The international ecosystem for accelerating the transition to Safe-and-Sustainable-by-design materials, products and processes.

Safe by design methods and criteria mapping

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Abbreviations and Acronyms

Abbreviation	Definition
CEFIC	The European Chemical Industry Council
Chesar	Chemical Safety Assessment and Reporting tool by ECHA
CLEPA	European Association of Automotive Suppliers
CLP	The Classification, Labelling, and Packaging Regulation
COSHH	COSHH Essentials by the British Institute of Occupational Safety (Health and Safety Executive, HSE)
CSS	Chemical Strategy for Sustainability
EC	European Commission
ECETOC TRA	Targeted Risk Assessment tool by ECETOC
ECHA	European Chemicals Agency
EFCC	European Federation for Construction Chemicals
EMIRI	Energy Materials Industrial Research Initiative
EMKG	Easy-to-use Workplace Control Scheme for Hazardous Substances Tool
EoL	End-of-Life
ERA	Environmental Risk Assessment
ETP	The European Technology Platform
EU	The European Union
GHS	German Hazardous Substances Column Model
HRA	Human Risk Assessment
ILO	International Labor Organization
IPC	Industrial Technical Centre for Plastics and Composites
JRC	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

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OSHA	Occupational Safety and Health Assessment
QNAR	Quantitative Nanostructure-Activity Relationship
QSAR	Quantitative Structure-Activity relationship
RA	Risk Assessment
REACH	Regulation on the Registration, Evaluation, Authorization, and Restriction of Chemicals
REGETOX	Belgian REGETOX Model
SbD	Safe-by-Design
SEA	Socio-Economic Assessment
SME	Small and Medium Enterprise
SSbD	Safe and Sustainable-by-Design
Stoffenmanager	Dutch Stoffenmanager Model
SusChem	European Technology Platform for Sustainable Chemistry

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1. Summary

With the introduction of the Joint Research Center (JRC) and the European Commission's Safe and Sustainable-by-Design (SSbD) framework, the interest in ensuring the safety and sustainability of materials at the early stages of innovation has skyrocketed. However, before the launch of the SSbD framework, the Safe-by-Design (SbD) approach was already prevalent in the nanomaterials sector. This study aims to preserve and carry forward valuable learnings and knowledge from previous SbD work to benefit SSbD while also identifying shortcomings of the former that could also plague the latter.

In this assessment, all available SbD literature has been compiled and analyzed. Firstly, a general landscape of the SbD studies has been painted. This is followed by a detailed analysis of studies reviewing SbD tools, applying SbD in case studies, and describing SbD frameworks. The reviews of SbD tools have been categorized as quantitative, qualitative, or toolboxes and repositories. SbD case studies on the other hand have been assessed and classified into three newly defined but non-standardized SbD categories: safe(r)-by-modelling, safe(r)-by-selection, or safe(r)-by-redesign. Moreover, the pre-existing SbD frameworks have been studied and contextualized against the SSbD framework. Finally, recommendations for future research have been proposed based on the deficiencies identified within the SbD and SSbD approaches, because of the extensive literature mapping exercise undertaken within this study.

Recommendations proposed include: the need for preservation of and effective transfer of past SbD, green and sustainable chemistry, and benign-by-design knowledge to SSbD; using proven material functionality and its benefits to support the 'hazard-based' approach of the SSbD framework; reconciling concepts of lifecycle thinking and the stage-gate innovation model for SSbD; need for further development of high throughput SSbD models and conducting case studies for the same; and finally, undertaking regular literature SSbD mapping exercises.

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2. Introduction

Safe and Sustainable-by-Design (SSbD) is a key component of the European Commission's (EC's) Chemical Strategy for Sustainability (CSS) and it is a pre-market 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 Aguirre, et al., 2022). The integration of safety and sustainability assessment methods has been a key research area in the discipline of environmental sciences; despite their interlinkages, the challenge of combining these two assessments has persisted over the last few years (Nawaz et al., 2019). In the past, the integration of environmental risk assessment (RA) and lifecycle assessment (LCA) would be considered a successful attempt at combining safety and sustainability (Harder et al., 2015; Salieri et al., 2021; Subramanian et al., 2023). However, the perception about, objectives of, and motivations behind combining the safety and sustainability methods has changed in academia since the introduction of the Joint Research Centre's (JRC's) Safe-and Sustainable-by-Design (SSbD) framework (European Commission, Joint Research Centre, Caldeira, Farcal, Garmendia Aguirre, et al., 2022) that is backed by the European Union (EU).

The interest in finding ways to practically apply SSbD is currently very 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 REACH (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 corporates as well as small and medium enterprises (SMEs) in the EU (Directorate-General for Research and Innovation, 2022). The SSbD framework issued by JRC 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 risk of rejection at compliance stage is minimized (OECD, 2020; Soeteman-Hernández et al., 2020). To achieve this, the JRC's SSbD framework comprises of 8-design principles and 5 assessment steps of which 3 design principles and 3 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 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 hazardous materials without considering the exposure aspects and consequent risks from the use of hazardous chemicals. This intrinsic hazard (Lynch et al., 2014) based elimination approach at an early development stage of the framework, if legalized, will bring about a paradigm shift in the development of new chemicals, materials, processes, and products because hazard considerations will become pivotal to the design process.

The JRC has already conducted case studies (Caldeira et al., 2023) to test the implementation of the SSbD framework, and several practical challenges have been identified including obtaining and

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generating data, gathering internal and external expertise, and identification of valid tools (Stringer, 2023). The breadth of the framework also implies that implementation of all five steps is time-consuming and therefore expensive. Furthermore, the comprehensive nature of the framework demands a high level of expertise for the SSbD assessment making its implementation early in the innovation process difficult, particularly for SMEs that often face resource and time restrictions. Apart from SMEs, large corporates, often utilizing materials for precisely their toxic functionality, may also suffer because of the hazard-based approach of the SSbD framework. Consequently, the hazard-based approach is not readily accepted by industrial lobbies as evident from the competing risk-based SSbD approach proposed by the European Chemical Industry Council (CEFIC, 2021).

Despite all its challenges, the SSbD framework provides the necessary building blocks and is a step in the direction to protect human health and the environment and to ensure that we operate within the planetary boundaries. This assessment aims to particularly abate possible challenges to SSbD by considering and mapping similar work already done on early-stage safety assessments. As acknowledged within the JRC's framework (European Commission, Joint Research Centre, Caldeira, Farcal, Moretti, et al., 2022), before the SSbD framework, the concept of Safe-by-Design (SbD) was developed by the nanotechnology sector (Krans et al., 2021; Schmutz et al., 2020; van de Poel & Robaey, 2017). Novel nanomaterials, with their specific and high functionality, can create many different and pose new toxicological challenges and threats that are not of concern in 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 generated 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 to therefore map and analyze the current landscape of SbD literature and contextualize it against the SSbD framework. There are detailed studies (Furxhi, Costa, et al., 2023; Guinée et al., 2022; Kraegeloh et al., 2018; Subramanian et al., 2023) in the past reviewing SbD methods and framework originating the nano sector however, this assessment aims to have a wider scope and considers the newly-changed and actual policy background (since the introduction of the JRC's SSbD framework). Furthermore, the goals of this study are: a) to identify key SbD literature that can be useful in resolving current issues in the JRC's framework; b) to highlight additions that can supplement the SSbD framework; and finally, to identify the research needs and deficiencies in a very targeted manner that already existed in the SbD sector that need to be bridged to further facilitate and operationalize SSbD.

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3. Methods

3.1 SbD Literature Compilation and Analysis

In the first step of this assessment, a literature search was carried out on Google Scholar until 15th March 2023 using the keywords "safe by design". Apart from the google scholar search, all articles in the special edition of the journal Nanoimpact focusing on SbD (Sánchez Jiménez, Rodríguez Llopis, et al., 2022) were considered for the assessment. Furthermore, the Zotero library maintained by the NanoSafety Cluster (EU NanoSafety Cluster, 2023) contains a list of publications from EU projects on nanomaterials; to obtain more literature, this library was queried for the keywords "nanosafety" and "safe(r)-by-design". Finally, case studies conducted within the Gov4Nano project (Gov4Nano, 2023) were included in the assessment.

