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Rules and Benefits of Life Cycle Assessment in Green Chemical Process and Synthesis Design: A Tutorial Review

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The implementation of Life Cycle Assessment and related methods in green chemical process and synthesis design strongly supports the development of greener concepts on the basis of deep and profound insights in the dependencies between the selection of compounds and process parameters and the resulting environmental impacts. This review article provides an overview about things to know about LCA in general, specifics to be considered during its application in the field of chemical (re-)designs and current application examples from emerging research areas such as active pharmaceutical ingredient manufacturing, nanotechnology, flow chemistry, process intensification by harsh synthesis conditions, process integration, waste treatment, use of alternative energy sources or solvents as well as chemistry based on renewable resources.

Introduction

Within the last decade, consciousness has risen for the finiteness of resources, and the serious impact of industrialisation on the environment in various ways is no longer denied. Consequences have been drawn: scientists have started research to understand the coherences of environmental changes with human behaviour, politicians have adopted laws restricting emissions and encouraging resource efficiency, consumers have started asking for more environmentally benign products and industry has to deal with the increasing demand for environmentally benign ways of production.

But, how can the environmental impact of a novel chemical process or material design be determined in a quantitative manner right from the start to support sustainable developments? Over the last decades, the concept of life-cycle thinking became more and more important. Consequently, the method of Life Cycle Assessment (LCA)[1, 2] has been developed and is now established as one of the major tools for the analysis of anthropogenic environmental impacts.[3] LCA is outstanding in its scope of applicability and its holism. It considers the whole life cycle of a product or process and evaluates environmental impacts in terms of various environmental impact categories that go beyond the consideration of mass or energy flows.

LCA was developed in the early seventies and has since then been refined and supported with inventory databases and impact assessment methodologies. Today, it can be applied to very

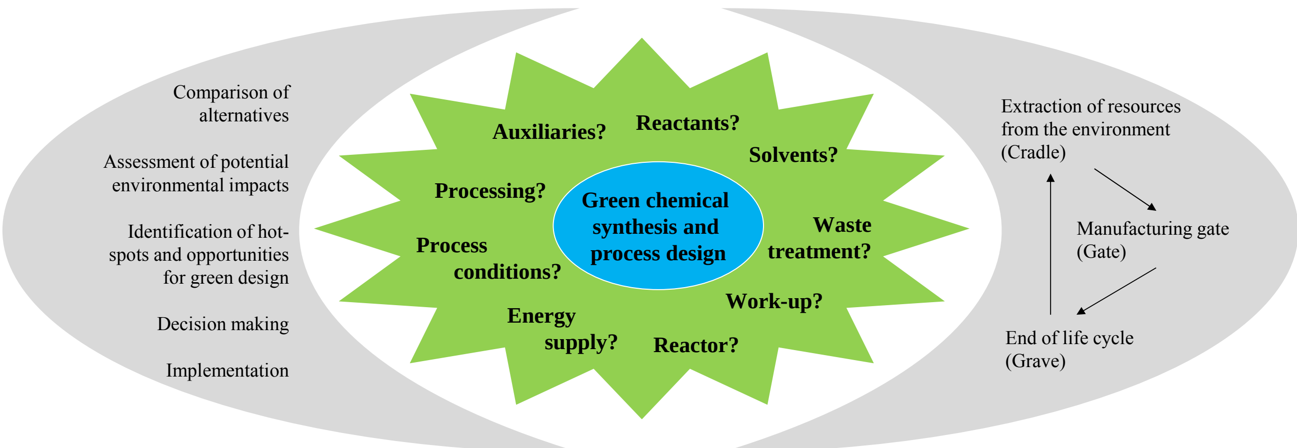


Figure 1. Life-cycle thinking in green chemical synthesis and process design.

complex issues. Aiming to compare the eco-friendliness of products and processes, LCA is nowadays an integral part of decision-making in industry, governmental and non-governmental organisations. LCA can be used as standalone tool or in combination with other environmental, risk, economic or social assessment tools, see also Jacequim *et al.*[3] or Guinée *et al.*[4] and the references therein.

For those who want to learn more about the methodological aspects of LCA investigations during chemical process and synthesis design, this review article provides an introduction into the topic, indicating further interesting literature to read on. Against the background of the LCA theory, recent case studies derived from emerging research areas such as active pharmaceutical ingredient manufacturing, nanotechnology, flow chemistry, process intensification by harsh synthesis conditions, process integration, waste treatment, use of alternative energy sources or solvents as well as chemistry based on renewable resources are presented, emphasising the usefulness and importance of LCA in today's green chemical design.

The Methodological Rules of LCA

As the name 'Life Cycle Assessment' implies, the perspective of LCA is the entire life of the product or process under investigation (see figure 1). This means that all the mass- and energy-flows within the life of a product are recorded, from the acquisition of the raw material, over the distribution and the use, to the final deposition of the wastes after its use (also called "cradle-to-grave").[5]

The defined structure of LCA studies consists of the following stages: i) Goal and Scope Definition, ii) Life Cycle Inventory Analysis (LCI), iii) Life Cycle Impact Assessment (LCIA), and iv) Life Cycle Interpretation. LCA is usually an iterative process. While working at one of the stages, difficulties in the acquisition of data might appear or new information gives rise to a necessary change in settings made before. Thus, it is often useful and necessary to go back to earlier parts and change these settings.[5]

Goal and Scope Definition

During Goal and Scope Definition, the cornerstones of the study are defined. The precise determination of the intention of the study is important to have a basis for decisions that have to be made during the execution of the study. It includes the motivation, the audience addressed and the purpose of the study. The definition of the scope also includes the phrasing of certain rules concerning the methodological procedure of the study. Here, also the investigated chemical product or process is set in terms of a functional unit as a comparable performance characteristic. All inputs and outputs are assigned to this functional unit.

Life Cycle Inventory Analysis

The second step of the LCA is the inventory analysis. During Life Cycle Inventory (LCI) all the mass and energy flows within the scope of the study are recorded. Focus is given on the structuring of the entire life cycle in separate unit processes as well as on the collection and calculation of data. Data collection means the assembly of all (energy and material) inputs (resources extracted from the environment) and outputs (products, wastes, emissions). Data calculation includes the validation and the relation of the data to the functional unit. At this, the LCI database ecoinvent[6] is often used in case of missing measured or gathered data especially with regard to up- and downstream processes of the chemical synthesis under investigation, Provided by the ecoinvent Centre, the database includes the most consistent, transparent, and up-to-date Life Cycle Inventory (LCI) data worldwide. Within the several thousands of LCI datasets, relevant LCI data concerning bulk and

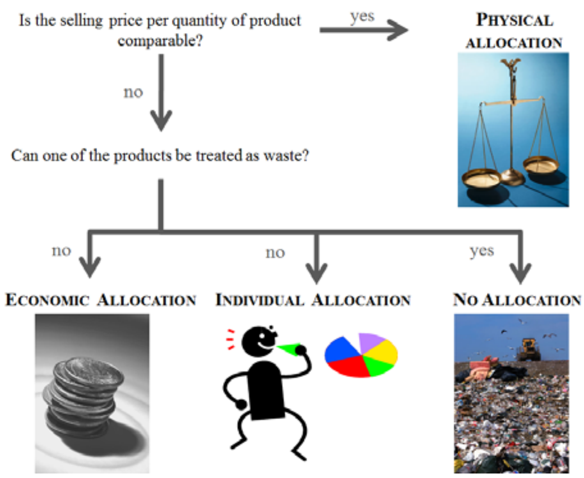


Figure 2: Illustration of the decision pathway for the most appropriate allocation method.

speciality chemicals, but also energy supply, transport, biofuels and biomaterials, construction and packaging materials, basic and precious metals, metals processing, as well as waste treatment can be found based on industrial data.

In case of a process involving more than one commercially useful product as well as recycled materials, an allocation of the energy and material flows has to be applied.[5] In general, various allocation methods are present and are controversially discussed.[7-9] Two of the more common allocation procedures refer to the mass or market-value of these products (see figure 2).

Life Cycle Impact Assessment

The Life Cycle Impact Assessment (LCIA) is conducted with the results of LCI. Certain potential environmental consequences (namely 'impact categories') are assigned to the mass- and energy-flows according to the chosen characterisation model. This way, the LCIA leads to statements about the environmental performance of the process, the particular process step or product under investigation. There exist many different ways of assigning environmental impacts to the inventory, but they all follow a common procedure fixed in the standards EN ISO 14040[5] and 14044[5]: i) selection of characterisation model, ii) classification, iii) characterisation, and optional, iv) normalisation.

The impact categories are selected according to the goal and scope of the study. The category indicator is the quantifiable representation of a certain impact category. The category indicator and the characterisation model are developed according to the environmental mechanism that is known for the particular impact category. The potential environmental impacts of the elementary flows that are identified in the LCI are classified within these impact categories. During characterisation, the potential impact of an inventoried item is quantified in terms of a representative unit, *e.g.*, in carbon dioxide equivalents in case of emissions causing climate change. The normalisation step is the calculation of the characteristic value of the category indicator relative to a reference value, *e.g.,* in relation to an emission limit or per capita. The normalisation step is optional and does not have to be included in the LCIA.[5]

Life Cycle Impact Assessment Methods

Nowadays, a number of LCIA methods have been established. They all use different kinds of characterisation models and therefore consist of different impact categories. The inclusion of these LCIA methods in software tools commonly used for LCA enables the LCA practitioner to focus on the data for the LCI, but the choice of the LCIA method and the considered impact categories has to be well conceived with respect to the goal and scope of the study.[10]

There are two different kinds of impact categories, the input- and the output-related categories. The theoretical model behind an input-related category could be described as follows: If the elementary flow is the extraction of 1 kg mineral oil, the effect (and the indicator) will be the depletion of a particular share of the remaining fossil oil resources. In order to define the impact of this depletion the scarcity, the renewability and the availability of a resource have to be considered. Therefore the evaluation of input-related indicators is already a complex issue.[11] The output-related categories are even more difficult to quantify, because the effects of the outputs is more multi-layered. There are primary, secondary and tertiary (and even more) effects of an output that can all serve for the indication of the characterisation. For the impact category of Climate Change (CC) the effect chain could be described as follows:

i) Primary effect: increase of the concentration of gases in the atmosphere that absorb radiation (the indicator here could be the measured value of the relevant gases),
ii) Secondary effect: increase of the temperature,
iii) Tertiary effect: variations in climate (different effects on the climate in different regions of the world): higher temperature peaks (cooler and warmer) drought, storms.

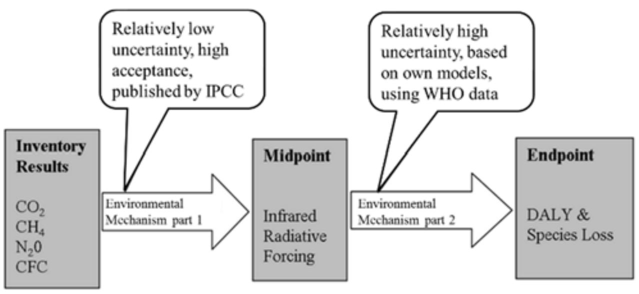


Figure 3. Illustration of a harmonised midpoint-endpoint model for climate change, linking to human health and ecosystem damage applied within ReCiPe.[10]

This list can be continued with further possible effects such as changes in abiotic conditions, effects on living nature and eventually effects on human health. If the indicator of a certain impact category is close to the inventory (close to the emission), it is called a midpoint indicator. If the indicator is describing a tertiary effect, it is called an endpoint indicator. As shown in figure 3, the indication of the effects becomes more complex due to the chain of events between cause and effect. Tertiary effects and beyond are difficult to measure and the number of impact categories rises, since the emission of one substance often has multiple effects (for example considering different areas of protection). Still, the use of endpoint categories would describe the actual impacts that the areas of protection are affected by, rather than the changes of the environment that result in potential effects. Therefore, the implementation of endpoint categories is one of the major goals of the current progress of LCA methodology, but cannot be recommended without objections yet.[12]

The characterisation model, which is the foundation of the association of the LCI results with the LCIA results, is based on confirmed scientific insight. Still, the resulting impacts should not be interpreted as verified predictions. Often, the environmental mechanism is complex and the theoretical models do not include spatial or temporal dimensions.[13] The assessment of impacts is always a balancing act between scientific precision and feasibility. Therefore the results of the LCIA are afflicted with uncertainties (that are often not defined, yet) and should be seen as statements on the potential impacts.

The ISO standards EN ISO 14040 and 14044[5] also refer to the analysis of the data quality as a mandatory part of the LCIA. Since it is part of the Life Cycle Interpretation as well, it will be further explained in the next section.

Methodologies for Life Cycle Impact Assessment

For the association of the inventory data with potential environmental impacts it is useful to choose one consistent LCIA method, which is a collection of characterisation models concerning a variety of impact categories. The choice LCIA method and their underlying characterisation models determined by standardisation organisations should be based on an international approval or agreement.[5] There are a number of LCIA methods existent, partly still on the stage of development. A comprehensive overview about these methods is given by Hauschild and colleagues.[11] Some of the well-established ones are for example CML 2002[14], IMPACT 2002[15] (both midpoint oriented methods) or Eco-Indicator 99[16] (endpoint oriented indicator).

