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Metrics of Green Chemistry and Sustainability: Past, Present, and Future

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ABSTRACT: The first green chemistry metrics—the E factor (kgs waste/kg product) and atom economy (mol wt of product/sum of mol wts of starting materials)—were introduced in the early 1990s and were actually green chemistry *avant la lettre*. In the last two decades, these two metrics have been adopted worldwide by both academia and industry. The E factor has been refined to distinguish between simple and complete E factors, for example, and to define the system boundaries. Other mass-based metrics such as process mass intensity (PMI) and reaction mass efficiency (RME) have been proposed. However, mass-based metrics need to be augmented by metrics which measure the environmental impact of waste, such as life cycle assessment (LCA), and metrics for assessing the economic viability of products and processes. The application of such metrics in measuring the sustainability of processes for the manufacture of pharmaceuticals and other fine chemicals is discussed in detail. Mass-based metrics alone are not sufficient to measure the greenness and sustainability of processes for the conversion of renewable biomass vs fossil-based feedstocks. Various metrics for use in assessing sustainability of the manufacture of basic chemicals from renewable biomass are discussed. The development of a sustainable biobased production of chemicals meshes well with the concept of a circular economy, based on resource efficiency and waste minimization by design, to replace traditional linear, take−make−use−dispose economies.

KEYWORDS: *E factor, Atom economy, Carbon economy, Step economy, Circular economy, Biobased economy, Ethanol equivalent, Life cycle assessment*
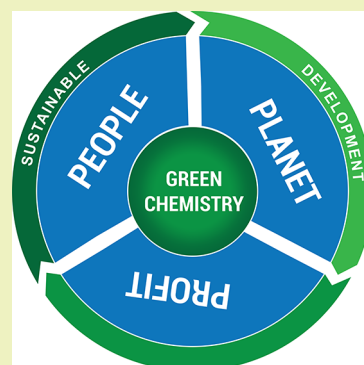
■ INTRODUCTION: ORIGINS OF GREEN CHEMISTRY

The essence of Green Chemistry can be paraphrased as follows:[1]

- Efficient utilization of (preferably renewable) raw materials, including energy resources in the manufacture and application of chemicals.
- Elimination of waste and the use of toxic and or hazardous solvents and reagents in the manufacture and application of chemicals.

In the 1980s, there was a growing concern regarding the generation of waste and the use of toxic and hazardous materials in chemicals manufacturing, in particular, in the fine chemical and allied industries. A pertinent example is provided by the fine chemical phloroglucinol, a pharmaceutical intermediate and reprographic chemical with a global production of ca. 200 tons per annum. The major producer in 1980s was Océ Andeno, based in Venlo in The Netherlands, a company that was later acquired by DSM. The manufacturing process, which had been known since the 19th century,[2] involved the conversion of the high explosive 2,4,6-trinitrotoluene (TNT) in three steps (Scheme 1).

In the first step, the TNT is dissolved in fuming sulfuric acid (oleum) followed by the addition of potassium dichromate to oxidize the TNT to trinitrobenzoic acid. The latter is subsequently reduced, with iron powder and hydrochloric acid (the Bechamp reduction), to triamino benzoic acid which undergoes spontaneous thermal decarboxylation to afford 1,3,5-triaminobenzene. Refluxing the aqueous acidic solution results in the hydrolysis of the triaminobenzene to phloroglucinol. The process is highly selective, affording phloroglucinol in an overall yield of ca. 90%. Hence, a cursory examination would suggest that it is a selective, efficient process.

However, phloroglucinol is not the only product formed. As shown in the overall stoichiometry of the process, in addition to phloroglucinol, substantial amounts of the following inorganic salts are formed: $Cr_2(SO_4)_3$, NH_4Cl, $FeCl_2$, and $KHSO_4$. Indeed, for every kilogram of phloroglucinol produced ca. 40 kg of solid, chromium containing waste were formed. Based on the reaction stoichiometry one would expect ca. 20 kg of waste. The fact that double that amount is formed can be attributed to the use of more than stoichiometric amounts of reagents and the fuming sulfuric acid is used in large excess, that is, as a solvent, and has to be neutralized with base.
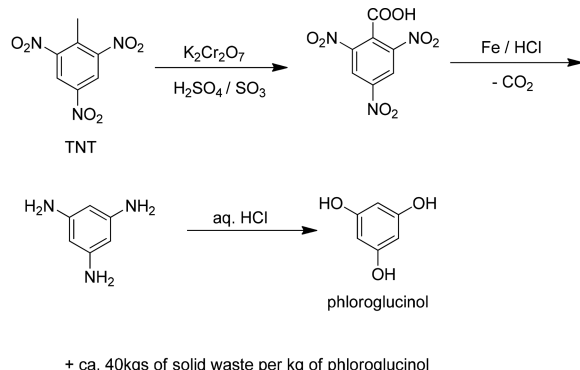
Although organic chemists would, certainly in 1980, have considered this to be an efficient process, it is actually the antithesis of green chemistry. The substrate (TNT) is a hazardous material, the oxidizing agent consists of a

Scheme 1. Phloroglucinol Manufacture before 1980
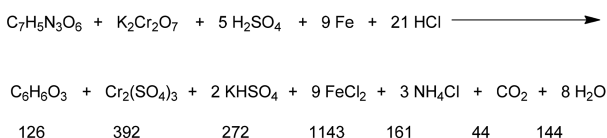

+ ca. 40kgs of solid waste per kg of phloroglucinol

Reaction Stoichiometry:

$$C_7H_5N_3O_6 + K_2Cr_2O_7 + 5\,H_2SO_4 + 9\,Fe + 21\,HCl \longrightarrow$$

$$C_6H_6O_3 + Cr_2(SO_4)_3 + 2\,KHSO_4 + 9\,FeCl_2 + 3\,NH_4Cl + CO_2 + 8\,H_2O$$

| 126 | 392 | 272 | 1143 | 161 | 44 | 144 |

Atom economy = 126/2282 = ca. 5 %

carcinogenic chromium(VI) reagent, and copious amounts of chromium-containing waste are generated. Indeed, operation of the plant was discontinued in the Mid-1980s when the cost of disposal of the chromium-containing solid waste rapidly approached the sales value of the product.

Our edifying experience with the phloroglucinol process led us, in the late 1980s, to conduct an inventorization of the amounts of waste formed per kg product in processes used for the manufacture of chemicals in various industry segments. We called it the E(nvironmental) factor: defined as the mass ratio of waste to the desired product. The now well-known table of E factors for the various segments of the chemical industry, based on this inventorization, was published in 1992.[3] The publication of Table 1 provided an important challenge to

Table 1. E Factors in the Chemical Industry

Industry Sector	Tonnage	E Factor (kg waste/kg product)
Oil refining	10^6–10^8	<0.1
Bulk chemicals	10^4–10^6	<1–5
Fine chemicals	10^2–10^4	5 to >50
Pharmaceuticals	10–10^3	25 to >100

the industry, particularly the fine chemical and pharmaceutical sectors, to reduce the amount of waste formed in their manufacturing processes. What was needed was not end-of-pipe remediation of waste but waste prevention at source by developing cleaner processes, that is Green Chemistry *avant la lettre*. The goal was zero waste manufacturing plants.

Clearly a new paradigm was needed for efficiency in organic synthesis.[4] An environmental factor was clearly missing in the traditional efficiency metric of chemical yield of product. The latter needed to be replaced or, at least, supplemented by an alternative metric that assigns value to eliminating waste and avoiding the use of hazardous and toxic materials. At roughly the same time that we were wrestling with the environmental implications of waste generation in fine chemicals manufacture, Barry Trost was considering the question of selectivity in

organic synthesis, in the context of growing environmental concern.[5] This led him to propose atom economy,[6] calculated by dividing the molecular weight of the desired product by the sum of the molecular weights of all substances produced in the stoichiometric equation and expressed as a percentage, as a metric for comparing the efficiency of synthetic routes to a target molecule. Atom economy (AE) is an extremely useful tool for quickly assessing the mass of waste that will be generated in alternative routes to a particular product.

At the same time, in the late 1980s, increasing environmental awareness was driving another fundamental shift in the historical focus in chemicals manufacture, from pollution control and abatement to pollution prevention. In the 1970s and 1980s, the scientific subdiscipline of environmental chemistry focused on pollution control, that is, on the identification, monitoring, and decontamination of industrial pollutants, primary examples of which were polychlorinated biphenyls (PCBs), chlorinated fluorocarbons (CFCs), and heavy metal salts. This was primarily the realm of analytical chemists who developed the tools and methods needed to trace and monitor man-made pollutants in air and water. It was not exactly the world of process chemists and engineers and was of limited interest to all but a few academic chemists. The majority saw it as "soft" science compared with their own "hard" science of chemical synthesis, reaction mechanisms, and catalysis. In short, mainstream chemists and engineers were, generally speaking, not interested in research on cleaning up the mess of industrial pollutants.

