Green Chemistry

CRITICAL REVIEW

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Cite this: *Green Chem.*, 2022, **24**, 7787

# The meaning of life … cycles: lessons from and for safe by design studies†

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Received 25th July 2022,
Accepted 14th September 2022

DOI: 10.1039/d2gc02761e

rsc.li/greenchem

The concepts of Safe by Design (SbD) and Safe and Sustainable by Design (SSbD) are receiving increasing attention. The definitions of both concepts include the term 'life cycle' in combination with the terms 'chemical', 'material' and 'product', but their meanings are not further elaborated and defined in scholarly publications on SbD/SSbD. Here, we address two research questions: (1) How are the terms chemical, material and product used and defined in the scholarly literature on SbD and SSbD; (2) How are life cycles defined and which are considered in the scholarly literature on SbD/SSbD? We found largely consistent, though still confusing, uses of the terms product, material and chemical and we found four types of life cycles in the reviewed papers. Using consistent definitions of the terms product, material and chemical, we reduce the four types of life cycles found to three types of distinctive life cycles: (1) the life cycle of a product; (2) the life cycle of a chemical in a specific product; (3) the life cycle of a chemical in all its product applications. We discuss the different trade-offs that each of these life cycle approaches can identify and argue that they are complementary and should preferably all be applied in SbD/SSbD studies.

## Introduction

The concept of Safe by Design (SbD, also termed Safer by Design) focuses on the inclusion of safety aspects in the early stages of the design of new chemicals, materials and products. SbD is a relatively new concept and has among others emerged from the field of Green Chemistry that amongst others aims "to design safer chemicals across all stages of the chemical life cycle and to reduce the risk, by minimizing the hazard, from the earliest stage of the production process".[1–3] SbD has already received ample attention from chemical engineers,[4] but over the past years, SbD has particularly been applied and evolved in the context of nanomaterials and nano-enabled products.[5,6]

Besides Green Chemistry, the SbD concept also builds on concepts such as the Collingridge dilemma[7] (impacts cannot be easily predicted until a technology is extensively developed and widely used, while changing or adapting the technology is difficult when the technology has matured and marketed), eco-design (referring to the design and development of products aiming at reducing the environmental impact of these products while taking the complete product life cycle into account),[8] and cleaner production (strategy to prevent emissions at the source and to initiate a continuous preventive improvement of environmental performance of organizations, while focusing on prevention rather than on cure in avoiding environmental problems).[9] Until recently, however, the SbD approach was not very well defined. In 2012, the U.S. National Institute for Occupational Safety and Health defined safety by design – called prevention through design (PtD) in the U.S. at that time – as "a management tool for protecting workers from potentially unsafe work conditions […] through the design, construction, manufacture, use, maintenance, and ultimate disposal or reuse of tools, equipment, machinery, substances, work processes, and work premises […] by eliminating hazards and minimizing risks to workers throughout the life cycle of the process".[10] Based on a review of SbD research in the context of nano-enabled products in EU Horizon 2020 projects, the Organization for Economic Co-operation and Development (OECD) recently redefined SbD as "identifying the risks and uncertainties concerning humans and the environment at an early phase of the innovation process so as to minimize uncertainties, potential hazard(s) and/or exposure. The SbD approach addresses the safety of the material/product and

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† Electronic supplementary information (ESI) available: Detailed set-up and results of the literature review. See DOI: **https://doi.org/10.1039/d2gc02761e**

associated processes through the whole life cycle: from the research and development phase to production, use, recycling and disposal."[11] For a more extensive review of the history of SbD, we here further refer to Caldeira *et al.*[5]

Expanding the SbD concept, the World Business Council on Sustainable Development (WBCSD) launched a roadmap for the Chemical Industry Methodology for Portfolio Sustainability Assessments providing guidance documents on how to perform and report on the environmental footprint of products and social impact of chemical products based on a life cycle approach.[12] Building on this WBCSD report, the EU Chemicals Strategy for Sustainability (CSS)[13] introduced the Safe and Sustainable by Design (SSbD) approach for chemicals, which was embraced by the European Chemical Industry Council (CEFIC).[14] The CSS defines SSbD as: "a pre-market approach to chemicals that focuses on providing a function (or service), while avoiding volumes and chemical properties that may be harmful to human health or the environment, in particular groups of chemicals likely to be (eco) toxic, persistent, bio-accumulative or mobile". In addition, "overall [environmental] sustainability should be ensured by minimizing the environmental footprint of chemicals in particular on climate change, resource use, ecosystems and biodiversity from a life-cycle perspective",[13] thus preventing unintended trade-offs in non-chemical related impact categories. SSbD adds a broader perspective to SbD, although safety is sometimes considered to be a part of environmental sustainability[15–18] and the CSS definition of SSbD does not (yet) include the economic and social pillars of sustainability. In the following we will write SbD as also including SSbD.

The various definitions of SbD include the term 'life cycle' in combination with the terms 'chemical', 'material' and 'product'. However, the meaning of life cycle is different for a product, a material or a chemical and also different in various scientific disciplines including environmental sciences,[19] biology,[20] marketing,[21] management[22] or psychology.[23] Focusing on environmental sciences and product-, material-, and chemical-related life cycles, we find that in scholarly literature on life cycle assessment (LCA), the definition of the life cycle of a product is adopted from ISO Standards[24] and defined as comprising 'the consecutive and interlinked stages of a product system, from raw material acquisition or generation from natural resources to final disposal'. There is no ISO definition for 'material life cycle', but according to the General Multilingual Environmental Thesaurus (GEMET),[25] a material life cycle is defined as "all the stages involved in the manufacturing, distribution and retail, use and re-use and maintenance, recycling and waste management of materials". GEMET also defines 'product life cycle' but different from the ISO definition above: "a product life cycle includes the following phases: acquisition of raw materials, production, packaging, distribution, use, recycling, and disposal". Compared to a product life cycle, the material life cycle excludes all stages of the product life cycle dealing with other materials than the material focused on, while it should include all possible uses of a material. The latter is not what we find in material LCA case studies generally; they rather exclude the use and sometimes disposal stages.[26–28] This illustrates that the definition of the terms 'material life cycle' – as far as defined explicitly – resembles the 'product life cycle' while in practice the 'material life cycle' is only a tiny part of a 'product life cycle' and should thus not have the same definition. The life cycle of a chemical or substance – which are often used mixed while not explicitly defined as being the same – is the core topic of particularly substance flow analysis (SFA)[29] and risk assessment (RA).[30] SFA captures the imports, exports, and production of a specific substance of focus in a certain region and a certain time period including all applications of the chemical and all possible emissions of the chemical throughout the life cycles of all those applications. MFA "is a systematic assessment of the flows and stocks of materials within a system defined in space and time".[31] This is consistent with SFA but takes a wider scope: not only substances but also materials. How materials exactly differ from substances as well as what the difference is with chemicals, however, remains undefined (see Discussion below). MFA has also a special mode called economy-wide MFA focusing on all materials flowing to, within and form a specific economy, *e.g.* the USA, Germany or Japan.[32] RA has been defined by the United Nations as "the quantitative and qualitative evaluation of the risk posed to human health and/or the environment by the actual or potential presence of an exposure to particular pollutants".[33] The life cycle in RA literature often refers to two distinct concepts: the biological life cycle, *e.g.* as a "series of stages, from a given point in one generation to same point in next generation",[30] and the chemical life cycle, which comprises production, formulation, use, service life and waste treatment.[30] It will be clear that the definition of 'life cycle' has a different meaning in relation to chemical, material and product and also to different scientific communities. If scholarly papers are unclear as to what the life cycle refers to, it will also be unclear what the findings of that study represent since each life cycle will provide different insights. In this article we focus on the life cycle as used in SbD studies due to the increasing attention for these studies. However, the analysis and findings reported here might also apply to differences found for life cycles as used in MFA, SFA, LCA and RA in general. As a first step towards such a broader analysis, we here focus on SbD studies.

