Chapter 2
Green Metrics, an Abridged Glossary

Abstract Green chemistry is an aspiration, and the advancement in this field must be recognized and quantitatively assessed. Various proposals of a green metrics have been put forward, based on the consumption of resources, the coproduction of waste, the environmental performance. These are briefly presented, pointing out the specific advantages and limitation of each one. In general, such metrics must blend high level of information supplied with accessibility. Software for several such metrics is freely available.

Keywords Green metrics · Mass metrics · Energy metrics · Environmental metrics · Life cycle

2.1 Environmental Parameters for a Chemical Reaction

What chemists strive to obtain, and what is asked from them, has traditionally been obtaining as much as possible of the desired (saleable) compound. The key parameters have thus been the *reaction yield* (RY) and the *selectivity* (S).

Reaction yield (*RY*) is the *quantity of a product* (usually expressed as a fraction or a percentage) generated by a chemical reaction from a given reactant. A more correct, but not commonly used praxis should be referring the yield to the balanced chemical equation, thus taking into account the fact that one of the reagents is often used in excess. *Selectivity (S)* is referred to the ratio of one of the products (usually the desired one) arising from the conversion of a certain reactant with respect to the other ones, or to the conversion of the starting material. When a chemical reaction is carried out on industrial scale, the occupation of the available reactors must be taken into account, through parameters such as *productivity* (amount of the desired product per time unit) and *space time yield* (STY), defined as the amount of reaction product formed *per unit volume* of the reactor *per unit time*.

Table 2.1 Current E-Factor value for different industrial sectors from [6]

Industrial sector	Production (Tons year^{-1})	E-factor (kg kg^{-1})	Waste produced (Tons year^{-1})
Petrochemical	10^6–10^8	ca. 0.1	10^6
Bulk chemicals	10^4–10^6	1–5	10^5
Fine chemicals	10^2–10^4	5–50	10^4
Pharmaceuticals	10–10^3	25–100	10^3

A different issue is having a process that is "green", that is one that causes as little as possible negative effects on the environment. Although good sense will help in judging what will be such effect, specific parameters for the assessment of the environmental performance of chemical reactions have been proposed over the years, with the aim of offering an objective set of metrics for making a process "greener" and making better use both of the materials and of the energy. Proposals have come from various laboratories, sometimes overlapping in some aspects. The metrics are summarily listed below according to their main goals, viz. optimization of the mass used, minimization of environmental damage and of the energy consumed. The most representative parameters are summarized in Table 2.1.

2.1.1 Mass Metrics

As for the mass balance, the parameter *Atom Economy* (AE or atom utilization), has been first defined by Trost in 1991 [1] as "*the ability of a chemical process to incorporate as many as possible of the atoms*" of the starting material into the final products, and thus to the ratio of the molecular weights (MW), see Eq. (2.1):

$$AE = \frac{MW\,(product)}{\sum MW\,(reagents)} \tag{2.1}$$

Convergent syntheses with two or more separate branches can be analyzed by taking into account the amount of the reactants involved in each chemical step, while ignoring the product intermediates [2]. A more elaborated AE expression for multistep synthesis has been proposed by Eissen et al. [3].

A variation, of obvious significance in organic synthesis, is *carbon economy* (CE), proposed by Curzons et al. [4] that is limited to the amount of *carbon* in the reactants that is incorporated in the end product, according to the equation below (Eq. 2.2):

$$CE = \frac{Amount\ of\ Carbon\ in\ product}{Amount\ of\ Carbon\ in\ reagents} \tag{2.2}$$

As originally defined, AE is referred to the chemical equation as such, and thus to a quantitative yield and the use of the reactants in exactly stoichiometric amounts.

