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Waste minimization

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Metrics of green chemistry: Waste minimization

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The increasingly apparent negative impact of human activities on the environment has heightened the urgency for the chemistry community to adopt greener and more sustainable practices. The E-factor can still be considered a valuable tool in this drive, particularly because of its broad acceptance and familiarity amongst both industrial and academic chemists. An important factor in broadening the adoption of green principles is ensuring that the academics responsible for training the next generation of chemists prioritise green and sustainable practices in their undergraduate and post graduate laboratories. Green metrics must be easy to use to motivate the broader chemistry community to develop greener syntheses. For maximum impact to be achieved the detail of the exact green metrics applied are less important than their adoption by the broader chemical community. Of growing importance is the replacement of fossil resources with renewable alternatives to reduce greenhouse gas emission that is a significant driver of climate change. The C factor is used to compare the carbon footprints of different routes to a particular product.

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Introduction

An important goal of green chemistry is to reduce or, preferably, eliminate waste generation in the manufacture and application of chemicals. In order to manage waste formation in chemical processes it is essential to have metrics for measuring it. Two important metrics for measuring the mass efficiency of chemical processes—atom economy (AE) [1] and the E-factor [2], were introduced 30 years ago. AE is the molecular weight of the product divided by the sum of the molecular weights of the starting materials. Calculation of the AE assumes the use of stoichiometric amounts of starting materials and a 100% chemical yield and is very useful for comparing different routes to a target molecule before any experiments are performed.

The E-factor: The environmental footprint of chemicals

The E-factor is the actual amount of waste, defined as "everything but the desired product" produced per kg of product, including solvent losses and chemicals used in work-up. E-factors of individual steps are additive and are readily calculated for single- or multi-step processes. The ideal E-factor is zero conforming to the first principle of green chemistry: "It is better to prevent waste than to treat or clean up waste after it is formed."

The substantial environmental footprint of chemicals manufacture, expressed as the E-factor, was illustrated with the now well-known Table of E-factors, derived from data of mature commercial processes, in various industry segments from oil refining to pharmaceuticals. Publication of Table 1 in 1992 provided an important challenge to the industry, particularly the fine chemicals and pharmaceuticals segments, to reduce the amount of waste generated in their manufacturing processes.

The pharmaceutical industry accepted the challenge and has spent the last 2–3 decades cleaning up their manufacturing operations [3]. However, in the intervening years APIs have become increasingly complicated molecules, compared with 40 years ago, thus requiring longer syntheses for their production. As Roschangar et al. have recently reported (ref. 50), the average cEF, which includes water and solvent with no recycling, of commercial scale syntheses of a selection of 97 APIs is 182 with a spread from 35 to 503.

An important driver for the widespread introduction of green chemistry in chemicals manufacture was always waste prevention at source [4], not only for its environmental benefits but also for its economic competitiveness through efficient and cost-effective use of raw materials. Higher E-factors correspond to more waste generated and greater environmental impact. Lower E-factors translate to smaller quantities of materials used and show a strong positive correlation

Table 1

Factors in the chemical industry.

Industry segment	Product tonnage (p/a)	E-factor (kgs 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	5–50
Pharmaceuticals	10–10^3	25 - >100

with reduced manufacturing and waste disposal costs [5—7]. Using the E-factor places emphasis firmly on designing cleaner, waste-free processes, and the ideal E-factor of 0 clearly reflects the ultimate goal of zero waste manufacturing plants.

So what does the E-factor include? Originally we considered all reagents used and assumed that solvents would be recycled. If the recycle figures were not known we assumed a 90% recycle of the solvent(s), that is we counted only 10% of the solvent used as waste in the process and work-up steps. In hindsight, this was in most cases rather optimistic. The propensity of organic chemists for optimizing the solvent for each step in a multi-step synthesis leads to cross-contamination and difficulties in solvent recycling. We excluded water because we thought that its inclusion would lead to a skewing of E-factors. However, disposal or reuse of process water will involve some sort of pretreatment and current thinking is to calculate E-factors both with and without water [8,9]. This has led to the use of simple E-factors (sEF), that disregard solvents and water in early route scouting, and complete E-factors (cEF) that include solvents and water with no recycling [5]. The true commercial E factor will fall between the sEF and cEF and can be calculated when reliable data for recycling and solvent losses are known.

The inclusion of the energy requirements of a process in the E-factor was always implicit since energy consumption generates waste as carbon dioxide. However, fine chemicals and pharmaceuticals are often produced in multi-purpose facilities where energy usage is not allocated to particular processes, making it difficult to assign waste derived from energy to individual products. In contrast, bulk chemicals are produced in dedicated units and energy consumption is an important component. In order to improve the energy accounting of the original E-factor, the E^+ factor, which considers the greenhouse gas emissions generated from electricity used for processes such as cooling, heating, stirring, and pumping, was recently proposed [10].