In many of the scholarly papers on SbD it is not specified what the term 'life cycle' refers to. Moreover, in our definitions above we implicitly assumed clear and distinguishable definitions of basic terms as 'product', 'material' and 'chemical' while these may have different meanings for different disciplinary communities and SbD require interdisciplinary collaboration of different scientific and R&D communities,[34–39] or may have quite similar meanings as shown by expressions such as 'chemical products' and 'chemical materials', and by some of the publications reviewed in this article (see Results section below). To prevent misunderstandings in such collective endeavours, unambiguous definitions are crucial for creating mutual understanding between different communities and to further the interdisciplinary SbD debate. Several (excellent) reviews of SbD and its applications have already been published,[1,5,6] but none of them noted nor explicitly discussed the possible ambiguities in these definitions. In this article we therefore address the following research questions: (1) How are the terms chemical, material and product used and defined in the scholarly literature on SbD; (2) How are life cycles defined and which are considered in the scholarly literature on SbD? The answers to these questions may learn what SbD studies focus on, if studies taking different life cycle perspectives deliver the same or complementary results, *etc*. But for this we need to know first what different scholarly articles mean by chemical, material and product and by life cycle.

Below, we first discuss our method for searching, selecting, and reviewing relevant SbD literature for our review. Then, we present our results for the two research questions defined above. We then discuss our findings regarding definitions and what can be learned from considering different life cycles, and finally we present our conclusions and recommendations.

# Method

To answer the research questions, we performed a focused review of the conceptual and methodological SbD literature. We did not include SbD case studies as a majority of these appear not to look at life cycles at all. Focusing on SbD conceptual literature is expected to provide sufficient hits and information to answer our research questions.

First, a simplified literature search was performed (on 13-03-2022) using Web of Science for studies published from 2010 to 2022 (March) using the following keywords: Title: ('safe by design') or Title: ('safer by design') or Title: ('safe and sustainable by design').‡ These keywords were searched in the titles targeting for the most focused hits. The titles and the abstracts of publications identified (136) with these keywords were screened, and studies meeting the following criteria were excluded:

- Editorial or commentary on another article.
- Studies that do not include a 'life cycle' approach.
- Studies with an exclusive focus on the following aspects – toxicity or case study only – procedures – socioeconomic – ethical – computational/IT – safety of operations, construction, informatics or hospitals.

Finally, three publications identified through snowballing or recently published and of special relevance for our research questions, were manually added.[15,37,40]

The stepwise selection procedure is documented in the ESI.† The selection procedure resulted in a list of 20 studies (Table 1) that were further reviewed.

We next defined two main criteria and reviewed all the included studies against these criteria:

(1) How are the concepts of chemical, material and product defined in these articles; and

(2) Which life cycles are considered in these articles?

# Results

The detailed results of our literature review can be found in the sheet 'review of conceptual S(S)bD lit' of the ESI.† It appears that 5 out of 20 reviewed studies use both the terms SbD and SSbD,[15,37,38,40,45] and another 4 studies add sustainability assessments to safety assessment without mentioning the term SSbD explicitly.[1,6,36,47] Another general finding is that most (18 out of 20) of the reviewed studies focus on engineered nanomaterials (ENMs) and nanoparticles (NPs).[1,6,16,17,34–39,41–48] We note that all the reviewed studies have been published in between 2017–2022 and that 18 out of the 20 reviewed studies focus on nanomaterials and/or nanoparticles. This short timeframe and focus are most likely explained by the short history of the term SbD (see above) and the recent interest for nano-safety studies.[1] The other two studies focus on chemicals.[15,40]

Below we summarize our findings for the two main criteria.

### Chemical, material and product definitions

Regarding the use and definitions of 'chemical', 'material', and 'product' we find that none of the reviewed studies defines these terms explicitly, except one. Only Caldeira *et al.*[15] extensively discuss definitions of material, chemical product and product. The discussion is based on the definitions adopted in the EU chemicals legislation REACH (Registration, Evaluation, Authorization and Restriction of Chemicals).[49] Although this legislation does not define the term 'chemical', it distinguishes between 'substance' (defined as "a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition") and 'mixture' (defined as "a mixture or solution composed of two or more substances"). The definition of mixture is a circular definition ('mixture defined as mixture […]') but appears not to be correctly based on REACH,[49] since REACH defines 'preparation' as 'a mixture or solution composed of two or more substances', not 'mixtures'. 'chemical' is not defined in REACH or other legislation, but Caldeira *et al.* suggest that a chemical can be a substance or a mixture. Caldeira *et al.* also provide a definition for the term 'material' based on a study by Amodio *et al.*:[50] materials "denote either substances or mixtures which may or may not yet fulfil the definition of an article under REACH and may be of natural or synthetic origin (EC, 2021e)': The authors note that in REACH 'materials' are mostly considered as 'mixtures'. Next, Caldeira *et al.*[15] also provide a definition for chemical or material product based on a study by Amodio *et al.*:[50] "a chemical or material intended for consumers or that is likely – under reasonably foreseeable conditions – to be used by consumers". Finally, Caldeira *et al.*[15] provide a definition for the term 'product' that is based on EU Ecolabel regulation:[51] "any goods or services which are supplied for distribution, consumption or use on the Community market whether in return

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‡ Ti = (safe by design) or Ti = (safer by design) or Ti = (safe and sustainable by design).

