defined as:

Risk = f(the inherent hazard of a material, the potential or likelihood for exposure).

Risk is often expanded to include a severity rating at given frequencies and probabilities of occurrence.

For most of the world, chemical hazard is seen as a driver for policy and regulation. For industry, there is a desire to make risk-based assessments of chemicals. You might ask why this distinction is important to a discussion of green chemistry metrics. Basically, all chemicals are hazardous in some fashion depending on the context. You can drink too much water and die, or drown in a 2″ puddle of water, if the conditions are correct, yet our lives depend on water and humans are mostly water in chemical composition. This example is perhaps overstating the issue, but most policy and regulation of chemicals is driven from the perspective that any exposure to hazardous chemicals constitutes an unacceptable degree of risk. Another related idea, the precautionary principle, states that if the chemical hazards of a chemical compound are not known, or are suspected of being harmful to people or the environment, one should not create or use that chemical unless or until there is proof that there is no risk of harm from that chemical. While regulators promote hazard-based assessments as a means for managing chemicals, industry operates using a wide variety of hazardous substances and rigorously controls exposure to decrease risk to human health and the environment and consequently, this often puts industry at odds with regulators.

For a chemist in a laboratory, risk is generally not something that is top of mind when they are performing an experiment. In the case of hazard, hazard is accepted as a normal part of chemistry and most chemists are rather cavalier about chemical hazards since the hazard is related to why chemicals react, and chemists are very interested in making chemicals react. For the second part of risk, that is, exposure, this may be easy for chemists to ignore because they work in hoods and wear personal protective equipment as a well-accepted, routine, and expected practice while working in the laboratory. The emphasis is on making something new and chemically interesting, not on protecting the environment or human health. It is also conventional wisdom that interesting chemistry cannot be done unless one is using hazardous chemicals to make a reaction proceed to completion in as quantitative and rapid a fashion as possible.

1.4
General Chemistry Considerations and Chemistry Metrics

The traditional way of thinking of efficiency in chemical synthesis is to think of it in terms of chemical selectivity, rates of reaction, and yield. It is worth having a brief, closer look at each one of these ideas.

Chemical Selectivity

One could argue that a lack of selectivity in a reaction is perhaps one of the biggest drivers of waste in most chemical reactions, so it is worth a deeper dive thinking about the ways chemists think about selectivity. In the case of chemoselectivity, a chemoselective reagent is one that reacts with one functional group (e.g., a halide, R-X), but not another (e.g., a carbonyl group, R-C=O). The problem for many reagents is that they can be somewhat promiscuous and will react with more than one portion of the molecule and that leads to the formation of impurities or undesirable by-products. This lack of selectivity also leads to the use of protecting groups as a synthetic strategy, but this is an inherently wasteful strategy. In the case of enantioselectivity, an inactive substrate (a molecule of interest) is converted selectively to only one of two enantiomers. Enantiomers are isomers (i.e., compounds with the same numbers and types of atoms but possessing different structures, properties, etc.) who differ only in the left- and right-handedness of their orientations in molecular space. Enantiomers rotate polarized light in equal but opposite directions and typically react at different rates with other chiral compounds. In drug synthesis, or in the case of certain crop protection agents, for example, a lack of enantioselectivity can lead to as much as 50% of the product being lost, although there are many synthetic strategies like dynamic kinetic resolution that are used to drive the synthetic product toward a single enantiomer. In the case of stereoselectivity, an inability to direct a synthesis toward the exclusive or predominant formation of a specific isomer results in the formation of many undesirable compounds. Finally, reactions can potentially lead to the formation of two or more structural isomers (e.g., R-O-C≡N or R-N=C=O); that is, chemicals possessing the same chemical formula but very different chemical properties. Regioselective reactions are reactions that lead only to the formation of one of the structural isomers. In each of the mentioned cases, a lack of selectivity can lead to tremendous waste of the starting materials, reagents, and catalysts that were used in the synthetic process.

Kinetics

Kinetics is the study of reaction rates; that is, how quickly or slowly a reaction proceeds to completion. Reaction rates are fundamentally controlled by the difference in chemical potential that exists between the reactants and the product, but rates can be dramatically influenced by, to name a few of the most important, reactant concentrations, solvent/solubility effects, applied energy (e.g., temperature, light, etc.) mixing, or the degree of steric hindrance in either or both of the reactants. Each of these influences can lead to a reduction in chemical selectivity and a loss of efficiency. In many synthetic organic chemistry papers, it is not uncommon to see reactions that take a very long time to go to completion. Stated differently, in synthetic organic chemistry the emphasis is usually on obtaining the desired product – not on how quickly one obtains it, or at what temperature, or for how many days the reaction proceeds – in a yield that is high enough to isolate the desired product.

