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Learning from Safe-by-Design for Safe-and-Sustainable-by-Design: Mapping the current landscape of Safe-by-Design reviews, case studies, and frameworks

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ABSTRACT

With the introduction of the European Commission's "Safe and Sustainable-by-Design" (SSbD) framework, the interest in understanding the implications of safety and sustainability assessments of chemicals, materials, and processes at early-innovation stages has skyrocketed. Our study focuses on the "Safe-by-Design" (SbD) approach from the nanomaterials sector, which predates the SSbD framework.

In this assessment, SbD studies have been compiled and categorized into reviews, case studies, and frameworks. Reviews of SbD tools have been further classified as quantitative, qualitative, or toolboxes and repositories. We assessed the SbD case studies and classified them into three categories: safe(r)-by-modeling, safe(r)-by-selection, or safe(r)-by-redesign. This classification enabled us to understand past SbD work and subsequently use it to define future SSbD work so as to avoid confusion and possibilities of "SSbD-washing" (similar to greenwashing). Finally, the preexisting SbD frameworks have been studied and contextualized against the SSbD framework.

Several key recommendations for SSbD based on our analysis can be made. Knowledge gained from existing approaches such as SbD, green and sustainable chemistry, and benign-by-design approaches needs to be preserved and effectively transferred to SSbD. Better incorporation of chemical and material functionality into the SSbD framework is required. The concept of lifecycle thinking and the stage-gate innovation model need to be reconciled for SSbD. The development of high-throughput screening models is critical for the operationalization of SSbD. We conclude that the rapid pace of both SbD and SSbD development necessitates a regular mapping of the newly published literature that is relevant to this field.

1. Introduction

Safe and Sustainable-by-Design (SSbD) is a key component of the European Commission's (EC's) Chemicals Strategy for Sustainability (CSS). It is a premarket approach that aims to integrate safety and sustainability as early as possible in the innovation process and throughout the entire product lifecycle (European Commission, 2020a; European Commission, Joint Research Centre, Caldeira, Farcal, Garmendia

Abbreviations: CEFIC, The European Chemical Industry Council; CLP, The Classification, Labelling, and Packaging Regulation; CSS, Chemical Strategy for Sustainability; EC, European Commission; ECHA, European Chemicals Agency; EoL, End-of-Life; EU, The European Union; ISC3, International Sustainable Chemistry Collaborative Centre; RC, Joint Research Centre; LCA, Lifecycle Assessment; MCDA, Multiple-Criteria Decision Analysis; NAM, New Approach Methodologies; NM, Nanomaterial; OECD, Organization for Economic Co-operation and Development; QNAR, Quantitative Nanostructure-Activity Relationship; QSAR, Quantitative Structure-Activity Relationship; RA, Risk Assessment; REACH, Regulation on the Registration, Evaluation, Authorization, and Restriction of Chemicals; SbD, Safe-by-Design; SEA, Socio-Economic Assessment; SME, Small and Medium Enterprise; SSbD, Safe and Sustainable-by-Design.

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Aguirre, et al., 2022). The integration of safety and sustainability assessment methods has been a key research area (Nawaz et al., 2019), and an example of said research would be the integration of risk assessment (RA) and lifecycle assessment (LCA) (Harder et al., 2015; Linkov et al., 2017; Salieri et al., 2021; Som et al., 2010; Subramanian et al., 2023). Particularly since the publication of the SSbD framework, this research area has received an enormous boost in attention.

The interest in finding ways to practically apply SSbD is currently high in policy, academic, and industrial players around the EU due to its key role in CSS and meeting the Green Deal goals (European Commission, 2019). SSbD is presently a soft and voluntary policy measure that supports current regulations such as the Registration, Evaluation, Authorization, and Restriction of Chemicals (ECHA, 2020), the Corporate Sustainability Reporting Directive (European Commission, 2023), the EU taxonomy (European Commission, 2020b), and the Sustainable Product Initiative (European Commission, 2020c). Thus, SSbD is relevant to all manufacturers, large corporations as well as small and medium enterprises (SMEs) in and outside the EU (Directorate-General for Research and Innovation, 2022). The SSbD framework, issued by EC in December 2023, is a premarket approach aimed at steering and supporting innovation, i.e., not just the development of novel chemicals, materials, processes, and products, but also the redesign of existing ones. It is aimed at ensuring regulatory preparedness of innovation by eliminating the use of hazardous and high-impact substances already at the design stage so that the risk of rejection at the compliance stage is minimized (OECD, 2020; Soeteman-Hernández et al., 2020). To achieve this, the EC's SSbD framework comprises eight design principles and five assessment steps of which three design principles and three steps directly deal with safety aspects. Furthermore, the framework follows a hierarchical approach according to which, chemical safety is considered a prerequisite for sustainability, and therefore steps 4 and 5 (dealing with environmental and socio-economic sustainability) are to be executed after the fulfillment of the safety pillar in the first three steps. In fact, the first step of the framework aims to eliminate the use of the most harmful substances based on their hazards without considering the exposure aspects and consequent risks from their use. This hazard-based elimination approach (Lynch et al., 2014; Nordlander et al., 2010) at an early development stage of the framework brings about a paradigm shift in the development of new chemicals, materials, processes, and products because hazard considerations will become pivotal to the design process.

EC's Joint Research Centre (JRC) has already conducted case studies (Caldeira et al., 2023) to test the implementation of the SSbD framework, and several practical challenges have been acknowledged including obtaining and generating data, gathering internal and external expertise, and identification of valid tools (Stringer, 2023). The breadth of the framework, while promising significant long-term gains for societal and environmental wellbeing, also implies that implementation of all five steps is time-consuming and therefore expensive in the short term. Furthermore, the comprehensive nature of the framework is likely beneficial for and less regrettable in the future but demands a high level of expertise for the SSbD assessment in the present. These aspects make SSbD implementation early in the innovation process challenging, particularly for SMEs that often face resource and time restrictions. Apart from SMEs, large companies may also suffer in the short term because the hazard-based approach of the SSbD framework restricts the use of most hazardous chemicals that are used otherwise precisely for their inherent toxic functionality. Consequently, the hazard-based approach is not readily accepted by industrial organizations as evident from the competing risk-based SSbD approach proposed by the European Chemical Industry Council (CEFIC, 2021) that allows the use of vital chemicals that are also hazardous as long as exposure is minimized. Debates about the risk versus hazard-based approaches originate in environmental chemistry and predate the SSbD framework (Lofstedt, 2011); yet this debate is critical to SSbD. Despite such challenges, the SSbD framework provides the necessary building blocks and opportunities for new products and is a necessary step in the direction of sustainability, protecting human health and the environment, and ensuring that we operate within the planetary boundaries (Persson et al., 2022; Steffen et al., 2015).