**Table 1** List of studies reviewed on the two main criteria

| Main author + reference | Title |
|---|---|
| Bastús (*Curr. Med. Chem.*, 2018)[41] | Nanosafety: towards safer nanoparticles by design |
| Bottero (*Environ. Sci. Nano*, 2017)[39] | SERENADE: safer and ecodesign research and education applied to nanomaterial development, the new generation of materials safer by design |
| Caldeira (2020)[15] | Framework for the definition of criteria and evaluation procedure for chemicals and materials – draft report for consultation |
| Cobaleda-Siles (*J. Phys.: Conf. Ser.*, 2017)[42] | Safer by design strategies |
| Dekkers (*NanoImpact*, 2020)[16] | Safe-by-design part I: proposal for nanospecific human health safety aspects needed along the innovation process |
| Furxhi (*Front. Bioeng. Biotechnol.*, 2022)[38] | ASINA project: towards a methodological data-driven sustainable and safe-by-design approach for the development of nanomaterials |
| Hauschild (*Environ. Sci. Eur.*, 2022)[40] | Risk and sustainability: trade-offs and synergies for robust decision making |
| Sánchez Jiménez (*NanoImpact*, 2022)[36] | Safe(r) by design guidelines for the nanotechnology industry |
| Sánchez Jiménez (*NanoImpact*, 2020)[43] | Safe(r) by design implementation in the nanotechnology industry |
| Kraegeloh (*Nanomaterials*, 2018)[6] | Implementation of safe-by-design for nanomaterial development and safe innovation: why we need a comprehensive approach |
| Labille (*Front. Environ. Sci.*, 2020)[17] | Assessing sunscreen lifecycle to minimize environmental risk posed by nanoparticulate UV-filters – a review for safer-by-design products |
| Nguyen (*Nanomaterials*, 2022)[44] | Risk analysis and technology assessment of emerging $(Gd,Ce)_2O_2S$ multifunctional nanoparticles: an attempt for early safer-by-design approach |
| Pavlicek (*Sustainability*, 2021)[45] | Testing the applicability of the safe-by-design concept: a theoretical case study using polymer nanoclay composites for coffee capsules |
| Rose (*Nano Today*, 2021)[34] | The SERENADE project; a step forward in the safe by design process of nanomaterials: the benefits of a diverse and interdisciplinary approach |
| Rose (*Nano Today*, 2021)[46] | The SERENADE project – a step forward in the safe by design process of nanomaterials: moving towards a product-oriented approach |
| Salieri (*NanoImpact*, 2021)[1] | Integrative approach in a safe by design context combining risk, life cycle and socio-economic assessment for safer and sustainable nanomaterials |
| Schmutz (*Front. Bioeng. Biotechnol.*, 2020)[35] | A methodological safe-by-design approach for the development of nanomedicines |
| Semenzin (*Environ. Sci. Pollut. Res.*, 2019)[47] | Guiding the development of sustainable nano-enabled products for the conservation of works of art: proposal for a framework implementing the safe by design concept |
| Tavernaro (*NanoImpact*, 2021)[48] | Safe-by-design part II: a strategy for balancing safety and functionality in the different stages of the innovation process |
| Tsalidis (*Int. J. Environ. Res. Public Health*, 2022)[37] | Safe-and-sustainable-by-design framework based on a prospective life cycle assessment: lessons learned from a nano-titanium dioxide case study |

for payment or free of charge". All definitions provided by Caldeira *et al.*[15] are based on EU regulations or studies and include therefore some limitations for generic application (*e.g.*, "consumption or use on the Community market"). Moreover, the distinction between the terms 'chemical' and 'material' appears to be non-existent depending on the interpretation of "may or may not yet fulfil the definition of an article under REACH".

Almost all studies reviewed use the terms 'product', 'material' and 'chemical' and even if they do not provide definitions, the use of these terms is generally consistent. One study[42] raises some confusion as it is about nanoparticles (NPs), but it refers to these NPs as 'products' and nanomaterials (NMs) mixed. All other studies do not raise similar confusion except for some minor issues. For example, sometimes 'product' refers to a 'chemical' as in "production data for a similar product, *i.e.*, copper(II) hexafluoro-acetylacetonate hydrate";[37] or 'material' refers to 'chemical' as in "safety/reactivity/crystallinity/*etc*. of the material"[48] and in "applying low toxic and low hazard materials";[1] and phrases like "chemical products",[1,47,48] "transformation products"[45] and "by-product" (mostly referring to 'chemical emissions'),[17,39] which are very common in specific scientific communities, while possibly confusing for other scientific (adjacent) disciplines and their communities.

Finally, we plotted the number of occurrences of the terms 'product(s)', 'material(s)' and 'chemical(s)' in each of the reviewed publications and normalized them to the number of occurrences found for 'chemical(s)' for each reviewed publication (Fig. 1). A normalized count of 2 for 'product' for a given publication, for example, means that in that publication the term 'product' is used 2 times more than the term 'chemical'. The resulting graph shows that there are huge differences in normalized counts for each study, but that it is particularly striking to see that the normalized counts on the term 'chemical' are lowest for 16 out of 22 studies. This is probably largely due to the fact that the term 'material' is used in the nano-related publications rather than 'chemical'. The word 'nano' refers to size, and virtually every material can be made in its nanoform. Therefore, nanomaterials are particles for which size and shape matters as well as chemicals and thus inherently they are a combination of particles and chemicals for which the preference for the term 'material' becomes obvious.

Fig. 1 also shows that:

- Caldeira *et al.*[15] – proposing an SSbD-based framework for the definition of criteria and evaluation procedure for

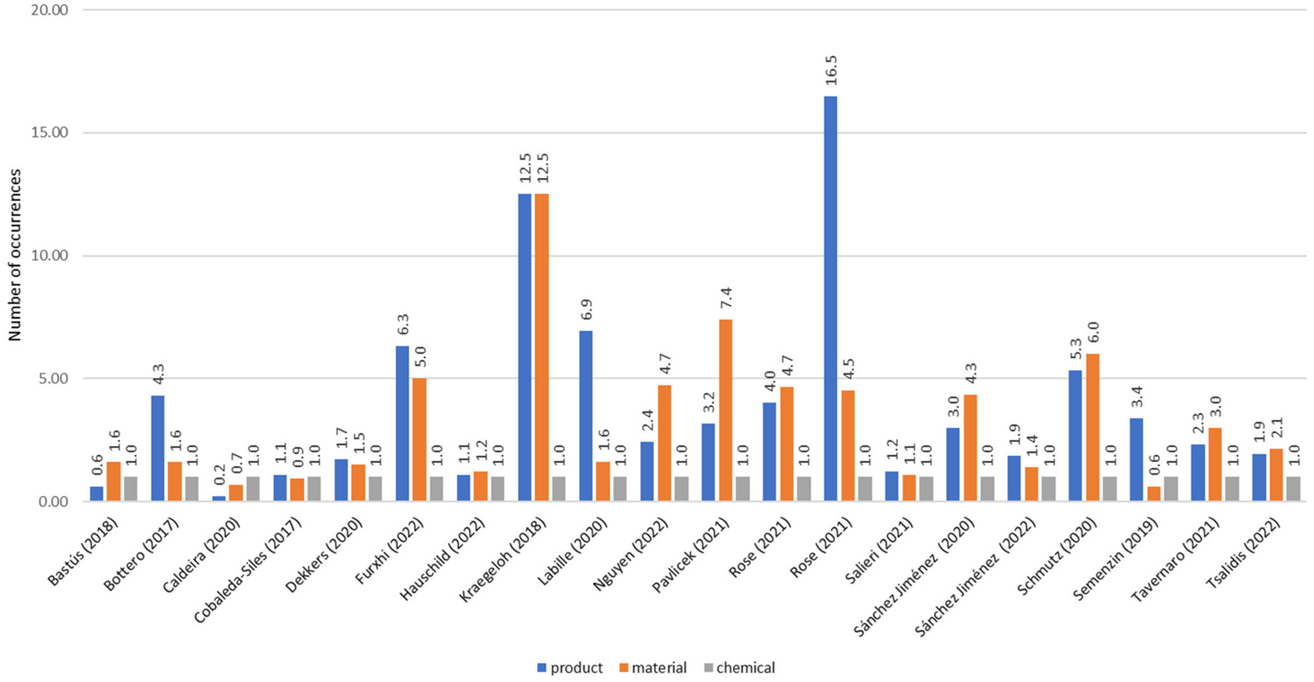

**Fig. 1** Plot of the number of occurrences of the terms 'product(s)', 'material(s)' and 'chemical(s)' in each of the reviewed publications, normalized to the number of hits found for 'chemical(s)' for each reviewed publication.

chemicals and materials – shows lowest normalized counts for 'product' and 'material'.