The U.S. Pollution Prevention Act of 1990[7] was probably the stimulus for a turning point in environmental awareness. It focused attention on the pressing need for pollution prevention rather than end-of-pipe waste treatment, recognizing that chemistry is the solution rather than the problem. It promulgated the premise that waste prevention at source is not only good for the environment but also strengthens economic competitiveness by circumventing the costs of waste treatment and, thus, providing for more efficient usage of raw materials. This precipitated a fundamental change in the environmental protection strategy of the U.S. Environmental Protection Agency (EPA)—from waste remediation to waste prevention—culminating in the introduction of the term Green Chemistry at the EPA in the early 1990s.[8]

The term "Green Chemistry" had been used synonymously with "minimum impact chemistry" in a publication in 1991,[9] but it was through the initiatives of the EPA that green chemistry was adopted globally to describe the design of chemical processes and products that reduce or, preferably, eliminate the generation of waste and avoid the use of toxic and/or hazardous substances. Originally, it was known as "benign by design chemistry",[10] and the first and second Gordon Research Conferences on "Environmentally Benign Organic Synthesis" were held in 1996 and 1997, respectively. For the third conference, in 1998, the name was changed to the Gordon Conference on Green Chemistry. The Presidential Green Chemistry Challenge Awards were instituted in 1995, and the Green Chemistry Institute (GCI) was incorporated in 1997 as a not-for-profit organization devoted to promoting and advancing green chemistry. In 2001, the GCI became part of the American Chemical Society in order to pursue their common interests in the discovery and design of chemical products and processes that eliminate the generation and use of hazardous substances. The term gained formal recognition with the publication of the 12 Principles of Green Chemistry (Table

Table 2. Twelve Principles of Green Chemistry

1. Waste prevention not remediation	7. Renewable rather than depleting raw material
2. Atom efficiency	8. Shorter synthesis (avoid derivatization)
3. Less hazardous/toxic materials	9. Catalytic rather than stoichiometric reagents
4. Safer products by design	10. Design products for degradation
5. Innocuous solvents and auxiliaries	11. Analytical methods for pollution prevention
6. Energy efficient by design	12. Inherently safer processes

Scheme 2. High Atom Economy Processes
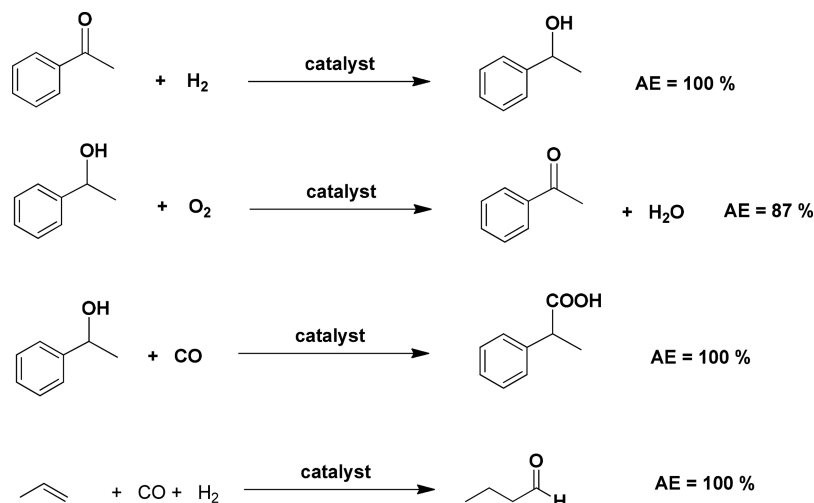
CATALYSIS: THE SOLUTION TO POLLUTION

As the phloroglucinol example clearly showed, a major source of waste, particularly in the fine chemicals and pharmaceuticals industries, is the use of stoichiometric reagents in organic synthesis. Illustrative examples are stoichiometric oxidations with chromium(VI) reagents, permanganate and manganese dioxide, and reductions with metal hydride reagents ($LiAlH_4$, $NaBH_4$) and metals (Na, Mg, Zn, Fe). Similarly, mineral acids (H_2SO_4, HF, H_3PO_4) and Lewis acids ($AlCl_3$, $ZnCl_2$, BF_3), employed as reagents in a wide variety of reactions such as Friedel−Crafts alkylations and acylations, and bases, used in stoichiometric quantities in many classical organic syntheses, are major sources of waste. The solution to waste minimization in (fine) chemicals manufacture is evident: substitution of archaic stoichiometric methodologies with atom economic catalytic alternatives.[12,13] After all, a catalyst is a substance that accelerates the rate of a chemical reaction without being consumed and, therefore, not generating waste. Relevant examples of high atom economy processes are catalytic hydrogenation, oxidation, carbonylation, and hydroformylation (Scheme 2).

Solvent losses are another major source of waste in industrial organic synthesis, and in our original inventorization of the E factors of industrial processes if solvent losses were not known, we assumed that they would be 10% of the amount used in the process. In hindsight, this was probably overly optimistic, certainly in the case of multistep syntheses of advanced pharmaceutical intermediate (APIs), where different solvents are often used for the various steps and cross-contamination becomes an issue. It is also worth mentioning that solvents are not always needed or can be used in much lower amounts, for example, in slurry to slurry processes. In short, the key to green and sustainable chemistry is the use of catalysis—heterogeneous, homogeneous, organocatalysis and biocatalysis—in organic synthesis.[14]

Since the solution is so obvious, why have catalytic processes not been as widely used in pharmaceuticals and fine chemicals manufacture as in bulk chemicals? One reason is that much smaller production volumes are involved, and therefore, the need to minimize waste was less acute than in bulk chemicals manufacture. A second reason is that the economics of bulk chemicals manufacture dictate the use of the least expensive reagents which, generally speaking, were the most atom economical. For example, O_2 and H_2O_2 are not only the least expensive oxidants (per mole), they also have the highest atom economy in oxidation processes. Similarly, H_2 and CO are highly atom economical reagents for reduction and C−C bond formation, respectively. Additional reasons are the fact that time-honored classical stoichiometric reagents generally exhibit broad applicability and shorter development times compared with that of cleaner, catalytic alternatives. Consequently, environmentally (and economically) inferior technologies are often used to meet stringent market deadlines, and subsequent process changes are prohibitive owing to problems associated with regulatory approval. Nonetheless, driven by the pressing need to reduce waste, in the last two decades, more emphasis has been placed on the use of catalytic methods in organic synthesis, in particular, in the manufacture of advanced pharmaceutical intermediates (APIs).[15]

MASS-BASED METRICS OF GREENNESS

Atom Economy and the E Factor. In order to perform meaningful comparisons of different routes to a particular product, we need metrics to measure greenness.[16−20] The two oldest green metrics, the above-mentioned atom economy

2) by Anastas and Warner in 1998,[11] in which the overall guiding element is "benign by design".

(AE) and the E factor, are the simplest and most popular green metrics. AE is a theoretical number which assumes the use of exact stoichiometric quantities of starting materials and a theoretical chemical yield and disregards substances, such as solvents and auxiliary chemicals which do not appear in the stoichiometric equation. The strength of AE, and what its critics tend to forget, is that it can be applied without the need for experimentation. This makes it an extremely useful tool for rapid prediction and evaluation of the amounts of waste that will be generated in alternative routes to a particular target molecule.

The E factor, in contrast, is the actual amount of waste produced in the process and takes waste from all auxiliary components, for example, solvent losses and chemicals used in workup, into account. Another difference is that AE is applied to individual steps, but the E factor, on the other hand, can easily be applied to a multistep process thus facilitating a holistic assessment of a complete process.

A higher E factor means more waste and, consequently, greater negative environmental impact. The ideal E factor is zero, perfectly in line with the first of the 12 Principles of Green Chemistry: "It is better to prevent waste than to treat or clean up waste after it is formed". It can be calculated, for a particular product, manufacturing site, or even a whole company, from a knowledge of the number of tons of raw materials purchased and the number of tons of product sold. Importantly, lower E factors correlate well with reduced manufacturing costs of APIs since they are a direct reflection of lower process materials input, reduced costs of hazardous and toxic waste disposal, improved capacity utilization, and reduced energy demand. In short, there are strong economic incentives for the pharmaceutical industry to integrate green chemistry into the entire process research, development, and manufacturing life cycle.[21]

Originally, waste was defined as "everything but the desired product". However, water was excluded based on the rationale that including it would result in a skewing of E factors. Thus, an otherwise "clean" process that used substantial amounts of water could appear to have more environmental impact than an alternative process, generating copious amounts of waste but using much less water. On the other hand, in many cases, disposal or reuse of the water would involve some sort of pretreatment, which argues for including it in the waste generated. Indeed, the current trend in the pharmaceutical industry is to include water in the E factor, and in an assessment of a biocatalytic process for an advanced intermediate for atorvastatin (Lipitor), we calculated the E factor both with and without water.[22]

A major source of waste in chemicals manufacture, particularly in the pharmaceutical industry, is solvent losses. Thus, an inventorization of waste formed in pharmaceuticals manufacture revealed that solvents and water accounted for 58% and 28%, respectively, of the process waste compared to 8% for the raw materials.[23] More recently, the use of simple E factors (sEF) and complete E factors (cEF), depending on the stage of development of the process, has been suggested.[23] The sEF does not take solvents and water into account and is more appropriate for early route scouting activities, whereas the cEF accounts for all process materials including solvents and water, assuming no recycling, and is more appropriate for total waste stream analysis. The true commercial E factor will fall somewhere between the sEF and cEF and can be calculated when reliable data for solvent losses are available.