Before the introduction of SSbD, and as recognized within the SSbD framework, toxicological and sustainability considerations at early-innovation phases were already introduced to chemists through principles of green chemistry (Anastas & Warner, 1998) and sustainable chemistry (Blum et al., 2017; ECOSChem, 2023; Kümmerer, 2017; Kümmerer et al., 2021). More specifically, in the pharmaceutical sector, the "benign by design" concept (R. S. Boethling et al., 2007; Kümmerer, 2007; Kummerer & Hempel, 2010) already existed as a strategy to manage pharmaceuticals in the environment. However, these existing early-stage safety concepts from the chemicals sector could only consider lifecycle and environmental impact aspects either indirectly or to a limited degree (Carney Almroth et al., 2022; Wang & Hellweg, 2021). Through the five-step SSbD assessment procedure, both JRC and EC have created a platform to simultaneously assess and address concerns related to toxicity within the safety assessments and adherence to the planetary boundary conditions (Steffen et al., 2015) in the sustainability assessments.

Our work aims to particularly abate possible challenges to SSbD by considering and mapping similar work already done on early-stage safety assessments. Our work here is focused on the concept of Safe-by-Design (SbD) developed in the nanotechnology sector (Kraegeloh et al., 2018; Schmutz et al., 2020; van de Poel & Robaey, 2017) and its relevance to SSbD. Novel nanomaterials with their specific functionality may pose many new toxicological challenges and threats not posed by conventional materials and chemicals. In fact for some nanomaterials, conventional toxicity tests applied at the compliance stage are insufficient in identifying potential risks (Hartmann et al., 2017). Hence, the nanotechnology sector has already learned many lessons from the application of SbD early in the innovation process and has been engaged in the development of tools, methods, guidance, and frameworks to diagnose potential environmental and human health risks from the use of nanomaterials under the SbD umbrella (Kraegeloh et al., 2018; Yan et al., 2019).

The objective of this assessment is therefore to map and analyze the current landscape of SbD literature and contextualize it against the SSbD framework. As stated earlier, the first 3-steps in the SSbD framework pertain to safety and thus the SbD analysis presented in this paper hierarchically holds a higher precedence to the sustainability assessment concepts from the SSbD framework. Recent studies (Furxhi, Costa, et al., 2023; Guinée et al., 2022; Kraegeloh et al., 2018; Subramanian et al., 2023) have reviewed SbD methods and framework originating from the nanotechnology sector. However, our assessment aims to have a wider scope by not restricting itself to the nano sector and actively considering the newly-changed and present-day policy background, i.e. the introduction of the EC's SSbD framework. Furthermore, this assessment focuses on identifying and categorizing the relevant SbD case studies and using them as a basis to better understand and also define types of SbD (and consequently also SSbD) research; this is necessary as looking into past SbD work can aid in the development of a clearer definition of SSbD and avoid confusion or possibilities of "SSbD-washing" (similar to greenwashing). Finally, this study proposes recommendations by identifying SbD concepts that could be incoporated to strengthen and facilitate the operationalization of EC's framework while SSbD is in its nascent stages and receptive to amendments.

2. Methods

2.1. SbD literature compilation and analysis

A literature search was carried out until 15th March 2023 using the keywords "safe by design". Since the goal was to be as inclusive as possible and compile the maximum amount of literature (irrespective of their impact) remotely relevant to SbD, Google Scholar was selected over other academic databases and search engines for the literature search (Martín-Martín et al., 2018). Apart from the google scholar search, all articles in the special issue of the journal NanoImpact focusing on SbD (Sánchez Jiménez, Rodríguez Llopis, et al., 2022) were considered for the assessment. Furthermore, to capture gray literature on SbD, the Zotero library maintained by the NanoSafety Cluster (EU NanoSafety Cluster, 2023) containing a list of publications from EU projects on nanomaterials was queried for the keywords "nanosafety" and "safe(r)-by-design". Finally, more gray literature in the form of case studies conducted within the Gov4Nano project (Gov4Nano, 2023) was included in the assessment.

The resulting research publications included SbD in their title, abstract, and/or keywords; owing to the use of Google Scholar, many resulting publications also contained the words "safe" and "design" in proximity to each other while not including SbD in their title, abstract, and/or keywords. The majority of the literature obtained was about safety to prevent accidents in engineering and product design, i.e., Engineering SbD (Hale et al., 2007; van Gelder et al., 2021), and was thus excluded from the scope of this assessment. All literature remotely pertinent to environmental safety (i.e., Environmental SbD) and sustainability was included in the assessment. Many studies were not labeled or classified as SbD but were still included in the scope of this assessment because they contained SbD information. The filtration criteria for studies were deliberately lax to ensure maximum coverage of valuable information relating to SbD (and by extension SSbD).

All the compiled literature can be found in Table S 1 and it was further objectively analyzed in the Supplementary table.xlsx to understand literature trends based on the following aspects:

- **Use of 'SbD':** It was assessed whether the 'SbD' or 'Safe-by-Design' term was used in the title, keywords, or abstract because the use in these sections implies high relevance to SbD (as perceived by the authors of those publications).
- **Origin/Applicability:** The research field of the literature source was identified. The identified origin/applicability sectors are categorized into conventional chemicals, nano or advanced materials, conventional materials, products, biotechnology, pharmaceuticals, and production processes. For example, if a case study focuses on chemical safety, then its origin/applicability will be 'chemicals'.
- **Safety Category:** It was analyzed whether the study addresses environmental and/or human safety endpoints.
- **Tool Proposed/Applied:** The relevance of the proposed tool to each step of EC's SSbD framework was assessed, i.e., toxicity (hazard assessment), exposure (occupational health and safety), risk (environmental and human risk), or LCAs (sustainability).
- **Literature Coverage:** To have a broad literature overview, we checked if the SbD studies propose a new tool, use an existing tool, promote an adapted tool, conduct a case study, offer guidance, review literature or tools, offer scientific commentary, including stakeholder feedback, and somehow incorporate the 'by-design' aspect by considering the stage-gate model (Cooper, 1990) or early-stage design considerations. Moreover, the reviews, case studies, and frameworks identified from this analysis were assessed in detail as explained further to map the current SbD landscape, understand where the gaps lie, and attempt to extract beneficial aspects for SSbD.

A single study may fulfill multiple groupings in the same aspect, i.e., double counting within the same aspect is possible. For example, a study by Shandilya and Franken (2020) covered both environmental and human toxicity aspects and was thus counted in both safety categories.