- Some studies adopt a clear product-oriented angle looking not just at one chemical or material but also how that chemical or material influences other aspects of a final product,[17,39,46] while others are more (nano)material-oriented and do not (or to a lesser extent) account for these other aspects, *e.g.* by rather focusing on the toxicity aspects of nanomaterials.[41,44]

One reason for the low counts of 'chemical' may again be that the majority of publications that we reviewed either focus on nanomaterials and not so much on the chemical differences of different nanomaterials,[6,34,35,38] on just one specific nanomaterial,[35] on the material properties rather than on the chemical differences behind those properties,[48] and/or mention specific chemicals (Ag, $TiO_2$, *etc.*) instead of 'chemicals' in general.[37,39,43,46]

## Life cycle definition

Since it was a selection criterion in our literature search, all reviewed studies include the 'life cycle' concept as part of their definition of SbD. However, what 'life cycle' refers to in each of the studies reviewed, is mostly unclear. Only one study[48] defines what its authors mean by 'life cycle': "the life-cycle comprises the consecutive and interlinked stages of a product system, from raw material acquisition or generation from natural resources to final disposal". This definition is adopted from LCA ISO Standards[24] as mentioned previously. As a 'stage' represents a group of industrial or economic processes in this definition, it is surprising to see that some studies[1,17,37,38] also link 'life cycle' to a single process.

Since 'life cycle' is such an important concept in SbD, we tried to determine more precisely or, if that appeared not possible, conjecturing for each study what the 'life cycle' refers to. In Table 2, we present for each study reviewed what the authors state and/or what we conjecture: the life cycle of a product (system), the life cycle of a material (system), the life cycle of a chemical, or any other type of life cycle. In the column 'Comments' we explain how we have arrived at our classification of 'life cycle' for each study. In the column 'Which LC is considered: chemical or product?' of the sheet 'review of conceptual S(S)bD lit' of the ESI,† we have included several quotes from each study providing the context in which the term 'life cycle' was used. Eventually, we found four types of life cycles – the life cycle of a product (system), the life cycle of a material/chemical in a product (system), the life cycle of a material (system), or the life cycle of a chemical/material as applied in all of its possible applications/product (systems) – that we will further discuss below.

The results displayed in Table 2 show that none of the reviewed studies seem to focus on the life cycle of a chemical. Pavlicek *et al.*[45] state that life cycle relates to a nano-enabled product, *e.g.*, a coffee capsule. But in their study, they perform a material flow analysis (MFA) of nanoclays applied in coffee capsules as a theoretical example to identify exposure pathways and potential risks. However, an MFA or substance flow analysis (SFA) would trace a specific material or specific chemical (substance), and only that material or substance, throughout its entire life cycle, from extraction to manufacturing to inter-

**Table 2** Overview of what the 'life cycle' adopted in each of the reviewed studies refers to: the life cycle of a product (system), the life cycle of a material, chemical in a product (system), the life cycle of a material (system), the life cycle of a chemical as applied in all of its possible applications/product (systems)

| | Type of life cycle considered | | | | | |
|---|---|---|---|---|---|---|
| Main author + reference | (1) Product | (2) Material/chemical in product | (3) Material | (4) Chemical | LC flowchart provided | Comments |
| Bastús (*Curr. Med. Chem.*, 2018)[41] | — | X? | X? | X? | No | It is unclear whether the authors mean LC of engineered inorganic nanoparticles (NPs) or LC of NPs in a final product. |
| Bottero (*Environ. Sci. Nano*, 2017)[39] | X | — | — | — | No[a] | LC of nano-products (*e.g.*, paints containing $TiO_2$) but also life cycle of exposure is mentioned without any further explanation what those entail |
| Caldeira (2020)[15] | X | X | X | X | Yes[b] | LC of chemical and material in product in first tier (steps 1–3) and optionally LC of product in next tier (step 4) of framework proposed. What the difference is between the LC of a chemical and the LC of a material is not further explained. |
| Cobaleda-Siles (*J. Phys.: Conf. Ser.*, 2017)[42] | X? | X? | X? | — | No | NPs in this article refers to nanoparticles and NMs to nanomaterials. Both are no final products, while the authors several times refer to the "life cycle of products". It is thus unclear what 'life cycle' exactly refers to in this publication. |
| Dekkers (*NanoImpact*, 2020)[16] | | X | | | No | This study considers nanomaterials (NMs) throughout the life cycle of its nano-enabled products. |
| Furxhi (*Front. Bioeng. Biotechnol.*, 2022)[38] | X? | X? | X? | — | No | Life cycle of nano-enabled products. However, the NEP is not defined as a final or consumer-product but focuses on the nano-part only (self-cleaning/air-purifying/antimicrobial coatings and nano-structured capsules delivering active phases in cosmetics). |
| Hauschild (*Environ. Sci. Eur.*, 2022)[40] | X | X | — | — | No | LC of a product system or a material system ("the life cycle of the plastic materials"). |
| Sánchez Jiménez (*NanoImpact*, 2022)[36] | X | X | X | — | No | The life cycle of a nano-enabled product (NEP), of a nanomaterial (NM), and of an NM in a NEP. If there is a difference between these three types of LCs is not further explained. |
| Sánchez Jiménez (*NanoImpact*, 2020)[43] | X? | X? | X? | — | No | The life cycle of a nano-enabled product (NEP). However, also the life cycle of the NM is mentioned in the first sentence of the abstract and the life cycle of the NM in a NEP seems to be suggested. If there is a difference between the LC of an NM (in an NEP) and the LC of an NEP is not further explained. |
| Kraegeloh (*Nanomaterials*, 2018)[6] | X | X? | X | — | No | In this article LC refers to the LC of manufactured nanomaterials (MNMs) and to the LC of nanoproducts. If there is a difference between the LC of an NM and the LC of a nanoproduct is not further explained. But LC might also refer to MNMs throughout or along a nanoproduct's life cycle. |
| Labille (*Front. Environ. Sci.*, 2020)[17] | X | — | — | — | No[c] | LC in this article refers to product life cycle and explicitly including all parts and not just the nanomaterial part because. |
| Nguyen (*Nanomaterials*, 2022)[44] | — | X? | — | — | No | LC is only mentioned twice, and it remains unclear to what it exactly relates. From one of the two uses of 'life cycle', we derive that it relates to the 'life cycle of nanomaterials as applied in a functional product'. |
| Pavlicek (*Sustainability*, 2021)[45] | X | — | — | —? | Yes[d] | Life cycle of a nano-enabled product, *e.g.*, a coffee capsule. An MFA of nanoclays in coffee capsules was made as a theoretical example to identify exposure pathways and potential risks, which is kind of an unexpected mix between an LCA of a product (coffee capsules; normally including all substances and materials needed for a coffee capsule product) and an MFA of a chemical substance or a material (nanoclays; normally including all nanoclay life cycle related flows for a region and year in all products that nanoclays are applied to (and not just coffee capsules)). |