Another major cause of the high E factors of processes for the manufacture of APIs is their high molecular complexity and the correspondingly large number of chemical steps needed for their assembly from commercially available starting materials. Hence, there is a definite need for step-economic syntheses as advocated by Wender and co-workers.[24] In the Green Aspiration Level (GAL) concept,[23] the complexity of processes is taken into account, using a combination of Wender's step economy and Baran's process ideality metric,[25] in order to compare the E factor of a particular process to the industry norm as derived from the inventorization of routes to various APIs. Indeed, one way to enhance the greenness of multistep syntheses is to integrate several catalytic steps into step economic, one-pot procedures.[26] Such "telescoping" of multistep syntheses has numerous benefits: it avoids the need for isolating and purifying intermediates, it involves fewer unit operations, requires less solvent and reactor volume, and affords shorter cycle times, higher volumetric and space−time yields, and less waste (lower E factors). Moreover, coupling of reactions can drive equilibria toward product and avoid the need for excess reagents.

A higher E factor means more waste and, consequently, greater negative environmental impact. The ideal E factor is zero, in line with the goal of zero waste manufacturing plants. It can be calculated, for a particular product, production site, or even a whole company, from a knowledge of the number of tons of raw materials purchased and the number of tons of product sold. Importantly, lower E factors, since they are a reflection of lower process materials input, reduced costs of hazardous and toxic waste disposal, improved capacity utilization and reduced energy demand, correlate well with reduced manufacturing costs of APIs. In short, there are strong economic incentives for the pharmaceutical industry to integrate green chemistry into the entire process research, development, and manufacturing life cycle.

The AE and E factor concepts have motivated both industrial and academic chemists globally to explicitly consider waste generation, in addition to the more common criteria such as synthetic convergence, chemical yield, and cost of goods, when designing a synthesis of a target molecule. Furthermore, in the past decade, the E factor and AE concepts have been incorporated into chemistry text books[27] and chemistry curricula at both university[18,19,28,29] and high school levels.[30]

Other Mass-Based Metrics. A variety of alternative mass-based metrics have been proposed[16−20] for measuring the greenness of processes. They can be divided into two groups: those representing a percentage of the ideal analogous to AE and those based on kg/kg analogous to the E factor (Scheme 3).

An example of the former is reaction mass efficiency (RME),[31,32] a refinement of AE taking yield and use of excess reagents into account, that was proposed by Constable and co-workers at GSK. Similarly, carbon economy is the mass of carbon in the product divided by the total mass of carbon in the reactants, expressed as a percentage.[31] Effective mass yield (EMY) is the mass of desired product divided by the mass of nonbenign reagents and was proposed by Hudlicky and co-workers.[33] The problem with applying this metric is to define a "nonbenign reagent".

An example of the latter type is mass intensity (MI), defined as the mass ratio of total input of materials (excluding water) to final product, that is MI = E factor + 1.[31,32] The Green Chemistry Institute Pharmaceutical Round Table adopted this

Scheme 3. Mass-Based Metrics for Measuring Greenness

E factor (E)[3]

$$E = \frac{\text{Total mass of waste}}{\text{Mass of final product}}$$

Atom Economy (AE)[6]

$$AE\ (\%) = \frac{\text{Mol wt of product x 100}}{\text{Sum of mol wts of reactants}}$$

Mass Intensity (MI)[31,32]

$$MI = \frac{\text{Total mass in process}}{\text{Mass of product}}$$

Reaction Mass Efficiency (RME)[31]

$$RME\ (\%) = \frac{\text{Mass of product x 100}}{\text{Total mass of reactants}}$$

Process Mass Intensity (PMI)[34,35]

$$PMI = \frac{\text{Total mass in process (incl } H_2O)}{\text{Mass of product}}$$

Mass Productivity (MP)

$$MP\ (\%) = \frac{\text{Mass of product x 100}}{\text{Total mass (incl solvents)}}$$

Waste Water Intensity (WWI)

$$WWI = \frac{\text{Mass of process water}}{\text{Mass of product}}$$

Effective Mass Yield (EMY)[33]

$$EMY\ (\%) = \frac{\text{Mass of product}}{\text{Mass of hazardous reactants}}$$

Solvent intensity (SI)

$$SI = \frac{\text{Mass of solvents}}{\text{Mass of product}}$$

Carbon Economy (CE)[31]

$$CE\ (\%) = \frac{\text{Carbon in product x 100}}{\text{Total carbon in reactants}}$$

metric, including water in addition to solvent in the input of materials and renamed it Process Mass Intensity (PMI), to benchmark the environmental footprint of processes for APIs and to use this data to drive the greening of the pharmaceutical industry.[34,35] In our opinion, none of these alternative metrics offer any particular advantage over the E factor for describing how wasteful a process is, and waste elimination was always the major driving force behind the development of green chemistry. Using the E factor places emphasis firmly on designing cleaner, waste-free processes, and the ideal E Factor of 0 more clearly reflects the ultimate goal of zero waste manufacturing plants. In contrast, using the PMI focuses on reducing the costs of the raw materials input, and it has been argued[34] that "waste and waste reduction doesn't come anywhere near to capturing management attention to the extent that the cost of high-value materials does". Perhaps this says more about the perception of senior managers in the pharmaceutical industry than the

relative merits of the E factor and PMI as sustainability metrics. It is not necessarily the viewpoint of the chemical industry at large that tends to experience and understand this completely differently. The major driver for the introduction of green chemistry was and still is waste prevention at source that was seen as not only beneficial for the environment but also good for economic competitiveness by circumventing the costs of waste treatment and, thus, *providing for more efficient usage of raw materials*. When all is said and done, PMI and the E factor represent two sides of the same coin, one focusing on optimizing resource utilization and the other on reducing waste generation. An additional advantage of the E factor is that, in evaluating a multistep process, E factors of individual steps are additive but PMIs are not because PMI does not discount step products from the mass balance. Thus, for a three-step process, the overall E factor is $E_{total} = E_1 + E_2 + E_3$ whereas the overall PMI is $PMI_{total} = PMI_1 + E_2 + E_3$.

Christensen and co-workers[36] proposed the use of the C factor, defined as the total mass of CO_2 emitted divided by the mass of product formed, as a metric for comparing the CO_2 burdens of different processes to a particular product. It can also be used to compare biomass-based vs fossil resource-based processes and as one facet of a Life Cycle Assessment study (see below).

System Boundaries and Intrinsic E Factors. E factors, indeed all mass-based metrics, are very much dependent on the starting point of the synthesis; that is, it is necessary to define the boundary conditions for calculation of E factors.[23] In our original development of the concept, E factors were calculated on a gate-to-gate basis,[3] that is, the starting point is the raw material entering the factory gate and the end point is the product leaving it. The E factor relates only to those processes carried out at the manufacturing site. However, a raw material used in an API synthesis may itself be an advanced intermediate, prepared in a multistep process from readily available raw materials. Indeed, E factors can be dramatically reduced overnight by purchasing an intermediate rather than producing it on site. However, this can easily lead to inconsistencies in measuring the greenness of pharmaceutical processes. Hence, the intrinsic E factors associated with

Scheme 4. Pfizer's Commercial Process for Sildenafil (Viagra)
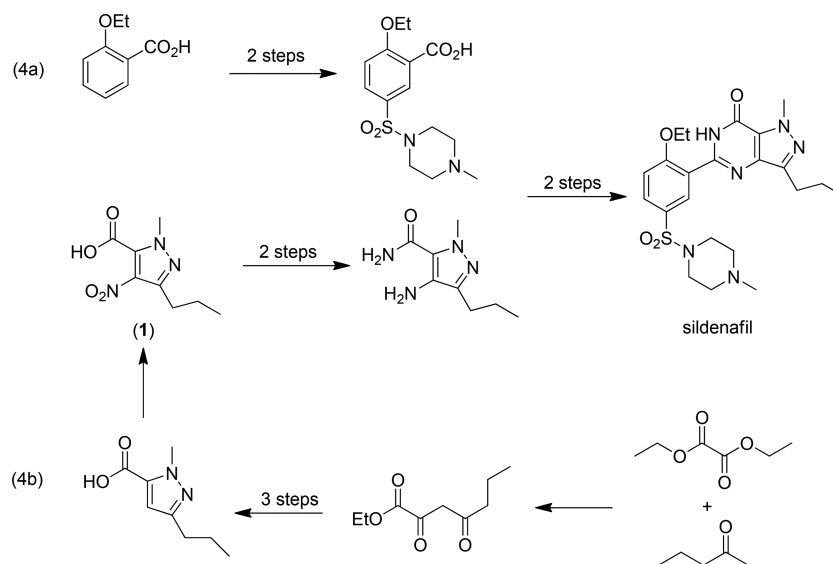
procured raw materials need to be considered. One possibility is to define the starting point as a commodity-type, commercially available, raw material. This can be illustrated by reference to the commercial process for the manufacture of sildenafil citrate (Viagra) shown in Scheme 4a.