One of the most up-to-date LCIA methods today is ReCiPe.[10] The focus during the development of this method was on the compatibility of mid- and endpoint methods in terms of the assumptions that create the measures defined in the model. ReCiPe is a combination of the established CML 2002 and the Eco-Indicator 99 methods. At midpoint-level, ReCiPe consists of the following 18 impact categories:

1. Climate Change (CC)
2. Ozone Depletion (OD)
3. Terrestrial Acidification (TA)
4. Freshwater Eutrophication (FE)
5. Marine Eutrophication (ME)
6. Human Toxicity (HT)
7. Photochemical Oxidant Formation (POF)

8. Particulate Matter Formation (PMF)
9. Terrestrial Eco-Toxicity (TET)
10. Freshwater Eco-Toxicity (FET)
11. Marine Eco-Toxicity (MET)
12. Ionising Radiation (IR)
13. Agricultural Land Occupation (ALO)
14. Urban Land Occupation (ULO)
15. Natural Land Transformation (NLT)
16. Water Depletion (WD)
17. Mineral Resource Depletion (MRD)
18. Fossil Fuel Depletion (FD)

To give an impression of the way the impact assessment works, the category Climate Change (CC) is further described in the following section. A description of the other 17 category indicators can be found in the ReCiPe main report.[10]
The impact category CC summarises the effects of elementary output substances that contribute to global warming. The calculation of the Global Warming Potential (GWP) of a certain substance appearing in the LCI is performed by the use of equivalence factors that have been defined in the report of the Intergovernmental Panel on Climate Change (IPCC).[17] These equivalence factors are calculated according to the following equation:[10]

$$GWP_{x,T} = \frac{\int_0^T a_x[x(t)]dt}{\int_0^T a_r[r(t)]dt}$$

With:

$GWP_{x,T}$	-	Global Warming Potential of substance x
T	-	Time horizon under consideration
a_x	-	Radiative efficiency due to an increase in abundance of x
$x(t)$	-	Time dependent abundance of the substance x
r	-	Reference substance

The term a_x describes the power of the substance x to increase the radiative forcing and the term x(t) describes the lifetime of the gas, as the gases in the atmosphere are subjected to different kinds of effects that influence their concentration, like chemical reactions with other gases or degradation caused for example by UV-radiation. As can be seen from the equation, the quality that is used to describe the CC is the increase of radiative forcing caused by a greenhouse gas relative to a reference gas. In this case, the reference gas is CO_2, the most important anthropogenic greenhouse gas.[18] The direct relative radiative forcing per ppbv (part per billion, volume basis) are derived from infrared radiative transfer models based on laboratory measurements of the molecular properties of each substance and considering the molecular weights.[10] Originating from the IPCC, the characterisation model is consensus-based and undisputed. It is classified satisfactory and recommended by the Joint Research Centre of the European Commission (JRC). Table 1 gives an overview of the characterisation model for CC. Since most production processes are connected with a significant energy demand causing additional environmental impacts, the Cumulative Energy Demand (CED) was established as a LCIA category nearly twenty years ago.[19, 20]

Table 1. Short description of the impact category CC[10] modified from [5].

Impact Category	**Climate Change**
LCI results	Greenhouse gases
Characterisation Model	Baseline model of 100 years as in IPCC[17]
Category Indicator	Infrared radiative forcing
Characterisation Factor	Global Warming Potential (kg CO_2-eq./ functional unit)
Environmental Relevance	Infrared radiative forcing is a proxy for potential effects on the climate, depending on the integrated atmospheric heat absorption caused by emissions and the distribution over time of the heat absorption

CED represents the energy demand during the entire life cycle of a product or process, and is nowadays accepted as a suitable screening indicator, predicting environmental burdens of production [21] and reflecting many of energy-related life cycle impacts typically considered in an LCA study, *e.g.*, global warming, resource depletion or acidification.[22]
During early stages of green fine chemical process design, the Finechem software tool by Wernet *et al.* [23, 24] can be used for CED estimation, in front of a detailed LCI modelling. The related Cumulative Exergy Demand (CExD) depicts instead the total exergy removal from nature to provide a product, summing up the exergy of all resources required.[25]
Some years ago, the group of Dewulf and colleagues developed the more sophisticated LCIA category Cumulative Exergy Extraction from the Natural Environment (CEENE) for the impact assessment of process alternatives with a high share of energy supply on the overall environmental impacts.[26] Exergy data on fossils, nuclear and metal ores, minerals, air, water, land occupation, and renewable energy sources were taken into account as "taken away" from natural ecosystems. They applied this measure also in the context of life-cycle based evaluation of pharmaceutical processes.[27, 28]

Life Cycle Interpretation

The Life Cycle Interpretation can be subdivided into the following constituents according to EN ISO 14044[5]:

i) Identification of significant issues,
ii) Evaluation,
iii) Conclusions.

The identification of significant results is mainly achieved by structuring the results of the LCI and LCIA. The evaluation is concerned with the completeness of the data base, the consistency of the data (data quality indication) and the analysis of the sensitivity of the results for changes in data. Having checked for these criteria, conclusions can be drawn concerning the resulting recommendations but also the limitations of the LCA study.

Sensitivity and Uncertainty Analysis

Most data used in a typical LCA study comes from secondary sources such as LCA databases, process simulation tools, information from similar processes, literature references, *etc.* Due to this fact as well as the inhomogeneity of those collected data, a

distinct uncertainty is inherent.
Furthermore, unclear definitions, the cut-off of relevant up- and downstream processes, the choice for unsuited environmental impacts, and incorrect interpretations, *e.g.,* caused by overdone aggregation, or the combination of data from different temporal or geographic origin may affect the overall LCA weakening the powerful validity and reliability of life cycle analyses compared to simple green metrics. It is the responsibility of each evaluator to reduce these causes for uncertainty carefully without losing sight of practicability and to document the quality of the data used. One approach to reduce the data gathering effort are sensitivity analyses based on expert knowledge. As an example, a variation of typical synthesis or process parameters and the analysis of the resulting effect on the overall environmental balance supports the selection of most influencing process modules.[29, 30] In a next step, those process modules can be evaluated in more detail than others showing only a minor contribution.
Monte Carlo simulations can further help to determine whether the calculated differences between alternatives evaluated within a comparative LCA are significant. The method relies on repeated stochastic calculations within a mostly pre-defined uncertainty band in order to obtain the distribution of the unknown probabilistic entity (*e.g.* [31, 32]).

Table 2: Data quality indicators and data quality scores for the indication of data quality modified according to Weidema[33] for use in early chemical process and synthesis design and optimisation.

	1	2	3	4	5
Completeness	Complete data including information on masses, energies, by-products and recycling	Nearly complete data, data gaps filled with qualified assumptions	Incomplete data, gaps filled with qualified assumptions	Incomplete data, important data gaps filled with standard assumptions	Incomplete data, data gaps not filled
Representativeness	Primary experimental data from the research area under study, provided by experts, recent time period	Data from area under study, from experts related to the topic of the study, from one time period	Data from a currently conducted procedure, from area with similar synthesis conditions, technology that could be applied	Data from former production procedure, area or different production conditions and technology of different scale	Data age older than 20 years or unknown, unknown area and unknown or inapplicable technology
Reliability	Data based on repeated measurements	Data based on measurements or calculated from trustworthy models	Data based on literature or on models	Data based on qualified estimations	Data based on non-qualified estimation or unknown origin

Indication of Data Quality

The description of the experimental procedures within a scientific study for greener chemical process and product design is mostly precise and comprehensive and the data quality goals can be achieved. The availability of secondary data is typically lower and therefore quality goals can only be accomplished partially. Hence, the quality of the data varies depending on the available sources within the specific study. In order to take these variations into account, the data quality of each aspect of this study should be indicated *via* indicators. A common procedure to indicate the data quality in an LCA is the so-called 'Pedigree Matrix' which has been established for this purpose by Weidema.[33] The data quality indicators used by Weidema are:

i) Completeness,
ii) Temporal correlation,
iii) Geographical correlation,
iv) Further technological correlation,
v) Reliability.

The data quality is evaluated by giving scores to each data set (forming the lines of the matrix) for each of these categories (the columns of the matrix). Every score is defined beforehand, and only if all the criteria in this definition are fulfilled a particular score can be assigned. The Pedigree matrix system for qualitative assessment of data quality within LCA studies has been modified and used for many different LCA studies in the past, but mostly not in the context of chemical process and synthesis design. Table 2 shows a modified pedigree matrix applicable for data quality indication for this specific application.
One major difference between Weidema's established valuation system and the one introduced here is the aggregation of the indicators for time-, space- and technological correspondence into one indicator called representativeness. Weidema reasons that the division is useful in order to figure out spots for improvement more easily. Nevertheless, in early stages of chemical process or synthesis design the simplification suggested herewith has been found useful for purposes of clarity and last but not least due to typically limited information about the time-, space- and technological implications of the novel process or material under development in a future industrial environment. The indicator score is always guided by the single aspect that scores the worst. If, for example the time-correlation scores '1' and the technological correlation scores '5' or is unknown, the score for representativeness is '5'.

Why using LCA?

The method of LCA has many advantages compared to other methods of measuring the environmental impact of products or processes. Due to its broad applicability and its validity, the LCA methodology has gained worldwide acceptance as a useful tool for strategic planning, process development as well as policy-making. Thanks to the development of this method in the last 40 years there is a set of guidelines for this method available that provides precise information on the implementation.[13] These guidelines take care of the consistency and the transparency of LCA.
The LCA-approach ensures the avoidance of a problem shifting to other stages of the process (*e.g.* raw material production, waste treatment) because of their comprehensiveness. When selecting the

system boundaries in a life-cycle-way of thinking, the increase of environmental impacts outside these boundaries is avoided.

The evaluation of products or processes in an LCA is typically performed in a relative way. In the case of comparative studies this can mean that completely different amounts of different chemical compounds are needed to serve the same purpose can be compared. Nevertheless, the decisions that follow the conduct of a LCA study are still a matter of values and opinions.

The handling of uncertainties or data gaps of the study as well as a securing of comparability of alternatives are important criteria, whether the study is conducted in a scientific way. Only the precise definition of rules, the scientific discourse concerning the methodology, the scientific base of the impact assessment and, after all, the transparency of each individual LCI data set ensure the high quality of LCA studies.

As mentioned before, the LCA method is not specially designed for the evaluation of chemical processes or its application for decision-making purposes during process design (for more detailed information see [34]). Thus, the practitioner has to select from the high number of LCA approaches (see *e.g.* dynamic LCA[35], spatially differentiated LCA[36], risk-based LCA[37], environmental input-output based LCA (EIO-LCA)[38], hybrid LCA[39] or Eco-OptiCAD[40]) the best-fitting strategy without losing the holistic, comprehensive evaluation idea behind the LCA approach.

Simplifying LCA

The benefits of applying LCA for the evaluation of green chemical processes and products, syntheses pathways and technologies have been stated above. The results of a LCA study can be used to highlight the attractiveness of a novel production pathway; they can help making decisions on which chemical compound to use or it can show optimisation potentials within an existing procedure.[41]

The most beneficial way of employing LCA is to apply it in the early development of new compounds or procedures. In this stage, relevant weak points cannot only be fixed by after care or so-called end-of-pipe solutions, but they can be identified and avoided in advance.[42] However, the complexity and the time and effort needed to conduct an LCA study are often the reason to prefer other, less complicated ways of evaluation at this stage. This is especially the case when new, non-established developments with little available data are to be assessed. In order to enable LCA in such cases without neglecting its high life-cycle based standards there are different ways to decrease the amount of work and data requirements that comes with it.

In an attempt to enable an LCA in a smaller scope, the Society of Environmental Chemistry and Toxicology (SETAC) developed a framework for Simplified Life Cycle Assessment (SLCA)[43] (also called Streamlined LCA), which describes the possibilities of simplification for every phase of the LCA. According to this framework, the simplification consists of three steps which are iteratively linked:

i) Screening: identification of elements of the LCA, that can be omitted or where generic data can be used without significantly affecting the accuracy of the final result,
ii) Simplifying: application of the simplifying options identified in the screening step to produce a simplified LCA,
iii) Assessing reliability: making sure that results are reliable enough to justify the conclusions drawn.

These steps are intended to be applied to all four phases of the 'common' LCA, because this way the holistic approach is still ensured. Just like the 'common' LCA, the simplification is an iterative procedure. Today, Simplified LCA is an established part of the toolbox for decision support towards more environmentally benign chemical developments. [42, 44]

Another possibility to decrease the amount of work afflicted with LCA is to concentrate on the most relevant life cycle stages: Some LCA studies are not concerned with the entire life cycle of a product, but with the potential impacts that are caused by a particular life stage (gate-to-gate analysis). More often, a cradle-to-gate assessment is performed, including all life cycle impacts caused up to the production and work-up of the final chemical compound. It is used for comparative studies evaluating different processing alternatives or synthesis pathways resulting in the same product, characterised by a comparable product quality. The further life-cycle impacts of all alternatives considered are equal and therefor excluded.

Another simplification approach was followed by GlaxoSmithKline (GSK). They developed the FLASC™ software tool[45] for fast LCA in synthetic chemistry especially for Active Pharmaceutical Ingredients (API). Material classes were chosen where it was possible to generate average LCI profile data that could be used for materials where LCI data did not exist. Then, a methodology to predict the cradle-to-gate life cycle impact profile for a typical batch chemical process used to synthesise APIs was developed based on the LCI of the materials used in the process, using a combination of actual or average data, and the mass of the material. Based on a core set of life cycle impact profiles for well-developed GSK processes including separation and/or isolation steps, a series of formulae was developed that enabled a score to be calculated for different impact categories. The average FLASC™ score was finally calculated from the individual scores for each impact category. The FLASC™ tool is now used to determine, compare and benchmark the 'greenness' or relative sustainability of synthetic processes in order to facilitate more informed and sustainable business choices. The motivation for the development of this tool was again the particular high optimisation potential at an early stage in research and development (R&D) activities when route and processes are being selected and detailed environmental data are not available.

Coupling with Other Assessment Methods

Since sustainability is not only characterised by environmental but also by cost and societal criteria, LCA investigations are often coupled with other evaluation tools. As an example, every investment decision in green chemical processes and technologies is finally a cost-based decision. Therefore, the life-cycle based assessment can be extended by the economic dimension of sustainability using appropriate cost assessment tools such as Life Cycle Costing (LCC)[46]. The results of both, plotted in two-dimensional graphs, can show the effectiveness of certain measures in environmental as well as economic terms.[47] Additionally combined with the results of a Societal LCA[48], all aspects of sustainability can be covered in a methodologically profound approach.

Another important issue especially in chemical process and product design is the appropriate analysis and management of risks concerning human health, environment and safety.

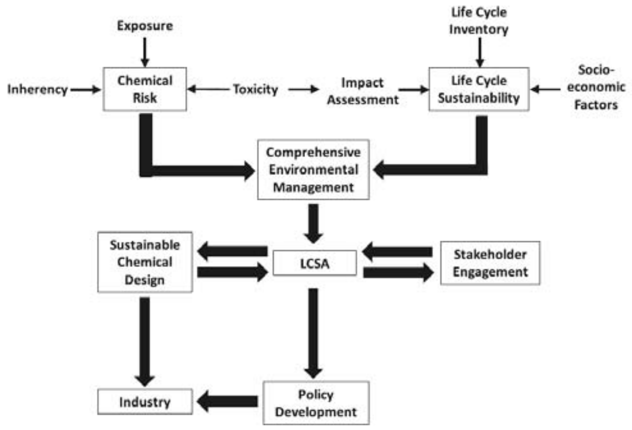


Figure 4: Risk management strategy for Life Cycle Sustainability Assessment (LCSA) of nanotechnologies[49] with kind permission from Springer Science and Business Media.