Yield

The most ubiquitous measure of chemical efficiency employed by chemists and chemical engineers alike is undoubtedly percentage yield. For any given reaction

$$A + B \rightarrow C$$

$$\begin{aligned}\text{Theoretical yield} &= (\text{[A] moles of limiting reagent}) \times (\text{stoichiometric ratio:}\\ &\quad \text{[C/A] desired product/limiting reagent}) \times\\ &\quad (\text{FW of desired product [C]})\\ \text{Percentage yield} &= (\text{actual yield/theoretical yield}) \times 100\end{aligned}$$

The interesting thing about yield is that it really is a very poor measure of the overall efficiency of a process and from that perspective, it is effectively useless when assessing whether or not a particular chemical or process is green. Yield ignores the reality that you rarely have only chemicals A and B reacting in isolation, and in many cases, B is added in large stoichiometric excess to drive the reaction to make as much of C as possible. Reagents, catalysts, solvents, and so on are not included in yield and in most cases, kinetics are not considered. So, a chemist can heat a reaction to 120 °C, hold at reflux for 3 days to obtain a yield of 50%, and subsequently claim victory for an awesome reaction no one has done. It does not matter that such a reaction would never be used in a manufacturing situation, nor would it matter if one had to employ massive amounts of solvent in workup or isolation.

1.5
Evolution of Green Chemistry Metrics

For anyone who has worked in the chemical manufacturing and processing industries and who also had responsibility for managing their company's environmental performance, using the traditional chemistry metrics already described as a means for measuring and tracking company's environmental, safety and health performance, efficiency, or compliance would find measures of chemical efficiency woefully inadequate. This is why there has been a focus on metrics that looked at waste and put that in terms of mass and energy rather than in moles. A brief review of the evolution of green chemistry and engineering metrics follows.

Atom Economy

In 1991, noted synthetic organic chemist Barry Trost introduced the term atom economy to prompt synthetic organic chemists to pursue “greener chemistry” as part of their search for synthetic efficiency [118]. Briefly stated, atom economy is a calculation of how many atoms in two chemicals that react remain in the final molecule or product. Final product applies equally to a single chemical transformation, a series of chemical transformations in a single stage of a multistage synthetic route, or to all the reactants in a complete synthetic route to a final product. Unfortunately, atom economy does not include a consideration of yield, stoichiometric excesses, or any of the other things that usually go into making a reaction proceed to completion. A complete review of atom economy and its weaknesses may be found elsewhere [119,120], although it is recognized that atom economy continues to be used by chemists [121–124]. Atom economy is mentioned here for the sake of its historical place, but as a metric to drive green chemistry or for greening a reaction, it is not a particularly practical, informative, or useful metric. It should be noted that the idea of atomic or molecular efficiency; that is, how much of a molecule in a reaction is retained in the final product, is one that has been explored by a number of groups over the years. For example, carbon efficiency [8], bond economy (Curzons, A.D., Constable, D.J.C., and Cunningham, V.L. (2002) *Bond Economy: An Alternative Approach to Synthetic Efficiency*, Unpublished, GlaxoSmithKline.), and molar efficiency [76] have all been proposed and investigated for their usefulness as metrics for assessing synthetic efficiency and their ability to promote greener chemistry. However, none of these measures have proven to be as useful as hoped since they don’t correlate well with mass, energy, or waste associated with chemical reactions. Unfortunately, it is a fact that chemistry lacks atomic and molecular precision, especially for complex molecules; it usually takes a relatively large amount of mass and energy to get molecules to react.

E-Factor

E-factor, proposed by Roger Sheldon in the early 1990s [4,5], is defined as follows:

$$\text{E-factor} = \frac{\text{Total waste (kg)}}{\text{kg product}}$$

In the original publication, it is not explicitly stated whether or not this metric included or excluded water, but it could be used to describe either case. E-factor is relatively simple to understand and its application has drawn attention to the waste produced for a given quantity of product. As part of his original publication, Sheldon produced a comparison of the relative wastefulness of different sectors of the chemical processing industries as diverse as petrochemicals, specialties, and pharmaceuticals and this comparison has been tremendously influential over the past nearly 25 years.