Furthermore, neither solvent nor additives (when present) appear in the chemical equation and thus are likewise not considered. This is obviously a significant limitation, and this parameter is better used in conjunction with other metrics. A simple improvement is obtained by considering the yield of the process and introducing a composite parameter, indicated either as the *actual atom economy* (AAE) or as the reaction mass efficiency of the process (RME$_{Kernel}$), defined as the ratio of the actual mass of the products obtained with respect to the reagents used (Eq. 2.3) [5].

$$AAE = RME_{Kernel} = RY \times AE = \left(\frac{mass}{mass}\right) \tag{2.3}$$

This concept can be extended to the *global Reaction Mass Efficiency* (RME$_{global}$ also defined by Sheldon as Material Efficiency, see Chap. 4) that takes into account all of the materials involved in the process, viz. solvents, auxiliaries and chemicals used for the work up procedure. This results in Eq. (2.4), with inclusion of the stoichiometric factor SF for the reagent used in excess, viz.

$$SF = 1 + \frac{\sum mass\ excess\ reagents\,(\mathrm{kg})}{\sum mass\ stoichiometric\ reagents\,(\mathrm{kg})} \tag{2.4}$$

as well as of a *material recovered factor* (MRP) including all of the recovered and reusable materials (starting materials used in excess and recovered at the end of the process, solvents and auxiliaries, see Eq 2.5) [5]. All of these parameters are fractions between 0 and 1.

$$RME_{Global} = AAE \times \frac{MRP}{SF} \tag{2.5}$$

The other way around, one may focus on the concept of waste, which is implicit in the above parameters. Thus, any output from the reaction other than the desired product (that is what is sold) is considered *waste*. The definition thus includes the unreacted starting material, the solvent used (when not recovered), as well as any catalyst or additive, when present. Further to be considered are other products formed beside the desired one, viz. byproducts and coupled products (that is compounds arising from the same pathway that yields the desired product) as well as side-products (that in contrast are produced from the same starting materials used for the synthesis of the target product, but arise from an entirely different mechanism). Furthermore, as mentioned above, often one (or more) of the reactants is used in stoichiometric excess with respect to the other ones. This may well increase the yield of the desired products, but at the same time obviously increases the amount of waste produced. Finally, any purification method used to isolate the product from the crude reaction mixture generates a further amount of waste.

An approach to assess the greenness of a chemical process based on the waste produced was proposed by Sheldon [6, 7] at about the same time as Trost (1992), during the analysis of the industrial production of pharmaceutical intermediates such

as phloroglucinol (1,3,5-benzenetriol) [7]. This is the *E-Factor* (E), defined as the ratio between *the mass of waste produced for mass unit of final product* (Eq. 2.6).

$$E = \frac{\textit{Mass of waste (kg)}}{\textit{Mass of product (kg)}} \tag{2.6}$$

According to Eq. 2.6, recyclable materials such as solvents, reused reactants or catalysts are not considered as waste and thus ignored, and the ideal value of E is 0. Different parts contribute to the value of the total E-factor (E_{global}). In a detailed analysis, Andraos [8] proposed a more articulated view of this parameter, defined as the sum of different contributions deriving from the core chemical equation (by-products, side-products, and unreacted starting materials, E_{kernel}), from excess reagent (E_{excess}), and from auxiliary materials used in the process, including work-up and purification operations (E_{aux}).

$$E_{global} = E_{kernel} + E_{excess} + E_{aux}. \tag{2.7}$$

As pointed out by Sheldon (see Table 2.2), the value of E-Factor strongly depends on the type of product and on the scale in which it is produced. Thus, in the