This process afforded[23] a (traditional) E factor, including 10% of solvents used and excluding water, of 6.4 kg/kg, corresponding well with Pfizer's reported 6 kg/kg.[37] The sEF (excluding solvents and water) is 3.9 kg/kg, and the cEF is 50.3 kg/kg. However, one of the primary raw materials, 1-methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic acid (1), does not meet the starting point criterion of a readily available commodity-type chemical, defined as being commercially available at a price not exceeding \$100 mol^{-1} for the largest quantity offered. Hence, it was argued[23] that the intrinsic E factor of (1), which is derived from readily available diethyl oxalate and 2-pentanone in a five-step process (Scheme 4b), should be included in the calculation. Indeed, its inclusion afforded significant increases in the overall E factors: the sEF increases from 3.9 to 9.9 kg/kg, the cEF from 50.3 to 85.5 kg/kg, and the E factor from 6.4 to 13.8 kg/kg. It is immediately clear, from this example, that agreement is needed on an industry-wide standardized starting point concept for analyzing process greenness.

SUSTAINABILITY METRICS AND THE ENVIRONMENTAL IMPACT OF WASTE

The mass-based metrics discussed in the preceding section give a good initial indication of the greenness and sustainability of a process, particularly from the viewpoint of waste prevention and resource utilization, but this constitutes only a part of the analysis of the sustainability of a chemical process. The concept of sustainable development was first introduced in 1987 and is defined as *development that meets the needs of the present generation without compromising the ability of future generations to meet their own needs.*[38]

Sustainability is dependent on the rates of both resource utilization and waste generation.[39] A sustainable technology needs to fulfill two conditions: (i) Natural resources should be used at rates that do not unacceptably deplete supplies over the long-term. (ii) Residues should be generated at rates no higher than can be readily assimilated by the natural environment. It is evident, for example, that nonrenewable fossil resources—oil, coal, and natural gas—are being used at a much higher rate than they are replaced by natural geological processes. Consequently, their use is unsustainable in the long term. By the same token, the extraction and use of fossil resources is generating carbon dioxide at rates that cannot be assimilated by the natural environment. This is widely accepted to be a root cause of climate change.[40] This marked discrepancy between the time scales for the formation of natural resources and their exploitation is referred to[41] as the "ecological time-scale violation".

In order to preserve the planet's resources, to enable future generations to fulfill their own ambitions regarding living standards, the current rate of resource extraction has to be restrained. A balance needs to be found between economic development, environmental impact, and societal equity, referred to as the triple bottom line. This is reflected in the three types of sustainability metrics or indicators: economic, ecological, and societal, or the three Ps, profit, planet, and people, represented by three overlapping circles in Scheme 5.[42−44] Two-dimensional metrics—socio-economic, eco-effi-

Scheme 5. Sustainability metrics Venn Diagram
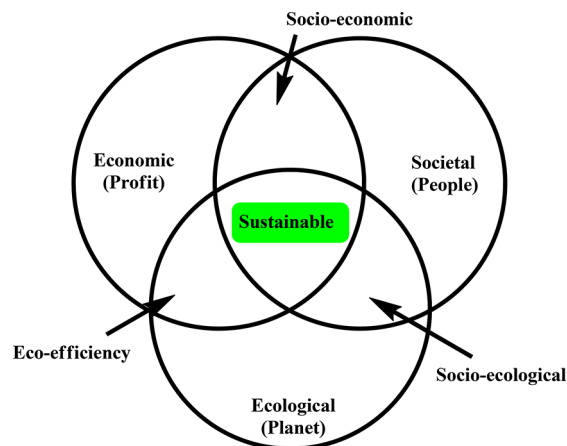
ciency, and socio-ecological—are obtained where two of the circles intersect and a fully sustainable technology where three circles overlap, corresponding to all three aspects of sustainability being fulfilled.

Mass efficiency metrics pertain to five of the 12 principles (numbers 1, 2, 5, 8, and 9) of Green Chemistry and are, therefore, at the heart of green process design. However, for a holistic analysis of the greenness of a chemical process, more aspects need to be delineated, namely, the energy efficiency of the process (principle 6), the renewability of the raw materials (principle 7), health and hazard risks for workers involved (principles 3, 11, and 12), and the environmental impact of the chemicals used and the waste generated (principle 3). [Principles 4 and 10 are associated with the product rather than the process for making it.] Moreover, in order to assess its overall sustainability, the economic and societal metrics, that is, the socio-economic indicators, of the process need to be considered. In short, green chemistry is an integral part of sustainable, benign-by-design processes for chemicals manufacture.

Energy Efficiency Metrics. The inclusion of the energy requirements of a process in the E factor was always implicit since energy consumption generates waste, mainly in the form of carbon dioxide. However, since many fine chemicals and pharmaceutical intermediates are produced in campaigns in multipurpose production facilities, energy usage is often not allocated to particular processes. In the production of commodity chemicals, in contrast, energy consumption plays a prominent role in comparing, for example, biomass-based with petrochemical-based routes (see below). As is the case with mass efficiency metrics, energy efficiency metrics can be based either on raw materials consumed or waste generated, in methane equivalents consumed or in CO_2 equivalents generated, respectively, for example.

In the context of energy consumption in chemicals manufacture, it is worth noting that manufacturing plants use steam, in many cases "waste" heat generated by other exothermic reactions, for heating reactions. This means that heating reactions often does not involve any "extra" energy input. In contrast, cooling reaction mixtures consume substantial amounts of "extra" energy. Hence, reactions at say −20 °C should be avoided.

Cumulative Energy Demand (CED), defined as the total amount of primary energy potential used during the production cycle, is an often used energy metric in environmental

assessments of chemical processes.[45] On the other hand, emphasis is currently placed more on the global warming potential (GWP) of the CO_2 generated in the burning of fuels and the manufacture of chemical products. In the context of green chemistry and sustainable development, it is very important to establish if energy is derived from fossil resources or renewable biomass. Thus, the seventh principle of Green Chemistry is "A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable."

Environmental Impact of Waste. The prevention of waste generation, thereby eliminating its environmental impact, continues to be the underpinning tenet of green chemistry. It has been further strengthened and consolidated by the more recent emergence of the concept of a waste-free circular economy (see below). However, a shortcoming of mass-efficiency metrics is that all types of waste are assigned the same weighting. The original intention of the E factor and other mass-based metrics was to draw attention to the inefficiency of many batch chemical processes and the fact that this is the direct cause of the generation of copious amounts of waste, especially in the fine chemical and pharmaceutical industries. Nonetheless, not only the mass but also the environmental burden of the waste needs to be considered. One kilogram of sodium chloride does not have the same impact on the environment as 1 kg of a chromium(VI) compound or 1 kg of dichloromethane solvent. This was recognized when the E factor was introduced in 1992, and the term "environmental quotient", EQ, where Q is an arbitrarily assigned unfriendliness multiplier or weighting factor, was introduced shortly thereafter.[46] In the teaching of green chemistry at the high school level in The Netherlands, these are now referred to as the E factor and the Q factor.[47]

For example, one could arbitrarily assign a Q value of 1 to NaCl and, say, 100−1000 to a heavy metal salt, such as chromium, depending on its threshold limit value (TLV), ease of recycling, etc. Although arbitrary assignment of Q values is debatable, it was clear that (monetary) values could be assigned to waste streams. [One reason for choosing Q to represent the "unfriendliness multiplier" was that the pronunciation of EQ is the same as that of ECU (the European Currency Unit) which subsequently became known as the euro.] Much attention has been devoted, therefore, over the past two decades to quantifying Q. This generally involves completing a score sheet based on safety, health, and environment (SHE) hazards of the raw materials (input) and waste (output). We note, in this context, that any impact score assigned to waste would presumably include the raw materials, solvents, etc., as the waste will inevitably contain some of these materials.