That is why, LCA is sometimes coupled with a risk assessment as depicted in figure 4 on the example of nanotechnologies.

During early design stages, the environmental behaviour, potential hazards for humans and ecosystems of substances and their treatment when entering different environmental compartments, can be estimated using the Environmental, Health and Safety (EHS) risk assessment method[29]. The EHS tool developed by Hungerbuehler and colleagues [50, 51] is a user-friendly approach to derive risks resulting from the handling of chemicals. It is combinable with LCA (or Simplified LCA) and other evaluation approaches.

As mentioned before, the analysis and minimisation of future environmental impact potentials of a novel chemical process under development is most effective during early stages. This effect is contradictory to the profound data requirements of an LCA study, which can usually not be fulfilled (if no experiences with a similar process are on hand), until the process is implemented on industrial scale. Here, process simulation tools such as ASPEN Tech and HYSYS are very helpful to estimate the mass and energy balance of the process and its optimisation potentials on future production scale as data basis for the LCI stage (also called ex-ante LCA).[52, 53]

Coupling with Multi-Criteria Optimisation and Decision Making Tools

From the complexity of the LCIA on the one hand and the combination of the LCA with other evaluation methods described before on the other hand it becomes obvious that several, partly contradictory objectives are incorporated in a sustainable process or product design and evaluation process. Then, a multi-objective decision making problem occurs, especially in case of conflicting objectives (see figure 5). The problem of comparing several alternatives with respect to several objectives, *e.g.,* costs, environmental or social impact and risks, integrating also a Multi-Objective Optimisation (MOO) can be solved by Multi-Criteria Decision Analysis (MCDA). Multi-Criteria Decision Making (MCDM) techniques are gaining popularity in sustainable process management to find a good trade-off among various objectives, often considering economic, safety or ecological aspects in parallel. Several well-established MCDM methods are applicable, differing in the way preferences are handled. Widely used ranking methods are, *e.g.,* AHP (Analytical Hierarchy Process)[54, 55], ELECTRE (Elimination and Choice Expressing Reality)[56] and PROMETHEE (Preference Ranking Organisation Method for Enrichment Evaluations)[57, 58], see also [59-62].

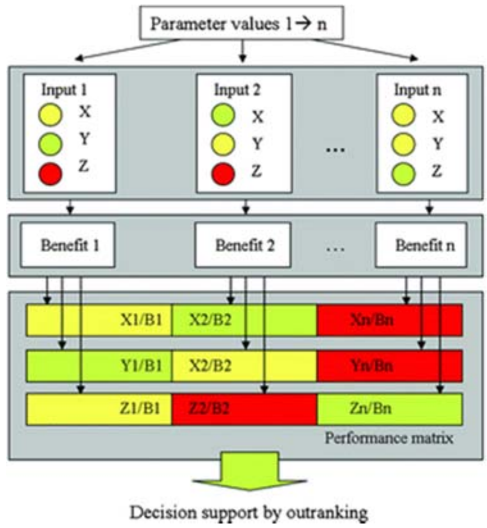


Figure 5: Performance matrix requiring decision support, taken from Kralisch *et al*.[63] reproduced by permission of The Royal Society of Chemistry.

Another established method is the NP (Nonlinear Programming) approach.[64] It involves the minimisation or maximisation of nonlinear objective functions subject to bound constraints, linear constraints, or nonlinear constraints.

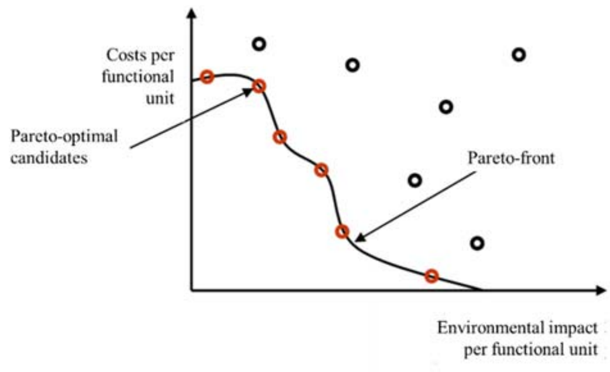


Figure 6: Best trade-off alternatives (Pareto-optimal candidates) at the Pareto-front.

The assessment of multi objective optimisation results can be done using the Pareto concept.[65] Standardised algorithms for identifying pareto-optimal solution candidates constitute for example the basis for partial ranking (out-ranking) procedures. Figure 6 shows a bi-objective Pareto-optimal curve (considering environmental and economic impacts). Parameter configurations and resulting impacts of alternatives at the Pareto-front cannot be changed or improved without worsening the other criterion/criteria.

Bi-objective Sustainability Analysis

Examples for bi-objective sustainability analyses performed during green process design and evaluation can be found, *e.g.*, in references[66-71].

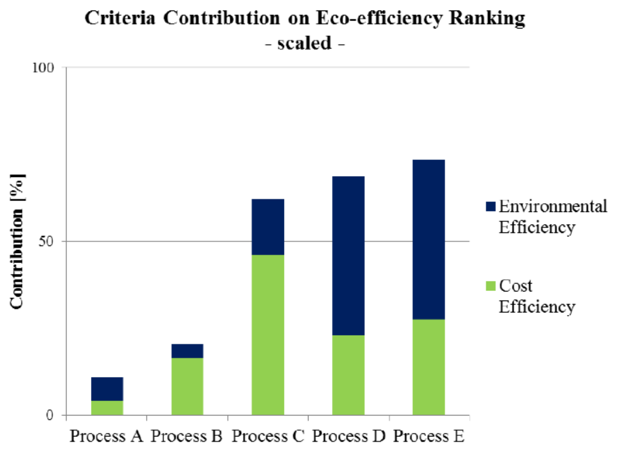


Figure 7: Criteria contribution (scaled) to overall eco-efficiency ranking of different biodiesel production alternatives utilising waste oil (Process A: pre-treated alkali-catalysed; Process B: acid-catalysed; Process C: heterogeneous acid-catalysed; Process D: supercritical process, Process E: supercritical, microreactor based process) according to Kralisch *et al.*[72]

In order to define a preference relation of multi-attributed alternatives, the outranking methods mentioned before can be applied. As a result of a total or partial outranking procedure regarding several LCIA results, preferences for specific, pareto-optimal options for environmental efficiency can be quantified. At this, the environmental efficiency can be determined based on the relative saving potentials in different LCIA categories referred to the worst as well as best case candidates (highest or lowest environmental impact potential, respectively) calculated in each of these categories. Finally, one aggregated environmental efficiency value can be calculated by means of weighting factors.[72, 73] Further, the results are transferable to, *e.g.,* a bi-objective eco-portfolio depiction showing environmental and cost efficiency in one graph. Thereby, cost efficiency is typically calculated taking into account relevant variable and fixed production cost criteria, *e.g.*, investment, material, energy, personnel, and waste treatment costs. High efficiency values in both categories put attention to preferential options.

Figure 7 shows an example of criteria contributions to the total eco-efficiency ranking of alternative biodiesel production pathways.[72] Despite of a lower cost efficiency of process D and E (being supercritical, waste oil based process alternatives), their environmental efficiencies are strongly preferred in contrast to conventional processing alternatives (processes A-C). In consequence, this results in a higher ranking score and thus in a preference against the other process alternatives.

Tri-objective Sustainability Analysis

In an even more holistic consideration, the efficiency regarding environmental, economic, health and safety aspects or social issues can be considered as well, resulting in a tri-objective analysis. Figure 8 demonstrates the SEEbalance® approach by BASF. This so-called "SEECube" combines LCA, cost and social impacts of a product or process.[74, 75]

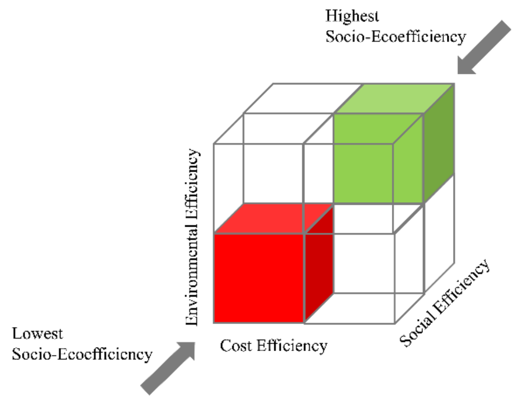


Figure 8: Simplified demonstration of the SEECube related to the BASF SEEbalance® concept [74]: consideration of environmental, cost and social impacts

For instance, Ouattara *et al.*[66] investigated the HAD process (hydrodealkylation of toluene) for the production of benzene focusing on optimised criteria configuration related to costs and selected, process outcome relevant life cycle impact categories in a three-dimensional evaluation.

Kralisch and co-worker[76] evaluated different biodiesel production pathways using a tetrahedral chart containing environmental, safety and cost criteria, see figure 9. Thereby, all of the three criteria consists of a *pre* outranking of sub-category performance matrices (*e.g.*, LCIA categories), resulting in a single ranking score for each criterion. The final tetrahedron emphasises the preference, but also potential for further development activities in dependency of the target criteria. If needed, a *post* outranking of LCA, LCC and EHS criteria can be performed by applying weighting parameters for each category, *e.g.*, depending on target constraints or expert knowledge.

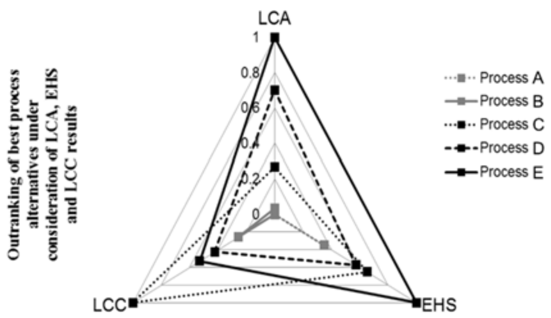


Figure 9: Three-dimensional criteria decision-making in the context of biodiesel manufacturing pathways. LCC: Life Cycle Costing, LCA: Life Cycle Assessment, EHS: Environmental, Health and Safety risk assessment. Tetrahedral graph according to Kralisch *et al.* [76]

Application of LCA for Green Chemical Process and Synthesis Design

Today, LCA is more and more accepted as assessment tool in green chemistry and engineering. It is applied on laboratory as well as production scale. In the following, selected studies performed during the last years in emerging fields of research and development will be introduced against the background of future challenges to be coped with.

LCA for Evaluating Chemical Transformation Pathways

Case Studies Dealing with Green Catalytic Synthesis Approaches
Van Kalkeren *et al.*[77] examined catalytic Appel and Wittig reactions, which were developed to avoid phosphine oxide waste produced in the classic phosphorus-consuming process alternatives (figure 10). They conducted an LCA study, in which the conventional reactions were compared with their catalytic counterparts in terms of CED and GWP. By means of this, they aimed to answer the question whether the requisite stoichiometric amounts of silanes may hinder environmental improvements.

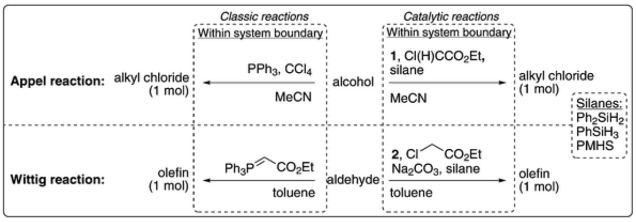


Figure 10: LCA system boundaries of the catalytic reactions investigated by van Kalkeren *et al.*[77] published by The Royal Society of Chemistry.

The results revealed that the replacement of phosphines by silanes can result in environmental improvements for the Wittig reaction, but that additional reagents and working in lower concentrated solutions would offset potential environmental improvements for the Appel reaction.
Griffiths and colleagues applied the LCA tool to measure the performance of a range of iron and palladium based nanoparticle catalysts for carbon dioxide utilisation at laboratory scale.[78] The catalysts combined the reverse water gas shift reaction with the Fischer–Tropsch process to convert CO_2 into hydrocarbons used as fuels and feedstocks for the chemical industry. The LCA results afforded insight into 'green' catalyst design, since palladium addition vastly improves catalyst performance. However, they also found scenarios in which the continual addition of palladium, although showing favourable CO_2 conversion and hydrocarbon yields, does not return a sufficient environmental offset to cover the embodied impacts present in its generation.
A novel approach for a catalytic synthesis of caprolactam was studied in an ex-ante environmental assessment by Roes and Patel (see figure 11).[79] By means of the indicators non-renewable energy use (NREU) and climate change (CC), they found that the production of caprolactam by a novel homogeneous transition metal catalyst can offer clear advantages compared to the petrochemical production of caprolactam. Furthermore, 3-pentenamide, *i.e.*, the precursor used in the novel catalytic process could be made from bio-based, instead of petrochemical butadiene, which would further reduce the environmental impacts. The same was pointed out for the syngas, which could be produced from biomass.

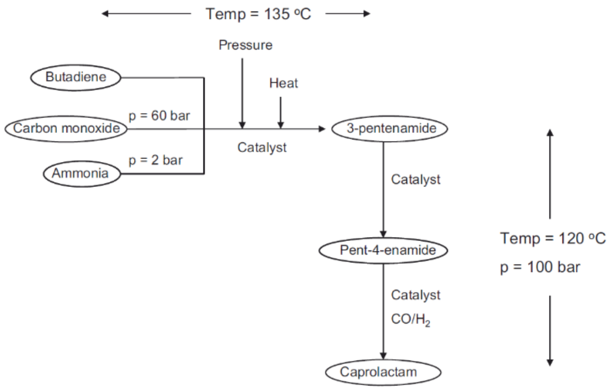
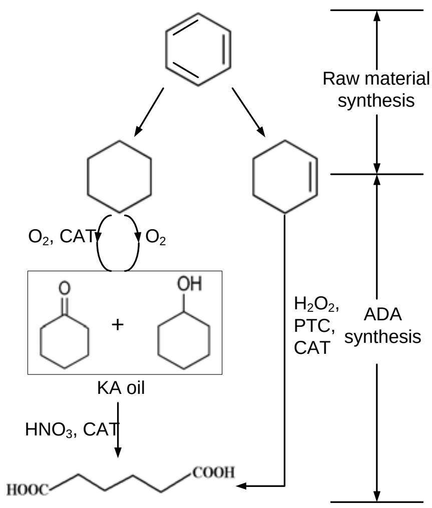


Figure 11: Flow sheet for the novel catalytic production of caprolactam studied by LCA[79] reprinted with permission from Elsevier.