Table 2.2 A summary of the main parameters discussed in this chapter

Metrics	Equation	Range of values (ideal value)
Mass metrics		
Reaction yield (*RY*)	$\frac{\text{mol (product) obtained}}{\text{mol (product) expected}}$	$0 < RY < 1$ (1)
Atom economy (*AE*)	$\frac{\text{MW (product)}}{\sum \text{MW(reagents)}}$	$0 < AE < 1$ (1)
Reaction mass efficiency kernel (*RME$_{Kernel}$*) or actual atom economy (*AAE*)	$\frac{\text{Mass of product (kg)}}{\text{Mass of reagents (kg)}}$	$0 < RME_{kernel} < 1$ (1)
Reaction mass efficiency global (*RME$_{Global}$*)	$AAE \times \frac{MRP}{SF}$	$0 < RME_{global} < 1$ (1)
Environmental factor (*E*)	$\frac{\text{Mass of waste (kg)}}{\text{Mass of product (kg)}}$	$0 < E < \infty$ (0)
Process mass intensity (*PMI*)	$\frac{\text{Mass of chemicals (kg)}}{\text{Mass of product (kg)}}$	$1 < PMI < \infty$ (1)
Environmental metrics		
Effective mass yield (*EMY*)	$\frac{\text{Mass of products (kg)}}{\text{Mass of non benign reagents (kg)}}$	$1 < EMY < \infty$ (∞)
E$_{IN}$ (*EATOS*)	$PMI \times Q_{IN}$	$1 < E_{IN} < \infty$ (1)
E$_{OUT}$ (*EATOS*)	E-factor $\times Q_{OUT}$	$0 < E_{OUT} < \infty$ (0)
Energy metrics		
Energy efficiency (E_E)	$\frac{\text{Mass product (kg)}}{\text{Energy consumption (kJ)}}$	$0 < E_E < \infty$

case of oil refining, highly evolved (catalytic) systems are used, where waste has been minimized through a long effort. On the other hand, the large volume involved would not make tolerable such processes if this were not the case, both because of the environmental effect and because this would reduce the profit margins. On the contrary, in pharmaceutical industry the tonnage produced is much lower, but the waste produced when preparing (by multistep syntheses) and purifying highly sophisticated materials is much larger, as apparent from the E factor (see Table 2.1).

Yet another approach makes use of the *Process Mass Intensity* (*PMI*, the reciprocal of Reaction Mass Efficiency RME_{global}) as proposed by the Glaxo group [9]. This is defined as *the total mass* of the materials required for the production of the *unit mass of desired product* (Eq. 2.8):

$$PMI = \frac{1}{RME\ global} = \frac{Mass\ of\ chemicals\ (kg)}{Mass\ of\ product\ (kg)} \tag{2.8}$$

As in the case of E, PMI takes into account the amount of (non reusable) reactants, auxiliaries and solvents employed in the process. In the ideal situation, the PMI value is unitary or close to it (and correspondingly, E = 0). Notice that, as it has been pointed out (see Eq 2.9), E factor and PMI differ by a unity [9]. This is important, since this difference corresponds to the amount of the target product obtained in the process, that is to the actual revenue of the process (see Fig. 2.1). PMI has been considered as a more convenient parameter than E when planning production, because the improvement of the productivity (of the saleable product) and not the waste reduction appears to be a more appealing target. Furthermore, the concept of PMI better matches with the first green chemistry principle of preventing waste production rather than having to find a way to manage it afterwards.
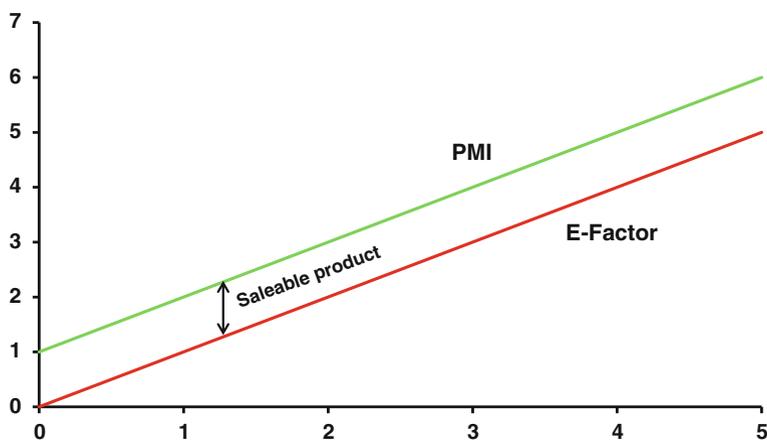

