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Green Chemistry

Cutting-edge research for a greener sustainable future

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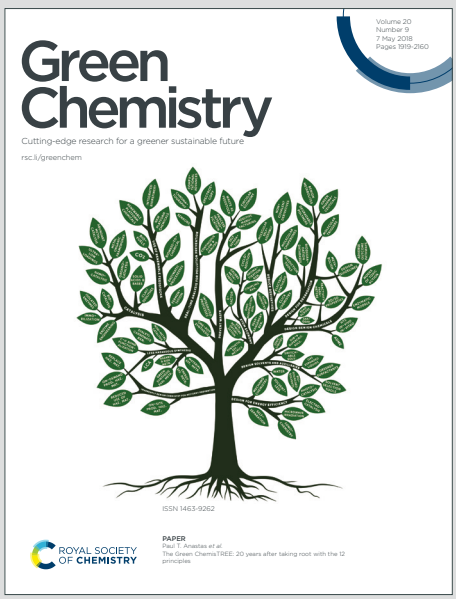

ROYAL SOCIETY OF CHEMISTRY

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Green Foundation Box

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1. What advances in green chemistry have been discussed?

   The development of twelve fundamental principles of Life Cycle Assessment (LCA) applied to chemicals can support practitioners in the field of green chemistry in adopting the LCA methodology to guide and enhance their research.

2. What makes the area of study of significant wider interest?

   LCA is a versatile tool; therefore, all branches of chemistry and chemical engineering may benefit from understanding the procedural approach needed to correctly apply the life cycle perspective within the discipline of green chemistry.

3. What will the future of this field hold, and how will the insight in your review help shape green chemistry science?

   Innovation from a life cycle perspective is aimed at embracing all dimensions of sustainability—environmental, social, and economic. I hope that proposing 12 fundamental principles of LCA applied to chemiclas may help in assessing the potential of new reactions from the outset, in line with one of the core pillars of green chemistry: benign by design.

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PERSPECTIVES

A proposal for twelve principles for LCA of chemicals

Daniele Cespi,*[a,b]

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Green chemistry, gained prominence after the publication of its 12 fundamental principles. Life Cycle Assessment (LCA) complements green chemistry by evaluating environmental impacts during the entire life cycle of products or part of it (cradle to gate). This perspective proposes 12 principles for LCA of chemicals a list of issues that should be addressed by the LCA practitioner, in a procedural way, in order to apply correctly the life cycle perspective within the green chemistry discipline.

Green chemistry is right now a well-established concept, spread around the World and consolidated among the variety of chemical disciplines. The term was first coined by Paul T. Anastas in 1991. However, it gains more relevance after the publication of the 12 fundamental principles in 1998.[1]
Those principles represent a recommendation for synthetic and industrial chemists, guiding them in performing more sustainable research activities in the field of chemistry.
Similarly, the life cycle thinking approach is gaining increasing attention within the chemical community due to its ability to be applied to syntheses, processes, and their components in order to identify inefficiencies and explore alternative solutions. The life cycle perspective represents a complex set of different tools which can be used singularly or in combination (in a life cycle sustainability perspective). Among those the Life Cycle Assessment (LCA) represents the more consolidated, since the oldest and thanks to its standardization.[2,3] It addresses the potential environmental impacts of products and systems in a cradle to grave approach, from raw material extraction up to the end-of-life (EoL) stage, by considering several impact categories oriented at the environmental problem (e.g., climate change potential, acidification potential, etc.) or at the damage to the final receptors (i.e., human health, ecosystem quality and resources consumption).
As highlighted by Gilbertson et al.,[4] "green chemistry looks at the entire life cycle through the application of a set of principles to optimize the design". Therefore, a strong connection between the green chemistry and LCA exists.
However, while green chemistry promotes the adoption of key principles to guide research towards more sustainable practices, it does not provide a standardized framework for classifying chemicals based on their environmental impact.
Although Kreuder et al.[5] have proposed an approach to assess chemicals and chemical processes in alignment with the 12 principles of green chemistry, they utilize information compiled for compliance with the Globally Harmonized System of Classification and Labeling of Chemicals (GHS). The green chemistry metrics (GCM) proposed by the authors enable the ranking of chemicals or processes using a hierarchical system: (1) scores corresponding to each of the 12 principles, (2) rankings across three categories for new and improved chemicals/processes (enhanced resource efficiency, improved energy efficiency, and reduced human and environmental hazards), and (3) an overall summary ranking for comparison.
Conversely, LCA is a versatile and powerful tool able to provide a standardized framework to assess the environmental sustainability of green chemistry choices (e.g., less hazardous or material intensive reagent, reduction in steps and waste prevention, etc.), even though it relies on specific case studies for its application.
Thus, green chemistry offers a set of guiding principles for designing safer and more sustainable chemical processes, whereas LCA provides quantitative and standardized metrics to evaluate their environmental impacts. Despite these differences, there are points of intersection between them. In fact, several approaches were already proposed *i)* to support the application of the LCA to the chemical sector, in order to structure a procedure to fill data gap in the inventory,[6,7,8,9] *ii)* to assist the researchers in the field of green chemistry to get