The resulting research publications included SbD in their title, abstract, and/or keywords; many resulting publications also contained the words "safe" and "design" in proximity to each other. Most of the literature obtained was about safety in engineering and product design and was thus excluded from the scope of this assessment. All literature remotely pertaining to environmental safety and sustainability was included in the assessment. Many studies were not labeled or classified as SbD but contained SbD information and were therefore included in the scope of this assessment. 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 was further objectively analyzed based on the following criteria:

- **Use of 'SbD':** assess whether the 'SbD' or 'Safe-by-Design' term has been used in the title, keyword, or abstract because use in these sections implies high relevance to SbD as perceived by the author.
- **Origin/Applicability:** answer exactly which research field is the literature source from or applicable to; for example, if a case study focuses on chemical safety, then it's origin/applicability will be 'Chemical'
- **Safety Category:** analyze whether the study addresses environmental and/or human safety endpoints
- **Tool Proposed/Applied:** corresponding to the JRC's framework (European Commission, Joint Research Centre, Caldeira, Farcal, Garmendia Aguirre, et al., 2022), to which SSbD step is the tool proposed or applied in the study relevant i.e. toxicity (hazard assessment), exposure (occupational health and safety), risk (environmental and human risk), or LCAs (sustainability).
- **Literature Coverage:** a broad landscape of the literature painted by assessing if the study proposes a new tool, uses an existing tool, promotes an adapted tool, conducts a case study, offers guidance, reviews literature or tools, offers scientific commentary, includes stakeholder feedback, and somehow incorporates the 'by-design' aspect by considering the stage-gate model (Cooper, 1990) or early-stage design considerations.

A single study may fulfill multiple groupings in the same criteria, i.e. doubling counting within the same criteria has been implemented in this assessment. For example, the JRC's SSbD framework (European Commission, Joint Research Centre, Caldeira, Farcal, Garmendia Aguirre, et al., 2022)

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addresses all kinds of environmental tools so for the tool proposed/applied criteria, it will be counted under toxicity, exposure, risk and also LCA. Similarly, a study (Shandilya & Franken, 2020) that covers both environmental and human toxicity aspects will be counted in both safety categories. Within the literature coverage criteria, a special emphasis is placed on the further analysis of reviews, case studies, and frameworks to map the current SbD landscape, understand where the gaps lie, and attempt to extract beneficial aspects for SSbD.

3.2 SbD Tool Reviews

'Reviews' is the first literature category analyzed here in detail. However, instead of just assessing all review literature on SbD, the assessment scope was limited to reviews focusing on available tools and methods. Focus on tools is necessary because the dearth of tools has been recognized as a challenge in the implementation of SSbD (Stringer, 2023). Thus, this scope was selected to broadly understand the availability of SbD tools and toolboxes and how they may be further applied to resolve the perceived challenges in the operationalization of SSbD. The analysis of tool reviews has been undertaken here while ensuring a broad definition of the term 'review'. In the present study, tool reviews have been classified as:

- **Quantitative Scoring:** 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 from tools designed for similar application
- **Toolboxes or Repositories:** They 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:** These also critically analyze each tool qualitatively without the use of scoring; ranking of tools is harder but the benefits and shortcomings of the individual tools are laid out along with details about possibilities and requirements for future development

Apart from the classification of reviews, the analysis also considers whether the stage-gate model has been 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. Hence, if reviews are capable of already ordering the tools along the stage gate, then they already provide valuable and actual SbD tools and toolboxes directly applicable (albeit with necessary modification) to SSbD.

3.3 SbD Case Studies

This assessment analyses SbD case studies 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.

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Hence, SbD frameworks without evidence of application in a case study would also have limited credibility.

Here, a 'case study' involves the application of methods and tools for specific chemicals, materials, processes, and products. Sectoral case studies (Robaey, 2018; Yan et al., 2019) that deal with general trends in a sector have been excluded from the assessment since they do not focus on the specifics of chemicals or materials and often do not apply specific methods and tools. As detailed in further subchapters, here case studies are firstly classified as *SbD studies* or *Conventional studies*, and then their *Sample Size* is assessed. The objective here is to underscore the state-of-art in SbD along with its deficiencies. An additional objective is to understand which studies are truly SbD and which ones have been mislabeled.

3.3.1 SbD Studies

SbD studies are true to their classification and illustrate how the safety of materials, chemicals, processes, and products can be ensured 'by design' at an early-innovation stage. This assessment identifies the following specific classes of SbD studies based on their respective methods:

- **Safe(r)-by-Modeling:** typically apply in-silico predictive methods and NAMs (such as QSARs and QNARs) for safety assessments at an early-innovation phase of chemicals, materials, and processes
- **Safe(r)-by-Selection:** This implies that from a list of materials considered for an application, the ones with superior safety profiles are selected during the design phase; conventional lab testing methods are applied for the assessment of safety profiles
- **Safe(r)-by-Redesign:** It entails that the safety profile of an existing material envisioned for a certain application is improved through human intervention, 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 at classifying SbD case studies and are by no means standardized. Experts are now slowly deliberating on the above-stated terms along with terms such as 'Safe(r)-by-Comparison' and 'Safe(r)-by-Substitution' to facilitate the classification of SSbD work. Despite the definitions provided above, studies cannot be categorically placed in one class versus another. Since all the classes 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 case studies 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 classification has been conducted. For example, a study will be classified as safe-by-redesign, if it involves multiple redesigns of existing material and then the selection of the best alternative.

3.3.2 Conventional Studies

Many conventional safety or sustainability assessments that use the SbD tag but are seemingly mislabeled have been identified in this assessment: for example, conventional toxicity assessments that have a 'safety' component but lack the 'by-design' element. The toxicity assessment of a

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chemical and its degradation products may be tagged as SbD (Bae et al., 2019) but this is a case of mislabeling if the study does not propose alternatives or recommend eschewing use in case of an observed environmental risk. To fulfill the 'by-design' criteria, studies need to apply some comparison, selection, and/or iterative approaches at an early stage of innovation and design. Conventional studies often mislabeled as SbD assessments identified in this assessment are: *a) Toxicity Analysis, b) Exposure Assessment, c) Risk Assessment, d) Literature Reviews,* and *e) General Guidance.* The classification of case studies as *General Guidance* was necessary in case the study lacked a 'safety' component, i.e. toxicity, exposure, or risk.

3.3.3 Sample Size

The sample size of the case study refers to the number of alternatives compared by the study for SbD purposes. The following categories have been defined:

- **Single:** refers to the assessment of one material; for example, safe-by-redesign of a material to produce one safer alternative or safe-by-selection of a material by comparison to a threshold or safe-by-modeling involving predicted toxicity of single material
- **Multiple:** implies more than one alternative has been considered and evaluated in the case study
- **High Throughput:** studies assess hundreds and thousands of alternatives simultaneously; typically, possible only during safe-by-modeling studies.

Assessing the sample size of a case study is relevant because, at 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 speed during application. It is also important to note that the sample size classification has been carried out based on exactly what the studies contain and demonstrate; for example, an in-silico case study handling one material would be classified as 'single' despite the tool could possess high-throughput capabilities.

3.4 SbD Frameworks

Since the SbD concept predates SSbD, SbD frameworks from the nano-sector are available that were conceived to guide the development of safe nanomaterials. Hence, as a last part of this assessment, we examine the available SbD frameworks to assess their strengths, weaknesses, and applicability considering today's policy landscape. For this assessment, *an SbD framework consists of at least one tool, guidance to use the tool, and finally some 'by-design' elements.* Past efforts and investments made to develop and refine SbD frameworks entail that they may have valuable content for the SSbD framework failing to incorporate which may create competition between frameworks.

The frameworks have been assessed in this article based on the following criteria:

- **Tools:** have been considered under a very broad definition in this assessment; numerical methods, computational models, decision trees, flowcharts, etc. are all classified as tools; furthermore, for the assessment of the frameworks, the 'specialization' of the tool has been ignored, so even frameworks free of safety tools such as LICARA nanoSCAN (van Harmelen

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et al., 2016) and Benefit Assessment Matrix (BAM) (Hong et al., 2023) have been considered in the framework assessment.

- **Applicability:** deals with the scope and origin of the framework; most frameworks originate in the nano sector and are apt for application to nanomaterials; nevertheless, this assessment also evaluates if the application of these frameworks (especially conceptually) may be extended beyond nanomaterials to chemicals, conventional materials, products, and processes
- **Guidance:** implies apart from the tool, what instructions or concepts the framework proposes. Again, the definition is general and considers aspects such as the 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 material safety already at the early-design phase and are therefore applicable under data and funding constraints
- **Lifecycle:** stages include production, use, and End-of-Life (EoL); the assessment involves analyzing which of the lifecycle stages is the framework applicable to; as observed from the review results (see Table S 2 in Annex S2), the lifecycle suitability and stage-gate incorporation seem to be mutually exclusive, and to validate this, the assessment criteria has been considered
- **Case studies:** conducted within the scope of the analyzed SbD frameworks are explored; case studies are important because they substantiate the real-world applicability (beyond theory) of the framework; the case studies identified in compiled literature are linked to corresponding frameworks at this stage
- **JRC's SSbD Framework:** criteria contextualize the assessed SbD frameworks against the SSbD framework; the aim is to first check if the said SbD framework is already acknowledged within the JRC's report and if not, to extract valuable concepts and ideas from the SbD frameworks for SSbD.