Fig. 2.1 PMI and E-factor differ for one unit which corresponds to the saleable product

$$\text{PMI} = \frac{Mass\ of\ chemicals\ (\text{kg})}{Mass\ of\ product\ (\text{kg})} = \frac{Mass\ of\ product\ (\text{kg}) + mass\ of\ waste\ (\text{kg})}{Mass\ of\ product\ (\text{kg})}$$

$$= E + 1$$

<div align="right">(2.9)</div>

Since five parameters (Reaction Yield, the reciprocal of stoichiometric factor SF, AE, RME and the material recovery parameter MRP) well account for the "greenness" of a process, a radial pentagon has been used in order to evidence which are the most sensitive points. Each axis ranges in value between zero and one and in the greenest situation each parameter is equal to 1 (see for review [10]), which results in a regular pentagon. This visual representation has been used by Andraos for the evaluation of different processes, including aldol condensation, Friedel Crafts acylation and cycloaddition (see in Fig. 2.2 an example involving the synthesis of diphenylmethanol via generation of a Grignard reagent and scenarios with different extent of reclaiming excess reagents are evaluated) [11].

It is apparent from the figure that a complete reclaiming is required for a reasonable environmental performance. When applied to a multistep procedure, as typical for Active Pharmaceutical Ingredients (APIs), the use of E-factor in the assessment procedure has the advantage that the contribution for each step is additive, while PMI is not, but is liable to inconsistent application, since the level of solvent recycling, when not measured, is estimated by the evaluator (a 90 % recycling

Fig. 2.2 Synthesis of diphenylmethanol with different extent of reclaiming excess reagent
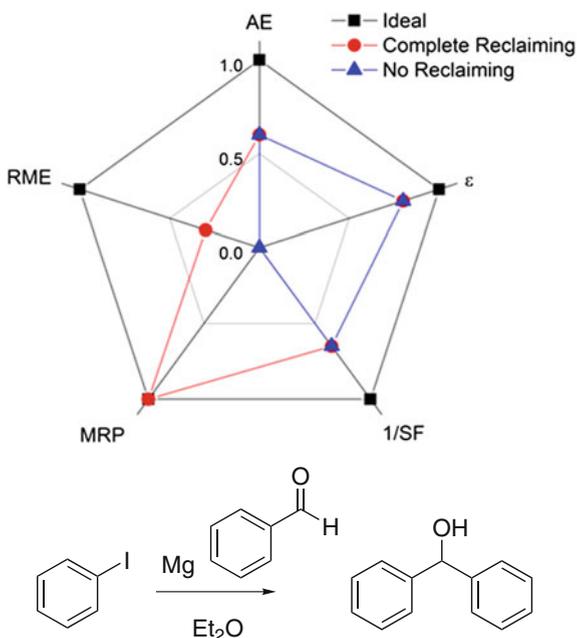
is often assumed). Thus, the use of a *complete* (cEF) and a *simple E-factor* (sEF) have been proposed by Roschangar et al. [12] as defined in Eqs. 2.10 and 2.11.

$$cEF = \frac{\sum m(raw\,materials) + \sum m(reagents) + \sum m(solvents) + \sum m(water) - m(product)}{m(product)}$$

(2.10)

$$sEF = \frac{\sum m(raw\,materials) + \sum m(reagents) - m(product)}{m(product)}$$

(2.11)

These authors suggests that cEF is applied in the post finalization stage, when optimization of the commercial procedure is being carried out, while at an earlier stage sEF is considered. Further determining is the choice of the starting point. Attention is often given to the steps carried out in house, starting from a purchased raw material, but this leaves out part of the environmental relevant processes. Actually, if a raw material is not a commodity, its synthesis must be considered as done especially for that particular API and included into the evaluation. It has been observed that at present 20–50 % of chemical steps are outsourced during the early development and 30–70 % during the late development or after commercial launch of a product. In order to obtain a fair evaluation, it has been proposed to label as raw materials only those that are offered in the Sigma Aldrich catalogue at a price below 100$ per mol (for the largest offered quantity). In the contrary case, the respective synthesis must be included [12].