Use and acceptance of the E-factor

The strength of the E-factor is its simplicity—both in terms of concept and application—and because it was introduced 30 years ago, it is familiar to many and is widely used. Other mass-based green metrics such as process mass intensity (PMI) and reaction mass efficiency (RME) have not reached the broad acceptance of the E-factor and their use is largely confined to small-molecule pharmaceuticals [11—13]. Of particular relevance, in our opinion, is the acceptance of the E-factor by university academics as evidenced by recent literature [14—19]. We believe that for universal adoption of greener and more sustainable processes, the concepts and practices need to be introduced to undergraduate students and rigorously applied in academic post graduate chemistry laboratories [20]. These practices will become second-nature to the students who will then ensure they are propagated in their places of future employment. It is gratifying to note that significant efforts are being invested in making green chemistry concepts accessible to undergraduate and post graduate students [21—26], but these efforts need to be accelerated. Simplicity is the key to stimulating broad adoption of the "greening of organic syntheses" by academics and we suggest continued use of the familiar E-factor for assessing process greenness.

The original E-factor has the serious limitation of not considering the nature of the waste, assigning all waste types the same weighting. However, the environmental impact of the waste generated is of paramount importance [12,25,27—29]. Consequently, the E-factor must be considered in conjunction with other metrics [30]. The environmental quotient (EQ) [31], where Q represents the nature of the waste, was suggested over two decades ago but the problem becomes how to quantify Q. Subsequently, Eissen et al. [32] developed the simple and easy-to-use EATOS (environmental assessment tool for organic synthesis) software to assess the potential environmental impact (PEI) of waste by assigning penalty points based on human and ecotoxicity. This approach was later further refined by various groups [12].

Which other metrics could be widely adopted by the broader chemistry community?

When deciding on which metrics should be a priority, it is useful to consider where the biggest impact can be achieved for relatively little effort. In pharmaceutical manufacture solvents account for 80—90% of the total mass of non-aqueous material used, the majority of waste formed and 75—80% of the environmental life cycle impacts [33—35]. Recognizing the importance of this, several drug companies have developed in-house solvent selection guides to stimulate replacement of environmentally undesirable solvents using a traffic-light inspired color coding—green, amber, and red—to signify "preferred," "useable," and "undesirable" solvents [36—39]. These can be readily adapted for use

in academic research laboratories, allowing students to make informed choices about solvent selection for reaction and work-up.

Traditionally, the E-factor is based on the chemical process conducted at the manufacturing site, that is, on gate-to-gate system boundaries, rather than cradle-to-grave [40]. Hence, the E-factor is dependent on the starting point of the synthesis and the E-factor of a multi-step synthesis can be significantly reduced overnight by purchasing an early intermediate instead of making it in-house. We recently used the E-factor alongside other metrics in selecting a route for the synthesis of a key intermediate for HIV protease inhibitors [41]. Overall, the E-factor fared well in route assessment, but inclusion of so-called intrinsic E-factors to account for the synthesis of advanced starting materials (ASMs) was essential. Hence, an agreed upon definition of starting material is essential. For example, in pharmaceuticals manufacture this has been defined as being readily available at a price of <$ 100 per kg from a reputable commercial supplier [5,12]. Since E-factors are additive, the intrinsic E-factor for the ASM synthesis may be simply added to the main synthesis E-factor to obtain an unbiased E-factor value for a complete synthetic pathway.

We found that using a range of metrics in addition to E-factor allowed for a more rigorous route evaluation. One of the most conceptually simple measures we applied was the Green Motion™ penalty point system [42]. Here seven fundamental concepts—raw material, solvent selection, hazard and toxicity of reagents, reaction efficiency, process efficiency, hazard and toxicity of final product and waste generation—are considered. Each process is assessed by means of a questionnaire requiring simple yes/no answers, pictograms, numerical values or a selection of multiple choice options that then assigns penalty points based on the answers. Deduction of the penalty points from 100 affords an overall score, meaning the higher the score the more sustainable and the lower the environmental impact of the process. Adaptation of this measure, specifically developed for the flavor and fragrance industry, or a similar measure [43–45], could lead to a penalty-point system ideally suited for use in academic laboratories. Another useful visual tool is the radial polygon that provides an overview of multivariable performance indicators. An ideal green synthesis corresponds to a regular polygon, while distortions towards the center identify weak points in a synthesis and provide guidance for optimization [46–48].

In order to set meaningful goals for industrial research it is necessary to compare processes with an industry benchmark. The green aspiration level (GAL™) [5] is such a benchmark and is based on the average waste generated per kg API in 46 commercial manufacturing processes from nine large pharmaceutical companies [49]. A further refinement, the innovative green aspiration level 2.0 (iGAL 2.0) was recently introduced [50]. However, these tools are only relevant for process evaluations of multi-step syntheses of relatively complex APIs.