While the metric has been tremendously helpful, it may in practice be subject to a lack of clarity depending on how waste is defined by the user. As in most of green chemistry and engineering, where one draws the boundaries in any given comparison or assessment impacts the outcome. For example, is only waste from one manufacturing plant in view, and is waste from emissions treatment (e.g., acid gas scrubbing, pH adjustment in wastewater treatment plants, etc.) included? Is waste from energy production (heating or cooling reactions, abatement technology, etc.) included? Or perhaps something like waste solvent passed on to a waste handler and burned in a cement kiln is not included. Depending on how these are handled, you can arrive at very different answers.

It is also generally true, at least based on industrial experience, that drawing attention to waste does not generally capture the attention or imagination of chemists, unless, of course, they have spent most of their careers trying to commercialize a chemical product and/or process. Among chemists, there may be a tendency to discount the importance of all the other things that go into the reaction and focus on the “good science” that goes into getting two reactants to proceed quantitatively to a desired product. Chemical process wastes also do not capture most business leader’s attention unless profit margins for their chemicals are very small.

Step and Pot Economy

In 1997, Paul Wender and colleagues published a paper introducing the concept of step economy in the context of an ideal synthesis for a new drug [125,126]. While it may seem obvious now, it was not appreciated that completing a synthesis in as few steps as possible is actually a desirable strategy or one that makes a synthesis greener. The connection between limiting steps and making a synthesis greener is especially true if there are a limited number of solvent switches, isolations, and recrystallizations in the overall synthesis route. A related idea to step economy reported by Clarke *et al.* is known as pot economy [127,128]. Basically, having a series or a set of cascade or multicomponent reactions in a single pot and of high efficiency means that you have fewer steps, fewer isolations, and fewer solvents, reagents, and/or catalysts. If the reaction mass efficiency of a step and pot economic synthesis is high, the overall process mass efficiency will also be quite high, a very desirable outcome from a green chemistry perspective.

Effective Mass Yield

In 1999, Hudlicky *et al.* proposed a metric known as effective mass yield [49], defined “as the percentage of the mass of desired product relative to the mass of all non-benign materials used in its synthesis.” Or, stated mathematically as follows:

$$\text{Effective mass yield} = \frac{\text{Mass of products}}{\text{Mass of nonbenign reagents}} \times 100$$

This metric was arguably the first in green chemistry that focused attention on the fact that not all mass that passes through a process has an equivalent impact and in fact, there is a relatively small amount of nontoxic mass associated with many processes to produce chemicals. The metric also tried to bridge from a commonly used term in chemistry, yield, and worked to tie that to the fact that many toxic reagents are used in chemistry. Adding reagent toxicity is an extremely important consideration in any assessment of what is “green” and toxicity is certainly something that is absent from any chemists discussion about yield.

Despite the positives of this metric, the attempt by Hudlicky *et al.* to define benign as “those by-products, reagents or solvents that have no known environmental risk associated with them for example, water, low-concentration saline, dilute ethanol, autoclaved cell mass, and so on,” suffers from a lack of definitional clarity. In addition to this lack of clarity, it should be understood that wastes, such as saline, ethanol, and autoclaved cell mass, have environmental impacts of one kind or another that would have to be evaluated and addressed. There is also a very practical problem that defining “nonbenign” is difficult, especially when you are working with complex reagents and reactants that have limited environmental or occupational toxicity information. Also, as noted previously, environmental risk is a function of hazard and exposure, and merely determining hazard for many materials in commerce is currently not possible. Adding to that the difficulty of assessing exposure and the challenge is even more daunting. Unless and until robust human and environmental toxicity information or credible quantitative structure activity estimates are routinely available for the wide diversity of chemicals used, trying to use this metric for most synthetic chemical operations is effectively impossible.

Reaction Mass Efficiency

In an attempt to get over some of the failings of atom economy while retaining a focus on reactants and the efficiency of a reaction, the metric reaction mass efficiency was investigated [8]. This is another mass-based metric that incorporates atom economy, yield, and stoichiometry and is the percentage of the mass of reactants in the final product.

There are two ways to calculate RME.

For a generic reaction $\mathrm{A} + \mathrm{B} \rightarrow \mathrm{C}$

$$\text{Reaction mass efficiency} = \left(\frac{\text{m.w. of product C}}{\text{m.w. of A} + (\text{m.w. of B} \times \text{molar ratio B/A})}\right) \times \text{yield}$$

or more simply

$$\text{Reaction mass efficiency} = \left(\frac{\text{mass of product C}}{\text{mass of A} + \text{mass of B}}\right) \times 100$$

This was a small step forward, but it still does not include all the other materials – reagents, solvents, catalysts – that go into making a reaction proceed to completion.