An early example of the development of methodologies for quantifying EQ, during the process design stage, is provided by the work of Heinzle and co-workers.[48] This involved combining mass-loss indices (MLI) with ecological and economic weighting factors to yield environmental (EI) and economic indices (CI). Environmental weighting factors were based on classification schemes related to environmental laws and regulations, and economic indices were based on raw material and waste treatment costs but could also include equipment and operating costs.

Subsequently, Eissen and Metzger[49] developed the simple and easy-to-use EATOS (Environmental Assessment Tool for Organic Synthesis) software for measuring the potential environmental impact of various routes to a target molecule.

Interestingly, for the input, that is the mass of all raw materials, including solvents, catalysts, and auxiliary chemicals used in workup, they used mass intensity, which they called the mass index, S^{1-}, and for the output they used the E factor. They also noted that it would be good to include energy use but that the necessary data are not usually available for bench scale reactions. They developed a relatively simple method, using readily available data, to assess the potential environmental impact, $PEI.kg^{-1}$, of each substance in both the input and output, Q_{input} and Q_{output}, respectively, by assigning a score of 1−10. For the input, this was based on risk phrases (R-phrases) used to designate toxic and hazardous substances.[50] For the output (waste), the score was based on potential eco-toxicological and human toxicological effects such as persistence, bioaccumulation, and ecotoxicity. The outcome is equivalent to EQ in that it constitutes an integration of the amount of waste with quantifiable environmental indicators based on the nature of the waste. It also introduced an economic component—the cost of raw materials—into the assessment.

Similarly, van Aken and co-workers[51] introduced a semi-quantitative post-synthesis tool, the EcoScale, for evaluating both economic and environmental impact factors of organic syntheses on a bench scale. As with EATOS, it is based on assigning a range of penalty points to six parameters—in this case yield, cost, safety hazards, technical setup, reaction conditions, and ease of downstream processing—and subtracting the sum of all penalty points from 100 to give the Ecoscale value of a particular synthesis.

Life Cycle Assessment. Life Cycle Assessment (LCA)[52−56] was specifically designed for assessing the environmental impact of a product, in all stages of its "life", that is, from raw materials acquisition through production and use to end-of-life treatment and disposal or recycling (cradle-to-grave). In addition to determining mass and energy balances LCA is concerned with the evaluation of quantifiable environmental impact categories, such as global warming potential, ozone depletion, acidification, eutrophication, smog formation, and human- and eco-toxicity as described by the ISO 14040:2006 standard.[57] It is used as a decision-making tool by both industry and governmental organizations.

LCA is an iterative process consisting of four phases: (i) definition of the goal and scope, (ii) inventory analysis (LCI), (iii) impact assessment (LCIA), and (iv) interpretation. The scope includes defining system boundaries and level of detail and can differ considerably depending on the goal of the study. The data collection phase (LCI) concerns the documentation of all the energy and material input and output flows within the boundaries of the study and the collection of data relating to the various environmental impact categories for the chemical substances involved from, for example, the LCI database Ecoinvent.[58,59]

The assessment phase (LCIA) is conducted with the data collected in the LCI phase. Environmental impact categories are assigned to the mass and energy flows and quantified in terms of representative units, for example, carbon dioxide equivalents for global warming potential of emissions. Particular categories are assigned a weighting based on their importance in the context of the goal and scope of the study. A number of LCIA methods have been described.[60] One of the most up-to-date examples is ReCiPe which consists of 18 impact categories related to human- and eco-toxicity, climate change, ozone depletion, smog formation, acidification and eutrophication,

Table 3. FLASC Sustainability Metrics Impact Categories

Sustainability Metrics Category	Measurement Unit
Net mass of materials used	kg
Energy consumed	MJ
Green house gas equivalents	kg CO_2 equivalents
Oil and natural gas depletion for materials manufacture[a]	kg
Acidification potential (AP)	kg SO_2 equivalents
Eutrophication potential (EuP)	kg PO_4^{3-} equivalents
Photochemical ozone creation potential (POCP)	kg ethylene equivalents
Total organic carbon (TOC) load before waste treatment	

[a]This concerns only the oil and natural gas resources used as feedstocks for materials manufacture and excludes those used for energy generation.

land use, and water, mineral, and fossil fuel depletion.[61] The interpretation phase should provide a readily understandable, complete, and consistent presentation of the results in accordance with the goal and scope of the study. It may well involve an iterative process of reviewing and revising the scope of the LCA and the nature and quality of the collected data in a way which is consistent with the defined goal.

Graedel[62] noted, in 1999, that "adding a life-cycle perspective to green chemistry enlarges its scope and enhances its environmental benefits". However, conducting a full scale cradle-to-grave LCA in the design or development phase of a process is generally too difficult and time consuming. Depending on the goal, an LCA of a chemical process (rather than a product) could be limited to the manufacturing domain (gate-to-gate).

Subsequently, integration of mass-based green chemistry metrics with quantitative assessment of environmental impact using LCA was described by several authors.[63–67] Domenich and co-workers, for example, compared two routes to maleic anhydride, by aerobic oxidation of benzene and 1-butene, respectively, using LCA with six impact categories: global warming potential (GWP; otherwise known as the carbon footprint, kg CO_2 equivalents), acidification potential (AP), eutrophication potential (EuP), ozone formation potential (OFP), energy consumption (EC), and solid waste production (SWP).[62] The results showed that the route from 1-butene was greener on all counts. The authors noted that they had not taken human- and eco-toxicity into account because there was no international consensus for the assignment of character-ization factors to these environmental impacts.

GREENSCOPE (Gauging Reaction Effectiveness for the Environmental Sustainability of Chemistries with a multi-Objective Process Evaluator) was introduced by the EPA for evaluating and designing more sustainable processes. The metrics/indicators used to compare processes to a target compound are divided into four categories: environment, energy, efficiency, and economics.[68,69] The energy intensity (kJ), atom economy, and yield (%) are used to assess the process efficiency. Net present value and payback period are used as economic indicators and toxic release (kg/kg), aquatic toxicity, and photochemical ozone potential as environmental indicators.

Some companies developed their own LCA methodologies, simplified and modified according to their own goals. Pharmaceutical companies, in particular, have shown consid-erable interest in using LCA-based methodologies to assess the greenness of their processes for API manufacture.[70] However, the application of LCA to the synthesis of fine chemicals and APIs is particularly challenging owing to the paucity of life cycle inventory data for many of the chemicals involved[71,72] and the

absence of a coherent framework for characterizing their toxicological impacts.[73] One approach to bridging this data gap is to use structure-based models, such as the Finechem tool developed by Wernet.[74–76] The latter is based on artificial neural networks and can estimate key inventory parameters and environmental impacts, such as cumulative energy demand and global warming potential based solely on molecular structures. Furthermore, LCA metrics are generally focused on emissions and need to be supplemented with Health, Safety, and Environment (HSE)[77] metrics to encompass potential risks posed by inherently hazardous chemicals. The EATOS methodology (see above) used R-phrases as the basis for assessing the toxicity and hazardous nature of the materials input. In the meantime R-phrases have been changed to Hazard (H) statements for use on material safety data sheets (MSDS).[78] The lacuna in data pertaining to hazardous substances led Eckelman[79] to propose the adoption of *life cycle inherent toxicity* as a new metric that, instead of just considering emissions, assigns degrees of inherent hazard to intermediate chemical flows.

Glaxo Smith Kline (GSK) has been particularly active in using LCA-based methodologies. Already in 2004 Jiménez-González and co-workers at GSK reported[80] a modular, cradle-to-gate LCA methodology for the evaluation of API manufacturing processes. The authors noted that it "proved to be a difficult, if not impossible, task since very little data were available for materials routinely used in the synthesis of chemically and biologically complex pharmaceuticals". More-over, there was no transparency with regard to how LCI data were derived. However, this early study provided the key insight that solvent use is a major contributor to the cradle-to-gate life cycle impacts of APIs, accounting for 75% of the energy use, 80% of total mass of materials, excluding water, 75% of photochemical ozone creation potential, and 50% of greenhouse gas emissions. This led GSK to incorporate LCA considerations into their solvent assessment and selection guides.[81]

Because of the problems encountered in obtaining and interpreting life cycle impact data, companies turned to using streamlined versions of LCA.[82] For example, GSK developed FLASC (Fast Life Cycle Assessment of Synthetic Chemistry), a web-based tool[83] to quickly screen synthetic routes to APIs at an early stage in research and development. FLASC is a cradle-to-gate methodology involving collation of LCI data associated with the manufacture of the materials used in a particular synthesis. It should be noted, therefore, that to enable complete environmental profiling of competing synthesis routes, the FLASC results need to be combined with gate-to-gate LCA impacts corresponding with the conversion of these materials to the API in question. The FLASC assessment is based on

eight core GSK sustainability metrics impact categories (Table 3).