3.5 Survey

Apart from the literature mapping, a survey was conducted as a part of this assessment to understand the status of SbD application and competencies in both academia and industry. This survey was shared amongst academic partners involved in EU projects such as PARC and IRISS. Furthermore, the survey was shared with non-academic participants of the IRISS workshop who consented to receive the survey. Finally, the connections between companies and the organizations representing the value chains in IRISS (CEFIC, SusChem, CLEPA, EMIRI, ETP, EFCC, and IPC) were leveraged to source responses from the former. The survey was active and open to responses for around four months between mid-November 2022 and end-of-February 2023.

The results obtained from the survey were further analyzed and segregated between academic (including Universities, RTOs, public authorities, NGOs, and others) and industrial (only including Companies) respondents. The reason for splitting the results in this manner was to understand the

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prevalent tools and methods relevant to SbD that are applied in practice for large-scale manufacturing and how these differ from the academic perspectives on the same.

The entire survey exhaustively covered questions on all different aspects of SSbD and specifically the SbD section of the survey is available in Annex S4. The SbD survey section was designed by considering the safety assessment aspects covered in the JRC's SSbD framework. There were essentially three queries posed to the respondents:

1. If they apply the SbD assessments, which past framework proposed by EU projects do they use? This was done to understand if there is any 'real-world' application of the past SbD work. The list of SbD frameworks was compiled based on the list provided in the JRC's SSbD framework and past reports reviewing SbD frameworks (Krans et al., 2021).
2. If they apply early-stage hazard assessment approaches for novel developments, which tools or methods do they use for the same? This question is relevant because the hazard-based approach of the SSbD framework prioritizes hazard assessment as the first step of the SSbD assessment.
3. Finally, if they conduct occupational health and safety assessments (OSHA), human risk assessments (HRA), and environmental risk assessments (ERA) for their novel products, which tools do they use for the same? These assessments correspond to steps two and three of the SSbD assessment approaches and there is a list of OSHA, HRA, and ERA tools in the JRC's framework which was also included in the survey.

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4. Results and Discussions

4.1 SbD Literature's General Trends

Based on the literature selection criteria, 89 SbD studies were identified. A list of the compiled studies can be found in Table S 1 in Annex S1 and their detailed analysis can be found in the digital appendix. As expected, the first trend observed in the analysis is that most SbD studies were funded by the EU or one of its member states (see Figure S 1 in Annex S1). Apart from funding, the usage of the 'SbD' term in the title, abstract, and keywords in the compiled literature can be seen in Figure 1(a). Neither in the title nor the abstract nor the keywords, the count of 'SbD' reaches 89; therefore, it is evident that some of the compiled literature, although SbD or SSbD oriented, showed up in the search due to the proximity of 'safe' and 'design' terms in the respective texts.

In Figure 1(b), the applicability and sector of origin of the study can be seen. As expected, most SbD literature was found to be oriented toward nanomaterials since the 'SbD' concept's origin lies in the nano sector. Because of this origin, the gathering of literature was also biased since some of it was collected in a targeted manner from nano-focused publications and projects. The subsequent coverage and applicability of methods in these studies to other sectors in comparison to nano are thus limited; this is particularly concerning for chemicals since currently the SSbD framework primarily targets the chemical sector. Interestingly, the literature does to some extent cover products and conventional materials too.

Regarding the safety categories considered, Figure 1(c) highlights that more literature covers human safety aspects than environmental safety aspects. A key reason for the same is that application of nanomaterials is often envisioned with close human contact; hence, most nano-safety and SbD literature focus on toxicity, exposure, and consequent risk to humans (examples would be use-phase exposure or debilitated occupational health, and safety due to nanoparticle dust during production). Consequently, the actual toxicity of nanomaterials has also been widely explored and to a greater extent than their exposure and risk impacts as depicted in Figure 1(d). This approach also seems to show an inclination of researchers towards the assessment of inherent hazards of materials that aligns more with the SSbD framework as well. Furthermore, there were a few SbD studies also applying LCA methods.

Figure 1(e) maps the current landscape of SbD literature and shows aspects such as the count of literature proposing novel tools, or simply adapting existing ones. More importantly, the number of review studies as well as case studies are found to be a significant proportion of the literature, which is beneficial because both can offer more guidance insights into operationalizing SbD and SSbD. Academic commentaries on SbD and its role have also been included within the scope of this assessment as offer insights into the development of a stronger conceptual basis for SbD and consequently SSbD. Implementation of the SSbD framework also affects many different stakeholders, so studies from SbD incorporating 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, this assessment emphasizes the inclusion of either the stage-gate model or an early-stage implementation as a prerequisite for SbD

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since both cover the 'by-design' aspects. Based on this mapping of literature, 29 out of 89 studies directly contain some element of 'by-design'.

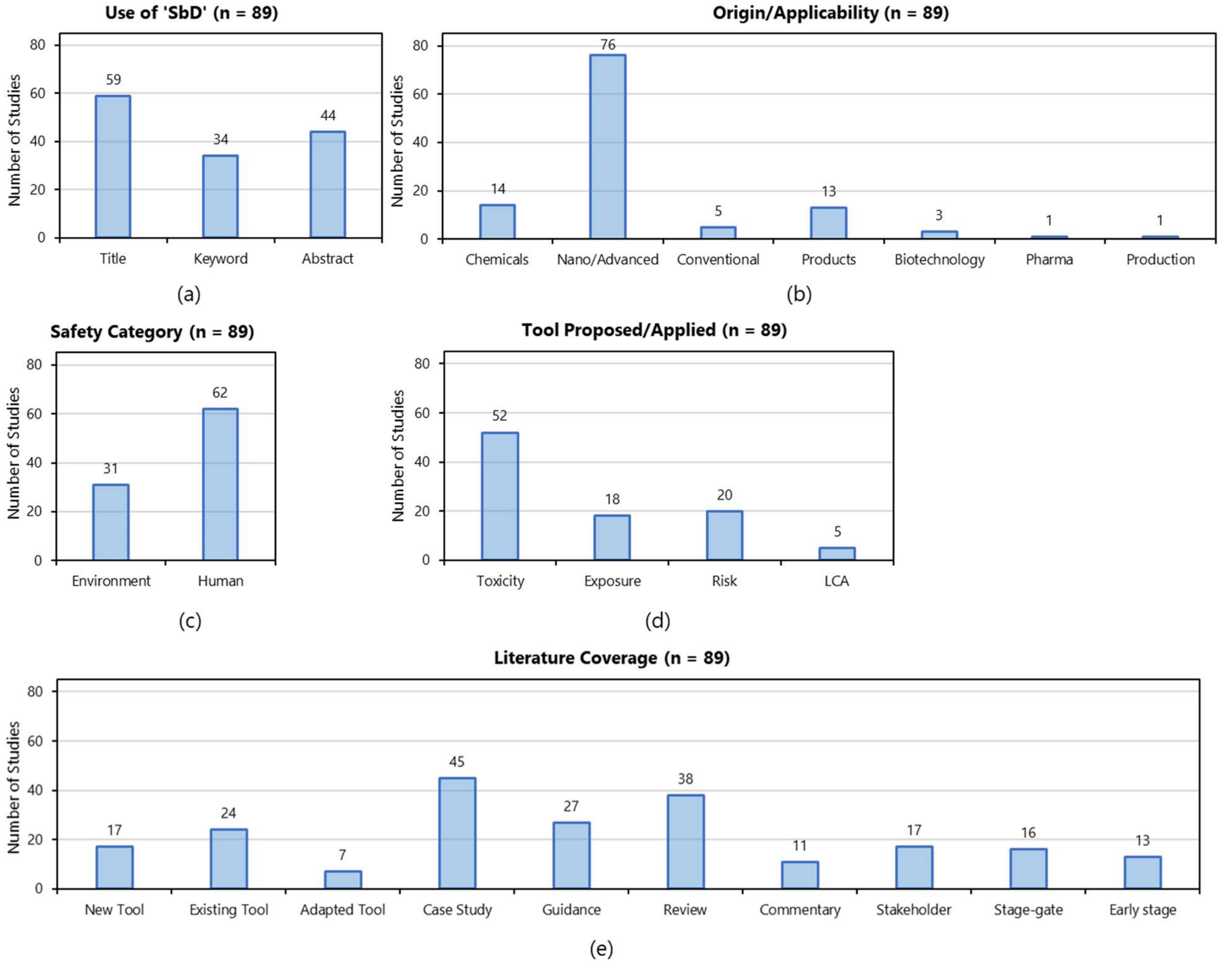

Figure 1 General trends of 89 SbD studies compiled along the different criteria: (a) use of 'SbD'; (b) origin/applicability; (c) safety category; (d) tools proposed/applied; and (e) literature coverage

4.2 SbD Tool-Review Trends

As depicted in Figure 1(e), 38 reviews in total were identified in this assessment out of which 19 were SbD tool reviews. Table 1 contains the summary of the tool reviews and classifies them based on a detailed background study analyzing each tool review (see Table S 2 in Annex S2).