[a] *Department of Industrial Chemistry "Toso Montanari", University of Bologna, Via Piero Gobetti 85, 40136, Bologna (BO), Italy.*
[b] *Center for Chemical Catalysis - C3, University of Bologna, Via Piero Gobetti 85, 40136, Bologna (BO), Italy.*
** Corresponding author: Daniele Cespi, daniele.cespi2@unibo.it.*
† Footnotes relating to the title and/or authors should appear here.

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familiar with the methodology,[10] by highlighting the benefits ascribable due to the usage of LCA within the green chemist,[11] and *iii)* to highlight the numerous methodological challenges to LCA studies of the chemical sector.[12]

However, to the best of my knowledge, nobody has proposed a list of issues that should be addressed by the LCA practitioner, in a procedural way, in order to apply correctly the life cycle perspective within the green chemistry discipline. Therefore, similar to green chemistry, in the following communication the 12 fundamental principles for LCA of chemicals are proposed as follow:

1 Cradle to gate
2 Consequential if under control
3 Avoid to neglect
4 Data collection from the beginning
5 Different scales
6 Data quality analysis
7 Multi-impact
8 Hotspot
9 Sensitivity
10 Results transparency, reproducibility and benchmarking
11 Combination with other tools
12 Beyond environment

The principles were ordered based on the logical sequence a practitioner should follow. Principles 1–2 pertain to system boundary definition (within the Goal and Scope definition, the first stage). Principles 3–6 address the life cycle inventory (the second and most time-consuming phase of the LCA). Principles 7–8 relate to the life cycle impact assessment (the third stage). Principles 9–10 are categorized as miscellaneous, as they include aspects of LCI, LCIA, and interpretation. Finally, Principles 11–12 focus on integrating the LCA with other tools and methodologies.

1 Cradle to gate: system boundaries of the study may vary, but at a minimum cradle to gate should always be ensured. Cradle to grave is the more established approach and consistently enables the comparison of two or more alternatives based on their function. However, very often chemicals represent intermediate products with several application in downstream and, thus, different EoL also depending from market. Therefore, other perspective may be acceptable, depending on the study's goal and scope. The one is the cradle to gate, which enables the analysis from the “roots” (raw material extraction) up to the production of the chemical in its finished form. In the case of some types of chemicals, like pharmaceuticals, the cradle to synthesis[13] approach is sometimes used including all steps up to the point where the purified active pharmaceutical ingredient (API) is obtained, while excluding tableting and packaging. This approach is particularly common in supporting R&D activities focused on optimizing API synthesis. The cradle to gate approach allows for a comprehensive analysis of alternatives, particularly when the main chemical or technical differences lie in the upstream and/or core stages. This could be the case of alternative pathways for producing the same molecule with equal usage and EoL. An example is represented by the comparison between the bottle grade polyethylene terephthalate (PET) derived from fossil respect to its bio-based counterpart. The molecule obtained is the same, as well as all the downstream stages (i.e., distribution, usage and EoL)[‡]. Therefore, downstream stages can be excluded from the analysis if they are not relevant to the intended audience. However, if the comparison extends to a different class of polymers, such as polylactic acid (PLA), which varies in reference service life and disposal method (e.g., PLA is compostable, while PET is not), the study must encompass all stages up to the grave. For chemical products, gate to gate boundaries (which generally focus only on Scope 1 flows) should be discouraged. In fact, to promote a 'benign by design' society, the harmful effects associated with material and energy extraction, purification, and the final fate of molecules and materials should always be taken into account—as also suggested by the principles of green chemistry—moving beyond what happens solely in the beaker.[14] For example, different catalyst substrates should be selected not only based on their efficiency within the reaction, but also by considering their criticality,[15] the resource intensity of their extraction,[16] and their recyclability potential.[17]