2.2. Analyzing the reviews of SbD tools

Instead of assessing all reviews on SbD, the analysis scope was limited to the reviews focusing on available tools and methods for SbD. Focusing on tools is necessary because the dearth of tools has been recognized as a challenge in the implementation of SSbD (Stringer, 2023). As detailed in Table S 2, individual tools such as databases, guidance documents, standards, decision trees, models, safety parameters, etc., can be found in the compiled tool reviews. This assessment follows the "review of reviews" approach rather than individually compiling and assessing tools in detail to avoid duplication and redundancy. Many studies assessed in Table S 2 (Shandilya et al., 2023; Sørensen et al., 2019; Subramanian et al., 2023) have already analyzed specific SbD tools in great detail while also listing the specific advantages and disadvantages of each tool. The "review of reviews" approach followed here assists in broadly understanding the availability of SbD tools and toolboxes, and how they may be further applied to resolve the perceived challenges in the operationalization of SSbD. In the present study, the reviews of SbD tools were categorized as:

- **Quantitative Scoring:** This refers to studies critically analyzing each tool and scoring them based on their applicability in different use cases using a well-defined scoring system. The outcome of these studies typically is an overall quantitative score that allows for the ranking of tools and aids in the selection of the best tool for a specific application.
- **Toolboxes or Repositories:** These are qualitative and typically consist of many tools compiled together. If these tools work in conjunction and serve a common objective, then they comprise a toolbox, otherwise a repository. These may be sophisticated and implemented in a web-based platform, or simply in an ordered list devoid of commentary and analysis of the tools.
- **Qualitative Reviews:** They also critically analyze each tool qualitatively without the use of scoring. Ranking of tools is harder, but the benefits and shortcomings of individual tools are laid out along with details about possibilities and requirements for future development.

Apart from the categorization of reviews, the analysis also considered whether or not the stage-gate model was incorporated into the review. Being able to order tools along the stage-gate model is presently perceived as a key determinant for SSbD to distinguish conventional tools (suitable for later innovation stages) from SSbD tools (Sørensen et al., 2019). The EC's SSbD framework (European Commission, Joint Research Centre, Caldeira, Farcal, Moretti, et al., 2022) does compile a list of many tools and methods for SSbD; however, many of the listed tools are already used in conventional risk and toxicity assessment studies performed during the later stages in the product development cycle. Therefore, there is a need to validate the applicability of many identified tools and methods at different stages of innovation, since the available data and resources differ at each stage of innovation (Subramanian et al., 2023). Hence, reviews that are capable of ordering the tools along the stage-gate model already provide valuable and actual SbD tools and toolboxes directly applicable to SSbD (albeit with necessary modification).

2.3. Analyzing the SbD case studies

The SbD case studies were assessed in detail because they are critical in validating the applicability of the SbD frameworks. On-ground implementation of a framework through a case study would not only illustrate proof-of-concept for the framework but also highlight the challenges encountered during implementation and the consequent revisions necessary for the framework. Hence, SbD frameworks without evidence of application in a case study would have limited credibility. Table S 3 lists and analyses the specific case studies showing how SbD concepts have been implemented to specifically improve nanomaterial design.

Here, a 'case study' involves the application of methods and tools for specific chemicals, materials, processes, and products. As detailed below, all collected case studies were first categorized as *SbD cases* or *Conventional studies*, and then their *Sample Size* was assessed. The objective here was to underscore the state-of-the-art in SbD along with its deficiencies. An additional objective was to understand which studies were truly SbD and which ones were mislabeled. By critically analyzing the motivation and methods of the compiled case studies, we hope to better understand what is and should be labeled as SbD (and consequently also SSbD).

2.3.1. SbD cases

SbD cases are true to the term “SbD” and thus illustrate how the safety of materials, chemicals, processes, and products can be ensured ’by design’ at an early-innovation stage. We define the following specific categories of SbD cases based on the respective methods they apply:

- **Safe(r)-by-Modeling:** They typically apply in-silico predictive methods such as Quantitative Structure-Activity Relationships (QSARs) and Quantitative Nanostructure-Activity Relationships (QNARs), rule-based systems, machine learning-based neural networks, and Novel Assessment Methodologies (NAMs) for safety assessments at an early-innovation phase of chemicals, materials, and processes.
- **Safe(r)-by-Selection:** This implies that from a list of chemicals or materials considered for an application, the ones with superior safety profiles are selected during the design phase. Typically, conventional lab testing methods are applied for the assessment of safety profiles.
- **Safe(r)-by-Redesign:** This entails that the safety profile of an existing material is improved through design solutions, i.e., introduction of barriers or coatings, changing of molecular structure, adapting the matrix or production process, etc.