**Table 2** *(Contd.)*

| | Type of life cycle considered | | | | | |
|---|---|---|---|---|---|---|
| Main author + reference | (1) Product | (2) Material/ chemical in product | (3) Material | (4) Chemical | LC flowchart provided | Comments |
| Rose (*Nano Today*, 2021)[34] | — | X | — | — | No[c] | LC of NM in a specific product is meant, since the focus is on NMs as applied in a number of (product case studies including food packaging, cosmetics and paint). |
| Rose (*Nano Today*, 2021)[46] | X | — | — | — | No | The LC of the product showing trade-offs of using a specific nanomaterial (*e.g.*, $TiO_2$) in a paint causing increased levels of volatile organic compounds (VOCs) emissions compared to focusing on the NMs only. |
| Salieri (*NanoImpact*, 2021)[1] | X | X | X | — | No | LC of manufactured nanoparticle (NPs) and of the nano-enabled (in-between and final) product. |
| Schmutz (*Front. Bioeng. Biotechnol.*, 2020)[35] | X? | — | — | — | No | LC of nanoproduct but the term life cycle is only mentioned twice, once referring to a "nanoproduct design" and the other time it seems to refer to medicine safety. |
| Semenzin (*Environ. Sci. Pollut. Res.*, 2019)[47] | — | X? | X? | — | No | LC refers to a nanomaterial (NM), but possibly the authors mean an NM in a specific product life cycle. |
| Tavernaro (*NanoImpact*, 2021)[48] | X? | X? | X? | — | No | LC of the NM and of the NEP, but the authors possibly mean the NM in a specific product life cycle, since they are "doing RA of the NM over the life cycle of the NP", and LCA is no part of their study. |
| Tsalidis (*Int. J. Environ. Res. Public Health*, 2022)[37] | X | — | — | — | Yes | LC refers to product life cycle as part of a prospective LCA. |

[a] Not of the paint system, but only of the safe-by-design process in general which has some resemblance with a life cycle. [b] Fig. 8 of this publication presents a "simplified representation of the life cycle of a chemical and its use in the life cycle of materials and products". [c] Only a very generic life cycle is presented with no detailed processes. [d] This study includes a simple product life cycle flowchart, while one would expect an MFA-based flowchart.

mediate and end uses to end-of-life for a specific period of time and region. For example, one could map all flows of cadmium for all processes and flows handling or containing cadmium in the European Union in 2020. Pavlicek *et al.*[45] claim that they perform an MFA but they do not provide a regional and temporal dimension for their MFA, consider all flows of nanoclays as applied in coffee capsules but ignore all other possible product applications of nanoclays. That does not reflect the life cycle of a nano-enabled product, but rather the life cycle of a (nano)material, *e.g.*, nanoclay, as implemented in a specific nano-enabled product, *e.g.*, coffee capsule.

Several studies mention the importance of considering the life cycle of a nano-enabled or chemical-enabled product.[1,6,15,17,36–40,45,46] A few recommend the use of LCA as part of an SbD framework, roadmap or working procedure proposed.[15,36,38,40] Only a few actually perform a cradle-to-gate[43] or cradle-to-grave/cradle LCA.[1,37] Salieri *et al.*[1] even performed LCAs at three different levels: on the manufacturing of three nanoparticles (NPs), on the application of these NPs in the anode of a Li-ion battery, and on the use of these NP-containing batteries in a battery-electric vehicle (BEV). The authors explicitly mention that they also look at the final product (BEV) life cycle and not only at the material/chemical (NP) or material/chemical in a product life cycle (battery) because applying an alternative material/chemical will often also change and thus affect other ingredients and components of a product and may in this way also have indirect impacts that will only be identified by also looking at the final product life cycle. Except for Caldeira *et al.*[15] none of the studies considering the life cycle of products explicitly explains, however, what the difference is between the life cycle of a product and the life cycle of a (nano)material/chemical.

Other studies[16,34] and some of the abovementioned studies[15,36,40] (also) focus, or possibly focus,[6] on the (nano) material/chemical throughout the life cycle of its (nano-enabled) product application, rather than on the life cycle of the product. Focusing on the life cycle of a (nano)material/chemical as implemented in one specific (nano-enabled) product application (see also the discussion of the Pavlicek *et al.*[45] study above) is another type of life cycle that we did not yet define above. Focusing on the life cycle of a product system implies including all materials and chemicals needed for the functioning of that product system in the analysis, while focusing on the life cycle of a chemical/material as applied in a specific product system implies that all other materials and chemicals needed for the functioning of that product system are excluded of the analysis. As explained by Salieri *et al.*[1] above, this limits the opportunities for identifying indirect impact trade-offs.

For all other studies,[35,38,41–44,47,48] we could not exactly pinpoint down what the term 'life cycle' referred to, only conjecture (indicated by 'X?' in Table 2). One of the reasons that we could not get a grip on this, is that flowcharts of life cycles were only provided by three studies.[15,37,45] Flowcharts of life cycles can be very helpful to identify what is included in a study. For example, a flowchart as part of an LCA study can clarify which processes have been included in the assessment, and which have not; a flowchart as part of an SbD study could clarify whether an LCA, SFA/MFA, or RA is undertaken and which processes are included in the analysis and which not. These figures serve to communicate what a particular study has analyzed and focused on, and what was outside the study's scope. Other reasons are specific for each study and displayed in the column 'Comments' in Table 2.

Finally, some studies explicitly mention applying RA for a nanomaterial or chemical substance throughout the life cycle of the product, meaning that an RA was, or was recommended to be, performed for all emissions of an NM or substance over the life cycle of a nano-enabled or substance-enabled product.[15,17,34,36,39,40,45,47,48]

In summary, we find that:

- In many cases it is unclear what 'life cycle' refers to (product, material, chemical in all possible products, chemical in one specific product);
- Studies that claim that they look at the life cycle of a product are often unclear about what that means: the life cycle of the product system with all materials and chemicals needed for the functioning of that product system? Or is their focus on a chemical/material throughout the life cycle of a specific product (system) using that chemical/material, or even the life cycle of a chemical/material including all applications in final products ('chemical/material in all possible products')?
- Only three studies provide a flowchart of the 'life cycle' considered, and a clear definition of the system boundaries of the study object.

Additionally, if the meaning of product, material or chemical is also unclear, the confusion on what 'life cycle' relates to and thus what it represents and what is analyzed may further increase. In the next section we try to resolve this confusion.