2 Consequential if under control: according to the literature,[18] an attributional LCA focuses on describing the environmental characteristics of a life cycle and its subsystems. In contrast, a consequential LCA aims to capture the effects of changes within the life cycle. In other words, an attributional LCI modelling framework inventories the input and output flows of all processes within a system as they naturally occur. Conversely, consequential LCI modelling identifies and evaluates all processes in the background system that arise as a result of decisions made in the foreground system.[19] The primary LCI methodological approaches associated with these frameworks are allocation for attributional modelling and system expansion or substitution for consequential modelling.[19] In simple terms, a consequential approach is more action-oriented than an attributional one, though capturing changes in physical, technical, and socio-economic variables. Thus, while the attributional approach quantifies the potential environmental impacts of the system as it is, the consequential approach aims to assess the potential environmental impacts resulting from changes within the system under study. Therefore, a consequential approach is more complex, as it extends the analysis beyond the plant facility to include a broader portion of the industrial ecosystem. Considering multiple variables can affect the final results and provide the user with a more powerful tool to support decision-making by incorporating various scenarios. However, this approach in the chemical sector is far from easy. A typical example of a consequential approach is when LCA boundaries are expanded to account for credits from material extraction or energy production, such as using bio-based waste to generate energy in a cogeneration plant as a substitute for fossil fuels. For greater consistency, the application of a consequential model to part of the life cycle should ideally extend to the entire system boundaries. In cases

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of avoided impacts from material or energy recovery, this approach should ideally encompass the whole supply chain, where appropriate (i.e., when co-products generated by process units within the supply chain could potentially be used as substitutes for virgin materials). However, while this approach might offer consistency, it can also lead to an underestimation or overestimation of the overall environmental impacts. This is because the consequential model may not be consistently applied across all upstream and downstream processes, over which the LCA practitioner typically has no direct control. When direct control is not guaranteed, the data used to build the models are classified as background data. These data generally fall under the category of secondary data, although primary data may also be provided by suppliers in the form of self-declared information or, preferably, certified or verified by a third party. Databases are examples of tools that help fill data gaps. On the other hand, foreground data should represent all core activities under the control of the practitioner, where primary information (both qualitative and quantitative) should ideally always be collected (Figure 1).

As a general rule, consequential approaches—such as accounting for avoided products—should be limited to parts of the life cycle where direct control over substitution is ensured. Otherwise, they should be used only for sensitivity analysis (see Principle 9).

Figure 1 - insert here

3 Avoid to neglect: when evaluating a reaction, there may be instances where certain data are unavailable to the LCA practitioner. This often occurs when the reaction is outside of direct or indirect control,[9] leading to gaps in data availability. One of the most common examples is the energetic consumption of a reaction at laboratory or pilot scale. Another case is the inclusion of the full mass balance in the LCA model. Since the life cycle results reflect the amount and quality of data used in the inventory (Life Cycle Inventory, LCI), greater is the percentage of omitted information and lower will be the reliability of the study. Therefore, as a general rule of thumb, all the input and output flows within the system boundaries should be incorporated in the model. A complete mass balance must always be satisfied, accounting for all input and output flows within the system under study, including reagents and auxiliaries (e.g., solvents), products and co-products, as well as waste and emission flows. Cut-off criteria may be applied to flows contributing ≤1% of the overall mass (or volume) only if the material does not have a significant environmental footprint (e.g., substances of very high concern or noble metals). Catalysts may sometimes be excluded from the mass balance if they are recovered and reused in subsequent cycles (e.g., heterogeneous catalysts).[9]