Technically, all the tool reviews categorized in Table 1 list many tools and therefore could be all considered as 'repositories'; however, it is the final goal of the repositories of tools that allows their categorization. Evidently, 9 out of the 19 tool reviews are classified 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

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clearly identified suitable tools for the early-innovation stages. Additionally, it is also 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.

Table 1 Assessing and classifying the 19 studies reviewing SbD tools identified from a total of 38 compiled reviews; detailed analysis of individual tool reviews conducted in Table S 2

Type of Review	Stage-gate	References
Quantitative Scoring	Yes	**3**[a] (Franken et al., 2020; Shandilya et al., 2023; Sørensen et al., 2019)[b]
	No	-
Toolboxes or Repositories	Yes	**4** (caLIBRATE & Gov4Nano, 2023; Nymark et al., 2020; 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)

[a] represents the number or count of references categorized within the respective column

[b] the citations classified within the respective categories of the columns

Literature dealing with quantitative scoring of tools is typically considerate of the stage-gate model and incorporates it in the scoring of tools. 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 input. Data and financial constraints during early-innovation stages are readily acknowledged by and central to these quantitative assessments and thus, all quantitative assessments found in this assessment consider the stage-gate model.

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

Another aspect worth highlighting (as also observed in Table S 2 of Annex S2) is that some tool reviews (Guinée et al., 2022) ignore stage-gate in favor of a lifecycle approach, i.e. they either assess the suitability of tools at individual lifecycle stages (production, use, and EoL) or different stages of the stage-gate. Essentially, the consideration of lifecycle and stage-gate models in reviews is found

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to be mutually exclusive in tool reviews. This is a relevant outcome as it highlights a gap and a need to reconcile the lifecycle and the stage-gate models for SSbD.

4.3 SbD Case Study Trends

Table 2 summarizes the detailed analysis of case studies performed in Table S 3 of Annex S3 and categorizes the 45 case studies identified in this assessment as illustrated in Figure 1(e). The first split between 18 conventional and 27 SbD studies shows that most of the case studies contain actual SbD work and illustrate the application of the SbD concept in real practice. The number of case studies conducting conventional toxicity, exposure, and risk analysis while mislabeling them as SbD is a smaller proportion, indicating the misuse of the 'SbD' terminology is a problem. Literature reviews and general guidance dominate the conventional study category. Literature reviews compile safety considerations and challenges for materials from the available literature (Som et al., 2013). Whereas, general guidance documents omit the 'safety' component and instead exhibit general best practices or other complex topics such as the inclusion of material functionality in assessments (Hong et al., 2023).

Within the case studies classified as SbD, safe-by-selection (9 studies) and –redesign (14 studies) approaches are predominant. In fact, the recent case study from the JRC (Caldeira et al., 2023) showing the application of the SSbD framework is a safe-by-selection study. 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, which is why the safe-by-redesign category contains the largest number of studies in total. 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 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, they could be automated to assess thousands of substances simultaneously in high throughput testing which is not possible with lab testing due to the amount of human effort required (Nymark et al., 2020). However, as shown in Table 2, the number of safe-by-modeling case studies is low and only one case study was found to implement high throughput testing (van Dijk et al., 2022). This result underscores the challenges of the safe-by-modeling approach, i.e. it is easier to implement once the modeling infrastructure has been established, however, setting up this infrastructure (background databases for the models) is effort intensive and often requires results from the previously mentioned lab tests in large quantities.

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Table 2 Assessment and categorization of 27 SbD and 18 conventional studies of the 45 total case studies identified in this assessment

Type of Case Study		Sample Size		
		Single	Multiple	High Throughput
Safe(r)-by-Design Studies	Safe(r)-by-Modelling	**1**[a] (Rybińska-Fryca et al., 2020)[b]	**2** (Furxhi, Bengalli, et al., 2023; Varsou et al., 2019)	**1** (van Dijk et al., 2022)
	Safe(r)-by-Selection	**1** (Semenzin et al., 2019)	**8** (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	**7** (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)	**7** (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	**1** (Gautam et al., 2019)	**2** (Bae et al., 2019; Dzhemileva et al., 2021)	
	Exposure Assessment	**2** (A. J. Koivisto et al., 2015; Antti Joonas Koivisto et al., 2018)		
	Risk Assessment	**1** (Cazzagon, Giubilato, Pizzol, et al., 2022)	**1** (Hristozov et al., 2018)	
	Literature Reviews	**1** (Marques et al., 2020)	**5** (Donaldson et al., 2010; Guo et al., 2021; Halappanavar et al., 2020; Som et al., 2013; Tavernaro et al., 2021)	
	General Guidance	**2** (Hong et al., 2023; Karayannis et al., 2019)	**3** (López De Ipina et al., 2017; Micheletti et al., 2017; van Harmelen et al., 2016)	

[a] represents the number or count of references categorized within the respective column

[b] the citations classified within the respective categories of the columns

Hence, since SbD and therefore SSbD computational models are currently unavailable for the safe-by-modeling approach, the other two SbD case study categories (safe-by-selection and –redesign) are relevant despite their shortcomings. Further exploration is thus required to understand how the

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outputs from safe-by-selection and –redesign studies can be used to build up the requisite databases and enable safe-by-modeling: robust, reliable, and quick computational models that can cheaply and without expert input generate relevant pre-compliance data.

4.4 SbD Frameworks and SSbD

It is necessary to evaluate the past SbD work and its incorporation into the JRC's framework because the latter has high political relevance and is expected to become the first point of introduction to SSbD for different political, academic, commercial, and corporate actors in the EU. Therefore, to ensure that all valuable and relevant SbD work continues to have a life after the introduction of the SSbD framework, positive contributions from the former need to be transferred to the latter. The SSbD framework does address the SbD concept from the nano-sector 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. One key reason for this omission is that the publication of some recent and valuable SbD literature occurred after the publication of the SSbD framework.

Another trend highlighted by the evaluation 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: the actual functional benefit from the nanomaterials in question need to be substantiated sufficiently to warrant the development and application of nanomaterials that may give rise to many unconventional human and environmental safety hazards and risks. Such a comprehensive discussion about material functionality and durability is naturally missing in the current state of the JRC's framework as the focus is completely on the hazard-based approach. Incorporation of the material functionality and durability aspects can help in addressing abstract issues associated with 'essential use' (Cousins et al., 2019) to some degree and result in reduced competition and possibly the reconciliation between the industrial and political SSbD approaches issued by CEFIC and JRC respectively.

Regular mapping of SSbD studies and frameworks needs to be undertaken to assess the evolution of the landscape and understand which and how gaps identified in the past 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. Finally, another noticeable aspect from Table 3 is that there are SbD frameworks that do not account comprehensively for the lifecycle stages and in such frameworks, primarily the production phase impacts, particularly occupational health, and safety, and in some cases use-phase impacts to customers have been the focus. EoL is often only included by proxy when emissions into the environment are considered.