The conversion of the raw materials into the usually highly complex API involves several steps, and a first appreciation of the greenness of a synthetic plan may be obtained by checking that the number of chemical transformations required for achieving the final complex structure is reduced. Balan [13] has proposed the concept of ideal synthesis as shown in Eq. 2.12.

$$\% \text{ Ideality} = \frac{no.\,of\,construction\,reactions + no.\,of\,strategic\,redox\,reactions}{no.\,of\,reactions}$$

(2.12)

In order to standardize chemical processes across the pharmaceutical industry, the concept of green aspiration level has been introduced. In this way, one is able to define *SMART* (Specific, Measurable, Ambitious and achievable, Result-based, Time-bound) processes as green chemistry goals for the whole field. A standard *aspirational level* (GAL) is defined with reference to the average parameters of processes examined by the ACS Green Chemistry Institute. Roschangar and co-workers calculated the average values as cEF = 307 kg kg^{-1} for Phase 1 and 167 kg kg^{-1} for commercial projects, and sEF = 167 kg kg^{-1} for Phase 1 and 23 kg kg^{-1} for commercial projects. In average, the number of steps in these processes is 7 with 1.3 chemical transformations per step. Thus, the average

complexity per drug target is ca. 9 (7×1.3). The transformation GAL (tGAL) is therefore expressed by Eq. 2.13 and the process GAL by Eq. 2.14 [12].

$$tGAL = \frac{(s\,or\,c)EF}{Average \times complexity} \qquad (2.13)$$

$$GAL = (tGal) \times complexity \qquad (2.14)$$

The relative process greenness is thus defined as indicated in Eq 2.15).

$$RPG = \frac{GAL\,(s\,or\,c)EF}{(s\,or\,c)\,EF} \qquad (2.15)$$

A RPG > 100 % shows that the green character of the process is below the average industrial value and would benefit from further optimization.

An increased green character of a new process can be evaluated by the reduction of the EF, taking into account the change in complexity. Roschangar and coll demonstrated that decreasing the amount of waste in the overall process does not imply that the RPG doesn't decrease in every single step [12].

2.1.2 Environmental Metrics

E-factor and PMI are the most convenient (and the most easily calculated) parameters for a first assessment of the sustainability of a process. As shown in the following sections, these parameters are largely used as a benchmark in the literature. The main limitation is that these two parameters consider the mass of chemicals involved as a "lump sum", and no account is taken of the quality of such chemicals and the ecological risks related to them. A first attempt to introduce this issue in green metrics was carried out by Hudlicky [14] with the term *Effective Mass Yield* defined as the fraction of the percentage of the mass of desired product relative to the mass of all *non-benign materials* used in its synthesis, according to the equation below:

$$Effective\,Mass\,Yield = \frac{Mass\,of\,products\,(\mathrm{kg})}{Mass\,of\,non\,benign\,materials\,(\mathrm{kg})} \qquad (2.16)$$

This is based on the proportion of the mass of the product that arises from non-toxic materials. "Benign" components are defined as 'the by-products, reagents or solvents that have no known environmental risk associated with them, for example, water, low concentration saline solutions, dilute ethanol, autoclaved cell mass, etc.". However, the subjective definition of benign materials is open to criticism.

To date, the most extensive effort to quantify the risk related to a given process is represented by the *EATOS* (Environmental Assessment Tool for Organic Syntheses) facility. The software, developed by Eissen and Metzger in 2004, takes into account as entries a large number of data, which are however easily available, and evaluates a chemical synthesis through four indices, including the above mentioned mass index (PMI) and environmental factor E-factor, as well as two environmental quotients, the "unfriendliness" parameters Q.