Energy consumption is also critically important, as it often represents a major contributor to the overall environmental impact of a reaction. However, its estimation can be challenging. In such cases, an enthalpy balance is recommended to ensure that the model accounts for the minimum energy required by the process. A recent publication[9] presents a step-by-step procedure for completing the LCI of chemicals, discussing both limitations and advantages, and providing guidance and strategies to address data gaps.

4 Data collection from the beginning: LCA studies are often conducted after the experimental phase is completed, a practice commonly referred to in the literature as ex-post or retrospective LCA.[20] However, when life cycle thinking is integrated during the research process to support innovation, it is more valuable and appreciated. During lab-scale activities, scientists typically focus on optimizing system efficiency (e.g., product yield) or improving characterization (e.g., active surface area on catalysts), often overlooking variables that can significantly impact the final environmental footprint of the chemical process. These overlooked factors may include energy consumption, time requirements per stage, and the exact volumes of solvent used for sample storage. Unfortunately, recovering such information after the experiment is challenging, requiring multiple assumptions to fill in the gaps. To avoid this, data collection should begin from the outset, using dedicated checklists to gather both quantitative and qualitative data for each stage of the process. An exhaustive example of checklist was recently published in literature.[21] The spreadsheet file reported in ESI can be used by practitioners as starting point to build their own checklist.

5 Different scales: a life cycle approach can be valuable in supporting the scaling up of reactions by conducting an initial LCA at an early design phase, when the technology is at a low readiness level (TRL). This helps to identify potential challenges or advantages, particularly important for lab-scale reactions when the degree of freedom is significantly higher. However, to fully grasp the potential of the innovation being studied, the analysis should also be extended to higher TRL levels, by setting the basis for a future-oriented LCA and investigate the environmental impacts of currently immature pathway. Recently, Arvidsson et al. suggested using the term prospective LCA to refer to studies with a future temporal positionality.[22] In the case of chemical reactions the assessment should also investigate the effect of changes in background systems e.g., new materials for vessels and reactor to reduce heat dissipation, alternative energetic mix to reach future climate targets, innovative catalytic system to mitigate metal criticalities, etc.

The most challenging activity is LCI upscaling. The first and more consolidated option is using software engineering simulation considered, so far, the top level when primary data are not available.[23] Various commercial and open-source software programs are available (e.g., Aspen Plus®,[24] CHEMCAD™,[25] DWSIM,[26] Aspen HYSYS®,[27] ProSim,[28] etc.) for estimating heat duty in reactions and unit operations, as well as electricity consumption for pumps, compressors, and other electric drives. However, these tools require a minimum set of input data—such as reactor type, kinetic equations, and reaction conditions—to function effectively. Without access to this information, conducting simulations becomes virtually impossible. Moreover, the process demands specialized expertise and a dedicated budget, which are not always readily available.[9] Therefore, if not feasible, a simplified approach can

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be implemented by the practitioner based on constitutive equations for individual equipment units. Piccinno et al.[29] developed a framework to support the scale-up of chemical production processes for LCA studies when only laboratory-scale data are available. It is intended for LCA practitioners with limited expertise in chemical engineering and provides a logical, systematic approach to guide the scale-up process.

6 Data quality analysis: due to the varying availability of necessary information for compiling the synthesis inventory (e.g., thermodynamic values for energy balance, reaction stoichiometry to identify by-products, etc.), a data quality analysis should be incorporated into the study.

This analysis should begin during data acquisition to prevent the loss of information—an issue that often arises when a chemical process involves multiple unit operations carried out by different research groups. To streamline the procedure, the checklist file (ESI) can include an additional column to classify data based on their source and to rank them as primary or secondary. Qualitative information (e.g., direct measurements) can also be collected, and a scoring system (e.g., from 1 to 5) may be applied.