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Table 3 The 14 meaningful SbD frameworks and how they fit into the context of the JRC's SSbD Framework; the S. No. column is indexed according to Table S 1 in Annex S1

SbD Framework	Tools	Applicability	Guidance	By-design	Lifecycle	Case Study	JRC's SSbD Framework	S. No.
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; but could be included as quick guidance for SSbD in Nanomedicines	2
GoNanoBioMat SbD approach (Schmutz et al., 2020)	Questionnaire, Flowcharts	Specific: proposed only for NMs but universally applicable	Three-pillar design: - Safe nanomaterials - Safe production - Safe storage and transport	Early-stage	Not explicitly defined but production, use & partially EoL covered	Absent	Referenced and three pillar design for SbD mention	3
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	5
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	14, 16
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 like the NanoReg2 framework	26
GRACIOUS (Stone et al., 2020)	Decision Trees, Grouping,	Specific: NMs only; hypothetically, the methodology	- Facilitates the application of grouping of nanomaterials or nanoforms (NFs), in a	Stage-gate	Production and use emphasized	Present (Wohlleben & Stone, 2022)	Not included but approach relevant for quick and easy SbD	29

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SbD Framework	Tools	Applicability	Guidance	By-design	Lifecycle	Case Study	JRC's SSbD Framework	S. No.
	Read-across Lists	possible to extend to other chemicals and products	regulatory context and supports innovation - Hypothesis testing for novel NMs for which no data is available based on existing data				consideration when data is absent	
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)	39
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	46
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	50
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 NanoRag2 approach which is included in the SbD section of SSbD	55
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,	Early-stage	Production	Present	Referenced as a decision support tool	64

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SbD Framework	Tools	Applicability	Guidance	By-design	Lifecycle	Case Study	JRC's SSbD Framework	S. No.
			environmental, and societal) for novel materials					
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	65
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 LICARA nanoSCAN; however, the inclusion of material functionality, durability, and its consequent benefit is missing	83
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	88

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4.5 SbD Survey Results

The SbD survey was answered by 86 respondents in total from academia and industry. Figure 2(a) and Figure 3 deal specifically with the responses related to the SbD tools used. As seen in Figure 2(a), a significant share of academic respondents uses SbD tools developed within EU projects. In contrast, a minor set of respondents from the industry have applied SbD tools developed within EU projects. From the 26 total respondents in Figure 2(a) who claim to have used SbD tools from EU projects, Figure 3 highlights that the SbD tools proposed within the Gov4Nano and NanoReg2 projects are popular amongst academic practitioners. However, the majority of academic respondents along with the industry respondents have used the SbD tools developed within EU projects that were not explicitly listed in the survey. Hence, it is necessary to further investigate these other popular SbD tools from EU projects that were not covered within the survey and also to further promote the use of SbD tools from EU projects in industry.

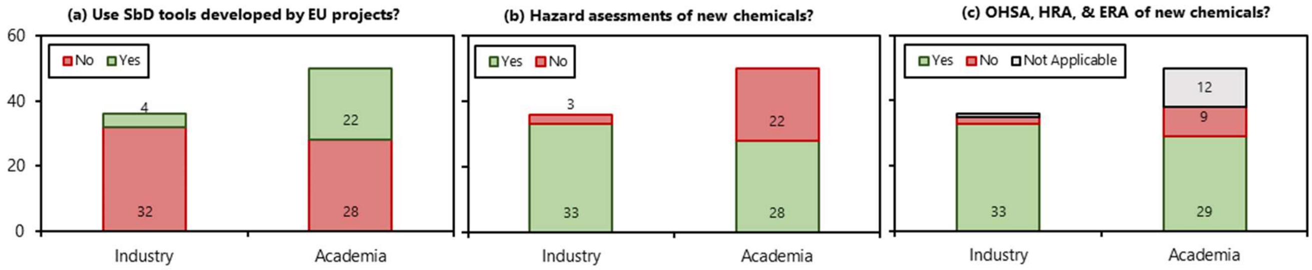

Figure 2 Survey results (n = 86) with classification based on the kind of respondents for: (a) use of tools developed in EU projects; (b) hazard assessment of new chemicals; and (c) occupational health and safety assessment (OSHA), human risk assessment (HRA), and environmental risk assessment (ERA) of new chemicals

Apart from SbD tools, the results in Figure 2(b) and Figure 4 illustrate the results of the inquiry about hazard assessments. As seen in Figure 2(b), a significant share of both academic and industrial respondents perform hazard assessments. Industrial respondents also shared that it is mandatory in the EU to ensure compliance of their products with REACH, as a consequence of which, the REACH framework is found to be the most prominent for hazard assessments in Figure 4. As seen in Figure 4, early stage-hazard assessments possible with NAMs and the JRC's SSbD framework are found to be more popular amongst the academic respondents as compared to their industrial counterparts. Furthermore, conventional hazard assessment frameworks such as the CSS and REACH are more popular amongst respondents from the industry due to the legislative and policy push for the same. These results highlight the popularity of hazard assessment for compliance purposes and the need for incentivization of hazard assessments during early-innovation phases that would be rooted in novel assessment methodologies.

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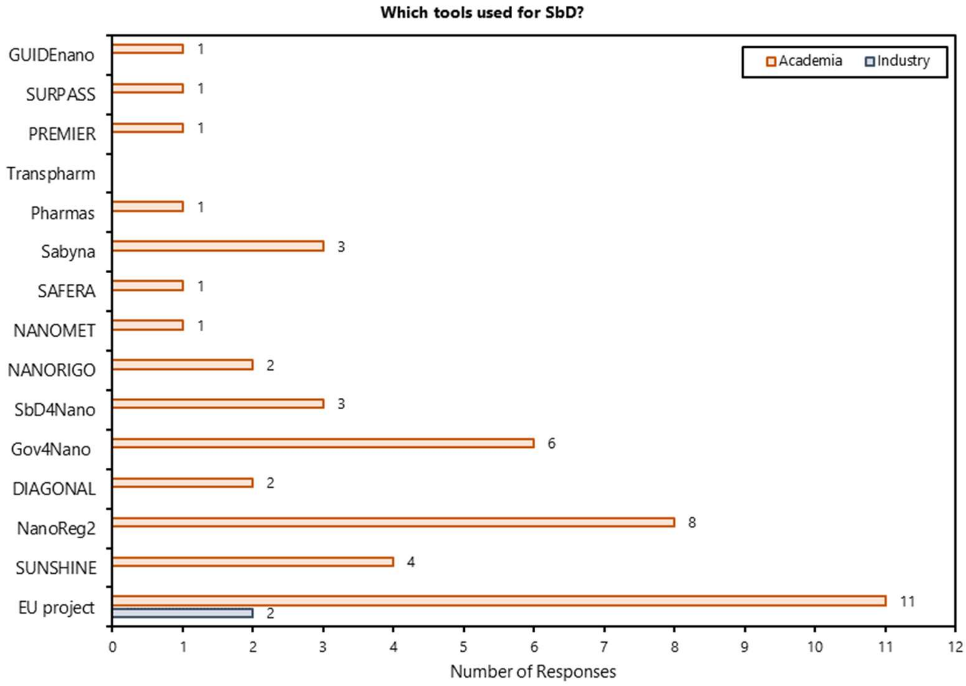

Figure 3 Responses (n = 26) classified based on the respondents and showing the SbD tools they use; here 'EU project' was offered as an option so that the respondents could specify a specific SbD approach that was excluded from the provided list, however, the respondents selecting this option never provided the names of these alternative approaches

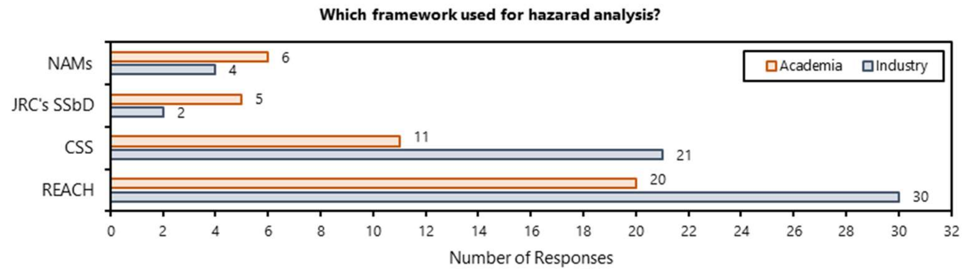

Figure 4 Responses (n = 61) classified based on the respondents and showing the hazard analysis tools they use; here NAMs refers to novel assessment methodologies and CSS refers to the EU's chemical strategy for sustainability