The environmental as well as economic benefits of recycling and reuse of catalytic plates typically used in microreactors were checked by Kressirer and colleagues by means of LCA (CML 2002 LCIA methodology) and cost analyses.[80] They found clear economic advantages especially in case of a combined reuse of the plates and recycling of the catalytic coatings, but the benefits for the environment were less conclusively. This was due to the additional demand for chemicals used for cleaning and recycling as well as for extra energy. Thus, further efforts for an optimisation of the overall *post* treatment and reuse process were required.

Case Example of Direct Adipic Acid Production
Due to its use as monomer precursor for nylon 6,6 production, adipic acid is the most important dicarboxylic acid[81], featuring a worldwide annual production of 2.6 million tons[82]. Wang *et al.*[83] discussed potential environmental benefits resulting from a simplification of the adipic acid (ADA) synthesis (scheme 1). The conventional process for ADA synthesis takes two steps, oxidation of cyclohexane by air followed by nitration oxidation. This process is characterised by capital- and energy-intensive downstream processes as well as an NO_x emission problem. In contrast, the direct route starts from cyclohexene and uses hydrogen peroxide as oxidant. Whereas the direct synthesis suffered in a batch process protocol from a long reaction time and increased safety issues, these drawbacks were overcome by micro-flow processing. The reaction rate of the two-phase reaction of cyclohexene oxidation by H_2O_2 was increased by an improved mass transfer and a higher temperature.By means of a comparative LCA using the CML 2002 LCIA methodology, the authors could demonstrate that the direct micro-flow route has advantages for the environment as well, but also disadvantages in impact categories such as Land Use, Human Toxicity Potential (HTP) or CED compared to the conventional route. This was reasoned by the high environmental burden of hydrogen peroxide supply.
An alternative approach was evaluated by van Duuren *et al.*[84] They performed a Simplified LCA of a combined biological and chemical process for the production of ADA. The LCA comprises the biological conversion of the aromatic feedstocks benzoic acid,

impure aromatics, toluene, or phenol from lignin to cis, cis-muconic acid, which is subsequently converted to adipic acid through hydrogenation.



Scheme 1: Two-(left) and one-step (right) production routes of adipic acid[83] reprinted with permission from Elsevier.

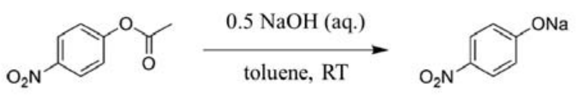
Their SLCA study focused on the LCIA categories CED, CExD, and CO_2 equivalent emissions (comparable to an assessment of GWP). The highest calculated reduction potential of CED and CExD were achieved using phenol from lignine, which reduced the CED up to 57 % compared to a petrochemical benchmark process. The bulk of the bioprocessing energy intensity was attributed to the hydrogenation reactor, directly related to the product concentration in the broth.

In conclusion, enhanced catalytic approaches have shown their great potential to improve the greenness of chemical processes. Of course, it has to be combined with the most material and energy efficient processing in order to exploit its full potential. But this is true also for any other concept for more environmentally benign chemical processing as discussed below.

Alternative Energy Sources

Ultrasound

Huebner *et al.*[85] investigated the acceleration of multiphase reactions by the application of ultrasound, increasing the specific interfacial areas and the corresponding mass transfer rates in microstructured devices. On the example of an ester hydrolysis of p-nitrophenyl acetate (scheme 2) they reported a yield increase by a factor of seven from 11 to 86% compared to the silent process.

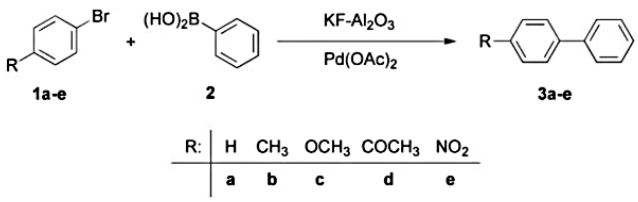


Scheme 2: Basic ester hydrolysis of p-nitrophenyl acetate (1) to sodium p-nitrophenolate.[85]

Although the new process alternative requires more energy compared to experiments without ultrasonication, a Simplified LCA utilising GWP and HTP as key indicators confirmed the development of a significantly greener process (*e.g.*, decrease of the GWP up to 80 % as a result of the yield increase).

Microwave Heating and Ball Milling

In other studies, the effect of microwave heating[30] and/or ball milling on the greenness of the overall process were investigated. To give an example, Schneider and co-workers[86] investigated the energy demand of different approaches to provide the required energy for the Suzuki–Miyaura reaction of aryl bromides with phenylboronic acid yielding to biaryls (scheme 3). Ball milling was found to be more energy efficient than microwave irradiation or the combination of both methods under the chosen reaction conditions. LCIA categories were not considered in this limited environmental assessment study.



Scheme 3: Suzuki–Miyaura reaction of aryl bromides (1) with phenylboronic acid (2) yielding biaryls (3)[86] reproduced by permission of The Royal Society of Chemistry.

Nevertheless, similar results were found by Kressirer and colleagues[30] for a comparative investigation of oil bath, microwave or direct electric heating, taking into account the impact categories GWP and HTP. Again, microwave heating did not result in any savings due to the low energy efficiency of the microwave apparatus (being in the range of 16 – 20 %).

Thus, using alternative forms of energy supply will not *a priori* result in a greener process. However, more effects than the energy efficiency ratio have to be taken into account in order to assess the environmental impact potential derived from the decision for a form of energy supply to a chemical reaction as shown by Huebner and colleagues.[85] Furthermore, if switching to continuous processing, batch technologies need to be replaced by continuously operated, time reducing modules for *pre* and *post* treatment as well. Here, microwave drying can provide an alternative technique to conventional time demanding vacuum drying, *e.g.,* within pharmaceutical processes [87, 88] Pharmaceutical powders have a relatively high dielectric loss factor compared to standard solvents and can therefore efficiently be dried using microwaves[89] meeting also the strict quality criteria. In such cases, life-cycle based analyses can again provide valuable support in terms of holistic decision making. The integration of CExD or CEENE analyses in future studies would further enhance the meaningfulness of a comparison taking into account alternative energy sources.

Green Solvents

Case Examples of Solvent Selection and Waste-Solvent Valorisation

Solvents are used in large quantities by chemical, and in particular pharmaceutical or specialty chemical industries. Besides safety and health issues, waste solvent management is an issue industry has to deal with steadily. Common technologies therefore are solvent recovery by distillation or incineration. For decision making already in R&D, Hungerbuehler and co-workers developed the ECOSOLVENT software tool. It allows to choose the most appropriate technology dependent on the solvent used, for assessing the life cycle impact of the solvent supply and waste treatment, but under consideration of EHS hazards directly connected with the considered solvents, see figure 12.[90-92] In the following, this tool was used several times for performing solvent related life-cycle based analyses (see. *e.g.*, Amelio *et al.*[93], Slater *et al.*[94] or Gaber *et al.*[95]).

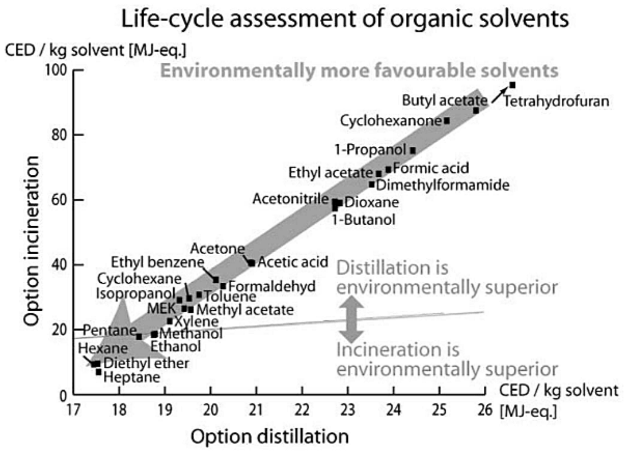


Figure 12: Combining LCA and EHS [50] method according to Capello *et al.*[90] reproduced by permission of The Royal Society of Chemistry.

Luis *et al.* [96] investigated the environmental burdens of batch and continuous distillation vs. incineration for the treatment of selected waste-solvent mixtures of different concentrations: acetonitrile-toluene, acetonitrile-toluene-tetrahydrofuran, ethyl acetate-water and methanol-tetrahydrofuran. The LCIA was performed by calculating the Eco-Indicator 99, UBP-97 (method of ecological scarcity)[97], GWP, CED and CO_2 emissions.[96]

Based on the LCA methodology, Amelio *et al.* further developed guidelines for solvent selection during the process design and evaluation of treatment alternatives. Therein, they investigated the environmental effect of treatment methods of 17 molecular solvents and their combined binary mixtures.[93] Both papers concluded, that the main impact arises from upstream processes of manufacturing these solvents. Thus, if the solvent supply is connected with high environmental burdens, a solvent distillation is preferred to its incineration. A comparison of the information, given by the different LCIA indicators used in this study, revealed that all indicators lead to the same conclusions for the evaluated mixtures with some exceptions only for UBP-97.

Case Example of Ionic Liquids

Ionic liquids can offer novel, potentially "green" perspectives and considerable advantages. They have been investigated as solvents as well as auxiliaries in a great number of applications, *e.g.*, in organic and catalytic syntheses such as Heck reactions, hydrogenations and Diels-Alder reactions, as well as solvents for extraction. Furthermore, the application potential of ionic liquids in enzymatic reactions, electrochemical applications, *e.g.,* the use of ionic liquids as electrolyte material for metal deposition or batteries, as well as sensors are some examples of the huge area of potential application, as also highlighted in, *e.g.*, Ott *et al.*[98].

Against the background of promising features of, *e.g.*, non-flammability, high thermal stability or negligibly low vapour pressure, ionic liquids were uncritically referred to green chemistry at first and discussed as "green" substitutes to molecular organic solvents. Then, first results concerning their partial toxicity, production effort and environmental impact have induced a more differentiated point of view. Nowadays, the assessment of their chemical and biological properties, and the resulting environmental impacts have become important research and development aspects. Zhang *et al.* [99] performed an LCA of the synthesis and application of an ionic liquid compared to selected molecular solvents. The authors emphasised the challenges and uncertainties of a product or process assessment in early stages of development of a new class of compounds, but pointed out the importance of ecological evaluations of ionic liquids in contrast to other solvent systems. In consequence, they decided to perform a cradle-to-gate LCA, neglecting downstream processes, particularly due to the fact that information on industrial disposal routes and the resulting emission pathway into the environment were not available.

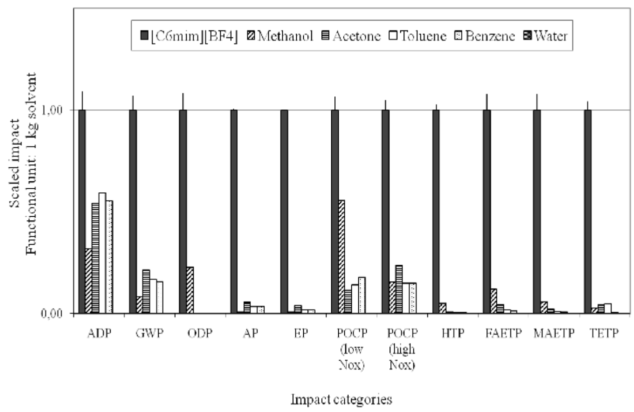


Figure 13: Comparison of the life cycle environmental impacts of the manufacture of ionic liquids with molecular solvents according to Ott and colleagues[98].

Reinhardt *et al.* performed Simplified (focussing on CED evaluation in combination with EHS criteria) up to holistic LCA studies to evaluate and optimise the synthesis of selected ionic liquids, and compared their ecological performance to molecular solvents for a Diels-Alder reaction.[63, 98, 100] The implementation of LCA strategies in ionic liquids R&D demonstrated the high optimisation potential for common synthesis strategies for these compounds and emphasised the need for a critical evaluation already at early process development stages. The life cycle impact of the ionic liquids was investigated to be much higher than for the selected molecular solvents, see figure 13, primarily due to the extensive pathway of its manufacture. The authors concluded that potentially the ecological and economic impacts resulting from the manufacture can only be counter- or outbalanced within the application phase, if proper recycling is ensured and the use of ionic liquids results in an essential improvement in the application stage. However, in the case studies of metathesis[101] and Diels-Alder reactions investigated[98] clear environmental benefits for the use of molecular solvents were found.

Altogether, solvent selection, reduction and recycling have become a big issue not only in academia but in particular also in industry. If this trend is continued, one very important source of environmental impacts caused by chemical and pharmaceutical industry will be distinctly reduced. Even simplified approaches, taking into account in particular energy demand and toxicological criteria in a life cycle based manner, are of great value here.

LCA for Evaluating Flow Processing

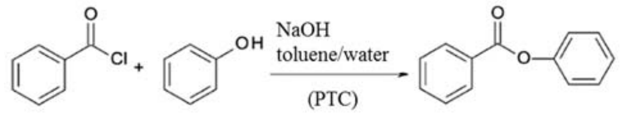
The chances of flow-chemistry to facilitate green processing was critically investigated by means of several (partly simplified) LCA studies (see, *e.g.*, references [29, 42, 76, 102, 103]) Some of them are introduced below.