Thus, the Environmental Index Input $E_{IN} = PMI \times Q_{IN}$, is *the Potential Environmental Impact* (PEI kg^{-1}) of chemicals used in the process. The factor Q_{IN}, quantifies the environmental and social costs involved in the use of such chemicals (based upon data generally available from the safety data sheet of the chemicals employed, such as risk phrases, the reclaiming of resources involved, transport information and cost).

Analogously, the Environmental Index Output ($EI_{OUT} = E \times Q_{OUT}$) is *the Potential Environmental Impact* (PEI kg^{-1}) on the ecosystem by the chemicals produced. Q_{OUT} is calculated from data available in the Material Safety Data Sheet, by using weighting categories such as human toxicity, chronic toxicity, and eco-toxicology. In addition to the mass and environmental indices, the EATOS software affords also the cost involved in the production of the desired product (expressed in € per kilogram of product). The above contributions well account for the environmental effect [15].

Furthermore, an easy to use semi-quantitative assessment method was reported by Van Aken and takes into account six different characteristics of the reaction, that is yield, cost, safety, technical set-up, temperature and feasibility of workup/purification procedures. In this approach, a range of penalty points is assigned to each of these parameters. As far as the safety is concerned, hazard warning symbols are used to quantify the penalty assigned. Such *ECOSCALE* software uses a scale from 0 to 100, the latter figure representing the ideal reaction, which the Authors defined as "Compound A (substrate) undergoes a reaction with (or in the presence of) inexpensive compound(s) B to give the desired compound C in 100 % yield at room temperature with a minimal risk for the operator and a minimal impact for the environment".

The contribution to the safety, health and environmental performances are detailed in the analogous SHE toolbox [16]. For each chemical and reaction step involved in the process, the SHE aspects are classed into 11 effect categories (fire explosion, reaction decomposition, acute toxicity, chronic toxicity and air mediated effects among others). These are not combined into a single index, but the effect of each substance to a given effect category is individually determined. An idea of the application of this method can be gathered from a paper by Hungerbhüler and coworkers where a reaction carried out in a pharmaceutical industry is considered. This is the methylation of 8-α-(tert-butyloxycarbonylamino)-6-methylergonin **1** to compound **2**, one of the six steps of the batch synthesis of building block 8-α-amino-2,6-dimethylergolin, see Fig. 2.3 [17].

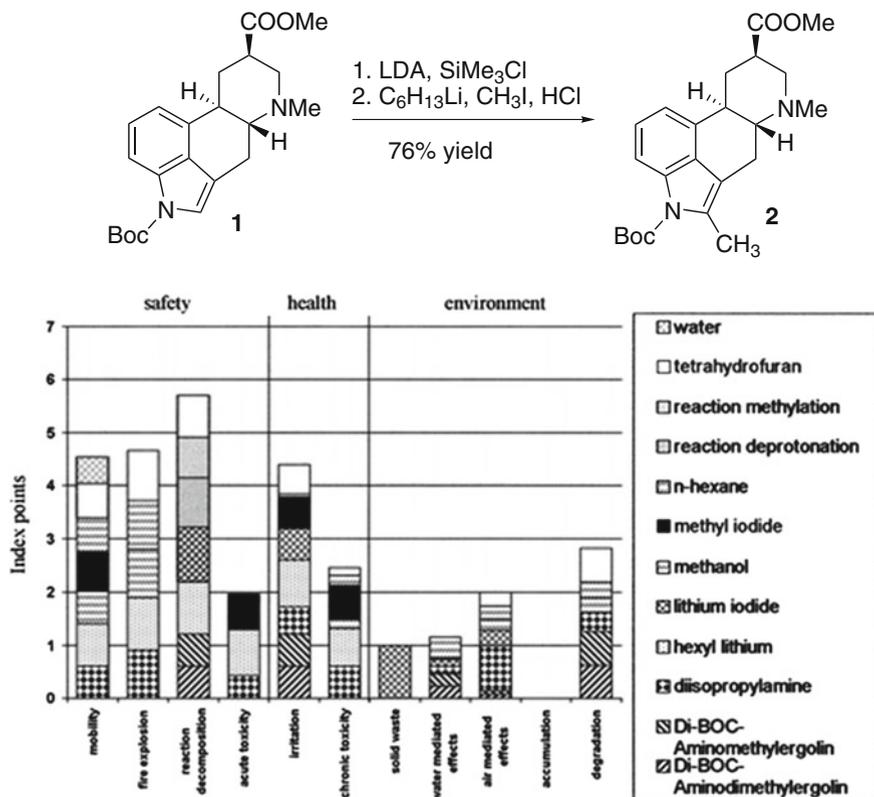**Fig. 2.3** Environmental performance of the materials used in the methylation of 8-α-(tert-butyloxycarbonylamino)-6-methylergolin **1**. Adapted with permission from Ref. [17a]