The definitions provided above are a first attempt by the authors at

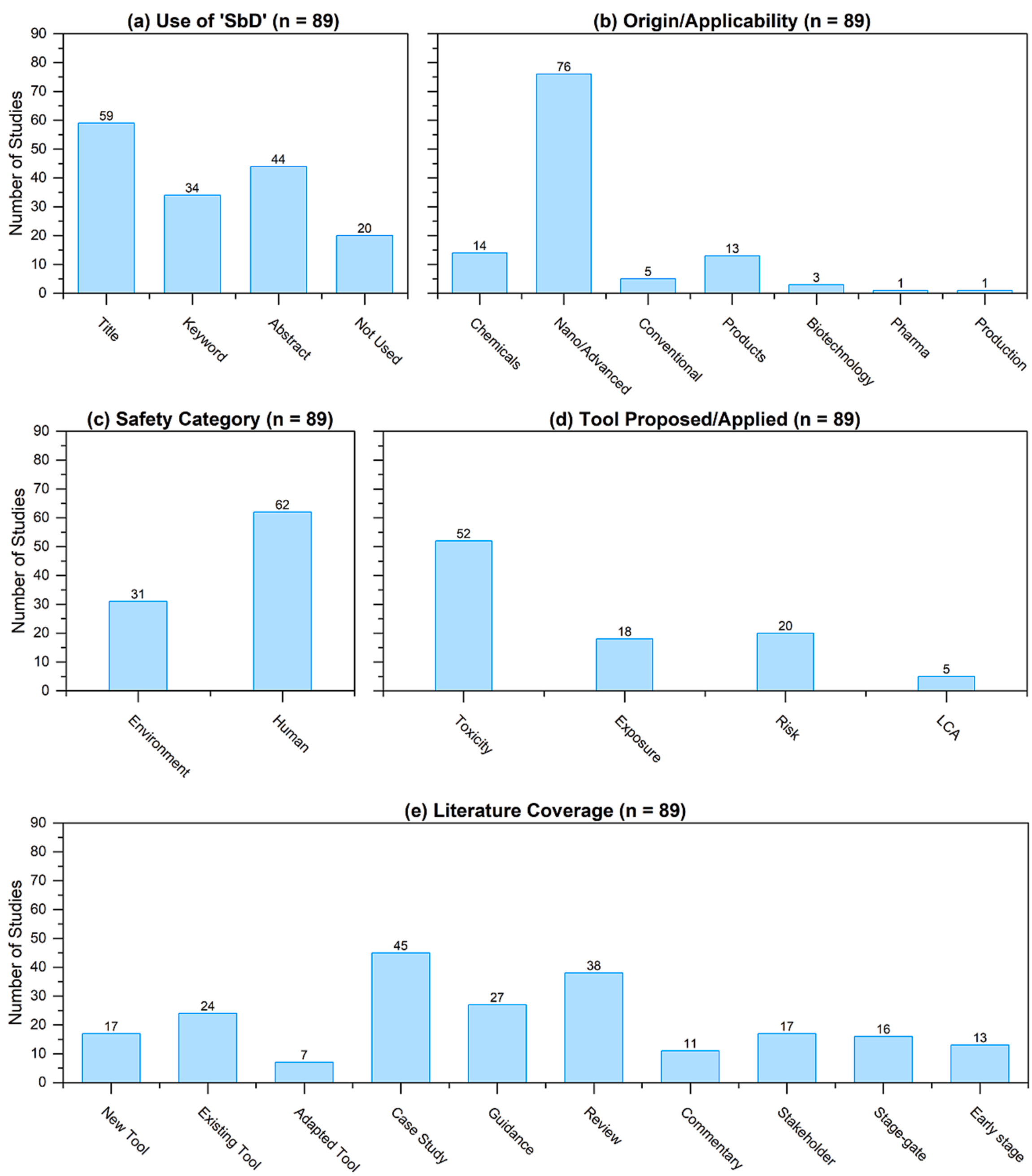

Fig. 1. General trends of 89 SbD studies compiled along the different criteria: (a) use of ’SbD’; (b) origin/applicability; (c) safety category; (d) tools proposed/applied; and (e) literature coverage.

Table 1
Analyzing and categorizing the 19 studies reviewing SbD tools; detailed analysis of individual reviews is provided in Table S 2.

Type of Review	Inclusion of Stage-gate	Number	References
Quantitative Scoring	Yes	**3**	Franken et al., 2020; Shandilya et al., 2023; Sørensen et al., 2019
	No	**0**	–
Toolboxes or Repositories	Yes	**4**	Nymark et al., 2020; RiskGONE et al., 2023; RIVM, 2017; Shandilya & Franken, 2020
	No	**5**	Jeliazkova et al., 2014; Joint Research Centre, 2021; NanoSolveIT, 2023; OECD, 2020; Ruijter et al., 2023
Qualitative Reviews	Yes	**1**	Subramanian et al., 2023
	No	**6**	European Commission et al., 2021; European Commission, Joint Research Centre, Caldeira, Farcal, Garmendia Aguirre, et al., 2022; Falk et al., 2021; Furxhi, Costa, et al., 2023; Guinée et al., 2022; Krans et al., 2021

categorizing SbD cases and broadly capturing the methods applied by SbD researchers; these categories of SbD cases are by no means standardized but very broadly help in defining SbD research and the general scientific methods that go into such research. Experts are now slowly deliberating on the above-stated terms along with terms such as 'Safe(r)-by-Comparison', 'Non-regrettable substitution', and 'Safe(r)-by-Substitution' to also facilitate the categorization of SSbD work however nothing has been published so far. Despite the clear definitions provided above, SbD cases cannot be categorically placed in one versus another. Since all the categories represent SbD, there are natural overlaps. For example, both Safe-by-Modelling and Safe-by-Redesign of multiple materials would naturally involve a selection component and thus arguably all SbD cases are Safe-by-Selection studies. However, in such scenarios, the objective of the study is considered, and depending on the precedence described in the study (which is more central to the study, redesign, or selection?), the categorization was conducted. For example, a study was categorized as safe-by-redesign if it involved multiple redesigns of existing material and then the selection of the best alternative.

2.3.2. Conventional studies

Considering the broad nature of the literature search, many conventional safety or sustainability assessments were identified that use the SbD tag but are seemingly mislabeled ('SbD-washing') based on this study's definition of SbD. Examples are the conventional toxicity assessments that have a 'safety' component but lack the 'by-design' element, i.e. the safety of materials, chemicals, processes, and products is not ensured 'by design' and/or implemented at later stages of innovation or product development. Furthermore, while toxicity assessments of a chemical and its degradation products may be tagged as SbD (Bae et al., 2019), it is a case of mislabeling if the study does not propose alternatives or recommend eschewing the use in case of an observed environmental risk. To fulfill the criterion of 'by-design', studies need to apply some comparison, selection, and even iterative approaches at an early stage of innovation and design. The mislabeled conventional studies were then categorized into *Toxicity Analysis, Exposure Assessment, Risk Assessment, Literature Reviews,* and *General Guidance*. Studies categorized as *Literature Reviews*, for example, Som et al., 2013 compile safety considerations and challenges for material development. In contrast, *General Guidance* documents, like Hong et al. 2023, omit the 'safety' component (i.e. toxicity, exposure, or risk) and instead exhibit general best practices or other complex topics such as the inclusion of material functionality in their assessments.

2.3.3. Sample size

The sample size of a case study refers to the number of alternatives compared by the study for SbD purposes. The following categories were used:

- **Single:** This refers to the assessment of one material, including the safe-by-redesign of a material to produce one safer alternative, the safe-by-selection of a material by comparison to a threshold, or the safe-by-modeling of a single material.
- **Multiple:** This implies more than one alternative was considered and evaluated in the case study.
- **High Throughput:** Such studies assess hundreds and thousands of alternatives simultaneously, typically possible only through safe-by-modeling.

Assessing the sample size of a case study is relevant because, for early-stage innovations, lack of data and funds implies that methods need to be quick, easy, and capable of evaluating many alternatives simultaneously. Hence, the sample size of the case studies here serves as a proxy for their rapidness. It is also important to note that the analysis of sample size was carried out based on exactly whatever the studies demonstrated. For example, an in-silico case study handling one material would be categorized as 'single' despite the tool possessing high-throughput capabilities.