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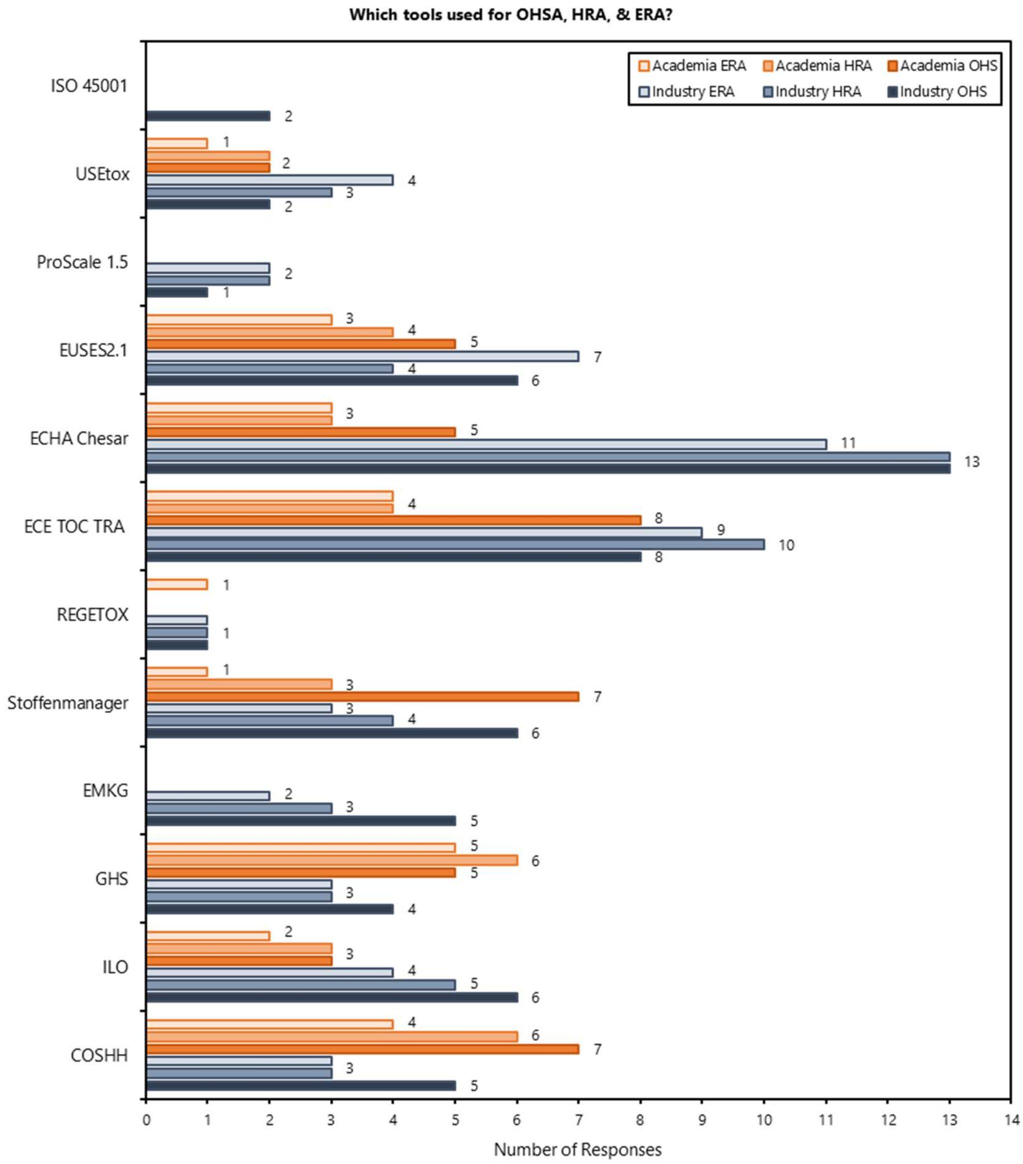

Figure 5 Responses (n = 62) classified based on the respondents and showing the respective tools they use for OHSA, HRA, and ERA

Finally, the results in Figure 2(c) and Figure 5 shed light on the current state of (the safety pillars in) the SSbD assessment in academia and industry. Again Figure 2(c) highlights the large share of industrial respondents involved in OSHA, HRA, and ERA because OSH and risk assessments in manufacturing facilities are mandated by law to ensure safe working conditions for their employees. Academic respondents who claimed to perform safety assessments also stated that they offer OSHA, HRA, and ERA services to industrial partners. Figure 5 shows which tools compiled by the JRC are applied for what kind of safety assessments and by which kind of respondents. The popularity of the ECHA's Chesar tool amongst industrial respondents due to REACH is evident in Figure 5. Apart from this, all other tools given in the SSbD framework for safety assessments seem to enjoy similar popularity and a good split in shares amongst industrial and academic institutions for all assessments: OSHA, ERA, and HRA. Two industrial respondents did specifically mention that the ISO 45001 standard is a critical OSHA tool that was absent from the survey as it is currently not mentioned in the JRC's SSbD tool list. Another valuable aspect worth noting is that all the tools listed by the JRC as SSbD tools are conventional safety assessment tools that are typically applied during later stages of product development when sufficient data and expertise on the developed materials are available. The validity of these listed tools at lower technology readiness levels (TRLs) is unclear and therefore, so is their true utility as SSbD tools. It is however clear that the JRC's framework sufficiently captures the current state-of-art of compliance-stage tools as no other tools, except for ISO 45001, were recognized as missing from the list by the respondents.

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5. Reflections

One key conclusion drawn after conducting the present study is the restrictive and exclusive nature of the term 'SbD'. Because of its origin in the nano sector, the use of the SbD keyword for the literature search has resulted in a lopsided assessment that sufficiently covers the area of nanosafety but only to a limited extent covers other application sectors such as chemicals, products, and processes. Therefore, it may be said that 'SbD' is not an all-inclusive term and unfortunately does not capture the essence of 'safe-by-design' universally in literature from all sectors.

In order to overcome this limitation, it is advisable to also use other relevant keywords to select literature. A key focus of the SSbD framework currently is on chemicals and the concept of developing safe chemicals predates (and is thus more mature than) the SbD of nanomaterials. In the (organic) chemical sector, widely recognized frameworks and concepts that integrate safety aspects into the chemical product design are "green chemistry" (Anastas & Warner, 1998), "circular chemistry" (Keijer et al., 2019), "sustainable chemistry" (Blum et al., 2017; ECOSChem, 2023; Kümmerer, 2017; Kümmerer et al., 2021), and "benign by design" (R. S. Boethling et al., 2007; Kümmerer, 2007; Kummerer & Hempel, 2010). In particular, the feasibility of the "benign by design" concept has been demonstrated several times in different case studies that could be classified based on the categories presented in Chapter 2.3.1: 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). Chemical frameworks and concepts show a huge overlap with SSbD. Enlarging the scope to literature from the chemical sector would therefore result in further useful tools and case studies, that could help to resolve current issues in the JRC framework.

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6. Recommendations

Based on this mapping, the following research needs have been highlighted and recommended for future funding opportunities:

- A lot of concepts and ideas relevant to SSbD, which are currently absent from the JRC's framework, were already funded under SbD research in the past; therefore, preservation of previously generated SbD knowledge and ensuring its effective transfer to SSbD is necessary.
- Apart from theoretical concepts, also the available SbD tools and toolboxes offer a great potential to support the operationalization of the SSbD framework; this study highlights that 9 of the 19 tool reviews may be classified as toolboxes or repositories and these should find some use also for SSbD, especially after their sufficient refinement, adaptation, and organization along the stage-gate model.
- A point of contention between the industrial and academic perspectives on SSbD is the intrinsic hazard approach of the latter; a possible means to reconcile both perspectives may be through a deeper focus on proven functionality and functional benefits of innovation in SSbD to justify the use of hazardous materials within tolerable risk limits for 'essential-use' cases.
- Currently, a mutual exclusivity in the adoption of the lifecycle thinking and the stage-gate model is evident in SbD frameworks since the latter only focuses on the development and production (i.e. pre-use) phases of the lifecycle; thus, research is required to combine (to avoid potential conflict between) these different approaches for SSbD
- Based on the present mapping, high throughput SbD studies are scarce; therefore, it is necessary to further develop and demonstrate the use of computational SSbD tools that can operate under data and time constraints to truly operationalize 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 JRC's framework underscores the need to regularly map the landscape of newly published literature on tools and methodologies for SSbD

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Annexes

Annex S1 - List of Reviewed SbD Articles

Table S 1 List all complied SbD literature; detailed analysis of the literature along the different criteria provided in the digital appendix

S.No.	Reference	Year	Funding	Title
1	(van de Poel & Robaey, 2017)	2017	Netherlands	Safe-by-Design: from Safety to Responsibility
2	(Yan et al., 2019)	2019	China	A Safe-by-Design Strategy towards Safer Nanomaterials in Nanomedicines
3	(Schmutz et al., 2020)	2020	EU (GoNanoBioMat)	A Methodological Safe-by-Design Approach for the Development of Nanomedicines
4	(Kraegeloh et al., 2018)	2018	EU (NanoReg, NanoReg2, ProSafe)	Implementation of Safe-by-Design for Nanomaterial Development and Safe Innovation: Why We Need a Comprehensive Approach
5	(Salieri et al., 2021)	2021	EU (NanoReg2, Porous4App)	Integrative approach in a safe by design context combining risk, life cycle and socio-economic assessment for safer and sustainable nanomaterials
6	(Marques et al., 2020)	2020	EU (GoNano-BioMat)	How the Lack of Chitosan Characterization Precludes Implementation of the Safe-by-Design Concept
7	(Robaey, 2018)	2018	Netherlands	Dealing with risks of biotechnology: understanding the potential of Safe-by-Design
8	(Le et al., 2016)	2016	Australia and China	An Experimental and Computational Approach to the Development of ZnO Nanoparticles that are Safe by Design
9	(Damasco et al., 2020)	2020	USA	Understanding Nanoparticle Toxicity to Direct a Safe-by-Design Approach in Cancer Nanomedicine
10	(Janko et al., 2017)	2017	Germany	Strategies to optimize the biocompatibility of iron oxide nanoparticles – "SPIONs safe by design"
11	(Lynch et al., 2014)	2014	EU (NanoMILE)	A strategy for grouping of nanomaterials based on key physico-chemical descriptors as a basis for safer-by-design NMs
12	(Naatz et al., 2017)	2017	USA	Safe-by-Design CuO Nanoparticles via Fe-Doping, Cu–O Bond Length Variation, and Biological Assessment in Cells and Zebrafish Embryos
13	(Guo et al., 2021)	2021	EU (NanoSolveIT, RiskGone, and NanoCommons)	Surface Functionalization of Graphene-Based Materials: Biological Behavior, Toxicology, and Safe-By-Design Aspects
14	(Dekkers et al., 2020)	2020	EU (NanoReg2)	Safe-by-Design part I: Proposal for nanospecific human health safety aspects needed along the innovation process