A valuable method to estimate data uncertainties and screen the entire dataset is the quality pedigree matrix.[30] This approach often needs to be adjusted to better align with the specific case study. Once the analysis is complete, the scores are used to assign standard deviation values to each input/output flow, which are then applied in an uncertainty analysis using Monte Carlo simulation. Formula for standard deviation calculation is commonly reported in literature.[31] There is no fixed number of iterations recommended to accurately capture data variability in the final results; software can perform the analysis with a very high number of iterations (e.g., over 10,000). .

7 Multi-impact: ISO 14044 clearly defines the need for a multi-impact approach in life cycle assessment studies. However, LCA models in green chemistry innovation studies often focus on a single indicator at a time (e.g., carbon footprint),[32] rather than considering multiple impacts simultaneously. Although a single-indicator approach may be easier and more cost-effective, a comprehensive and holistic assessment can be achieved using methods that encompass a wider range of impact categories.[33,34] Among the more consolidated examples several methods exist: ReCiPe 2016 (18 midpoint categories and 3 endpoint receptors)[35], IMPACT World+ (18 midpoint categories and 3 endpoint receptors)[36] and EF 3.0 (28 midpoint categories and no endpoint)[37] are some of them. Except for the Environmental Footprint methodology,[38] there is no fixed rule for the inclusion or exclusion of specific impact categories in traditional LCA. As a general rule of thumb, when a method is selected, the full set of impact categories should be included in the evaluation. For example, when using ReCiPe 2016, [35] all 18 midpoint categories should be considered at the characterization level and reported in the manuscript or in the electronic supporting information. The discussion, however, can focus on a subset of these categories by highlighting those that are most relevant.

This selection should follow a rational approach: depending on the type of process or material being assessed, certain categories cannot be omitted. For instance, in the case of bio-based products, the use of dedicated biomass necessitates the inclusion of impact categories such as land use, eutrophication, and ecotoxicity. Similarly, for battery production, the consideration of mineral resource consumption is essential.

Another option—often used in combination with the above—is to identify the impact categories that contribute most to the cumulative single score after applying a weighting step. However, weighting is not mandatory in all multi-impact assessment methods. It is considered an optional element, as it introduces a degree of subjectivity that can influence the final results, even though most methods include predefined weighting schemes.

8 Hotspot: green chemistry innovation should prioritize reagents, solvents, auxiliaries, or process steps that have the greatest impact across the entire life cycle. To effectively target efforts—often constrained by limited budgets—a hotspot analysis[39] should always be conducted to identify where improvements are most needed. Results of this evaluation, also called contribution analysis, allow the identification of dominating hotspots. In this context, a preliminary LCA can be valuable in pinpointing inefficiencies and assessing how alternative approaches might reduce the overall environmental footprint. When a database is presented in the form of unit processes (a list of elementary flows entering and leaving each unit), hotspot analysis reveals the step(s) with the greatest contribution. A further network analysis can then be conducted to identify the flow(s) with the highest contribution, which can serve as a basis for exploring potential alternatives. Replacement is sometimes challenging, as the availability of practical chemical alternatives on the market is limited. However, this limitation drives continuous innovation and improvement in the development of greener and more sustainable solutions.

9 Sensitivity: the traditional LCA approach typically represents a stable scenario with fixed geographical, technical, and temporal boundaries, producing a snapshot of the system under study during the impact assessment stage. However, how do changes in variables affect the results? To assess the robustness of the LCA model, sensitivity analysis is highly recommended, especially in the chemical sector. Factors such as process efficiencies (yield, conversion, and selectivity), chemical and physical conditions, catalyst quantities, raw material sources, energy mixes, transportation, and other variables can be adjusted to reflect a wider range of scenarios. Often, the sensitivity by evaluating the variations of parameters is beyond practical and feasible due to the high number of variables. Therefore, the practitioner can limit the sensitivity analysis to only dominant hotspots and substances. The simplest example is represented by the energy vector(s) used to run the reaction. The practitioner can evaluate how the results are affected by switching from a traditional energy carrier (e.g., natural gas)[40] to electricity,[41] and then perform a further sensitivity analysis to identify the optimum under different energy mix scenarios.