Utilising Strongly Exothermic Reactions in Flow

The very first study concerning green potentials of flow chemistry in microreactors dealt with the two-step lithium-organic synthesis yielding *m*-anisaldehyde.[102] The LCA study applying the CML 2002 impact assessment method pointed out promising ecological advantages gained from microreaction technology in comparison to batch technology, which is typically utilised in the fine chemical industry. Savings in environmental impacts could be obtained for the laboratory scale syntheses as well as for the newly implemented industrial scale process. On laboratory scale, the advantages mainly consisted in savings in energy consumption, a reduction of the solvent amount and the increase of the reaction yield achieved by the micro-scale setup. On the industrial scale, the avoidance of a cryogenic system by increasing the reaction temperature was the most important benefit. Compared to these saving potentials (being in the range of 10 – 40 % depending on the environmental impact category investigated), the fabrication of the reactors and of the peripheral equipment played a minor role.
An LCA comparison of a batch versus continuous flow processing of the exothermic anionic polymerisation of styrene again resulted in environmental benefits for the flow process due to the avoidance of a cryogenic cooling system.[104]

Case Study of Phase Transfer Catalysis in Flow

Huebschmann *et al.*[103] investigated the biphasic esterification of phenol and benzoyl chloride resulting in phenyl benzoate under moderate reaction conditions (Scheme 4). They combined a Simplified LCA (LCIA method: CML 2002) with a cost analysis. Due to missing data at an early stage of process design, they used partly also theoretical expert knowledge, *e.g.*, concerning best work-up strategies in order to provide decision support for the most sustainable process design alternatives for the phenyl benzoate synthesis already during the R&D stage.
An improvement of the mixing of the biphasic reaction system was realised by transferring the synthesis from batch to flow processing using different types of micromixer in combination with ionic liquids as phase transfer catalysts.



Scheme 4: Phase transfer catalysis (PTC) of benzoyl chloride and phenol evaluated by Simplified LCA.[103]

The performance of the micromixing structures was significantly influenced by the process parameters chosen, especially by the utilisation of ionic liquids such as [C_{18}MIM]Br, [MIM][$BuSO_3$] or [BMIM]Br as phase transfer catalysts. The ionic liquids showed strongly positive results on the yield of the esterification reaction compared to non-catalysed syntheses. Despite the high environmental burden of these compounds resulting from their material and energy demanding synthesis, the overall environmental balance was improved even when the ionic liquids were used only once without recycling. Sensitivity analyses were performed by varying relevant process parameters including the amount of solvent, the yield and flow rates. Based on this, the work-up step was found to be a major bottleneck for green process design, independently from the decision for batch or flow processing. Another critical element was the higher energy demand of the flow processing plant including pumps and process control systems compared to the batch system. As a result, substantial savings up to 70 % for the microreaction process were forecasted only under the constraint that the high electricity demand of the peripheral equipment can be reduced in an optimised production process.

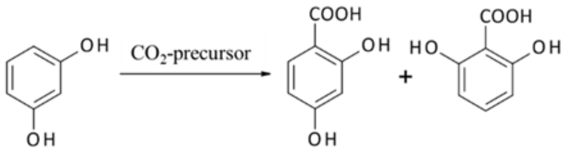
These and further studies have shown that flow chemistry can provide powerful options to improve the environmental balance of chemical processes, but has to come along with benefits in yield/selectivity, energy management or solvent demand. Otherwise, the additional effort for increased process control will counterbalance the advantages.

Assessment of the Environmental Impacts of Flow Chemistry Coupled with *Novel Process Windows* Conditions

Some years ago, Hessel introduced the concept of *Novel Process Windows* (NPW) in flow chemistry using microreaction technology.[105] He argued that these smart devices allow the exploitation and intensification of chemistry under harsh process conditions. In the meantime, a broad range of experimental investigations in this area has been performed.[106] Some of them were accompanied by comparative LCA studies in order to answer the question, whether NPW conditions will also result in a more environmentally efficient processing.

Case Example of CO_2 Utilisation under Harsh Process Conditions

On the example of the Kolbe-Schmitt synthesis (scheme 5), Krtschil *et al.*[107] and Stark *et al.*[42] investigated different measures of process intensification and CO_2 activation as carbon source for chemical reactions on laboratory scale.



Scheme 5: Kolbe-Schmitt synthesis starting from resorcinol with a CO_2-precursor giving 2,4 DHBA (target product) and 2,6 DHBA as by-product (Krtschil *et al.* [107]).

The process was intensified using a microreaction process under NPW conditions applying high temperature (up to 250 °C) and pressure (up to 120 bar). Process design alternatives and several solvent concepts were critically compared by means of Simplified LCA in order to develop a green process (figure 14). [30] In addition, the application of microwave irradiation instead of oil bath heating was tested in order to increase the energy efficiency of the process. As active media, hydrogen carbonate containing water or ionic liquids, supercritical CO_2 as well as Dimcarb, a liquid dimethylamine:CO_2 (1.8:1) adduct, were investigated under different reaction conditions (*e.g.*, temperature, pressure, concentration and molar ratio).
The design accompanying Simplified LCA using the LCIA methods CML 2002 and CED pointed out several hot spots for process design improvements compared to the reference, a batch process utilising aqueous $KHCO_3$ at a reaction temperature of 100 °C under normal pressure. The application of supercritical carbon dioxide had an adverse impact on the reaction performance, but aqueous [EMIM][HCO_3] or [BMIM][HCO_3] led to significantly increased yields. Nevertheless, a greener process using these active solvents can only be realised in combination with an efficient recycling of these compounds.[108] The authors explained this outcome with the high environmental impacts caused by the supply chain of the ionic liquids. All in all, the evaluation pointed out that the environmental balance of the Kolbe-Schmitt synthesis is rather benefiting from efficient work-up strategies and the utilisation of recyclable ionic liquids as active solvents than from harsh synthesis conditions or alternative forms of energy supply.

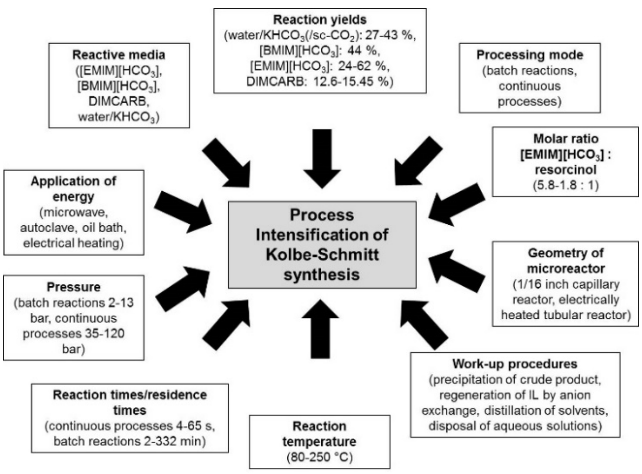


Fig. 14: Concepts for PI of Kolbe-Schmitt synthesis by Kressirer *et al.*[30] reprinted with permission from the American Chemical Society.

Case Example of Epoxidised Soybean Oil

Kralisch and colleagues performed a process design accompanying LCA and LCC study analysing the NPW concept for the re-design of an existing production process of epoxidised soybean oil.[29] Based on experimental data and process simulation results for syntheses under high temperature (T > 150 °C) conditions, an environmental screening to identify the best suited flow process conditions was done in a first attempt. In contrast to the last two examples, a real case industrial production of epoxidised soybean oil was used as benchmark. The results showed that the expected innovations by microreaction technology and chemical intensification under NPW conditions depended on the fluid–fluid and fluid–wall interactions, which were mostly unknown factors when starting the investigations. Thus, the hydrogen peroxide demand was found to be a critical factor, if solid–liquid interactions with the large internal steel surfaces of the microchannels lead to considerably enhanced decomposition rates. Consequently, the LCA results pointed out that this aspect was one of the key criteria for the success of the whole flow process design. Nevertheless, parameter configurations were found, which allow for an improvement of the overall environmental balance compared to the industrial reference fed-batch process. However, due to the dominance of the upstream process of agricultural soybean oil generation in the overall environmental impact of the process, the optimisation potential was estimated to be 5 – 16 % maximum depending on the environmental impact categories considered, again applying the CML 2002 method. Such information, gathered at an early stage of process design can be of great value for further decision making. In the specific case described here, the company decided against an investigation into the new technology.

Case Examples of Biodiesel Synthesis

In other studies, the NPW concept was transferred to biodiesel processing, since process intensification and optimisation of biodiesel generation is still an open issue for many research groups worldwide.[76, 109, 110] Especially the transesterification of triglycerides with supercritical methanol under high temperature and pressure conditions received much attention.[111] It is a catalyst-free process with high reaction rates being insensitive to the presence of impurities in the oil, such as water and free fatty acids. Three LCA studies were performed evaluating this topic in detail. In all cases, the same LCIA method, namely CML 2002, was used. This allows a good comparability of the results and provide the opportunity to build upon each other. At first, Morais *et al.* reported about the potential environmental impacts of different process design alternatives for biodiesel production from waste vegetable oils.[109] The process design alternatives considered in this study included an alkali-catalysed process with a free fatty acid pre-treatment, an acid-catalysed process and a supercritical methanol process using propane as co-solvent. These processes were simulated using the process simulator ASPEN Plus®. The outcome of the study already proposed a supercritical processing of waste oil, using methanol as well as propane as co-solvent. The authors argued that although the supercritical methanol process is highly energy intensive, the downstream operation of methanol recovery and the product purification are much simpler, enabling a decrease in the overall energy consumption compared to the process alternatives with moderate reaction temperatures below

100 °C and normal pressure. An LCA study of Sawangkeaw and colleagues[110], again supported by process simulation, confirmed that supercritical processing at high temperature conditions of 400°C can be beneficial also in case of fresh vegetable oil (here: palm oil).

Based on this, Kralisch *et al*. [76] recently performed a systematic LCA based decision support procedure for the best-suited process design of a biodiesel production process before a pilot plant construction. The development of the novel biodiesel production alternative was accompanied by process simulation, LCA, cost and risk analyses nearly from the beginning using an iterative evaluation procedure. They pointed out favorable process parameter combinations in parallel to experimental optimisation. The transesterification of waste oil *via* supercritical processing at a temperature of 380 °C and a pressure of 200 bar in intensifying continuous flow reactors was found to be the most favourable option out of eighteen and was transferred to a newly developed mini-plant design. It will allow a reduction of the overall GWP up to 70 % referred to the industrial established benchmark utilising fresh vegetable oil under moderate process conditions, as well as a safe processing despite supercritical process conditions.

In summary, harsh process conditions in chemical production were found to be not *per se* critical for the environment. Despite the comparably high energy demand for heating, pressurizing or cooling, benefits in yield and/or simplified *pre* and *post* treatment can lead to green intensified processes.[106]

LCA and MOO for Evaluating Biomass to Fuels and Bio-Based Products

The use of biomass to produce bio-based fuel or commodity chemicals and its accompanying evaluation of eco-efficiency improvement, as shown in the above section, has gained increased importance within the last decade. This chapter will introduce some more selected examples.

Recently, Patel *et al.* presented an early-stage sustainability assessment framework to analyse new bio-based process alternatives.[112] The assessment relied on a multi-criteria approach, integrating the performance of chemical conversions based on five indicators into an index value. The indicators encompassed economics, environmental impact, hazards and risks, techno-economics and LCA. For each bio-based process, two R&D stages (current laboratory and expected future) were assessed against a comparable conventional process. The multi-criteria assessment in combination with an uncertainty and scenario analysis showed that the chemical production processes using biomass as feedstock can provide potential sustainability benefits over conventional alternatives, but requires further development especially in case of biomass gasification and pyrolysis processes for fuel production.

Gerber and colleagues integrated the LCA methodology in thermo-economic process models for the conceptual design of a combined fuel and electricity production from lignocellulosic biomass.[113] They formulated the LCI as a function of the design variables of the thermo-economic model and used a multi-objective optimisation algorithm to consider the environmental performance calculated by LCIA together with thermo-economic indicators as objectives functions in the process optimisation at an early stage of the process synthesis.

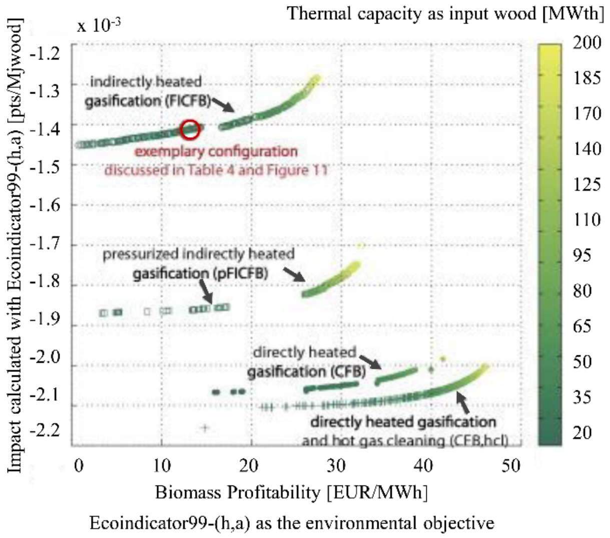


Figure 15: Results of multi-objective optimisation using the Eco-Indicator 99 impact as the environmental objective, biomass profitability as the economic objective, at multiple scale[113] reprinted with permission from Elsevier.

They argued that with a classical LCA approach, changes in process configuration or design conditions, effects of process integration, future installation size and technology evolution are often not considered or cannot be evaluated. Thus, typically only a few scenarios based on average technologies are discussed. The results of the study showed a non-correspondence of the thermodynamic optimum with the environmental optima, determined by means of the Eco-Indicator 99[16] method(figure 15). The energy service substitution and therefore the increase in energy efficiency were key points for the reduction of environmental impacts, especially in case of a process producing multiple energy services. The results of the multi-objective optimisation further highlighted the importance of the impact caused by logistics, auxiliary materials and off-site emissions associated with the process operation which are usually not accounted in a process design considering only thermo-economic objectives.

The optimal design and operation of a hydrocarbon bio-refinery via fast pyrolysis, hydrotreating and hydrocracking for crude bio-oil production was investigated by Gebreslassie and colleagues.[64] The authors applied a model that seeks to maximise the economic performance measured by the net present value (NPV) and to minimise the environmental impacts, described by means of the LCIA category GWP in a gate-to-gate analysis. The Pareto curve in figure 16 shows the optimal trade-off of several designs of the hydrocarbon bio-refinery. Each Pareto point represents an optimal design strategy for the hydro-carbon bio-refinery with a trade-off between the economic and environmental criteria NPV and GWP. As shown in Figure 16, relative to the maximum NPV design (point C), the global GWP can be reduced to 63 % at the expense of decreasing the NPV by 43 %. In the other direction, the NPV is increased if GWP is increased as well.At the trade-off point B, the best compromise between these contradictory objectives were found. The study was complemented by an extended model of the bio-refinery including a number of major processing stages, such as drying of the cellulosic biomass feedstocks, the air separation unit, gasification, syngas conditioning, the Fischer-Tropsch synthesis, hydroprocessing, power generation, and the diesel and gasoline production.[68]

These examples together with the case studies of utilising biomass under harsh process conditions, as discussed before, provide a mixed message. The life cycle step of agricultural biomass generation is most often connected with significant environmental impacts, dominating the overall LCA balance.