S.No.	Reference	Year	Funding	Title
15	(Bae et al., 2019)	2019	South Korea	Hazard potential of perovskite solar cell technology for potential implementation of "safe-by-design" approach
16	(Tavernaro et al., 2021)	2021	EU (NanoReg2)	Safe-by-Design part II: A strategy for balancing safety and functionality in the different stages of the innovation process
17	(Sánchez Jiménez, Puelles, et al., 2022)	2022	EU (NanoReg2)	Safe(r) by design guidelines for the nanotechnology industry
18	(Sánchez Jiménez et al., 2020)	2020	EU (NanoReg2)	Safe(r) by design implementation in the nanotechnology industry
19	(Giusti et al., 2019)	2019	EU (NanoReg2)	Nanomaterial grouping: Existing approaches and future recommendations
20	(Soeteman-Hernández et al., 2020)	2020	EU (NanoReg2)	Challenges of implementing nano-specific safety and safe-by-design principles in academia
21	(Marcoulaki et al., 2021)	2021	EU (EC4SafeNano)	Blueprint for a self-sustained European Centre for service provision in safe and sustainable innovation for nanotechnology
22	(Cummings et al., 2021)	2021	USA	Barriers to responsible innovation of nanotechnology applications in food and agriculture: A study of US experts and developers
23	(Soeteman-Hernández et al., 2021)	2021	EU (NanoReg2)	Modernizing innovation governance to meet policy ambitions through trusted environments
24	(Cazzagon, Giubilato, Bonetto, et al., 2022)	2022	EU (BIORIMA SUNSHINE, and ASINA)	Identification of the safe(r) by design alternatives for nanosilver-enabled wound dressings
25	(Varsou et al., 2019)	2019	EU (NANOGENTOOLS RISE and NanoCommons)	A safe-by-design tool for functionalised nanomaterials through the Enalos Nanoinformatics Cloud platform
26	(Som et al., 2013)	2013	EU (NanoHouse and MARINA)	Toward the Development of Decision Supporting Tools That Can Be Used for Safe Production and Use of Nanomaterials
27	(Rybińska-Fryca et al., 2020)	2020	EU (NanoSolveIT)	Structure–activity prediction networks (SAPNets): a step beyond Nano-QSAR for effective implementation of the safe-by-design concept† Check for updates
28	(Halappanavar et al., 2020)	2020	EU (SmartNanoTox and PATROLS)	Adverse outcome pathways as a tool for the design of testing strategies to support the safety assessment of emerging advanced materials at the nanoscale
29	(Stone et al., 2020)	2020	EU (GRACIOUS)	A framework for grouping and read-across of nanomaterials-supporting innovation and risk assessment
30	(Afantitis et al., 2020)	2020	EU (NanoSolveIT)	NanoSolveIT Project: Driving nanoinformatics research to develop innovative and integrated tools for in silico nanosafety assessment
31	(Choi et al., 2018)	2018	South Korea	Towards a generalized toxicity prediction model for oxide nanomaterials using integrated data from different sources
32	(Himly et al., 2020)	2020	EU (NANORIGO, PANDORA, and	When Would Immunologists Consider a Nanomaterial to be Safe? Recommendations for Planning Studies on Nanosafety

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S.No.	Reference	Year	Funding	Title
			NanoCommons)	
33	(Labouta et al., 2019)	2019	Canada	Meta-Analysis of Nanoparticle Cytotoxicity via Data-Mining the Literature
34	(Papadiamantis et al., 2020)	2020	EU (NanoSolveIT)	Predicting Cytotoxicity of Metal Oxide Nanoparticles Using Isalos Analytics Platform
35	(Saarimäki et al., 2021)	2021	EU (Nano-SolveIT)	Manually curated transcriptomics data collection for toxicogenomic assessment of engineered nanomaterials
36	(Rodrigues et al., 2020)	2020	EU (Graphene Flagship)	Size-Dependent Pulmonary Impact of Thin Graphene Oxide Sheets in Mice: Toward Safe-by-Design
37	(Donaldson et al., 2010)	2010	UK	Identifying the pulmonary hazard of high aspect ratio nanoparticles to enable their safety-by-design
38	(Bouchaut & Asveld, 2020)	2020	Netherlands	Safe-by-Design: Stakeholders' Perceptions and Expectations of How to Deal with Uncertain Risks of Emerging Biotechnologies in the Netherlands
39	(Semenzin et al., 2019)	2019	EU (NANORESTART)	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
40	(Gautam et al., 2019)	2019	South Korea	Plug-In Safe-by-Design Nanoinorganic Antibacterials
41	(Azmi et al., 2016)	2016	Denmark	A structurally diverse library of safe-by-design citrem-phospholipid lamellar and non-lamellar liquid crystalline nano-assemblies
42	(Movia et al., 2014)	2014	EU (NAMDIATREAM, MULTIFUN and CRANN)	A safe-by-design approach to the development of gold nanoboxes as carriers for internalization into cancer cells
43	(Miao et al., 2020)	2020	China	Safe-by-Design Exfoliation of Niobium Diselenide Atomic Crystals as a Theory-Oriented 2D Nanoagent from Anti-Inflammation to Antitumor
44	(Motta et al., 2023)	2023	EU (ASINA)	Preliminary Toxicological Analysis in a Safe-by-Design and Adverse Outcome Pathway-Driven Approach on Different Silver Nanoparticles: Assessment of Acute Responses in A549 Cells
45	(Remzova et al., 2019)	2019	Czech Republic	Toxicity of TiO_2, ZnO, and SiO_2 Nanoparticles in Human Lung Cells: Safe-by-Design Development of Construction Materials
46	(Karayannis et al., 2019)	2019	EU (MEDLOC)	3D-Printed Lab-on-a-Chip Diagnostic Systems-Developing a Safe-by-Design Manufacturing Approach
47	(Mantecca et al., 2017)	2017	EU (PROTECT)	Airborne Nanoparticle Release and Toxicological Risk from Metal-Oxide-Coated Textiles: Toward a Multiscale Safe-by-Design Approach
48	(Wolska-Pietkiewicz et al., 2018)	2018	Poland	Safe-by-Design Ligand-Coated ZnO Nanocrystals Engineered by an Organometallic Approach: Unique Physicochemical Properties and Low Toxicity toward Lung Cells
49	(Fiandra et al., 2020)	2020	EU (PROTECT)	Hazard assessment of polymer-capped CuO and ZnO nanocolloids: A contribution to the safe-by-design implementation of biocidal agents Author links open overlay panel