E-factors of commodity chemicals

The E-factor was always intended to be used in pharma, fine and bulk (commodity) chemicals manufacture. Although the E-factors for pharmaceuticals are higher, in absolute terms bulk chemicals produce more waste, for example, if the total annual production of a chemical is 500,000 tonnes and the E-factor is 5 then 2.5 million tonnes of waste are generated. Indeed, it was becoming increasingly obvious in the 1990s, to anyone paying attention, that bulk chemicals manufacture was responsible for the generation of copious amounts of chemical waste, mainly owing to the use of antiquated technologies using stoichiometric amounts of (inorganic) reagents. The solution was obvious: substitution of stoichiometric reagents with catalytic alternatives.

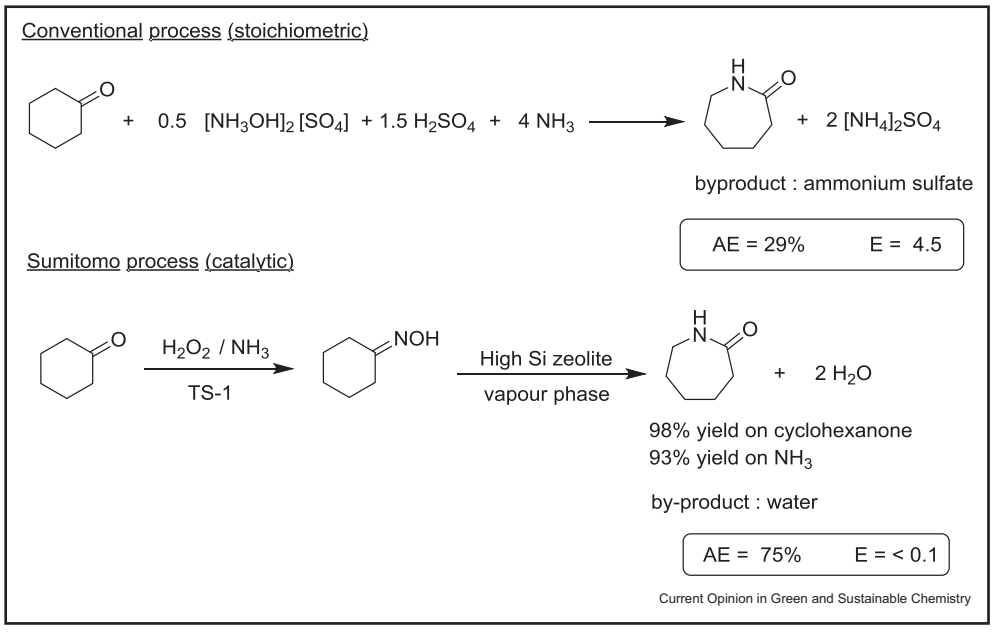
A case in point is caprolactam manufacture [51]. The conventional process involves production of cyclohexanone oxime, by reaction of hydroxylamine sulfate with cyclohexanone, followed by sulfuric acid promoted Beckmann rearrangement (Figure 1). It generates ca. 4.5 kg of ammonium sulfate per kg of caprolactam. In contrast, the Sumitomo process involved two catalytic steps generating two molecules of water as the sole co-product, that is, it is salt-free with an E-factor of <0.1. It was gratifying, therefore, that Sumitomo used the E-Factor to showcase the merits of their new, catalytic process.

Measuring the carbon footprint of chemicals: The C factor

In 1992, the number one environmental problem was the hole in the ozone layer caused by ozone depleting chemicals in the atmosphere. Thirty years later it is climate change caused by greenhouse gases, particularly carbon dioxide. The number one priority is climate change mitigation, which is motivating a transition from an economy based on fossil resources to a bio-based economy based on renewable energy and raw materials. We are on the cusp of the decarbonisation of the energy sector and the defossilization of the chemicals sector.

Christensen et al. [52] proposed the use of the climate factor, defined as the total mass of CO_2 emitted divided by the mass of product formed (kg CO_2/kg product), as a metric for comparing the CO_2 burdens of different processes to a particular product. It is the sum of kg CO_2 emitted in the production of the raw material(s) and in the conversion of the raw materials to the product(s). It is also useful for comparing biomass-vs fossil resource-

Figure 1



Sumitomo caprolactam process versus conventional process.

based processes [53] but, as is the case with E-factors, system boundaries will need to be defined for determining the C factor. More recently, Gallou et al. [54] used the C factor for measuring the ecological footprints of APIs.

Closing comments

Green metrics used to assess process greenness do not have to be perfect but they must be easy to use if they are to motivate the broader chemistry community to develop greener syntheses. Application of "imperfect metrics" by many will achieve more than application of "perfect metrics" by few.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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