## Discussion

### Chemical, material and product definitions

Consulting the Cambridge dictionary[52] for definitions of chemical, material and product, we find the following:

- The noun 'chemical' refers to 'any basic substance that is used in or produced by a reaction involving changes to atoms or molecules' (both in UK and US).
- The noun 'material' has several meanings (physical substance, information, cloth, equipment) but focusing on the physical meaning 'material' refers to (UK) "a physical substance that things can be made from (*e.g.*, building materials, such as stone, or crude oil is used as the raw (=basic) material for making plastics)" or to (US) "a type of physical thing, such as wood, stone, or plastic, having qualities that allow it to be used to make other things" (*e.g.*, a hard/soft material, or the sculpture was made of various materials, including steel, copper wire, and rubber).
- The noun 'product' has also several meanings (thing made, in mathematics, in chemistry) and we mention the first and third meaning as these are exactly the source of confusion between different scientific communities. 'Product' as 'thing made' refers to (UK) "something that is made to be sold, usually something that is produced by an industrial process or, less commonly, something that is grown or obtained through farming" or to (US) "something that is made to be sold, esp. something produced by an industrial process or something that is grown or raised through farming". Product as 'in chemistry' refers to (UK) "a substance formed in a chemical reaction" or to (US) "a substance that results from a chemical reaction between other substances".

While 'chemical' according to the Cambridge dictionary has a clear meaning, its distinction to the term 'material' remains problematic, even in the Cambridge dictionary, since both terms refer to 'substance'. In several studies of our review,[15,37,48] 'chemical' and 'material' are not or only partly defined while used mixed. In addition, all nano-related studies[1,6,16,17,34–39,41–48] use the term 'material' for something that is at least also 'chemical'. Generally, a materials scientist will not use the term 'material' as equivocal to 'chemical' while some nanotechnology engineers may do so for understandable reasons as discussed above.

Within the LCA community 'product' generally has the meaning of 'thing made' or 'function fulfilled' or 'service provided', *i.e.*, something that is to be sold, particularly to a client,§ while in the chemical and technical engineering communities 'product' may also have the 'chemistry' meaning referring to 'a substance or chemical formed in a chemical reaction'.[1,17,39,45,47,48] If the LCA community refers to the product 'hairspray' they refer to the 'hairspray' as sold to a consumer, which not only includes the chemical compound of the hairspray but also the tin packaging of the compound and the spraying system. A chemical engineer referring to the product 'hairspray', may only refer to the chemical compound (or the active ingredient and, if relevant, some additives). Both use proper definitions of the term 'product' but they refer to different things. This may create confusion in the discussion between these two communities. The confusion may not just be restricted to these two scientific communities, but we take it here just as an illustrative example. The message rather is that it may be of importance to determine in more detail what we mean by certain commonly used terms when involved in interdisciplinary discourses.

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§ In the LCA Handbook[63] we defined 'product' as 'a positively valued economic flow of goods, materials, energy or services produced in a unit process and possibly serving as an input to another unit process'. This is slightly different from the Caldeira *et al.*[15] definition that seems to focus more on the EU ('any good or service which is supplied for distribution, consumption or use on the Community market whether in return for payment or free of charge').

### Life cycle definition

In LCA literature life cycle is defined by ISO[24] and has a well-accepted, standard definition. Evaluating the life cycle of a product or material entails accounting for all up- and downstream stages (as aggregated processes) related to a final consumer product or service (see precise definition above). In the SbD literature, the definition of life cycle is more ambiguous.

Based on our review we found various interpretations of the term 'life cycle'. We can summarize them in four types of life cycles of which the first three are summarized in Fig. 2.

Fig. 2 represents a simple and hypothetical product system with four chemicals that are building blocks of two materials, which on their turn are the main constituents of a final consumer product. Let us assume for simplicity that all chemicals can also be emitted, thus resulting into 4 possible emissions that can occur all over the life cycle. The four types of life cycles that can now be distinguished include:

(1) **The life cycle of a product system** captures all 13 processes of Fig. 2 and includes emissions of all 4 chemicals over all 13 processes. Life cycle assessment (LCA) is a method that adopts this type of life cycle for mapping trade-offs between life cycle processes or stages (shifting emissions from the use phase to the end-of-life phase, for example) and between impact categories (such as climate change, resource use, human and ecotoxicity *etc.*) comparing two or more product systems fulfilling the same function (*e.g.*, a sunscreen with *versus* a sunscreen without a specific nanomaterial). An LCA is capable of mapping all kinds of trade-offs between processes or stages, also for example if that nanomaterial in the sunscreen example requires a stable formulation including several chemical options that determine the performance of the nano UV-filter[17] but could also cause other emissions and impacts.

(2) **The life cycle of a chemical** (as "any basic substance that is used in or produced by a reaction involving changes to atoms or molecules" including nanomaterials) **in one specific product application** captures only 6 out of the 13 processes represented in Fig. 2. For example, if a study focuses on the life cycle of chemical 1 in the product represented in Fig. 2, only the two fully blue boxes and the blue parts of the 'production of material 1', 'product manufacturing', 'product use', and 'end-of-life treatment' boxes would be included. This is what several studies of our review seem to do[15,16,34,36] and they mostly refer to this analysis as performing an LCA. The trade-offs mapped by this stripped down LCA is mapping possible shifting of emissions over different phases of the 'chemical in product' life cycle so that it becomes clear if emissions of an alternative chemical over the same life cycle are worse or not compared to the chemical analyzed. Another use of this type of life cycle is for so-called life cycle risk assessment or analysis (LCRA).[53] Then, the life cycle of the chemical in a product is used to trace down all emissions of that chemical over the life cycle and then perform an RA of each of those life cycle emissions. In this case no other impact than human and ecotoxic impacts of producing and using a chemical in a specific product application are mapped.

(3) **The life cycle of a material** (as "physical substance that things can be made of"), *e.g.* material 1 in Fig. (2), captures the production of material 1 (blue-green boxes in Fig. 2) and its four upstream processes including only the emissions of

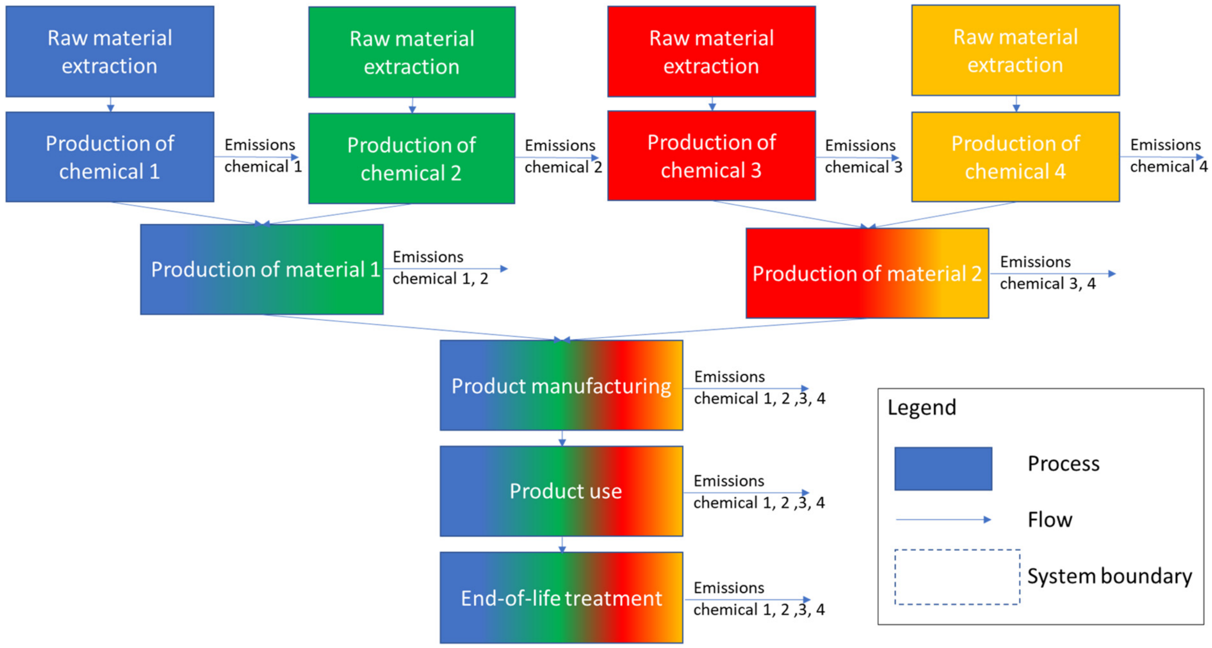

**Fig. 2** The life cycle of a hypothetical consumer product existing of four chemicals and two materials (material 1 manufactured of chemical 1 and 2, and material 2 manufactured of chemical 3 and 4).