2.4. Analyzing the SbD frameworks

Considering the past investments and efforts in developing and refining SbD frameworks, failing to incorporate their valuable content into the SSbD will be inefficient and may create competition between frameworks. In this analysis, the available SbD frameworks were examined by assessing their strengths, weaknesses, and applicability considering today's policy landscape. For our analysis, *an SbD framework consists of at least one tool, guidance for using the tool, and some 'by-design' elements.*

The frameworks were assessed in this article based on the following aspects:

- **Tools** were considered under a broad definition, including numerical methods, computational models, decision trees, flowcharts, etc. Furthermore, in our analysis of the frameworks, the 'specialization' of the tool was ignored so even frameworks without safety tools such as the LICARA nanoSCAN (van Harmelen et al., 2016) and the Benefit Assessment Matrix (BAM) (Hong et al., 2023) were considered.
- **Applicability** deals with the scope and origin of the frameworks. Here we evaluated if the application of these frameworks (especially conceptually) may be extended beyond nanomaterials to conventional chemicals, materials, products, and processes.
- **Guidance** implies apart from the tool, what instructions or concepts the framework proposes. Again, the definition is broad and considers aspects such as pillars of the framework, proposal of lifecycle thinking, hierarchical approaches, iterative improvements during developments, early-stage recommendations, etc.
- **'By-design'** refers to the inclusion either of the stage-gate model (Cooper, 1990) or the incorporation of early-stage innovation aspects. This is required as the key idea here is to distinguish conventional frameworks (applicable at the later-stage product development) from SbD frameworks that include safety already at the early-design phase and are therefore applicable under data and funding constraints.

Table 2
Analysis and categorization of 27 true SbD and 18 conventional studies of the 45 total case studies identified.

Type of Case Study			Single	Multiple	High Throughput
Safe(r)-by-Design Cases	Safe(r)-by-Modelling	Number	1	2	1
		References	Rybińska-Fryca et al., 2020	Furxhi, Bengalli, et al., 2023; Varsou et al., 2019	van Dijk et al., 2022
	Safe(r)-by-Selection	Number	1	8	
		References	Semenzin et al., 2019	Caldeira et al., 2023; Cazzagon, Giubilato, Bonetto, et al., 2022; Herva et al., 2011; Le et al., 2016; Mantecca et al., 2017; Rodrigues et al., 2020; Salieri et al., 2021; Tedesco et al., 2015	
	Safe(r)-by-Redesign	Number	7	7	
		References	Boulanger et al., 2013; Chang et al., 2016; Janko et al., 2017; Miao et al., 2020; Sánchez Jiménez et al., 2020; Soeteman-Hernández et al., 2020; Wolska-Pietkiewicz et al., 2018	Azmi et al., 2016; Fiandra et al., 2020; Motta et al., 2023; Movia et al., 2014; Naatz et al., 2017; Park et al., 2019; Remzova et al., 2019	
Conventional Studies	Toxicity Analysis	Number	1	2	
		References	Gautam et al., 2019	Bae et al., 2019; Dzhemileva et al., 2021	
	Exposure Assessment	Number	2		
		References	A. J. Koivisto et al., 2015; Antti Joonas Koivisto et al., 2018		
	Risk Assessment	Number	1	1	
		References	Cazzagon, Giubilato, Pizzol, et al., 2022	Hristozov et al., 2018	
	Literature Reviews	Number	1	5	
		References	Marques et al., 2020	Donaldson et al., 2011; Guo et al., 2021; Halappanavar et al., 2020; Som et al., 2013; Tavernaro et al., 2021	
	General Guidance	Number	2	3	
		References	Hong et al., 2023; Karayannis et al., 2019	López De Ipina et al., 2017; Micheletti et al., 2017; van Harmelen et al., 2016	

- **Lifecycle** stages include production, use, and End-of-Life (EoL). Here we analyze to which lifecycle stages the framework is applicable.
- **Case studies** applying the analyzed SbD frameworks were explored. Case studies are important because they substantiate the real-world applicability of the framework. Here, the SbD case studies identified in the compiled literature were linked to the corresponding frameworks.
- **EC's SSbD Framework** was used to contextualize the SbD frameworks. Our analysis first checked whether or not the SbD frameworks were already acknowledged in the JRC's report on the SSbD framework (European Commission, 2020a; European Commission, Joint Research Centre, Caldeira, Farcal, Garmendia Aguirre, et al., 2022). If not, we further extracted valuable concepts and ideas from the SbD frameworks intending to propose them for the operationalization of EC's SSbD framework.

3. Results and discussions

3.1. General trends of the SbD literature

Based on the literature selection criteria, 89 SbD studies are identified. As expected, the first trend observed in the analysis is that most SbD studies were funded by the EU or its member state(s) (see Figure S 1).

The usage of the 'SbD' term in the title, abstract, and keywords in the compiled literature can be seen in Fig. 1(a). Interestingly, 20 SbD or SSbD-oriented studies did not use these terms in the title, abstract, or keywords, and yet showed up in the search results due to the proximity of 'safe' and 'design' terms in the respective texts.

In Fig. 1(b), the applicability and sector of origin of the studies can be seen. Most SbD literature is found to be oriented toward nanomaterials since the 'SbD' concept's origin lies in the nano sector. Taking into account this origin, the gathering of literature was conducted in a targeted manner from nano-focused publications and projects and thus to some extent is biased. Hence, SbD studies compiled from other sectors, e.g., conventional chemicals, were thus limited. Interestingly, the literature does to some extent cover conventional materials and products as well.

Regarding the safety categories considered, Fig. 1(c) highlights that more literature covers human safety aspects than environmental safety aspects. The reason is that human safety is often by default a higher priority since the application of nanomaterials is often envisioned in human proximity. Hence, most nano-safety and SbD literature focus on toxicity, exposure, and consequent risk to humans (examples would be use-phase exposure or compromised occupational health and safety due to nanoparticle dust during production). The actual toxicity of nanomaterials has also been widely explored and to a greater extent than their exposure and risk/impacts as depicted in Fig. 1(d). These results highlight the inclination of researchers towards the assessment of inherent hazards of materials that also align with the SSbD framework.

Fig. 1(e) pictorially presents an overview of the compiled SbD literature and shows aspects such as the count of literature proposing novel tools, or simply adapting existing ones. Importantly, the number of review studies as well as case studies are found to be a significant proportion of the literature, which could be beneficial because both can offer more guidance for and insights into operationalizing SbD and SSbD. However, if in a nascent field, too many reviews exist without an appropriate number of actual studies providing input, then this could point to some underlying issues in actually concretizing the general concept. This could however also highlight that there is a high interest in the field from various stakeholders that request results before the actual work has been done. In addition, academic commentaries on SbD and its role have been included within the scope of this analysis as they offer insights into the development of a stronger conceptual basis for SbD and SSbD. Moreover, the implementation of the SSbD framework affects many different stakeholders, so studies from SbD incorporating

Table 3
The 14 SbD frameworks identified in this study and their relevance to the JRC's SSbD Framework; the S. No. indexed according to Table S 1.