10 Results transparency, reproducibility and benchmarking: The chemical sector is characterized by highly specialized corporate knowledge, making it difficult to fully reconstruct systems. Key information such as energy consumption, catalyst quantities, and regeneration flow requirements are often confidential.

Confidentiality is also a common characteristic of commercial databases (e.g., ecoinvent).[42] However, two essential pillars of the life cycle thinking approach are transparency and the reproducibility of data and outcomes. In line with the European Open Science policy,[43] researchers and practitioners in the field of LCA should provide at least the system boundaries flowsheet (Principle 1), the complete LCI with assumptions and exclusions (in line with Principle 3), and the characterization factors used during impact assessment (Principle 7). This information constitutes the minimum knowledge required for reproducibility, even though data sharing is also desirable (as encouraged by the Environmental Footprint methodology).[37] In this sense, sharing data in the form of elementary flows without further detail about the unit processes involved may help protect confidential information. While this approach may have some benefits, it reduces the amount of information that can be extracted from the results to support eco-design.[44] Furthermore, an independent third-party critical review of the study should be ensured when the results are intended for external communication, particularly at the company level.

In fact, the results of the LCA study are intended for both internal and external stakeholders, depending on the target audience. In the latter case the study has to undergo a critical third-party review, as required by the reference standards. In accordance with the ISO 14044 the critical review process is necessary to decrease the likelihood of misunderstanding, by ensuring:

- the methods used are consistent with the ISO standard;
- the methods used are scientifically and technically valid;
- the data used are appropriate and reasonable, in relation to the goal of the study;
- the interpretation reflects the limitation;
- the transparency of the study report.

As reported above, the principles of green chemistry and LCA are considered key approaches to support innovation. LCA is comparative in nature, and its results should be interpreted by comparing them with one or more benchmarks. Many standards[45,46,47] support claims by evaluating a product's performance relative to an average product (with the same function) available on the market. Another common approach is to compare a greener chemical or pathway with a traditional one (e.g., patented route vs commercial route;[13] fossil vs bio-based[48]). However, benchmarking can be challenging during the early design stage of a new chemical, especially when no comparable products are yet available on the market. In such cases, applying a streamlined LCA[49,50] from the outset can support decision-making throughout the optimization process. In these cases, the benchmark is the chemical product/process synthesized or developed in the stage prior to optimization.

11 Combination with other tools: the structure and nature of LCA allow for seamless integration with other approaches, enhancing insights into reactions and effectively supporting R&D efforts. Combining LCA with green metrics is recommended, since they can act as complementary sets of indicators.[51] Chemists often use tools like the E-factor,[52,53] atom economy,[54] or process mass intensity (PMI)[55] to evaluate their syntheses at the laboratory scale. While these tools are simple to apply and can help identify key performance indicators for tracking over time and during scaling up, combining them with LCA ensures a more comprehensive assessment by quantifying potential environmental impacts from significant waste generation (high E-factor) and/or excessive resource consumption (high PMI). A recent quantitative study by Lucas et al.[51] found weak correlations between mass- and energy-based metrics and life cycle impacts across environmental and human protection categories (i.e., climate change, pollution, toxicity, and resource depletion). Their findings suggest that metrics like PMI and E-factor alone are not reliable indicators of the overall environmental impact of chemical production processes. From a practical standpoint, researchers may adopt standardized process metrics (e.g., PMI, E-factor, and energy intensity) in combination with LCA-based indicators. As a general rule of thumb, the combination of multiple indicators into a single score (i.e., green metrics + LCA indicators) should generally be discouraged. However, if it is applied, it should always be accompanied by an analysis of each investigated impact factor separately.