After consolidating the metrics for the eight impact categories, processes are given a score of 1 (bad) to 5 (good), and a simple color-coding system is used to flag differences in scores. A "green" rating is given to processes with a score of greater than 4 and corresponds to, for example, a LCA mass and energy impact of less than 25% of that of the benchmark. A yellow rating is given for a score of 2−4 and red for less than 2. Further refinement of streamlined, easy-to-use LCA methodologies for measuring the greenness of chemicals manufacture remains a top priority, and the evolution of LCA in pharmaceutical and chemical applications was recently reviewed.[84]

More recently, Isoni and co-workers[85] developed an interesting LCA-based methodology for use in solvent selection during early process development of an API. Quick Sustainability Assessment via Experimental Solvent Selection (Q-SA$\sqrt{}$ESS) is a three-stage LCA approach in which the full cradle-to-grave life cycle of a solvent is evaluated. In stage 1, the origin and production of 1 kg of each of the 10 different solvents were evaluated. This involved the use of metrics that reflect their impact on the environment (carbon footprint, acidification potential, and eutrophication potential), human health (toxicity levels), and costs (total energy required and kg API produced per batch). Manufacture from both fossil and renewable biomass feedstocks were also compared. This afforded a mini cradle-to-gate database for the 10 solvents studied.

Stage 2 involved the collection of mass and energy balance data pertaining to the process in which the solvent is used. This also included the mass and type of solvent(s) used to clean the reactor before and after each operation. In stage 3, end-of-use treatment is evaluated. In general, this involves recover and reuse, most commonly by distillation, or disposal by incineration.

The methodology was designed to evaluate solvents in the process development stage where the chemistry has been selected but final decisions have to be made before proceeding to pilot-plant production. It was developed as an Excel spread sheet in which a decision-making table is automatically generated.

Various companies have developed methods for assessing the environmental footprint of their processes based on their own specific goals and needs. For example, Chimex, a subsidiary of L'Oreal that produces primarily cosmetic ingredients, introduced Eco-footprint, a new tool for assessing their processes.[86] The Eco-footprint covers the supply chain from the supplier's gate to the product leaving the Chimex gate and consists of a manufacturing footprint and an eco-design footprint (Table 4).

The manufacturing footprint is based on five indicators: water footprint, carbon footprint of the transportation of raw materials from their manufacturing sites to Chimex plants,

aqueous waste valorization, used solvents valorization, and energy consumption.

The eco-design footprint also consists of five indicators: the E factor of the process, synthetic pathway efficiency which combines the number of steps with yields, raw materials of renewable origin, and potential environmental impacts of raw materials and waste. The latter two indicators are intended to represent the unfriendliness quotient, Q, that the authors renamed the hazard quotient. Presumably, inspired by the EATOS methodology (see above) the authors developed their own calculation tool, taking only toxicological and eco-toxicological parameters that are mandatory in REACH material safety data sheets (MSDS)[87] into account, to determine the potential environmental impacts of raw materials input and waste output. This comprised the following five criteria: chronic and human toxicity, acute eco-toxicology, bioaccumulation, and biodegradability based on data extracted from supplier MSDS or the European Chemical Agency (ECHA) Web site.[88] Each of the 10 indicators is assigned a score on a scale of 1 to 4 where the larger the environmental impact is the higher the score.

Similarly, Phan and co-workers[89] at the flavor and fragrance company, Mane, introduced Green Motion as a gate-to-gate green metric tool to evaluate the efficiency and health, safety, and environmental impacts of their manufacturing processes on a 0−100 scale. Their starting point was to group the 12 Principles of Green Chemistry into seven fundamental concepts as shown in Table 5.

Penalty points are then allocated within each category based on well-defined criteria, such as renewable or synthetic origin of raw materials, yield, number of steps and solvents in the process, and amount of waste as expressed by the E factor. The E factor was favored over PMI because it fitted better with the objective of zero points for an E factor equal to zero.[89] For a given criterion, the higher the impact on health, safety, or environment is, the higher the number of penalty points is. Interestingly, the hazard and toxicity ratings are based on the hierarchy of GHS pictograms used on labels and safety data sheets to denote various hazards and toxicity.

The method was used to rate more than a thousand products in 12 months, thus building a useful database for further benchmarking, and each new product which is scaled up and transferred into production is rated. The authors concluded that GREEN MOTION is a simple and quantitative method and noted that a full assessment can be made in only half an hour. Allocation of penalty points was arbitrary by definition, but the authors noted that they were carefully cross checked and are well suited to the evaluation of flavor and fragrance ingredients.

Clearly, full-scale cradle-to-grave or cradle-to-cradle LCAs are useful for comparing products and processes which have already been commercialized, but conducting a full scale LCA in the design or development phase is generally too difficult and time consuming. In the final analysis, an assessment of the "greenness" of a process or product requires a multivariate approach that includes impacts across all the different metrics. However, the assessment tools for process industries can be simplified by splitting the system boundaries into two domains: the raw materials production and supply domain and the gate-to-gate manufacturing domain.[90]

Integration of mass-based green metrics with LCA affords an extremely useful tool for evaluating the environmental impact of processes for the manufacture of bulk and fine chemicals,

Table 4. Eco-Footprint Metrics

Manufacturing Footprint	Eco-Design Footprint
Carbon footprint	E factor of the process
Water footprint	Synthetic pathway efficiency
Aqueous waste valorization	Raw materials of renewable origin
Used solvents valorization	Environmental impacts of raw materials
Energy consumption	Environmental impacts of waste

Table 5. Green Motion Methodology

Concept	Major Criterion	Unit
Raw material	Origin	Category Yes/No
	Process naturalness	
Solvents	Solvent category	Category
Hazard/toxicity reagent	GHS pictogram	Pictogram
Reaction	Yield	%
	No. of steps	Number
	No. of solvents	Number
	C economy	%
	No. of protection/deprotection steps	
	Overall processing time	
Process	Heating/cooling	Category
	Pressure/vacuum	
Hazard/toxicity of product	GHS pictogram	Pictogram
Waste	E factor	kg/kg

Table 6. Eco-Efficiency Analysis (BASF)

Main Impact Categories	Emission Categories		
	Air	Water	Solid waste
1. Raw materials consumption	GWP	COD	Special waste
2. Energy consumption	ODP	BOD	House
3. Resulting emissions	POCP	NH_4^+	Building
4. Toxicity potential	AP	PO_4^{3-}	
5. Abuse and risk potential		SO_4^{2-}	
6. Land use		Cl^-	
		Heavy metals	
		Hydrocarbons	

and the methodology continues to be further refined.[91] However, in order to be sustainable, a technology must address all three components of the sustainability triple bottom line: environmental, economic, and societal.

■ FROM ENVIRONMENTAL IMPACT TO SUSTAINABILITY

If a technology is not cost effective, it will not be sustainable in the long term. Indeed, the fact that there is no economic component implicit in green chemistry was always seen as a major shortcoming by industry that preferred, therefore, the more encompassing concept of sustainable development. However, economic assessments are very much dependent on geographical location. The cost of raw materials, equipment, and labor, for example, can vary enormously depending on the location. Moreover, economic comparisons of different technologies must be conducted on a level playing field with no "hidden costs". This is particularly important in comparing the economics of fossil-based fuels and chemicals with their biobased counterparts (see below). It is also important at the macro-economic level, where the commonly used indicator— gross domestic product (GDP)—is woefully inadequate for comparing the output of economies of different nations since it does not take the hidden costs of resource depletion and ecological degradation into account.

Similarly, if a technology is not at least *perceived* to have societal benefits it is unlikely to be sustainable. However, one could argue that avoiding toxicity and safety hazards in chemical products and processes, in order to protect both production workers and consumers, are not only desirable environmental goals but are also important societal objectives. Moreover, the weighting of various environmental impact factors can be conducted on the basis of societal considerations. However, it is important to remember that economic and societal indicators are very subjective and vary substantially with the geographical location, the market segment involved, and even from one company to another within a particular industry segment. On the other hand, gauging environmental impact by assigning scores to various environmental criteria, albeit based on quantitative data, is also subjective and can vary very much from one company to another. As Isoni et al.[85] put it, "*Sustainability is an anthropocentric concept based on human judgement of the delicate balance of social, environmental and economic factors, and as such it is not uncommon to observe trade-offs in borderline situations.*"

A prime example of a societal factor in sustainability deliberations is the food vs fuel debate that is the subject of an ongoing discussion in the context of fossil-based fuels vs biofuels. The situation has been summed up admirably by Rosillo-Calle:[92] "*The debate has been for most parts, sterile, driven by moral/ethical, policy concerns, vested interest, and generally, a*

negative press, rather than by science. The movement towards pragmatism is welcome." Hence, there is a move toward "food *and* biofuel" with the realization that renewable biomass can make an important contribution to energy and socio-economic development without affecting food security. Moreover, the whole discussion is a nonissue in parts of the world, for example, in Brazil, that have more than enough arable land to produce all the food and fuel that is needed. Other prime examples of societal factors associated with technological advances are job creation (or loss) and the genetically modified organisms debate.