S. No.	SbD Framework	Tools	Applicability	Guidance	By-design	Lifecycle	Case Study	JRC's SSbD Framework
2	SbD Strategies for Safer Nanomaterials in Nanomedicines (Yan et al., 2019)	Review	Specific: NMs used in Nanomedicine	SbD strategies for Nanomedicine: - Current approaches and best practices - General principles for safer design	Early-stage	Not a focus so only production covered	Absent but based on case studies of others	Not included; could be included as quick guidance for SSbD in Nanomedicines
3	GoNanoBioMat SbD approach (Schmutz et al., 2020)	Questionnaire, Flowcharts	Specific: proposed only for NMs but universally applicable	Three-pillar design of SbD: - Safe nanomaterials - Safe production - Safe storage and transport	Early-stage	Not explicitly defined but production, use & partially end-of-life (EoL) covered	Absent	Referenced and three-pillar design of SbD briefly described
5	Integrative SbD Approach (Salieri et al., 2021)	RA, LCA, Socio-economic Assessment (SEA)	General: chemicals, materials, products & processes	Iterative design guidance is provided according to which SbD analysis, LCA, and SEA should be carried out sequentially	Stage-gate	All included in LCA	Present	Referenced; the sequential order of RA, LCA, and SEA proposed is also seen in the SSbD framework
14, 16	NanoReg2 Approaches (Dekkers et al., 2020; Tavernaro et al., 2021)	Questionnaire, Flowcharts	Specific: proposed for NMs but applicable universally	- Three pillars of safe(r) material, production and EoL - Relevant human health safety aspects for consideration mapped along Stage-gate - "go or no-go" strategy to balance functionality and safety to support decision-making in the innovation process	Stage-gate	All stages are included indirectly in the questionnaire and pillars	Present (Sánchez Jiménez, Puelles, et al., 2022; Soeteman-Hernández et al., 2020)	Referenced and described under SbD
26	Decision Supporting Tools for Safe NMs (Som et al., 2013)	Decision Trees, RA	Specific: proposed for NMs but applicable universally	Relevant physical and toxicological properties of NMs are relevant during the production and product life phase	Early-stage	Production and use	Absent	Not directly referenced but conceptually similar to the NanoReg2 framework
29	GRACIOUS (Stone et al., 2020)	Decision Trees, Grouping, Read-across Lists	Specific: NMs only; hypothetically, the methodology possible to extend to other chemicals and products	- Facilitates the application of grouping of nanomaterials or nanoforms (NFs), in a regulatory context and supports innovation - Hypothesis testing for novel NMs for which no data is available based on existing data	Stage-gate	Production and use emphasized	Present (Wohlleben & Stone, 2022)	Not included but approach relevant for quick and easy SbD consideration when data is absent
39	SbD for the conservation of works of art (Semenzin et al., 2019)	EU CLP, Ecotoxicity assessment, RA, LCA, SEA	Specific: proposed for NMs but applicable universally	Iterative assessment of: State of the art; Initial formulation; Hazard Screening (EU CLP); Advanced toxicology; Safety; and Sustainability	Stage-gate	All stages considered	Hypothetical one presented	Not included but heavily inspiring the overall SSbD methodology (scoring system)
46	Developing a Safe-by-Design Manufacturing Approach (Karayannis et al., 2019)	Decision Trees, Flowcharts, Step Hierarchies, Hazard Assessment	Specific: only to pilot production line (PPL)	A pilot production system described for manufacturing of microchips and possible hazards or risks in the production line and their mitigation plans mapped	Early-stage	Production	Present	Not included but study relevant to illustrate possible application and development of SSbD production processes
50	ASINA (Furxhi, Bengalli, et al., 2023)	Hazard criteria assessment	Specific: proposed for NMs but applicable universally	Using Bayesian network structure and expert reasoning to determine intrinsic hazard criteria relevant for safety during synthesis	Early-stage	Production	Present	Published recently so not included but relevant as it shows in-silico methods can assist in identifying relevant hazard criteria and their relationships for novel materials
55	NANoREG Safe Innovation Approach (Micheletti et al., 2017)	RA, Stakeholder Dialogue	Specific: proposed for NMs but applicable universally	Safe Innovation Approach Elements: - SbD approach to include RA in all innovation stages - Regulatory preparedness using stakeholder dialogue	Stage-gate	Production	Present	Not included but essential concepts preserved in the NanoReg2 approach which is included in the SbD section of SSbD

(*continued on next page*)

Table 3 (*continued*)

S. No.	SbD Framework	Tools	Applicability	Guidance	By-design	Lifecycle	Case Study	JRC's SSbD Framework
64	LICARA nanoSCAN (van Harmelen et al., 2016)	RA, SEA, LCA, Precautionary Matrices	Specific: proposed for NMs but applicable universally	A modular approach to estimate both risks (environmental, occupational, and consumer) and benefits (economic, environmental, and societal) for novel materials	Early-stage	Production	Present	Referenced as a decision support tool
65	NanoCRED (Hartmann et al., 2017)	Questionnaire, Assessment Criteria, Decision Support	Specific: NMs for which conventional toxicity tests are insufficient	Reliability and relevance evaluation of ecotoxicity data for NMs obtained from non-standardized tests to ensure regulatory validity	Early-stage	Production	Absent but a user manual is available	Not referenced but relevant because non-regulatory testing of NMs and assessing their validity is critical for SbD
83	Benefit Assessment Matrix (Hong et al., 2023)	Decision Matrix	Specific: proposed for NMs but applicable universally	- Contrasts benefits of NM products with conventional reference products - Evidence of perceived benefit needs to be validated - Along with inherent risks, does the proposed innovation truly bring value?	Stage-gate	Production and use	Present	Published recently so not referenced directly but overarching concepts are covered also in the LICARA nanoSCAN; however, the inclusion of material functionality and its consequent benefit is missing
88	Computer-based SSbD for Chemicals (van Dijk et al., 2022)	QSAR, MCDA	Specific: proposed for chemicals but applicable universally	Early-stage determination of biodegradability of chemicals belonging to certain class should be considered for the successful realization of a circular economy	Early-stage	EoL	Present	Published recently so not included but a great example of an in-silico high-throughput multi-criteria SSbD decision optimization

stakeholder input can guide the implementation of the frameworks in a manner that is satisfactory for stakeholders while also highlighting key 'human' challenges associated with operationalizing the frameworks. Finally, our analysis emphasizes the inclusion of either the stage-gate model or an early-stage implementation as a prerequisite for SbD since both of these cover the 'by-design' aspects. Based on this mapping of literature, 29 out of 89 studies directly contain some element of 'by-design'.