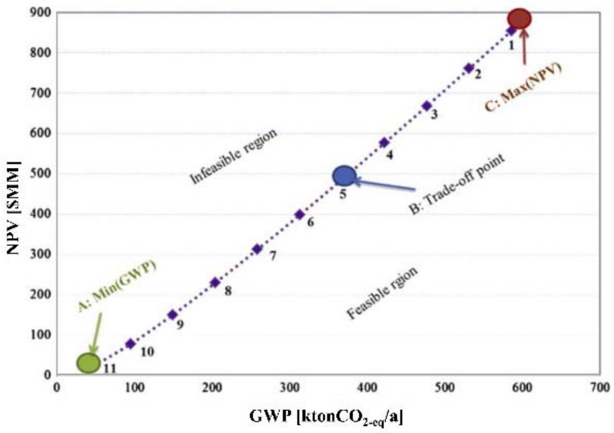


Figure 16: Pareto optimal curve for a hydrocarbon bio refinery[64] reprinted with permission from Elsevier.

Thus, careful process optimisation for high material and energy efficiency is required to come up with the best trade-off. MCDM and MOO are tools of high value bringing forward today`s approaches for biomass utilisation.

LCA for Green Pharmaceutical Processes

Within the last years, also the life cycles of pharmaceuticals have become a concern for many environmental scientists. However, so far only a few studies exist, since detailed production data on pharmaceuticals are not publicly available and their production parameters are usually kept confidential. Nevertheless, the following studies provided important insights into the optimisation potential of existing pharmaceutical production processes.

LCA Investigation of an Established API Production Process
The complex synthesis of a pharmaceutical compound produced by F. Hoffmann-La Roche in Basel was analysed in a cradle-to- -gate LCA by Wernet and colleagues.[114] As major contributors to the environmental impacts of this process, resource consumption and emissions from energy production were found. Process emissions from the pharmaceutical manufacturing plant itself were less of a concern. The LCIA results found by applying several LCIA methods such as CED, GWP, Eco-Indicator 99, UBP-97 and ReCiPe in parallel are in line with the considerable efforts required for the complex synthesis and the complexity of the pharmaceutical production, as compared to a basic chemical production. Thus, a difference of up to and sometimes over two orders of magnitude between basic chemical and pharmaceutical production impacts was forecasted based on the results of this study. The difference was explained by the greater complexity of API molecules, the higher demands of the complex synthesis processes, and the shorter development times of APIs, allowing less time for optimisation of the processes.

Exergetic LCA of API Production
Van der Vorst *et al.*[27, 28] performed an exergetic LCA of a Galantamine·HBr synthesis for anti-Alzheimer medication produced by Johnson & Johnson. They explored the potential environmental improvements within the established synthesis of the API. At this, thermodynamics and a systematic data inventory methodology for the quantification of the resource efficiency were emerged into impact value exergy loss, or CEENE, per mol API for fast benchmarking and evaluation. The first synthesis pathway included nine synthesis steps. In the second generation of the process, the fourth and fifth synthesis steps were optimised by replacing a solvent and by improving the efficiency of both steps (see figure 17).

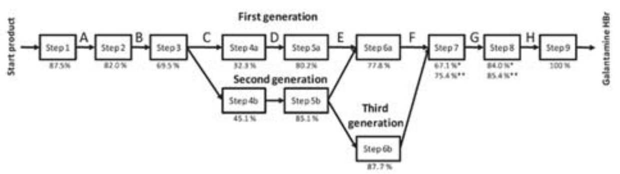


Figure 17: Synthesis steps and their yields for the production of Galantamine·HBr evaluated by the LCA indicator CEENE[15] reproduced with permission from The Royal Society of Chemistry.

Particularly the solvent switch had an effect on the reduction of resource requirements. In the third generation of the process pathway optimisation, the sixth step was replaced by a continuous process using a flow reactor. The increased resource efficiency by changing from first till third generation resulted in a reduction of the overall resource consumption up to 41 %, realised by new chemistry in combination with flow processing.

Case Study of LCA-based MCDM for API Process Re-Design
Recently, Ott and colleagues[73] published the first comparative LCA applied as MCDM tool within pharmaceutical process optimisation and intensification. A low volume, high value active pharmaceutical ingredient production process at Sanofi was re-designed by a transfer from batch to continuous processing in combination with an alternative catalytic system. In order to provide decision support, different existing as well as hypothetical process options were evaluated regarding their environmental impacts and costs[115] to identify bottlenecks and improvement potentials for further process development activities. The results of the LCIA using ReCiPe pointed out saving potentials of 765 kg CO_2 equivalents (GWP) and 65 kg Fe equivalents (MDP) per kg API by transition from the conventional API manufacturing process (scenario AP) at Sanofi to the best case within the analysed process evaluation scenarios. This outcome was complemented by cost saving potentials of 33 %. A multi-criteria outranking of API production alternatives investigated in this study concerning the resulting eco-efficiency is shown in figure 18.

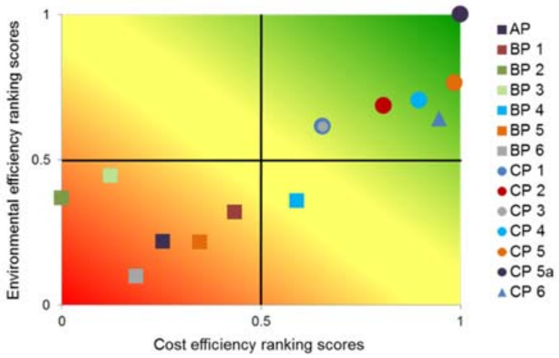


Figure 18: Multi-criteria outranking of API production alternatives according to their environmental and cost efficiency compared to the existing process AP; criteria weights: equal, linear minimisation of LCIA criteria and costs[73] reproduced with permission from The Royal Society of Chemistry.

These case studies show that the high effort required in case of LCA studies of complex pharmaceutical processes is justified by the substantial improvement potentials towards greener processing in this sector. Although the application of LCA metrics is still not widespread practiced in pharmaceutical industry, the use is more widespread today than a decade ago in order to, *e.g.*, compare different chemical routes, assess and select materials or to perform holistic LCAs of products, see also examples collected by Jiménez-González and Overcash.[116]

LCA Applied in the Nanotechnology Sector

Nanotechnology is widely cited as “the defining technology for the 21st century”.[117, 118] The broad-impact nanotechnology sector offers advantages, but probably can also cause serious problems regarding environmental aspects within the life cycle of engineered nanomaterials, nanoproducts or nanostructured materials (as defined in, *e.g.*, Som *et al*. [119]).

Case Study of Multi-Walled Carbon Nanotubes

Griffiths *et al.*[120] published the first LCA study dealing with the growth of multi-walled carbon nanotubes (MWNTs) *via* catalytic chemical vapor deposition in a high-temperature process (T = 790°C). They used several data sources such as experimental investigations, process simulation as well as the ecoinvent database to be able to perform the study early in the development phase. Again, ReCiPe was used as LCIA method. The process was evaluated on laboratory scale by means of a cradle to-gate approach. The synthetic routes of the reactants, the process energy inputs, the equipment infrastructure and the resulting emissions were considered to determine the environmental impacts of the MWNTs. The results clearly show the high impact of energy demand for furnace electricity in the process as well as the infrastructure required at today`s state of development causes high environmental impacts. Thus, excellent performance of MWNTs in application as well as a significant increase in the overall processing efficiency during the scale-up of the MWNT generation is required in order to justify their application compared to alternative materials.

Case Study of Fullerenes

Anctil and colleagues[121] compared two energy demanding synthesis pathways of C60 and C70 fullerenes, *via* pyrolysis and plasma technique, in a cradle-to-gate LCA analysis. But, due to the unknown nature of carbon emissions from the pyrolysis process, they decided to compare the production methods not by means of typical LCIA categories, but calculated the embodied energy (the total of all direct and indirect energy inputs) of alternative fullerene production pathways. The results point out that the embodied energy mainly depend on how the carbon precursor is transformed into the desired fullerenes. Four synthesis methods were analysed: pyrolysis with either tetralin (1,2,3,4-tetrahydronaphthalene) or toluene as feedstock and radio frequency or arc plasma with graphite as a feedstock. The resulting carbon emissions depended on the specific process conditions, in particular from the temperature profile in the reactor, the precursor used, and the amount of oxygen. The pyrolysis of 1,4-tetrahydronaphthalene revealed to be the method with the lowest embodied energy (12.7 GJ/kg C60). Furthermore, the pyrolysis methods investigated had a much lower energy impact than the plasma methods by nearly one order of magnitude due to the lower amount of electricity required. Depending on the necessary purification level, the embodied energy for separation was found to additionally increase by at least a factor of 5 for high purity fullerenes (>98% by wt.). In conclusion, the life-cycle based study provided valuable hints concerning key factors for improvement of this energy-intensive process, although no established LCIA indicators were used.

Case Studies of Nanoparticles and Nanofibers

Walser *et al.*[122] performed a cradle-to-grave LCA of the production of nanosilver, its application on textiles (T-shirts) *via* flame spray pyrolysis and plasma polymerisation with silver co-sputtering, the use phase (including 100 washings) and final disposal, considering the LCIA categories GWP, FETP and METP. The results in this study show significant differences in the environmental burdens between different nanoparticle production technologies: Whereas the cradle-to-gate assessment of producing nano-enabled T-shirts by flame spray pyrolysis causes 2.70 kg of CO_2-equiv., the method of plasma sputtering resulted in 7.67–166 kg of CO_2-equivalents. In contrast, the production of conventional T-shirts with and without a finishing with the biocide triclosan resulted in emissions of 2.55 kg of CO_2-equivalents, whereas the share of triclosan in the resulting environmental impact was marginal. Nevertheless, the use phase of the nanosilver T-shirts, identified as most relevant life cycle stage, can decrease the GWP as compared to conventional (with and without biocidal treatment) clothing, depending on the consumer behaviour: an increased awareness of its biocidal functionality and benefits, and a subsequent change of washing procedures (*e.g.*, changing frequency). Thus, higher environmental impacts during the nanoparticle production must not result *a priori* in a more environmental problematic alternative. Further, the authors described that data on workplace exposure or chronic inhalation toxicity of silver nanoparticles and accompanied potential nano-specific effects are rather scarce. They stated that the development of LCA methodologies for nanomaterials requires the specific assessment of toxic impacts of nanomaterial emissions in the environmental compartments (within all life cycle stages) and suitable metrics for LCI and LCIA (i.e., quantification of output, assessment of its impact) to facilitate the performance of a nanomaterial focused LCA [122], also reported in, *e.g.*, [118, 119, 123].

Figure 19 summarises possibilities and limitations of LCA in the context of engineered nanomaterials.[123] Whereas data on material and energy input of engineered nanomaterials, *e.g.*, carbon nanotubes, carbon nanofibers, nanosilver or nanoscale silica are well covered and also well reported in publications, there is only a partial or no data coverage or information regarding output related data, *e.g.*, emissions to air, water and soil [118], often hindering a holistic LCA covering all life cycle stages.

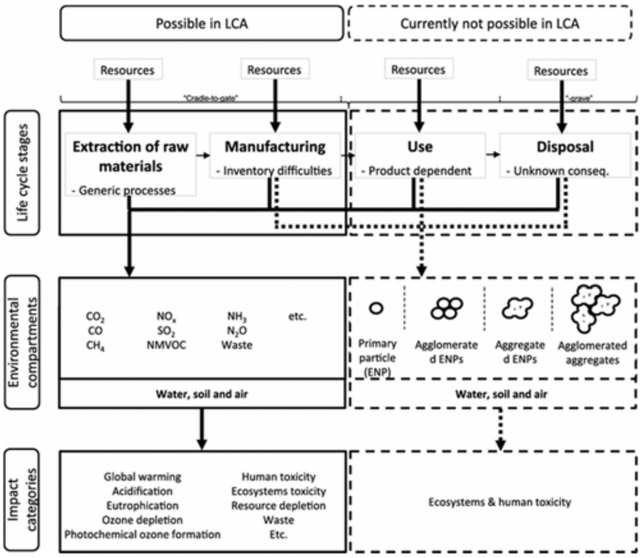


Figure 19: Limitations of LCA of engineered nanomaterials, according to Miseljic *et al*.[123] with kind permission from Springer Science and Business Media.

Hischier *et al*. further pointed out, that in many case studies the use phase of engineered nanomaterials is claimed as "stationary phase", *i.e.*, having no influence on the material or energy consumption in this stage.[118] Though, these life cycle stages can have a significant effect on the overall environmental performance as shown above. As an example, Hischier *et al.* compared the difference in the CED value of carbon nanofibers, polypropylene and steel during material production, composite production and use phase in cars, thus performing a comparison based on functionality issues. The data basis were life cycle studies performed by Khanna and his co-workers, dealing with the life cycle energy consumption and environmental impact from carbon nanofiber and carbon nanofiber composites production as possible replacement for steel in automobile body panels.[124, 125] From a material and composite production point of view, the LCA results indicated (partially significantly) higher life cycle energy intensities and environmental impacts of carbon nanofibers compared to conventional materials such as aluminium and steel. This assessment was based on a kilogram basis (see figure 20).[124] However, by substituting steel by nanocomposite materials in the automobile body panels, the environmental burdens resulting from upstream processes can be significantly reduced due to, *e.g.*, weight reduction, and thus reduced fossil energy consumption.[125]

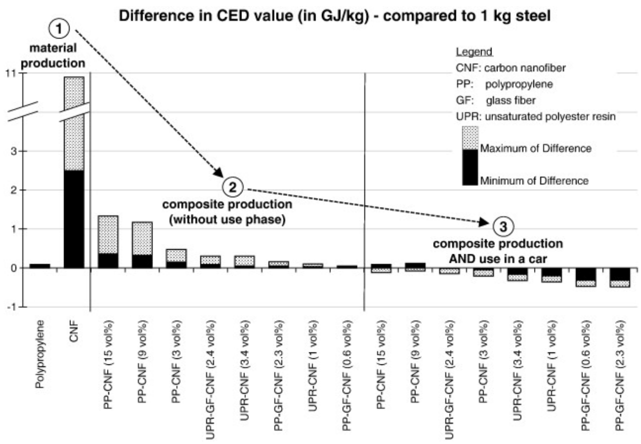


Figure 20: Difference in CED value for material production, composite production and use in cars: carbon nanofiber, polypropylene compared to steel according to Hischier et al.[118] using data from [124, 125] reprinted with permission from Elsevier.