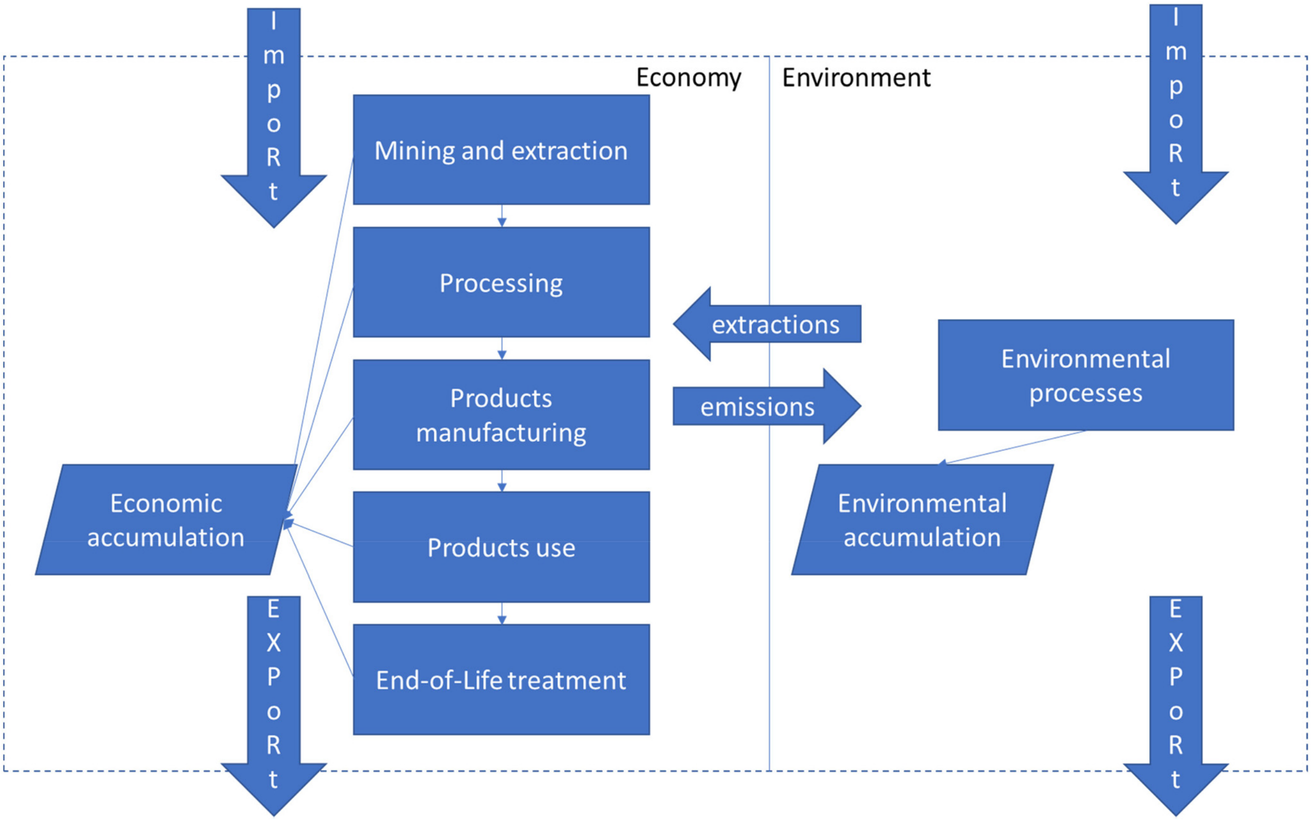

**Fig. 3** The LC of a chemical substance/material in all products for a given region and year.

chemical 1 (blue boxes in Fig. 2) and 2 (green boxes in Fig. 2) over its 5 processes, while the life cycle of material 2 (red-orange boxes in Fig. 2) captures the production of material 2 and its four upstream processes including only the emissions of chemical 3 (red boxes in Fig. 2) and 4 (orange boxes in Fig. 2) over its 5 processes. Downstream processes of material 1 and 2 and related emissions of the four chemicals depend on the application of the material in a final product and can therefore not be included or only unrealistically and partially (*e.g.*, representing the end-of-life treatment of the isolated material 1 or 2 independent from its application). Some cradle-to-gate LCAs[54] adopt this type of life cycle that excludes the application of materials in a final consumer product, the use of that product and also excludes the end-of-life treatment. When two materials could provide the same function for a product, the materials often need different auxiliary materials and different amounts. Adopting a cradle-to-gate life cycle would not be able to map the possible trade-offs in impacts related to the use of these different qualities and quantities of auxiliaries.

(4) **The life cycle of a chemical** (as "any basic substance that is used in or produced by a reaction involving changes to atoms or molecules" including nanomaterials) **including *all* its material and product applications** is a totally different life cycle since it would comprise of multiple product life cycles, *i.e.*, several product life cycles as displayed in Fig. 2. This can also be represented in a more simplified and aggregated way, which is illustrated in Fig. 3. Fig. 3 displays the imports, exports, and production of a specific chemical of focus in a certain region and a certain time period including all applications of the chemical and all possible emissions of the chemical throughout the life cycles of all those applications. Similar figures are used in the substance flow analysis (SFA)[29] and material flow analysis (MFA)[32] communities. SFA and MFA provide insights regarding how and where a chemical or material enters a region's economy, where that results in emissions and how and where these emissions could be most effectively prevented without shifting them to another life cycle phase or another region.¶

Whether these are 4 distinctive life cycles or not depends on the definition of product, material and chemical. Our review results show that the terms 'nanomaterials' and 'chemicals' are used mixed while meaning the same in many of the nano-related studies. Therefore, we propose to lump these two and classify them as 'chemical' referring to 'any basic sub-

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¶In a recent paper by Fantke *et al.*,[61] the life cycle of a chemical is explicitly separated from the life cycle of a product to which the chemical is applied. The life cycle of a chemical is defined as spanning 'the entire supply chain for harvesting resources, synthesizing, and processing a chemical, and related waste handling'. Fantke *et al.* recommend applying LCA for the product life cycle, but they do not mention or recommend SFA or MFA for the chemical life cycle.