1.6
Andraos: Tree Analysis

In 2005, Andraos published several papers [54,55] detailing his work to unify reaction metrics for green chemistry and performed detailed reaction analyses on a number of different synthetic routes to target molecules using routes available from the literature. This work was expanded a year later in a paper [56] that used tree analysis to quantify mass, energy, and cost throughput efficiencies of simple and complex synthesis plans and networks. Tree analysis provides a straightforward graphical illustration of key metrics for any reaction sequence, and a variety of spreadsheets have been created to facilitate the analysis. Andraos has continued to expand his work to include environmental, safety, and health metrics into his reaction analysis [68]. He and his coworkers have also developed a series of spreadsheets and educational modules for integrating green chemistry metrics into chemistry education [101–103]. More about Andraos' work may be found in Chapter 3. Given the extensive literature precedent that has been developed, and the ready availability of spreadsheets to facilitate calculations, it is a bit of a mystery as to why green chemistry metrics are not routinely reported by all chemists.

1.7
Process Metrics

A very good treatment of process metrics that is still very relevant was published in a prior book on green chemistry metrics, so the information found there will not be repeated here. Chapters 5–7 of this book also contain an extended treatment of metrics for batch, continuous, and bioprocessing that go well beyond what was covered in the earlier work. There has been, in general, an extensive amount published about process metrics in the green chemistry and engineering literature and the reader is referred elsewhere [129–154].

Process Mass Intensity

Process mass intensity was first published in 2001 [8], although it had been extensively applied within SmithKline Beecham for about 4 years prior to being described in a publication. Process mass intensity was an attempt to focus attention on the inefficiency associated with a typical pharmaceutical process, which at the time, was not the subject of much interest within the pharmaceutical industry. Process mass intensity was built on reaction mass efficiency and included all the reactants, reagents, catalysts, solvents, and any other materials used in product work-up and isolation. It is relatively straightforward to calculate

$$\text{Mass intensity (MI)} = \frac{\text{Total mass in reaction vessel (kg)}}{\text{Mass of product (kg)}}$$

It may also be useful to compare MI with E-factor where

$$\text{E-factor} = \text{MI} - 1$$

At the time the metric was introduced, the amount of water used in a process was excluded, despite the fact that this was routinely calculated. In recent years, water has been included in mass intensity calculations by most pharmaceutical companies for a variety of reasons, but at the time this metric was introduced, it was quite difficult to get chemists to think that organic solvents were important as significant process cost and environmental drivers let alone getting them to think about the total cost of producing high-purity water.

Mass intensity may also be expressed as its reciprocal and converting it to a percentage; in this form it may be compared to metrics like effective mass yield and atom economy although there is generally no correlation between these metrics. This metric is generally known as mass productivity or mass efficiency, and it was proposed as a means of making mass intensity more accessible to managers in business. Productivity and efficiency are more easily understood and valued than an intensity metric ever would be in the business world.

$$\text{Mass productivity} = \frac{1}{\text{MI}} \times 100 = \frac{\text{Mass of product}}{\text{Total mass in reaction vessel}} \times 100$$

1.8
Product Metrics

There has been increasing societal concern about chemicals in products, especially in food, water, personal care, and a growing number of other consumer products. As a result, leading consumer product companies have increased their focus and activities to ensure that chemicals in products they put on the market are safe for humans and the environment. Safer does not mean that there is no inherent hazard associated with any given chemical, but it does mean that under conditions of use, the product will not contain chemicals that will cause harm under normal conditions of use and if used as intended. Legislation like the Frank Lautenberg Chemical Safety Act of 2016 and REACH in the EU are illustrative of government responses to consumer's desires to ensure that chemicals in commercial production, and those that are ultimately in products, will not have adverse impacts on human health and the environment. In the United States, consumer concerns have also given rise to programs like the US EPAs Design for the Environment, Safer Choice program, a voluntary labeling program for companies that use chemicals in their products that are on the US EPAs Safer Chemicals List.