3.2. Trends of the reviews of SbD tools

As depicted in Fig. 1(e), 38 reviews in total were identified in this analysis, out of which 19 were reviews of SbD tools. Table 1 contains the summary of these reviews of tools and categorizes them based on a detailed background study analyzing each one (see Table S 2).

Evidently, 9 out of the 19 tool reviews are categorized as toolboxes or repositories implying that there is a significant number of SbD tools and toolboxes already available that could be utilized for SSbD. Furthermore, some toolboxes incorporate the stage-gate model and have thus clearly identified suitable tools for the early-innovation stages. Additionally, it is possible to use the existing toolboxes as inspiration for the future design of SSbD toolboxes to operationalize the framework and to understand the procurement and development of tools that fit in the different stages of the stage-gate model.

Literature dealing with quantitative scoring of tools is typically considerate of the stage-gate model and incorporates it in the scoring of tools. Data and financial constraints during early-innovation stages are readily acknowledged by and central to these quantitative scorings. Two studies (Franken et al., 2020; Sørensen et al., 2019) score the tools based on their applicability, fitness, and performance at individual stages of the stage-gate before ranking them. This approach is important to quantitatively assess and give preference to SbD tools that perform well under data constraints and can be implemented simply without requiring high time and effort.

Most qualitative reviews of tools have not considered the stage-gate model in their assessment approaches. The JRC published a review of tools and methods to support the operationalization of the SSbD framework that evades categorization of and ordering tools along the stage-gate model despite the latter being central in the SSbD framework (European Commission, Joint Research Centre, Caldeira, Farcal, Moretti, et al., 2022). Only one study considers the stage-gate model in detail and qualitatively analyzes the applicability of different tools at each stage (Subramanian et al., 2023).

As also observed in Table S 2, another aspect worth highlighting is that many reviews of SbD tools, e.g., Guinée et al. (2022), ignore stage-gate in favor of a lifecycle approach in their reviews. In other words, the reviews of SbD tools either assess the suitability of tools at individual lifecycle stages (production, use, and EoL), or different stages of the stage-gate. This is essential because both approaches have different scopes: the stage-gate only deals with the innovation process, i.e. it is limited to the production stage in the lifecycle (OECD, 2020). This underscores a gap and a need to reconcile the lifecycle and the stage-gate models for SSbD so as to apply these two different concepts simultaneously rather than favoring one over the other.

3.3. Trends of the SbD case study

Table 2 lists and categorizes the 45 case studies identified; more details are provided in Table S 3. The first split between 18 conventional studies and 27 true SbD cases shows that the majority of the case studies contain actual SbD work and illustrate the application of the SbD concept in reality. At the same time, the number of case studies that conducted conventional toxicity, exposure, and risk analysis but were mislabeled as SbD, is still a significant proportion (40 %), indicating that the misuse and misunderstanding of the 'SbD' terminology ('SbD-washing') is a prevalent problem. In Table 2, literature reviews and general guidance dominate the conventional study category.

Within the 27 true SbD case studies, safe-by-selection and –redesign approaches are predominant. For example, the recent case study from the JRC showing the application of the SSbD framework is a safe-by-selection study (Caldeira et al., 2023). The high number of safe-by-selection studies indicates that comparing the safety parameters of different alternatives for the same application is a prevalent SbD idea. Preceding the safe-by-selection approach is the idea of redesigning materials to reduce toxicity and improve their safety profiles. Both the safe-by-selection and –redesign approaches typically utilize conventional safety assessment methods, i.e., time-consuming, expensive, and expertise-hungry lab tests. Hence, safe-by-selection, and –redesign approaches, although conceptually SbD, do not offer a quick and cheap assessment of novel developments at an early-innovation stage. Furthermore, it must be highlighted that all of these safe-by-selection and –redesign studies have been carried out within EU projects and their true potential for industrial application is unclear.

In-silico safe-by-modeling approaches on the other hand are quick, require less effort, and could be simpler to implement. Furthermore, in-silico safe-by-modeling approaches could be automated to assess thousands of substances simultaneously, which is not possible with conventional lab testing due to the amount of human effort required (Nymark et al., 2020). Modern laboratory equipment and methods may allow for high-throughput chemical testing (Davenport et al., 2022), and yet, in the compiled SbD literature, no instances of high-throughput safe-by-selection or –redesign were observed. As shown in Table 2, the number of safe-by-modeling case studies is low, and only one case study for chemicals was found to implement high-throughput testing (van Dijk et al., 2022). This may highlight the unavailability of validated computational models, particularly in the nano-sector, for the safe-by-modeling approach. In the chemicals sector, it could be easier to implement the safe-by-modeling approach because models to predict various physicochemical and hazardous properties of chemicals have been developed over the past decades (Davenport et al., 2022). Thus, it is necessary to properly acknowledge and map existing computational chemistry and cheminformatics work (Sessions et al., 2020; Stratton et al., 2015), and to contextualize all of it for SSbD (the relevant models likely exist and need to be repurposed and used for SSbD).

This result underscores the challenges of the safe-by-modeling approach. For example, it is fairly easy to implement once the modeling infrastructure has been established. However, setting up such infrastructure, including building databases for the models and validating them, is effort-intensive and often requires results from high-quality lab tests in sufficient numbers. Furthermore, even after the establishment of necessary models, regular retraining and validation of the models would be required to ensure a good data basis and expand the models' applicability domain. Otherwise, the model prediction would be unreliable and their use would be futile, particularly for novel chemicals and materials. Further research is thus required to utilize the outputs from safe-by-selection and –redesign studies to enable safe-by-modeling with robust, reliable, user-friendly, and quick computational models.

3.4. SbD frameworks and SSbD

It is helpful to evaluate existing SbD work and its incorporation into the EC's SSbD framework to ensure that everything valuable and relevant in the formercontinues to be applied and developed further in the latter. The SSbD framework does address the SbD concept but as depicted in Table 3, not all literature deemed as a framework in this research has been referred to in the JRC's document. Out of the 14 SbD frameworks proposing valuable concepts relevant also to SSbD in Table 3, only 4 are directly referenced in the JRC's SSbD framework. One key reason for this omission is that the publication of some recent and valuable SbD literature (Furxhi, Costa, et al., 2023; Hong et al., 2023; van Dijk et al., 2022) occurred after the publication of the SSbD framework.