**Table 3** Potential trade-offs identified when looking at the life cycle of a product or material, of a chemical in a specific application, or of a chemical including all its application

| Reference point of 'life cycle' (LC) | Color in Fig. 2 or 3 | Possible trade-offs identified |
|---|---|---|
| LC of a product or material | Blue, green, red, and orange in Fig. 2 | Cradle-to-grave/cradle-to-cradle (product):<br>• Trade-offs between all processes/stages needed for the functioning of several product systems fulfilling the same function<br>• Trade-offs between different impact categories (*e.g.*, global warming, resource use, acidification, human toxicity, ecotoxicity, …) of several product systems fulfilling the same function<br>Cradle-to-gate (material):<br>• Trade-offs between selected processes/stages needed to produce several materials fulfilling the same function<br>• Trade-offs between different impact categories (*e.g.*, global warming, resource use, acidification, human toxicity, ecotoxicity, …) of several materials fulfilling the same material function[54] |
| LC of a chemical in one specific application | Blue, green, red or orange only in Fig. 2 | • Trade-offs due to shifting of emissions over different processes/stages of the 'chemical in one specific product' life cycle<br>• Trade-offs between processes/stages of actual risks of a specific chemical in one specific product |
| LC of a chemical including all its applications | Blue in Fig. 3 | • Trade-offs of measures intended to effectively prevent emissions of a chemical and all its related product applications, such as shifting emissions to another life cycle phase or another region |

stance that is used in or produced by a reaction involving changes to atoms or molecules' adopting the Cambridge dictionary definition for 'chemical'. 'Product' applying one or more of these 'chemicals' would constitute a separate class referring to 'something that is made to be sold, usually something that is produced by an industrial process or, less commonly, something that is grown or obtained through farming' adopting the Cambridge dictionary definition for 'product'. Full life cycle assessments (cradle-to-grave or cradle-to-cradle) focus on final consumer products while partial life cycle assessments may focus on cradle-to-gate products. The latter includes 'materials' as (UK) "a physical substance that things can be made from" (*e.g.*, building materials, such as stone, or crude oil is used as the raw (=basic) material for making plastics) or to (US) "a type of physical thing, such as wood, stone, or plastic, having qualities that allow it to be used to make other things" (*e.g.*, a hard/soft material, or the sculpture was made of various materials, including steel, copper wire, and rubber) adopting the Cambridge dictionary definition for 'material'. In this way we reduced the number of distinctive life cycles to three:

(a) **Life cycle of a product or material** (*e.g.*, analyzed through a full or partial LCA);

(b) **Life cycle of a chemical in a specific product system** (*e.g.*, analyzed through risk assessment of all life cycle processes/stages emitting the chemical);

(c) **Life cycle of a chemical in all of its product applications** (*e.g.*, analyzed through substance of material flow analyses either or not combined with RA[55] and/or LCA[56]).

Each of these three life cycle perspectives and related analytical methods (LCA, RA, SFA/MFA) will provide different insights that essentially are complementary to each other (see Table 3). To prevent displacing of impacts to other life cycle stages, products, materials or chemicals and thus to prevent "regrettable substitutions" in SbD to the best we can, all three types of life cycles and related analyses should be performed, but of course we realize that that might be too demanding in practice.‖

Alternatively, a strategy to determine which applications of chemicals should be designed out with priority could be based on adopting the third life cycle perspective above and drafting SFAs of a chemical for a region (*e.g.*, the USA,[57] The Netherlands[55] or the globe[58]) and determining which applications are responsible for which parts of emissions of that chemical and developing generic strategies on how to best prevent these emissions (see also van der Voet[59] for illustrative examples on nitrogen and cadmium).

## Conclusions

In this paper, we addressed the following research questions: (1) How are the terms chemical, material and product used and defined in the scholarly literature on SbD; (2) Which life cycles are considered in the scholarly literature on SbD – the life cycle of a chemical, a material and or a product – and how are they defined by different disciplinary scholars involved in the field of SbD?

We found largely consistent, although still partly confusing, uses of the terms product, material and chemical and we found four types of life cycles in the reviewed papers. Using consistent definitions of the terms product, material and chemical, we reduced the four types of life cycles found to three types of distinctive life cycles: (1) the life cycle of a product; (2) the life cycle of a chemical in a specific product; (3) the life cycle of a chemical in all its product applications.

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‖ Particularly for a designer as such. However, designers are not solely responsible for this[64] and instead interdisciplinary design teams should be established including not only design engineers but also environmental, economic and social–ethical experts enabling to fully capture of important aspects for SbD.

We identified the different trade-offs that each of these life cycle approaches can identify and argued that they are complementary and should preferably all be applied in SbD studies. The third life cycle approach could also be used to prioritize specific product applications of chemicals for re-design.

SbD is an important emerging concept that requires interdisciplinary collaboration of different scientific communities.[34–39] Interdisciplinary collaboration requires a common language that is understood in the same way by each disciplinary partner. We have shown that the use of very common terms as 'product', 'material', and 'chemical' do not have the same meaning across disciplines and may thus create confusion and ambiguity. In combination with varying definitions of 'life cycle', applying SbD can result in different trade-offs being found and conclusions being reached depending on the life cycle perspectives or, in other words, system approach(es) adopted. Therefore, a clear definition of basic terms and life cycle is crucial. 'Life cycle' thinking is an important aspect of SbD. Several of the publications that we reviewed seem to focus on the life cycle of a chemical in a specific product system. However, the basic idea behind SbD and life cycle thinking is to map and prevent trade-offs at an early stage of development as possible and prevent "regrettable substitutions". Only focusing on the life cycle of a chemical as applied in a specific product may not map all possible trade-offs and still result in "regrettable substitutions". Only focusing on the life cycle of a product may not properly assess safety issues of a specific chemical and the other way around: combining the two (LCA and RA, and possibly also SFA/MFA) is the way forward.[40,60–62] For future scholarly publications on SbD, we thus recommend to clearly define what is meant by product, material and chemical, and to be as explicit as possible in what 'life cycle' refers to, preferably including a figure clearly defining the systems boundaries and what is out of the scope. Moreover, we recommend including flowcharts of life cycles adopted whenever relevant and possible, and to realize that in the end life cycles in sustainability sciences are all about mapping trade-offs and thus preventing regrettable substitutions. Also, including more than one life cycle perspective in SbD studies may considerably help achieving the best possible substitution. Finally, we recommend reiterating our review when more S(S)bD studies have become available focusing on other chemicals (including advanced materials) beyond nanomaterials and/or nanoparticles in order to analyze whether our findings might be biased due to the current focus on nanomaterials and/or nanoparticles (18 out of 20 reviewed studies). We also recommend broadening our analysis from only SbD studies to how 'life cycle' is defined and used in scholarly communities of MFA, SFA, LCA and RA in general, as a next step. The meaning of life is debated already for centuries; let us prevent that the meaning of life cycles gets the same destiny.

## Author contributions

Conceptualization: J. B. G. and R. H.; methodology: J. B. G., R. H.; visualization: J. B. G.; writing – original draft: J. B. G; writing – review & editing: R. H., M. G. V., W. J. G. M. P., G. V. M.

## Conflicts of interest

There are no conflicts to declare.

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