Many of the early approaches, such as that of the ETH group[48] and the EATOS[49] and Eco-scale[51] methodologies, included an economic metric. BASF developed Eco-efficiency Analysis[93−96] as a tool for quantifying the sustainability of products and processes over the whole life cycle (cradle-to-grave) taking both economic and ecological aspects into account. Ecological data are collected according to LCA rules of ISO 14040 and divided into six main categories: consumption of raw materials, energy consumption, emissions to air, water, and soil (wastes), toxicity potential of substances employed and produced, risk potential of misuse, and land use (Table 5). Emissions impacts are further subdivided into emissions to air, water, and solid wastes (Table 6). Solid wastes are further subdivided into three categories, and their impact potentials are calculated based on the average disposal costs.

For material consumption, individual materials are weighted according to their reserves. Toxicity potentials are based on EU classifications of hazardous materials. The abuse and risk potential reflects the potential dangers of accidents in the manufacturing process. The environmental impact data are normalized and subjected to societal weighting factors to give an overall environmental relevance factor. [The least attractive process is assigned a value of 1, and alternatives are set in relation to that.] An overall cost calculation takes the flow of material and energy and all relevant secondary processes into account and affords a cost relevance factor. The ratio of the environment relevance (E) to the costs relevance (C) gives the eco-efficiency ratio, E/C, of the product or process.

Dach and Roschangar and co-workers[97] described a methodology used by Boehringer Ingelheim to define a good chemical manufacturing process. The primary objective was to affect a smooth transfer of a well-developed, safe, scalable, robust, and economical process to the Production Department. Six of the total of eight criteria were grouped under the heading, Conversion Cost Factors, and the remaining two were Material Cost Factors and Ecoscale. Conversion costs related to the production of the externally procured materials, which were divided into commodity chemicals, raw materials, and custom-made proprietary intermediates, were considered to be reflected in their cost price.

Conversion Cost Factors were divided into Process Efficiency and Process Reproducibility. The former consisted of atom economy (AE), chemical yield, and Volume−Time−Output (VTO), defined as the nominal volume of all reactors (m^3) multiplied by the hours per batch and divided by the output (kg) per batch. If the VTO is less than 1, the process is acceptable, and if it is considerably more than 1, it needs to be improved. The conversion cost can be calculated readily from the VTO. The E factor is used as the indicator of the potential environmental impact of the process and PMI to measure the resource utilization. Process reproducibility and robustness are defined by a Quality Service Level (QSL) and a Process

Excellence Index (PEI). The latter is an indicator of the performance, in terms of yield and cycle time, of diverse operations. The EcoScale criterion is an assessment of the process quality using a penalty point-based analysis of the yield, cost, safety, conditions, and ease of downstream processing derived from the Eco-scale methodology of van Aken.[51]

The Circular Economy. Increasing global concern for anthropogenic climate change is the major driver in the transition from a traditional linear flow of materials in a "take−make−use−dispose" economy to a greener, circular economy.[98] The latter seeks to eliminate waste through deliberate design of products and processes with resource efficiency and recycling in mind, the underpinning philosophy of the European Commission's "Roadmap to a resource efficient Europe".[99]

Barry Commoner, an icon of industrial ecology, already recognized the linear vs circular economy dichotomy in the 1960s. He observed: "We have broken out of the circle of life, converting its endless cycles into man-made linear events: oil is taken from the ground, distilled into fuel, burned in an engine, converted thereby into noxious fumes that are emitted into the air."[100] However, the transition from the planned obsolescence of an unsustainable linear economy to a greener circular one is seriously hampered by the fact that economic comparisons are not being conducted on a level playing field. The true costs of established "take−make−use−dispose" production chains must include the costs of resource depletion, waste management, and environmental pollution that are currently externalized. New economic indicators are needed that take resource efficiency and circularity into account. We need to rethink how to close the loops of production chains, eliminate waste, and optimize resource efficiency.

■ THE BIOBASED ECONOMY

The seventh principle of Green Chemistry is "renewable rather than depleting raw materials", and one of the great challenges of the 21st century is to implement the transition from an unsustainable economy based on nonrenewable fossil resources—oil, coal, and natural gas—as raw materials to a biobased economy with renewable biomass as the feedstock.[101,102] The pressing need for climate change mitigation and the conservation of natural carbon resources is driving the switch to a carbon-neutral manufacture of commodity chemicals, materials, and liquid fuels[103,104] from renewable biomass in integrated biorefineries.[105,106] However, the use of first-generation biomass feedstocks, such as corn and edible oil seeds, is not (*perceived to be*) a sustainable option in the longer term because of direct or indirect competition with food production. An alternative, second-generation scenario, more in line with the concept of a circular economy, involves the valorization of waste biomass,[107] such as waste lignocellulose derived from agricultural and forestry residues, triglycerides from waste cooking oil, and even food supply chain waste.[108] This will require the development of efficient chemocatalytic and, in particular, biocatalytic methods as key enabling technologies for the conversion of lignocellulose to its constituent sugars and their further conversion to liquid fuels and commodity chemicals.[109]

Appropriate sustainability metrics will be an essential component of any comparison of lignocellulose-based with oil- and gas-based routes to commodity chemicals. Various metrics have been used to measure the sustainability of transportation fuels derived from renewable biomass,[110] but much less attention has been devoted to assessing the

sustainability of commodity chemicals from renewable biomass. In the first place, it will be necessary to measure and compare the suitability of different waste lignocellulosic feedstocks. Girio and co-workers[111] proposed a Biotechnological Valorization Potential Indicator (BVPI), based on biological, physicochemical, technological, economic, and geographical factors, for measuring the suitability of lignocellulosic materials as feedstocks for a biorefinery. Using their BVPI, they were able to identify several lignocellulosic waste streams from the Portuguese agro-industrial sector, for example, rice husks and tomato pomace, with high valorization potential.

Saling and co-workers[112,113] at BASF used eco-efficiency analysis for a cradle-to-gate assessment of biobased vs petroleum-based routes to, for example, vitamin B2 (riboflavin). However, there is a great need for concise methodologies for assessing the sustainability of biobased vs petrochemical-based routes to commodity chemicals. Patel and co-workers,[114] building on earlier work of Sugiyama and co-workers,[115] described a methodology for relatively quick, preliminary assessment of the sustainability of processes in the laboratory phase based on a multicriteria approach comprising green chemistry principles, techno-economic analysis, and some elements of LCA, reflecting the environmental impact of both the raw materials and the process. Five parameters contributed to the final score:

1. Economic constraints (weighting 0.3)
   - Raw materials costs/value of product and coproducts
2. Environmental impact of the raw materials (weighting 0.2)
   - Cumulative energy demand
   - GHG emissions
3. Costs and environmental impact of the process (weighting 0.2)
   - Mass loss index = total mass of all materials/ mass of product + coproducts)
4. Environment, Health, and Safety (EHS) index (weighting 0.2)
   - Hazards and persistency of emissions (environment)
   - Chronic toxicity and irritation (health)
   - Acute toxicity and fire/explosion hazards (safety)
5. Risk assessment (weighting 0.1)
   - For example, feedstock availability and supply

The method was used to compare biobased vs naphtha-based butadiene and was later extended to other early stage biobased vs petroleum-based products.[116,117] A more comprehensive study of biobased vs naphtha-based butadiene, using a simplified life cycle approach based on five indicators— cumulative energy demand, carbon footprint, water usage, and an economic index—was subsequently reported by Cavani and co-workers.[118] They concluded that the direct conversion of (bio)ethanol to butadiene has a lower burden than the naphtha-based route and that future efforts should be focused on this route.

The European Union COST Action CM0903 "Utilization of Biomass for Sustainable Fuels and Chemicals" (UBIOCHEM) was launched in November 2009 with special emphasis on the utilization of agricultural residues and nonedible or waste triglycerides. An important objective of UBIOCHEM was to shape a unified view and develop concise metrics for comparing

different processes to sustainable fuels and platform chemicals from biomass. A special issue of Catalysis Today, "*Sustainability Metrics of Chemicals from Biomass*", was devoted to this topic in 2015.[119] The goal was to produce a concise set of sustainability metrics which would enable a relatively quick, cradle-to-gate comparison of fossil-based vs renewable biomass-based routes to commodity chemicals. It soon became apparent that mass-based metrics alone were not sufficient to differentiate as the competing processes often had comparable E factors. Four criteria were eventually selected: material and energy efficiency, land use, and process economics.[120]

1. Material efficiency
   - Mass of useful products/total mass of useful products + waste, that is, it is $1/E + 1$
2. Energy efficiency
   - Caloric value of useful products/caloric value of fossil and renewable energy inputs
3. Land use
   - Hectares of land (in Champagne, France) of good agricultural soil per tonne product
4. Process economics
   - Raw material and capital costs
   - Starting point for petrochemical route
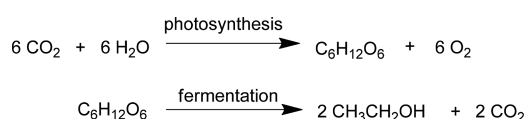   - Starting point for biobased route is sugar beet, corn, or rapeseed.