2.1.3 Energy Metrics

Importantly, none of the above described parameters takes into account the amount of energy supplied for carrying out a chemical process [18]. This is particularly relevant, since in some cases the advantage of using a method that is more eco-sustainable when considering the chemicals used may be lost due to energetic costs. Indeed, in the case of laboratory reactions, the electric energy employed can be measured with good accuracy with easily available, cost-effective energy counters, although only a fraction of the electric energy consumption is actually transferred to the reaction batch. Different energy metrics have been introduced to class a chemical process. One of first parameters defined is the *Energy Efficiency* (E_E) that is the ratio between the amount of the desired product obtained and the electric energy used in a synthesis [18].

$$E_E = \frac{mass\,product\,(\text{kg})}{Energy\,consumption\,(\text{KJ})} \tag{2.17}$$

Analogously, the *specific productivity* (sP) has been defined as the amount of product (expressed in molar unit, more often used by chemists) obtained for unit of work (in KWh), a definition suitable for any kind of activation, including irradiation by lamps or microwave [19].

$$sP = \frac{mol\,product\,(\text{mol})}{Electric\,work\,(\text{KWh})} \tag{2.18}$$

The reverse of E_E is defined as the *Energetic process expenditure* (A_P). Energy is consumed both during the reaction (energetic reaction expenditure, A_R) and during work up (energetic work up expenditure, A_E), but often the latter contribution is larger.

$$A_P = A_R + A_W$$
$$= \frac{Energy\,consumption\,(Reaction,\,\text{W}) + Energy\,consumption\,workup\,(\text{W})}{mass\,product\,(\text{kg})}$$
$$\tag{2.19}$$

The most used parameter is, however, the Energy-induced methane equivalents that quantifies the energy consumed as moles of methane required to produce the end product. For determining this value, it is assumed that electricity is exclusively obtained from burning methane, with an efficiency, in the power plant, of 43 %. Then, the amount of methane is calculated in mol (1 MJ = 3.052 mol methane). Alternatively, the amount of CO_2 produced for the process can be also easily calculated.