Another trend highlighted by the analysis of these frameworks is the focus of recent SbD frameworks (Hong et al., 2023; Rybińska-Fryca et al., 2020) on the assessment of material functionality, i.e., the actual functional benefits from the novel developments in question need to be sufficiently substantiated to warrant their development and application that may give rise to many human and environmental safety hazards and risks. Such a comprehensive discussion about chemical/material functionality is currently missing from the EC's SSbD framework. Additionally, incorporation of the chemical/material functionality aspects in SSbD can help identify cases of 'essential use' (Cousins et al., 2019) and to some degree reduce the competition between and possibly reconcile the different SSbD approaches recommended by CEFIC and EC, respectively (Roy et al., 2022). Incorporation of material functionality in SSbD is possible within the current EC framework either as an individual design principle or also as a step in the SSbD assessment. Nevertheless, challenges related to quantifying functionality may persist in SSbD and therefore further discussion about the precedence of such an assessment step or design principle and its effective integration in the SSbD framework would be necessary.

Furthermore, regular mapping of SSbD studies and frameworks needs to be undertaken to assess the evolution of the concepts, e.g., which gaps were identified in the past and how they have been bridged by different stakeholders. This of course considers that many more studies are expected to be published soon because of the launch of the SSbD framework itself and a high research interest in the topic.

4. Reflections

Our use of the keywords associated with SbD for the literature search has resulted in a lopsided analysis that sufficiently covers the area of nanosafety (since 'SbD' originates from the nano sector), but activities and principles in other sectors such as conventional chemicals, products, and processes safety were captured only to a limited extent.

To overcome this limitation, it is advisable that future studies also use other relevant keywords to select literature. For example, the concept of developing safe chemicals predates (and is thus more mature than) the SbD of nanomaterials; therefore, many important concepts and ideas pertinent to SbD and SSbD could be extracted from the frameworks on chemical safety. In the (organic) chemical sector, widely recognized frameworks and concepts that integrate safety aspects into the chemical synthesis' design and molecular design include "green chemistry" (Anastas & Warner, 1998), "circular chemistry" (Keijer et al., 2019), the broader "sustainable chemistry" framework (Blum et al., 2017; ECO-SChem, 2023; Kümmerer, 2017; Kümmerer et al., 2021), "benign by design" (R. S. Boethling et al., 2007; Kümmerer, 2007; Kummerer & Hempel, 2010), "alternatives assessments" (Arnold, 2016; Jacobs et al., 2016; Tickner et al., 2015), and "non-regrettable substitution" (Maertens et al., 2021; Zimmerman & Anastas, 2015). "Sustainable Chemistry", as characterized by the International Sustainable Chemistry Collaborative Centre (ISC3) (Kümmerer et al., 2021), specifically goes much beyond SSbD and addresses further issues such as transparency and justice, alternative business models, and alternative non-chemical approaches ("no need" for chemicals or omitting "non-essential" chemicals) to deliver a desired service, all of which are currently not explored in detail within the SSbD framework.

Furthermore, the feasibility of the "benign by design" concept has been demonstrated in different case studies, particularly pertinent to SSbD, that could be categorized according to the aforementioned SbD categories, i.e., safe(r)-by-redesign pharmaceuticals (Espinosa et al., 2022; Lorenz et al., 2022; Rastogi et al., 2015; Zumstein & Fenner, 2021), safe(r)-by-modeling pharmaceuticals (Kümmerer, 2019; Leder et al., 2021; Rastogi et al., 2014b, 2014c), safe-by-selection pharmaceuticals (Rastogi et al., 2014a), safe(r)-by-modeling fragrances (Robert S. Boethling, 2011), safe(r)-by-modeling ionic liquids (Beil et al., 2021), safe(r)-by-selection ionic liquids (Haiß et al., 2016; Suk et al., 2020), and safe(r)-by-selection biopesticides (Schnarr et al., 2022).

The aforementioned frameworks and concepts show a huge overlap with SSbD. These should therefore be utilized to refine the SSbD concept by inclusion of alternative business models and systems thinking ideas. Enlarging the scope of studies presented here to a wider range of literature would bring in further useful tools, case studies, perspectives, and insights that would benefit the operationalization of SSbD.

SbD has not been implemented in any policy but was a research tool designed to support the industry developing and making use of engineered nanomaterials in nano-enabled products. SSbD is somewhat different in this respect as it is a framework proposed as an EC Recommendation (European Commission, 2022) and is thus an official concept that is now undergoing a testing phase. Ideally, SSbD should be promoted by all EU-member states and used by industry and academia during the development of chemicals and materials. In the current testing and reporting phase, the experience gained from SbD as reported in this paper, in particular the SbD cases listed in Table 2, could be of invaluable help.

5. Recommendations

Based on our mapping and critical analysis of available SbD literature, the following recommendations may be made for further refining the SSbD concept while it is amenable:

- Preservation of existing and relevant SbD knowledge and ensuring its effective transfer to SSbD is necessary. This includes mapping and compiling nano-specific information, as well as knowledge from the conventional chemical/material sector.
- Apart from theoretical concepts and databases, available SbD tools and toolboxes offer great potential to support the operationalization of the SSbD framework, especially after their sufficient refinement and adaptation. Furthermore, it is important to go beyond nanoscience tools and toolboxes and consider the ones for conventional chemicals (e.g., benign by design, non-regrettable substitution). In particular, it is key to map safety and sustainability tools and toolboxes according to the innovation process and identify those that can be used early in the innovation process.
- SSbD should focus deeper on the proven functionality and functional benefits of innovation. Innovation is driven by societal needs. Thus, not only safety and sustainability benefits but also the functional benefits from innovation should be accounted for in SSbD.
- Currently, a mutual exclusivity in the adoption of the lifecycle thinking and the stage-gate model is evident in SbD frameworks. Thus, research is required to combine these different approaches for SSbD to avoid potential conflicts.
- Based on the present mapping, high-throughput SbD studies are scarce. Therefore, it is necessary to further develop and demonstrate the use of high-throughput and computational SSbD tools that can operate under data and time constraints for operationalizing SSbD.
- Past work and case studies from the sectors of chemical safety, sustainable and green chemistry, and benign-by-design should be explored further, as although not labeled as such, they are relevant to SbD and consequently SSbD.
- Finally, the skyrocketing interest of various academic, political, and industrial stakeholders in SSbD since the launch of the EC's framework underscores the need to regularly map the landscape of upcoming literature on tools and methodologies for SSbD.

CRediT authorship contribution statement

Akshat Sudheshwar: Methodology, Investigation, Formal analysis, Writing – original draft, Visualization. **Christina Apel:** Writing – original draft, Writing – review & editing. **Klaus Kümmerer:** Writing – original draft, Writing – review & editing. **Zhanyun Wang:** Writing – original draft, Writing – review & editing. **Lya G. Soeteman-Hernández:** Writing – original draft, Writing – review & editing. **Eugenia Valsami-Jones:** Writing – original draft, Writing – review & editing. **Claudia Som:** Writing – original draft. **Bernd Nowack:** Writing – original draft, Supervision.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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