Seven commodity chemicals were chosen for the study: lactic acid,[121] acrylonitrile,[122] 1-butanol,[123] 1,2-propane diol,[124] succinic acid,[125] isoprene,[126] and methionine.[127] An overall conclusion was that some chemicals (for example, lactic acid) can already be produced from biomass with less energy input and even at lower cost compared to established petrochemical routes, while others are currently more expensive and less energy efficient. Indeed, many biobased routes are at the beginning of the learning curve, and these concise metrics are useful in identifying bottlenecks and providing a basis for planning further research on optimization.

When the relevant processes have been demonstrated at an industrial scale, full-blown sustainability assessments can be used to compare different process strategies. For example, Morales and co-workers[128] carried out a sustainability assessment of technologies for the production of succinic acid by fermentation with metabolically engineered strains of *E.coli*, including isolation of the succinic acid from the fermentation broth. Technical, economic, environmental, and process hazard aspects were considered. They showed that fermentation with strains active at acidic pH together with reactive extraction of the product provide the most environmentally competitive process, while strains with resistance to high sugar concentrations afforded the most economically attractive one. Succinic acid is currently produced mainly from *n*-butane via maleic anhydride. Substitution of this petrochemical succinic acid by biosuccinic acid would afford greenhouse gas savings of ca. 5 tonnes of CO_2 per tonne of succinic acid. The authors noted that realization of a high market share is dependent on a future decrease in total production costs, and the product isolation step is responsible for 60−70% of the latter.

Interestingly, Horvath and co-workers[129] proposed "ethanol equivalent", a novel and relatively simple metric, as a common currency for assessing the sustainability of biomass-based routes to fuels and chemicals. An ethanol equivalent is defined as the mass of ethanol required to deliver the equivalent amount of energy from a given feedstock using energy equivalency or

produce the equivalent mass of a carbon-based chemical using molar equivalency. Since the "ethanol equivalent" can be produced by well-known fermentation, the required mass of biomass feedstock, the land area, and even the volume of water can be calculated. The calculations were based on the first-generation corn-based bioethanol technology commercially practiced in the United States and the stoichiometry shown in Scheme 6. Based on their calculations of ethanol equivalents,

Scheme 6. Stoichiometry of Carbon Dioxide to Ethanol via Glucose

$$6\,CO_2 + 6\,H_2O \xrightarrow{\text{photosynthesis}} C_6H_{12}O_6 + 6\,O_2$$

$$C_6H_{12}O_6 \xrightarrow{\text{fermentation}} 2\,CH_3CH_2OH + 2\,CO_2$$

the authors concluded, *inter alia*, that replacement of the 387×10^6 tons of gasoline used in the United States in 2008 is not a viable proposition by a long way. In contrast, the conversion of biomass to basic chemicals, such as ethylene, propylene, and xylenes, could be a sustainable option in the near future, especially with second-generation bioethanol from waste lignocellulose.

More recently, the same group[130] developed a novel set of metrics for assessing the sustainability of biomass-based carbon chemicals based on ethanol equivalents (EE) as the common currency. A sustainability value of resource replacement (SV_{rep}) and a sustainability value of the fate of waste (SV_{waste}) are determined and used to establish a sustainability indicator (SUS_{ind}). The latter is calculated with the following equation:

$$SUS_{ind} = [SV_{rep} \times SV_{waste}]/[SV_{rep} + SV_{waste}]$$

Sustainability is achieved when all resources are replaced ($SV_{rep} = 1$) and all waste can be recycled or the remaining parts treated within a reasonable time frame. $SUS_{ind} > 0.5$ is better than required sustainability. The SUS_{ind} values of six bioethanol-based basic petrochemicals—ethylene, propylene, toluene, *p*-xylene, styrene, and ethylene oxide—were determined based on the availability of bioethanol in 2008 and 2014. If the global production of all of these chemicals was from bioethanol, then the total amount of bioethanol feedstock needed would be 151.93 mio tonnes in 2008 and 150.26 mio tonnes in 2014. This is substantially more than the total bioethanol production of 27.8 and 42.8 in 2008 and 2014, respectively. The SUS_{ind} values of these chemicals were between 0.1 and 0.429 indicating that the global demand of none of these chemicals could be met with bioethanol-based production. The authors suggested that bioethanol-based carbon products should be labeled "sustainable" only when the necessary land is available to produce the required bioethanol.

The calculations are all based on the state-of-the-art technology for producing bioethanol from corn starch that requires 1 kg of additional bioethanol to produce 2.3 kgs of bioethanol. The authors noted that production of the bioethanol from second-generation lignocellulose in agricultural residues and food supply chain wastes could significantly improve this scenario.

■ SUMMARY AND FUTURE OUTLOOK

The green and sustainable manufacture of chemicals is an essential component of the transition from a linear economy that is devouring the planet's natural resources and degrading the ecosphere to a circular economy that is resource efficient and waste free by design. In order to facilitate this development, it is necessary to have reliable metrics for comparing the greenness and sustainability of competing technologies. The original green metrics, the E factor and atom economy, were focused on the elimination of waste and the maximization of resource efficiency, two sides of the same coin. Other mass-based metrics, such as process mass intensity and reaction mass efficiency, have also been developed. However, not only the amount but also the nature of the raw materials and waste are important in determining greenness. Hence, mass-based metrics need to be supplemented by metrics that measure the environmental impact of raw materials and waste. The life cycle assessment methodology has been adapted by many pharmaceutical and fine chemical companies to make it more suitable for the evaluation of process greenness. In order to assess the sustainability of a process, these metrics need to supplemented with energy efficiency, economic, and societal metrics.

It is also clear that different segments of the chemical industry focus on different aspects of green chemistry and sustainability. In the pharmaceutical and fine chemical industries, for example, solvent use is an important contributor to waste and has associated toxicity/hazard issues. Processes for commodity chemicals, on the other hand, are often solvent free. For some industry segments, the origin of the raw materials, including solvents, is important; for example, for cosmetics companies, they should preferably be renewable. The transition from an unsustainable economy based on fossil resources to a sustainable biobased economy driven by renewable biomass is another important cornerstone of sustainable development Hence, reliable sustainability metrics are needed for comparing biobased and petrochemical routes to commodity chemicals, materials, and fuels.

Another important development is that downstream manufacturers such as pharmaceutical and cosmetic ingredient producers increasingly realize that the sustainabilities of their processes are also influenced by the greenness of the raw materials they are using. Sustainability spans the whole gamut from resources extraction and conversion to raw materials on to their further elaboration to end products and disposal of waste. Hence, many companies now require their suppliers to guarantee the greenness of the materials they are delivering. Cosmetic ingredient manufacturers, such as L'Oreal and Mane, may require that a supplier guarantees that a particular material is derived from renewable biomass rather than being of fossil origin.

Looking to the future, there is still a great need for simple and reliable metrics for quick evaluation of processes in an early stage of development. In particular, a simple, back-of-the-envelope method for evaluating the process costs based on the initial technical data would be very useful. From a circular economy viewpoint, there is a definite need for metrics that readily identify and define "critical elements".[131] Finally, as we already mentioned, there is a pressing need for new economic indicators that incorporate the currently externalized costs of repairing the environmental damage caused by industrial activities.[132] It would be wise to heed the words of Kenneth Boulding, the British-American economist and philosopher: *"If the society toward which we are developing is not to be a nightmare of exhaustion, we must use the interlude of the present era to develop a new technology which is based on a circular flow of*

materials such that the only sources of man's provisions will be his own waste products."

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Notes
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Biography

Roger Sheldon (www.sheldon.nl) is a recognized authority on Green Chemistry and widely known for developing the E factor concept for assessing the environmental impact of chemical processes. He is currently Distinguished Professor of Biocatalysis Engineering at the University of the Witwatersrand (SA). He authored several books on catalysis, more than 460 papers, and 55 granted patents. He was Co-Chair of the 1999 Gordon Research Conference on Green Chemistry. Among other awards, he was a co-recipient of a Presidential Green Chemistry Challenge Award in 2006 and received the RSC 2010 Green Chemistry Award and the Biocat2010 lifetime achievement award for his important and lasting contributions to biocatalysis. He was elected a Fellow of the Royal Society in 2015. He has a Ph.D. (organic chemistry) from Leicester University (UK) and was Professor at Delft University (NL) (1991-2007), CEO of CLEA Technologies (2006−2015), VP R&D at DSM-Andeno (1980−1990), and with Shell Research Amsterdam (1969−1980).

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