Societal concerns have also spurred in the United States the promulgation of legislation, like the misnamed CA Green Chemistry Act. The California Act has, among other things, legislated that selected chemicals undergo an alternatives assessment; that is, an evaluation of chemicals that provide the same function as an existing chemical but which hopefully do not have the various kinds of human health or environmental hazards associated with that chemical. There are a few concerns with the alternatives assessment approach. First, there is a presumption that one or more alternative compounds are readily available, that these alternatives perform the desired function, and that they will be cost competitive with the incumbent. A second issue is the presumption that there are a sufficient number of alternatives available that do not have the human health and environmental impacts associated with the compound under review. A third issue is that there is still not a defined or agreed standard for how alternatives assessments are to be carried out, and one last issue that is of great concern to industry is that the assessments are all based on an assessment of the inherent hazards of a chemical and not the risk associated with that chemical in use.

Despite these concerns, there are at least two opportunities for green chemistry. First, the identification of compounds to be assessed may eventually be a direct result of the development of “safer” chemicals, safer at least from a human and environmental hazard perspective, through the systematic application of green chemistry and engineering principles during chemical design and development. The second is in contributing to a broader discussion that expands green chemistry considerations beyond merely inherent hazard or “safer” chemicals, and incorporates more sustainability considerations into the development of alternative chemicals. Much of what is covered in the remaining chapters of this book will be very helpful in equipping chemists to evaluate their chemistry from an objective sustainable and green chemistry and engineering perspective. Chapter 8, in particular, will cover in greater depth how some of what was discussed already about green chemistry and its application to products is being handled by a variety of organizations today.

1.9
Sustainability and Green Chemistry

For a very long time in green chemistry circles, there has been debate about what green chemistry includes and what it does not, what sustainable chemistry is, and how the two ideas relate to each other. Despite all the publications over the past 25 years, there are actually many different opinions about what defines something as being green chemistry, and more recently, there has been revived discussion about what sustainable chemistry is and is not. Restricting the discussion for the moment to green chemistry and speaking broadly, the two biggest camps in green chemistry are composed of people that believe green chemistry is restricted to the development of safer chemicals (i.e., pay attention to toxicity and secondarily, to waste) and that all other considerations are not as important, or more under the umbrella of sustainability than belonging to green chemistry. At the opposite end of the spectrum are those that believe the principles of green chemistry and engineering, that is, all the principles that have been written and best articulated in a recent publication on design principles of sustainable and green chemistry [155], encompass most sustainability considerations that are relevant to the integration of green chemistry and engineering into the practice of chemistry. More will be discussed about sustainability and green chemistry in the final chapter of this book, but it is important to state now that principles are not metrics and that metrics need to be derived that can be mapped to principles.

1.10
Making Decisions

As stated in Section 1.1, the purpose of metrics should be to help people make better decisions about their work. In the case of green chemistry, metrics should be guiding what kinds of choices people make in their use of reactants, reagents, solvents, catalysts, reactors, how they isolate and purify their chemical products, and how they make formulations or specify chemicals that are part of complex materials or consumer products. Unfortunately, the world is not very savvy when it comes to making decisions, and we have an especially poor understanding of how to use statistically valid, risk-based decision-making [156]. Ironically, when it comes to making important decisions that require some change in behavior, even when faced with one's own mortality, fewer than 1 in 5 are successful in making changes to develop positive habits that will increase their lifespan [157].

As mentioned previously, there has been increased interest and awareness in recent years for making better decisions about choosing “safer” chemicals that go into consumer products of one kind or another. A recent report by the US National Academy of Science has done a good job proposing a framework for chemical alternatives assessment and compiling, state-of-the-art information about alternatives assessment [158]. There are a variety of online resources becoming available as well [159,160]. Regardless of which alternatives assessment methodology or approach is taken, they all rely on some kind of multicriteria or multivariate decision-making process to guide decision-making. They are also invariably hazards based, and they do not generally include life cycle or systems level thinking in the decision frameworks.

The greatest value of chemical alternatives assessment work to date is in formalizing and standardizing the decision-making methodology, and in identifying the areas that require additional research. For example, data gaps are quite common and how one approaches data gaps in making decisions is critical. In general, there are a variety of strategies employed to fill data gaps such as read-across, nearest-neighbor estimations, quantitative structure activity relationships [161–163], and expert opinion, to name a few. At this point in time, it is fair to say that each approach has its strengths and limitations, with no clear winner; except obtaining the data through standard, accepted experimental protocols. However, lack of data is no excuse for ignoring or not using a multivariate approach to assessment. It is extremely important to undertake the assessment and be transparent about missing data and how decisions are made in the face of data gaps.

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