Thus, it is of high importance to evaluate nanomaterials in the context of their entire life cycle (cradle-to-grave LCA) including production, application, (recycling) and disposal in order to quantify their benefits *versus* environmental impacts in a profound comparison against conventional alternative materials.

LCA for Waste Water Treatment

Environmental issues related to wastewater treatment are numerous not only in the context of nanoparticles, and LCA applied to wastewater treatment is a field with approximately twenty years of experience. Corominas *et al.* have published a comprehensive review on this topic.[126] Emerging waste water treatment technologies and techniques are being developed, being already commonly evaluated by means of LCA in order to compare them to the environmental efficiency of conventional technologies, see, *e.g.*,[126-130]. Some examples are given below.

Microbial Fuel and Electrolysis Cells for Waste Water Treatment
Foley and colleagues[129] investigated the use of microbial fuel (MFC) and electrolysis (MEC) cells which gained much attention in the past years as an alternative to conventional wastewater treatment options being claimed as energy intensive and environmentally unfriendly. By comparing these techniques with conventional anaerobic treatment they found out that by applying electrolysis cells the environmental efficiency could be significantly increased, not at least due to the formation of hydrogen peroxide as valuable by-product in a cost-effective way.[129]

Case Study of Nanofiber-Supported Catalysts for Waste Water Treatment
Recently, Yasneva *et al.*[131] published a comparative LCA study investigating the application of a newly developed, carbon nanofiber supported catalyst *versus* a conventional Pd/Al_2O_3 catalyst for the reduction of bromates in waste water. Based on data gathered on experimental scale, they found a considerable decrease of environmental impacts (LCIA methods: CED and CML 2002), mainly due to the decreased amount of catalyst required in the case of the carbon nanofiber-based catalyst.

Despite the supporting function of LCA also in the chemical waste treatment, there are also some drawbacks and challenges to be handled in the future. Corominas *et al.* [126] emphasised the need to develop standardised guidelines to ensure the quality of the LCA methodology application. In addition, the impact assessment methods need to be extended by further human and ecosystem health indicators to avoid problem shifting. Specific materials such as pathogens, pharmaceuticals or nanomaterials have not been integrated in databases yet. Thus, LCA methodologies need to be adapted to these new compounds, and ideally combined with tools like chemical and microbial risk analysis to provide a holistic analysis and decision-making for stakeholders in this sector.[126, 132]

Conclusions

This review emphasises the need and usefulness of LCA approaches applied to chemical process and product design within various fields of research and development. Numerous case studies were presented, dealing with the assessment of applying emerging technologies and procedures, but also the optimisation of conventional processes to support the decision-making in research institutes, industry, governmental and non-governmental organisations. They allowed the profound comparison of alternative concepts and thus provided important support for the development of various green chemical processes and products during the last years.

Depending on the specific questions to be answered by the analysis, different life-cycle approaches (ranging from gate-to-gate to cradle-to-crave) and impact assessment methods were applied. Independent from the LCA software tool, the ecoinvent database[6] was used in most case studies to model LCI data of up- and downstream processes caused by the chemical synthesis under investigation. CML 2002 was found to be the most preferential LCIA method among the users in green chemical process design, whereas the follow-up method ReCiPe was applied so far only in a few studies. It is highly recommended to use this method in future studies (in combination with the latest ecoinvent dataset) in order to improve the actuality, comparability and consistency of LCA studies. The assessment of energy-intensive chemical processes further strongly benefits from the consideration of energy-related impact categories such as CEENE.

However, beside promising opportunities of LCA studies to support green chemical designs, there are also several challenges to be coped with in the future: standardised guidelines in dependency of the specific research field need to be developed in order to ensure the quality of the LCA methodology application.[133] Especially against the background of new emerging technologies such as nanotechnology, more LCI data is required allowing to consider the whole life cycle. LCIA assessment has to be extended by impact factors for a wider range of chemical and pharmaceutical compounds. Furthermore, only a few studies reported about sensitivity and/or uncertainty analyses or disclosed the quality of their database. Thus, standardised methods for data gap or uncertainty handling as well as common rules for sensitivity analyses are urgently required. Those measures would significantly improve the comparability and reliability of the wide range of studies dealing with chemical product or process design and implementation.

Abbreviations

API - Active pharmaceutical ingredient
CC - Climate Change
CED - Cumulative Energy Demand
CExD - Cumulative Exergy Demand
CEENE - Cumulative Exergy Extraction from the Natural Environment
CML - Institute of Environmental Sciences, University of Leiden, The Netherlands
EHS - Environmental, health and safety
GWP - Global Warming Potential
HTP - Human Toxicity Potential
IPCC - Intergovernmental Panel on Climate Change
LCI - Life Cycle Inventory
LCIA - Life Cycle Impact Assessment
LCA - Life Cycle Assessment
LCC - Life Cycle Costing
MCDM - Multi-criteria decision making
MOO - Multi-objective optimisation
MWNT - Multi-walled carbon nanotubes
NPV - Net present value
PI – Process Intensification
R&D - Research and development
SLCA – Simplified Life Cycle Assessment

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Notes and References

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1. *EN ISO 14040*, International Organisation for Standardisation, Geneva, 2006.
2. *EN ISO 14044*, International Organisation for Standardisation, Geneva, 2006.
3. L. Jacquemin, P.-Y. Pontalier and C. Sablayrolles, *International Journal of Life Cycle Assessment,* 2012, **17**, 1028-1041.
4. J. B. Guinee, R. Heijungs, G. Huppes, A. Zamagni, P. Masoni, R. Buonamici, T. Ekvall and T. Rydberg, *Environmental Science & Technology*, 2011, **45**, 90-96.
5. Deutsches Institut für Normung e.V., Beuth Verlag GmbH, Berlin, 2006.
6. Ecoinvent, v3.1, Ecoinvent Centre, Swiss Centre for Life Cycle Inventories, Dübendorf, Switzerland, 2014.
7. A. Azapagic and R. Clift, *International Journal of Life Cycle Assessment,* 1999, **4**, 357-369.
8. A. Azapagic and R. Clift, *International Journal of Life Cycle Assessment,* 2000, **5**, 31-36.

9. M. A. Curran, *International Journal of Life Cycle Assessment*, 2006, **12**, 65-78.
10. M. Goedkoop, R. Heijungs, M. Huijbregts, A. D. Schryver, J. Struijs and R. v. Zelm, *ReCiPe 2008 - A life cycle impact assessment method which comprises harmonised category indicators at the midpoint and the endpoint level*, Ministerie van Volkshuisvesting, Ruimtelijke Ordering en Milieubeheer, Den Hague, 2013.
11. M. Hauschild, M. Goedkoop, J. Guinée, R. Heijungs, M. Huijbregts, O. Jolliet, M. Margni, A. Schryver, S. Humbert, A. Laurent, S. Sala and R. Pant, *International Journal of Life Cycle Assessment*, 2013, **18**, 683-697.
12. J. Buchgeister, *Umwelt-Medizin-Gesellschaft*, 2012, **25**, 12-21.
13. W. Klöpffer and B. Grahl, *Ökobilanz (LCA)*, WILEY-VCH Verlag GmbH & Co kGaA, Weinheim, 2009.
14. J. B. G. Guinée, M.; Heijungs, R.; Huppes, G.; Kleijn, R.; Koning, A. de; Oers, L. van; Wegener Sleeswijk, A.; Suh, S.; Udo de Haes, H.A.; Bruijn, H. de; Duin, R. van; Huijbregts, M.A.J. , *Handbook on life cycle assessment. Operational guide to the ISO standards*, Kluwer Academic Publishers, Dordrecht, 2002.
15. O. Jolliet, M. Margni, R. Charles, S. Humbert, J. Payet, G. Rebitzer and R. Rosenbaum, *International Journal of Life Cycle Assessment*, 2003, **8**, 324-330.
16. M. Goedkoop and R. Spriensma, *Eco-indicator 99 Manual for Designers*, Ministry of Housing, Spatial Planning and the Environment, Den Haag, 2000.
17. P. Forster, V. Ramaswamy, P. Artaxo, T. Berntsen, R. Betts, D.W. Fahey, J. Haywood, J. Lean, D.C. Lowe, G. Myhre, J. Nganga, R. Prinn, G. Raga, M. Schulz and R. Van Dorland, in *Climate Change 2007: The Physical Science Basis. Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change*, ed. S. Solomon, D. Qin, M. Manning, Z. Chen, M. Marquis, K.B. Averyt, M.Tignor and H.L. Miller, Cambridge University Press, Cambridge, 2007.
18. S. Solomon, D. Qin, M. Manning, Z. Chen, M. Marquis, K.B. Averyt, M. Tignor and H.L. Miller (eds.), *Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change*, Intergovernmental Panel on Climate Change, Cambridge, United Kingdom and New York, NY, USA., 2007.
19. R. Frischknecht, R. Heijungs and P. Hofstetter, *International Journal of Life Cycle Assessment*, 1998, **3**, 266-272.
20. *Cumulative Energy Demand - Terms, Definitions, Methods of Calculation*, VDI, Düsseldorf, 1999.
21. M. A. J. Huijbregts, S. Hellweg, R. Frischknecht, H. W. M. Hendriks, K. Hungerbühler and A. J. Hendriks, *Environmental Science & Technology*, 2010, **44**, 2189-2196.
22. M. A. J. Huijbregts, L. J. A. Rombouts, S. Hellweg, R. Frischknecht, A. J. Hendriks, D. van de Meent, A. M. J. Ragas, L. Reijnders and J. Struijs, *Environmental Science & Technology*, 2005, **40**, 641-648.
23. G. Wernet, S. Hellweg, U. Fischer, S. Papadokonstantakis and K. Hungerbühler, *Environmental Science & Technology*, 2008, **42**, 6717-6722.
24. G. Wernet, S. Papadokonstantakis, S. Hellweg and K. Hungerbuhler, *Green Chemistry*, 2009, **11**, 1826-1831.
25. M. Bösch, S. Hellweg, M. J. Huijbregts and R. Frischknecht, *International Journal of Life Cycle Assessment*, 2007, **12**, 181-190.
26. J. Dewulf, M. E. Boesch, M. B. De, d. V. G. Van, L. H. Van, S. Hellweg and M. A. J. Huijbregts, *Environmental Science & Technology*, 2007, **41**, 8477-8483.
27. G. Van der Vorst, J. Dewulf, W. Aelterman, W. B. De and L. H. Van, *Environmental Science & Technology*, 2011, **45**, 3040-3046.
28. G. Van der Vorst, W. Aelterman, W. B. De, B. Heirman, L. H. Van and J. Dewulf, *Green Chemistry*, 2013, **15**, 744-748.
29. D. Kralisch, I. Streckmann, D. Ott, U. Krtschil, E. Santacesaria, M. Di Serio, V. Russo, L. De Carlo, W. Linhart, E. Christian, B. Cortese, M. H. J. M. de Croon and V. Hessel, *ChemSusChem*, 2012, **5**, 300-311.
30. S. Kressirer, D. Kralisch, A. Stark, U. Krtschil and V. Hessel, *Environmental Science & Technology,* 2013, **47**, 5362-5371.
31. M. A. J. Huijbregts, U. Thissen, T. Jager, D. van de Meent and A. M. J. Ragas, *Chemosphere*, 2000, **41**, 575-588.
32. M. J. Huijbregts, G. Norris, R. Bretz, A. Ciroth, B. Maurice, B. von Bahr, B. Weidema and A. H. de Beaufort, *International Journal of Life Cycle Assessment*, 2001, **6**, 127-132.
33. B. P. Weidema and M. S. Wesnæs, *Journal of Cleaner Production*, 1996, **4**, 167-174.
34. D. Kralisch, in *Green Chemistry Metrics*, John Wiley & Sons, Ltd, 2009, pp. 248-271.
35. M. Pehnt, *Renewable Energy*, 2006, **31**, 55-71.
36. G. Finnveden, M. Z. Hauschild, T. Ekvall, J. Guinee, R. Heijungs, S. Hellweg, A. Koehler, D. Pennington and S. Suh, *Journal of Environmental Management*, 2009, **91**, 1-21.
37. J. A. Assies, *Journal of Hazardous Materials*, 1998, **61**, 23-29.
38. C. Hendrickson, A. Horvath, S. Joshi and L. Lave, *Environmental Science & Technology*, 1998, **32**, 184A-191A.
39. S. Suh, M. Lenzen, G. J. Treloar, H. Hondo, A. Horvath, G. Huppes, O. Jolliet, U. Klann, W. Krewitt, Y. Moriguchi, J. Munksgaard and G. Norris, *Environmental Science & Technology*, 2003, **38**, 657-664.
40. D. Russo and C. Rizzi, *Computers in Industry*, 2014, **65**, 470-479.
41. Z. Cui, F. Meng, J. Hong, X. Li and X. Ren, *Journal of Bioscience and Bioengineering*, 2012, **113**, 765-770.
42. A. Stark, S. Huebschmann, M. Sellin, D. Kralisch, R. Trotzki and B. Ondruschka, *Chemical Engineering & Technology*, 2009, **32**, 1730-1738.
43. K. Christiansen, N. van den Berg, R. Haydock, M. ten Houten, S. Kotaji, E. Oerlemans, W.-P. Schmidt, H. K. Stranddorf, A. Weidenhaupt, P.R. White, *Simplifying LCA: Just a Cut?*, Society of Environmental Toxicology and Chemistry Europe, Brussels, 1997.
44. T. Hur, J. Lee, J. Ryu and E. Kwon, *Journal of Environmental Management*, 2005, **75**, 229-237.
45. A. D. Curzons, C. Jimenez-Gonzalez, A. L. Duncan, D. J. C. Constable and V. L. Cunningham, *International Journal of Life Cycle Assessment*, 2007, **12**, 272-280.
46. G. Rebitzer and D. Hunkeler, *International Journal of Life Cycle Assessment*, 2003, **8**, 253-256.
47. I. Sell, D. Ott and D. Kralisch, *ChemBioEng Reviews*, 2014, **1**, 50-56.
48. C. Benoît, G. Norris, S. Valdivia, A. Ciroth, A. Moberg, U. Bos, S. Prakash, C. Ugaya and T. Beck, *International Journal of Life Cycle Assessment*, 2010, **15**, 156-163.
49. D. Meyer and V. K. Upadhyayula, *Clean Technologies and Environmental Policy*, 2014, **16**, 757-772.
50. G. Koller, U. Fischer and K. Hungerbühler, *Industrial & Engineering Chemistry Research*, 2000, **39**, 960-972.