A general, advanced approach is offered by the *Life Cycle Assessment* (LCA), which follows a philosophy *"from the cradle to the grave",* where every section of the entire life of the product is assessed [20] including raw material supply, each chemical step, the product or service itself, including its final disposal and waste removal. This approach has been known since the early 1970s when only the energy consumption was investigated, but only in the early 1990s the LCA as we know it today started to emerge. Generally, LCA consists of four steps, namely (1) Goal and definition of the scope. (2) Life Cycle Inventory Analysis, where all the mass and energy flows of the process are recorded according to the defined scope. (3) Life Cycle Impact Assessment, where the results of Life Cycle Inventory process is analyzed in view of its environmental impact, including, among others, climate change, ozone depletion, freshwater and marine eutrophication, human toxicity and water depletion. 4) Life Cycle Interpretation, that involves pointing out the most significant issues related to the process and their evaluation. This approach is operated by a dedicate software regulated by the ISO standards (see the ISO 14000 series). The obtained results can be coupled with other environmental and
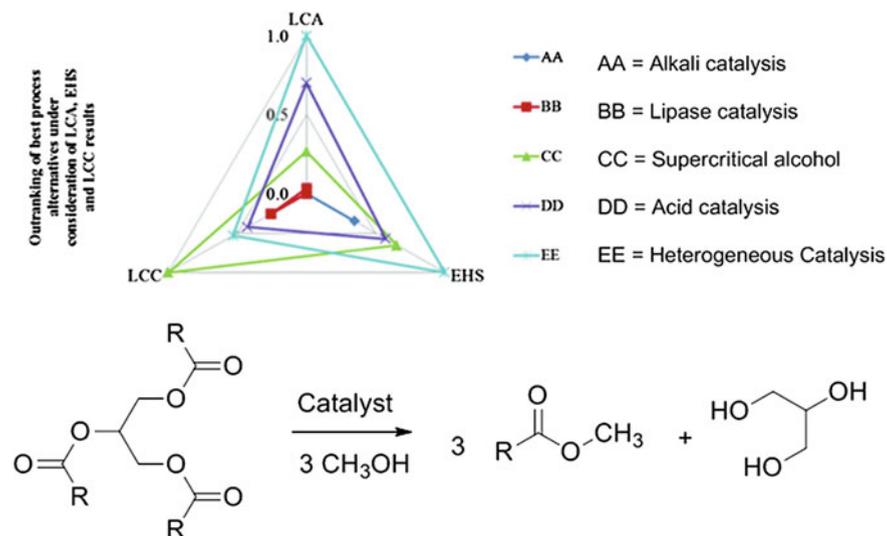
Fig. 2.4 Comparison between different conditions employed for biodiesel production. Adapted with permission from Ref. [21]

evaluation methods in three-dimension graphs, with the aim of affording a complete picture of the process. Kralish et al. analyzed different routes to biodiesel by taking into account the nature of the feedstock, the catalyst (both acid and alkali) and the reaction conditions (heating, microwave activation, use of supercritical fluids), finding that supercritical processing in an intensifying continuous flow reactors is the most favorable proposal (see Fig. 2.4). The results obtained were inserted in a tetrahedral chart including both safety (EHS, see below), environmental (LCA) and economic parameters (Life Cycle Cost, (LCC) that is the analysis of the cost of goods throughout its full life cycle) [21].

In any case, despite the capability of giving a precise idea of both the environmental and (in particular) of the energetic cost of the process, this approach has been substantially limited to a few large scale productions and hardly applied to fine chemistry, because of the fact that the required data are available only for a few chemicals in inventories already present in the LCA database [22].

In order to overcome this limitation, a *Simplified Life Cycle Assessment* (SLCA) has been proposed by the Society of Environmental Chemistry and Toxicology (SETAC), where some chosen approximations (e.g. the use of data of an analogous compounds, rather than exactly of the required one, a move that has been shown often not too largely affect the final result) are applied to the four phases of the traditional LCA [21]. In this way, the LCAs approach is increasingly adopted for the optimization of synthetic routes leading to Active Pharmaceutical Ingredients (APIs) despite the complexity of the problem, in some cases by accepting a reasonable compromise. LCA should offer a realistic measure of the "greenness" of the examined process, be easy to use and able to assess quantitatively the

environmental impact of the process, as well as to offer a guidance for the minimization of these impacts. An example is the web-based tool *FLASC™* (Fast Life cycle Assessment of Synthetic Chemistry) developed at GSK. In this approach, eight impact categories were taken into account, including mass, energy and environmental categories of chemicals such as organic and inorganic reagents and solvent employed in the examined process. FLASC affords, along with RME and PMI values, a score quantifying the LCA impact of the material employed in the process, as well as a quantitative measure of the health effects of the solvent used (EHS) [23]. Further applications of LCA to green chemistry are mentioned in the following chapters [24].

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