Another recommended approach for chemical reactions is risk assessment (RA). While LCA typically offers an overview of potential environmental impacts from actual releases, RA provides valuable insights into the potential risks faced by workers handling hazardous substances during synthesis, as well as the possible environmental and human health risks during the molecule's use and end-of-life stages. The combined use of both approaches was first proposed in the late 1990s,[56] and has since been reiterated by several researchers as a key strategy to support green chemistry innovation and policy development.[57,58,59]

In general, RA can support LCI by predicting the likelihood of exposure to specific substances during handling or reaction steps (e.g., emissions). This is achieved by identifying or assuming potential exposure routes (inhalation, dermal, ingestion), assessing release potential (e.g., volatility, dustiness, fugacity, temperature, pressure), and considering the risk management measures in place. This integration helps practitioners achieve more reliable results regarding toxicological impacts.

Recently Cefic (The European Chemical Industry Council) and JRC (Joint Research Center) have worked on the standardization of an innovative assessment scheme, the so-called Safe and Sustainable by Design chemicals and materials (SSbD).[60,61] SSbD integrates safety considerations, environmental sustainability, and social and economic sustainability (the latter two are discussed later in principle 12) into the design of new chemicals and materials by incorporating safety analysis (including

intrinsic, and risk during production, usage, and EoL stages) before the environmental and socio-economic dimensions.

12 Beyond environment: to fully advance the development of green chemistry, the life cycle approach should extend beyond environmental sustainability. Ideally, the economic and social dimensions of sustainability should also be considered in evaluations where feasible. Life Cycle Costing (LCC)[62] and Social-LCA (S-LCA)[63] are the primary globally recognized methods for assessing these potential impacts. Among them, only S-LCA is currently progressing toward standardization. The European ORIENTING (Operational Life Cycle Sustainability Assessment Methodology Supporting Decisions Towards a Circular Economy)[64] project has developed a unified approach for Life Cycle Sustainability Assessment (LCSA), a comprehensive methodology that integrates the results of LCA, LCC, and S-LCA into a single score.

In summary, twelve fundamental principles of LCA applied to chemicals are suggested here. These principles serve as a general guideline to support a more standardized and consolidated use of LCA within the field of green chemistry. While most principles should always be adhered to, any deviations should be clearly justified. Some aspects, such as integrating other methodologies like LCC and S-LCA or applying more complex frameworks (e.g., LCSA and SSbD), may be more challenging to implement. Although expanding the assessment beyond environmental factors requires specialized expertise, the scientific community strongly encourages the use of additional methodologies or comprehensive approaches to do that.
These principles are not intended to be definitive; rather, the author's aim is to share them with the LCA practitioner community working in the field of green chemistry, inviting interested parties to engage in a discussion regarding their potential expansion and/or refinement.

Conflicts of interest

There are no conflicts to declare.

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‡ If the same market scenario is assumed: same distribution, same usage and equal EoL.

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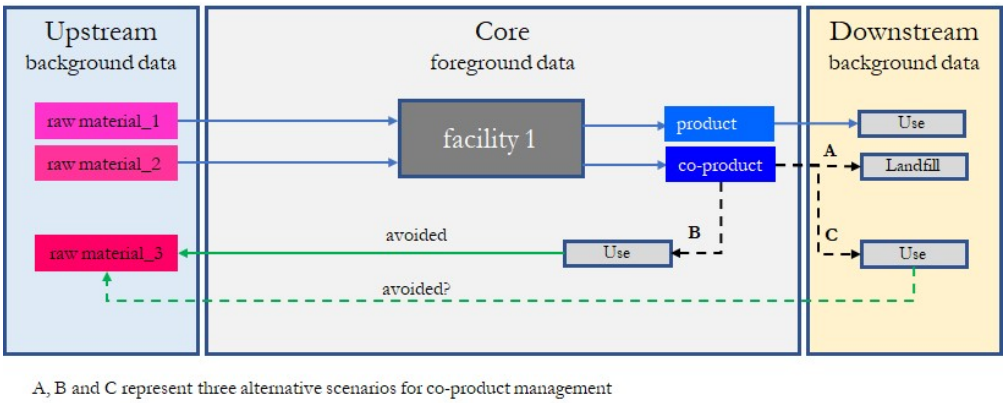

Figure 1: Simplified system boundaries

216x88mm (96 x 96 DPI)

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Data availability statements

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.