51. H. F. Sugiyama, U. Hungerbühler, K., ETH Zurich, Safety & Environmental Technology Group, Zurich, Switzerland, 2006.
52. H. Sugiyama, U. Fischer, K. Hungerbühler and M. Hirao, *AIChE Journal*, 2008, **54**, 1037-1053.
53. A. D. Bojarski, G. Guillen-Gosalbez, L. Jimenez, A. Espuna and L. Puigjaner, *Industrial & Engineering Chemistry Research*, 2008, **47**, 8286-8300.
54. T. L. Saaty, *The Analytic Hierarchy Process: Planning, Priority Setting, Resource Allocation*, McGraw-Hill, 1980.
55. T. L. Saaty and N. Begicevic, *International Journal of Economics and Business Research*, 2012, **4**, 266-283.
56. B. Roy, *La Revue d'Informatique et de Recherche Opérationelle (RIRO)*, 1968, **8**, 57-75.
57. J. P. Brans and P. Vincke, *Management Science*, 1985, **31**, 647-656.
58. M. Behzadian, R. B. Kazemzadeh, A. Albadvi and M. Aghdasi, *European Journal of Operational Research*, 2010, **200**, 198-215.
59. A. Azapagic and S. Perdan, *International Journal of Sustainable Development & World Ecology*, 2005, **12**, 98-111.
60. A. Azapagic and S. Perdan, *International Journal of Sustainable Development & World Ecology*, 2005, **12**, 112-131.
61. V. Polshettiwar and R. S. Varma, Non-conventional energy sources for green synthesis in water (microwave, ultrasound, and photo), 2010.
62. D. Bouyssou, in *Encyclopedia of Optimization*, eds. C. A. Floudas and P. M. Pardalos, Springer US, 2009, ch. 495, pp. 2887-2893.
63. D. Kralisch, D. Reinhardt and G. Kreisel, *Green Chemistry*, 2007, **9**, 1308-1318.
64. B. H. Gebreslassie, M. Slivinsky, B. Wang and F. You, *Computers & Chemical Engineering*, 2013, **50**, 71-91.
65. V. Pareto, *Cours D´Economie Politique, Lausanne*, 1896.
66. A. Ouattara, L. Pibouleau, C. Azzaro-Pantel, S. Domenech, P. Baudet and B. Yao, *Computers & Chemical Engineering*, 2012, **36**, 174-188.
67. L. Gerber, S. Fazlollahi and F. Marechal, *Computers & Chemical Engineering*, 2013, **59**, 2-16.
68. B. Wang, B. H. Gebreslassie and F. You, *Computers & Chemical Engineering*, 2013, **52**, 55-76.
69. F. You, L. Tao, D. J. Graziano and S. W. Snyder, *AIChE Journal*, 2012, **58**, 1157-1180.
70. D. Cerri, M. Taisch and S. Terzi, in *Advances in Production Management Systems. Competitive Manufacturing for Innovative Products and Services*, eds. C. Emmanouilidis, M. Taisch and D. Kiritsis, Springer Berlin Heidelberg, 2013, vol. 397, ch. 49, pp. 391-396.
71. A. Azapagic and R. Clift, *Journal of Cleaner Production*, 1999, **7**, 135-143.
72. D. Kralisch, D. Ott, S. Kressirer, C. Staffel, I. Sell, U. Krtschil and P. Loeb, *Green Processing and Synthesis*, 2013, **2**, 465–478.
73. D. Ott, D. Kralisch, I. Denčic, V. Hessel, Y. Laribi, P. D. Perrichon, C. Berguerand, L. Kiwi-Minsker and P. Loeb, *ChemSusChem*, 2014, doi: 10.1002/cssc.201402313.
74. P. Saling, in *Karlsruher Schriften zur Geographie und Ökologie*, 2007, vol. 22, pp. 1-115.
75. D. Kolsch, P. Saling, A. Kicherer, A. Grosse-Sommer and I. Schmidt, *International Journal of Sustainable Development*, 2008, **11**, 1-23.
76. D. Kralisch, C. Staffel, D. Ott, S. Bensaid, G. Saracco, P. Bellantoni and P. Loeb, *Green Chemistry*, 2013, **15**, 463-477.
77. v. H. A. Kalkeren, A. L. Blom, F. P. J. T. Rutjes and M. A. J. Huijbregts, *Green Chemistry*, 2013, **15**, 1255-1263.
78. O. G. Griffiths, R. E. Owen, J. P. O'Byrne, D. Mattia, M. D. Jones and M. C. McManus, *RSC Advances*, 2013, **3**, 12244-12254.
79. A. L. Roes and M. K. Patel, *Journal of Cleaner Production*, 2011, **19**, 1659-1667.
80. S. Kressirer, L. N. Protasova, M. H. J. M. de Croon, V. Hessel and D. Kralisch, *Green Chemistry*, 2012, **14**, 3034-3046.
81. Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH Verlag GmbH & Co. KGaA, 7th Edition, Weinheim, 2009.
82. T. Polen, M. Spelberg and M. Bott, *Journal of Biotechnology*, 2013, **167**, 75-84.
83. Q. Wang, I. Vural-Gürsel, M. Shang and V. Hessel, *Chemical Engineering Journal*, 2013, **234**, 300-311.
84. J. B. J. H. van Duuren, B. Brehmer, A. E. Mars, G. Eggink, V. A. P. M. dos Santos and J. P. M. Sanders, *Biotechnology and Bioengineering*, 2011, **108**, 1298-1306.
85. S. Huebner, S. Kressirer, D. Kralisch, C. Bludszuweit-Philipp, K. Lukow, I. Jänich, A. Schilling, H. Hieronymus, C. Liebner and K. Jähnisch, *ChemSusChem*, 2012, **5**, 279-288.
86. F. Schneider, T. Szuppa, A. Stolle, B. Ondruschka and H. Hopf, *Green Chemistry*, 2009, **11**, 1894-1899.
87. C. M. McLoughlin, W. A. M. McMinn and T. R. A. Magee, *Food and Bioproducts Processing*, 2000, **78**, 90-96.
88. H. K. Solanki, V. D. Prajapati and G. K. Jani, *International Journal of PharmTech Research*, 2010, **2**, 1754-1761.
89. N. G. Patil, A. I. G. Hermans, F. Benaskar, E. Rebrov, J. Meuldijk, L. A. Hulshof, V. Hessel and J. C. Schouten, *AIChE Journal*, 2012, **58**, 3144-3155.
90. C. Capello, U. Fischer and K. Hungerbuhler, *Green Chemistry*, 2007, **9**, 927-934.
91. C. Capello, S. Hellweg and K. Hungerbuehler, *Journal of Industrial Ecology*, 2008, **12**, 111-127.
92. C. Capello, S. Hellweg, B. Badertscher, H. Betschart and K. Hungerbuehler, *Journal of Industrial Ecology*, 2007, **11**, 26-38.
93. A. Amelio, G. Genduso, S. Vreysen, P. Luis and B. Van der Bruggen, *Green Chemistry*, 2014, **16**, 3045-3063.
94. C. S. Slater, M. J. Savelski, T. M. Moroz and M. J. Raymond, *Green Chemistry Letters and Reviews*, 2011, **5**, 55-64.
95. Y. Gaber, U. Tornvall, M. A. Kumar, M. Ali Amin and R. Hatti-Kaul, *Green Chemistry*, 2011, **13**, 2021-2025.
96. P. Luis, A. Amelio, S. Vreysen, V. Calabro and B. Bruggen, *International Journal of Life Cycle Assessment*, 2013, **18**, 1048-1061.
97. R. Hischier, *The method of ecological scarcity (Umweltbelastungspunkte, UBP`97), Implementation of Life Cycle Impact Assessment methods*, EMPA, Dübendorf, 2004.
98. *Handbook of Green Chemistry - Green Solvents*, eds. P. Wasserscheid and A. Stark, Wiley-VCH Verlag GmbH & Co. KGaA, 2010.
99. Y. Zhang, B. R. Bakshi and E. S. Demessie, *Environmental Science & Technology*, 2008, **42**, 1724-1730.
100. D. Reinhardt, F. Ilgen, D. Kralisch, B. Konig and G. Kreisel, *Green Chemistry*, 2008, **10**, 1170-1181.
101. D. Kralisch, A. Stark, S. Koersten, G. Kreisel and B. Ondruschka, *Green Chemistry*, 2005, **7**, 301-309.
102. D. Kralisch and G. Kreisel, *Chemical Engineering Science*, 2007, **62**, 1094-1100.

103. S. Huebschmann, D. Kralisch, H. Loewe, D. Breuch, J. H. Petersen, T. Dietrich and R. Scholz, *Green Chemistry*, 2011, **13**, 1694-1707.
104. S. Huebschmann, D. Kralisch, V. Hessel, U. Krtschil and C. Kompter, *Chemical Engineering & Technology*, 2009, **32**, 1757-1765.
105. V. Hessel, *Chemical Engineering & Technology*, 2009, **32**, 1655-1681.
106. V. Hessel, D. Kralisch, N. Kockmann, T. Noël and Q. Wang, *ChemSusChem*, 2013, **6**, 746-789.
107. U. Krtschil, V. Hessel, P. Loeb, D. Reinhard, S. Huebschmann and D. Kralisch, *Chemical Engineering Journal*, 2011, **167**, 510-518.
108. S. Kressirer, D. Kralisch, A. Stark, U. Krtschil, V. Hessel, *Environmental Science & Technology*, 2013.
109. S. Morais, T. M. Mata, A. A. Martins, G. A. Pinto and C. A. V. Costa, *Journal of Cleaner Production*, 2010, **18**, 1251-1259.
110. R. Sawangkeaw, S. Teeravitud, P. Piumsomboon and S. Ngamprasertsith, *Bioresource Technology*, 2012, **120**, 6-12.
111. D. Kusdiana and S. Saka, *Fuel*, 2001, **80**, 693-698.
112. A. D. Patel, K. Meesters, H. den Uil, E. de Jong, E. Worrell and M. K. Patel, *ChemSusChem*, 2013, **6**, 1724-1736.
113. L. Gerber, M. Gassner and F. Maréchal, *Computers & Chemical Engineering*, 2011, **35**, 1265-1280.
114. G. Wernet, S. Conradt, H. Isenring, C. Jiménez-González and K. Hungerbühler, *International Journal of Life Cycle Assessment*, 2010, **15**, 294-303.
115. I. Dencic, D. Ott, D. Kralisch, T. Noel, J. Meuldijk, M. De Croon, V. Hessel, Y. Laribi and P. Perrichon, *Organic Process Research & Development*, 2014.
116. C. Jimenez-Gonzalez and M. R. Overcash, *Green Chemistry*, 2014, **16**, 3392-3400.
117. A. Arnall and D. Parr, *Technology in Society*, 2005, **27**, 23-38.
118. R. Hischier and T. Walser, *Science of The Total Environment*, 2012, **425**, 271-282.
119. C. Som, M. Berges, Q. Chaudhry, M. Dusinska, T. F. Fernandes, S. I. Olsen and B. Nowack, *Toxicology*, 2010, **269**, 160-169.
120. O. G. Griffiths, J. P. O'Byrne, L. Torrente-Murciano, M. D. Jones, D. Mattia and M. C. McManus, *Journal of Cleaner Production*, 2013, **42**, 180-189.
121. A. Anctil, C. W. Babbitt, R. P. Raffaelle and B. J. Landi,Environmental Science & Technology, 2011, **45**, 2353-2359.
122. T. Walser, E. Demou, D. J. Lang and S. Hellweg, *Environmental Science & Technology*, 2011, **45**, 4570-4578.
123. M. Miseljic and S. Olsen, *Journal of Nanoparticle Researc*h, 2014, **16**, 1-33.
124. V. Khanna, B. R. Bakshi and L. J. Lee, *Journal of Industrial Ecology*, 2008, **12**, 394-410.
125. V. Khanna and B. R. Bakshi, *Environmental Science & Technology*, 2009, **43**, 2078.
126. L. Corominas, J. Foley, J. S. Guest, A. Hospido, H. F. Larsen, S. Morera and A. Shaw, *Water Research*, 2013, **47**, 5480-5492.
127. J. Foley, D. de Haas, K. Hartley and P. Lant, *Water Research*, 2010, **44**, 1654-1666.
128. I. Muñoz, J. Rieradevall, F. Torrades, J. Peral and X. Domènech, *Solar Energy*, 2005, **79**, 369-375.
129. J. M. Foley, R. A. Rozendal, C. K. Hertle, P. A. Lant and K. Rabaey, *Environmental Science & Technology*, 2010, **44**, 3629-3637.
130. N. Tangsubkul, K. Parameshwaran, S. Lundie, A. G. Fane and T. D. Waite, *Journal of Membrane Science*, 2006, **284**, 214-226.
131. P. Yaseneva, C. F. Marti, E. Palomares, X. Fan, T. Morgan, P. S. Perez, M. Ronning, F. Huang, T. Yuranova, L. Kiwi-Minsker, S. Derrouiche and A. A. Lapkin, *Chemical Engineering Journal*, 2014, **248**, 230-241.
132. S. Renou, J. S. Thomas, E. Aoustin and M. N. Pons, *Journal of Cleaner Production*, 2008, **16**, 1098-1105.
133. M. A. Curran, *Life Cycle Assessment Handbook: A Guide for Environmentally Sustainable Products*, Wiley, 2012.