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S.No.	Reference	Year	Funding	Title
50	(Furxhi, Bengalli, et al., 2023)	2023	EU (ASINA)	Data-Driven Quantitative Intrinsic Hazard Criteria for Nanoproduct Development in a Safe-by-Design Paradigm: A Case Study of Silver Nanoforms
51	(Robaey et al., 2018)	2018	Netherlands	The Food Warden: An Exploration of Issues in Distributing Responsibilities for Safe-by-Design Synthetic Biology Applications
52	(Park et al., 2019)	2019	South Korea	Plug-and-play safe-by-design production of metal-doped tellurium nanoparticles with safer antimicrobial activities
53	(Boulanger et al., 2013)	2013	France	Towards large scale aligned carbon nanotube composites: an industrial safe-by-design and sustainable approach
54	(Jeliazkova et al., 2014)	2014	EU (eNanoMapper)	The first eNanoMapper prototype: A substance database to support safe-by-design
55	(Micheletti et al., 2017)	2017	EU (NanoReg, ProSafe)	Implementation of the NANoREG Safe-by-Design approach for different nanomaterial applications
56	(Tedesco et al., 2015)	2015	Italy	Cytotoxicity and antibacterial activity of a new generation of nanoparticle-based consolidants for restoration and contribution to the safe-by-design implementation
57	(Herva et al., 2011)	2011	Spain	Sustainable and safe design of footwear integrating ecological footprint and risk criteria
58	(Mech et al., 2022)	2022	EU	Safe- and sustainable-by-design: The case of Smart Nanomaterials. A perspective based on a European workshop
59	(Chang et al., 2016)	2016	China	Crystallographic facet-dependent stress responses by polyhedral lead sulfide nanocrystals and the potential “safe-by-design” approach
60	(López De Ipina et al., 2017)	2017	EU (PLATFORM)	Implementation of a safe-by-design approach in the development of new open pilot lines for the manufacture of carbon nanotube-based nano-enabled products
61	(Dzhemileva et al., 2021)	2021	Russia	A large-scale study of ionic liquids employed in chemistry and energy research to reveal cytotoxicity mechanisms and to develop a safe design guide
62	(Kramer et al., 2007)	2007		The application of discovery toxicology and pathology towards the design of safer pharmaceutical lead candidates
63	(Gottardo et al., 2021)	2021	EU	Towards safe and sustainable innovation in nanotechnology: State-of-play for smart nanomaterials
64	(van Harmelen et al., 2016)	2016	EU (LICARA)	LICARA nanoSCAN - A tool for the self-assessment of benefits and risks of nanoproducts
65	(Hartmann et al., 2017)	2017	EU (ENVNANO)	NanoCRED: A transparent framework to assess the regulatory adequacy of ecotoxicity data for nanomaterials – Relevance and reliability revisited
66	(RIVM, 2017)	2017	EU (NanoReg2)	Safe Innovation Approach (SIA) Toolbox
67	(Sørensen et al., 2019)	2019	EU (CaLIBRAte)	Evaluating environmental risk assessment models for nanomaterials according to requirements along the product innovation Stage-Gate process
68	(Franken et al., 2020)	2020	EU (CaLIBRAte)	Ranking of human risk assessment models for manufactured nanomaterials along the Cooper stage-gate innovation funnel using stakeholder criteria

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S.No.	Reference	Year	Funding	Title
69	(Nymark et al., 2020)	2020	EU (CaLIBRAte, Gov4Nano, NanoSolveIT, etc.)	Toward Rigorous Materials Production: New Approach Methodologies Have Extensive Potential to Improve Current Safety Assessment Practices
70	(OECD, 2020)	2020	OECD	Moving Towards a Safe(r) Innovation Approach (SIA) for More Sustainable Nanomaterials and Nano-enabled Products
71	(Shandilya & Franken, 2020)	2020	EU (Gov4Nano)	D4.1 Review of existing and near-future next generation tools and models to support the nano-risk governance council and industrial safer-by-design.
72	(Falk et al., 2021)	2021	EU	Safe-by-design and EU funded NanoSafety projects
73	(European Commission et al., 2021)	2021	EU	European research on environment and health : projects funded by Horizon 2020 (2014-2020)
74	(Krans et al., 2021)	2021	Netherlands	Nanotechnology and Safe-by-Design. Inventory of research into Safe-by-Design Horizon 2020 projects from 2013 to 2020
75	(Joint Research Centre, 2021)	2021	EU (NANoREG)	NANoREG Toolbox for the Safety Assessment of Nanomaterials - Data Europa EU
76	(Shandilya et al., 2021, 2023)	2021	EU (Gov4Nano)	TRAAC framework for regulatory acceptance and wider usability of tools and methods for safe innovation and sustainability of manufactured nanomaterials
77	(European Commission, Joint Research Centre, Caldeira, Farcal, Garmendia Aguirre, et al., 2022; European Commission, Joint Research Centre, Caldeira, Farcal, Moretti, et al., 2022)	2022	EU	Safe and sustainable by design chemicals and materials : review of safety and sustainability dimensions, aspects, methods, indicators, and tools; Safe and sustainable by design chemicals and materials : framework for the definition of criteria and evaluation procedure for chemicals and materials
78	(Guinée et al., 2022)	2022	EU	The meaning of life … cycles: lessons from and for safe by design studies
79	(Furxhi, Costa, et al., 2023)	2023	EU	Status, implications and challenges of European safe and sustainable by design paradigms applicable to nanomaterials and advanced materials
80	(Ruijter et al., 2023)	2023	EU	The State of the Art and Challenges of In Vitro Methods for Human Hazard Assessment of Nanomaterials in the Context of Safe-by-Design
81	(Subramanian et al., 2023)	2023	Netherlands	Approaches to implement safe by design in early product design through combining risk assessment and Life Cycle Assessment
82	(caLIBRATE & Gov4Nano, 2023; RiskGONE et al., 2023)	2023	EU (RiskGONE, NANORIGO. and Gov4Nano)	Nano-Risk Governance Platform
83	(Hong et al., 2023)	2023	EU	Development of a Benefit Assessment Matrix for Nanomaterials and Nano-enabled Products—Toward Safe and Sustainable by Design
84	(Hristozov et al., 2018)	2018	EU (SUN)	Quantitative human health risk assessment along the lifecycle of nano-scale copper-based wood preservatives
85	(Cazzagon, Giubilato, Pizzol, et al., 2022)	2022	EU (BIORIMA)	Occupational risk of nano-biomaterials: Assessment of nano-enabled magnetite contrast agent using the BIORIMA Decision Support System

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S.No.	Reference	Year	Funding	Title
86	(A. J. Koivisto et al., 2015)	2014	EU (NanoValid)	Testing the near field/far field model performance for prediction of particulate matter emissions in a paint factory
87	(Antti Joonas Koivisto et al., 2018)	2018	EU (NanoPack)	Occupational exposure during handling and loading of halloysite nanotubes – A case study of counting nanofibers
88	(van Dijk et al., 2022)	2022	EU	Safe and sustainable by design: A computer-based approach to redesign chemicals for reduced environmental hazards
89	(Caldeira et al., 2023)	2023	EU	Safe and Sustainable by Design chemicals and materials. Application of the SSbD framework to case studies. JRC technical report for consultation. JRC131878

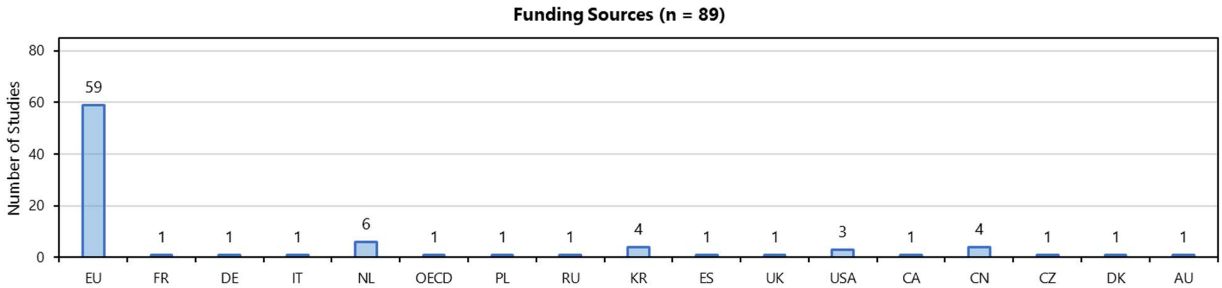

Figure S 1 Funding dources of the 89 SbD studies compiled in this assessment

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Annex S2 - SbD Tool Reviews

Table S 2 Overview of relevant literature reviewing and compiling SbD tools, frameworks, methods, and literature from (but not necessarily specific to the) nano/advanced materials fields

Reference	Safety Category		Number of Tools	Nature of Review	Consideration of Stage-gate	Incorporating Stakeholder Input	Additional Notes
	Environmental	Human					
(Jeliazkova et al., 2014)	Yes	Yes	104 identified but 34 publicly available	Qualitative: databases are compiled and then linked to produce meaningful toxicity estimates	No	Internal stakeholder support to compile databases	- Funded under eNanoMapper - Toxicological data management of nanomaterials through a computation infrastructure allowing: transparent data sharing, data analysis, and the creation of computational toxicology models - Relevant toxicological databases for chemicals and nanomaterials compiled - Supported include diverse formats (ISA-Tab, OECD Harmonized Templates, custom spreadsheet templates, various databases provided by consortia members
(RIVM, 2017)	Yes	Yes	24	Not a review but an SbD toolbox	Partially as early, mid, and late development phase	No	- Funded under NanoReg2 - Safe Innovation Approach (SIA) Toolbox - Tools assessing Risks, Costs, and Benefits classified based on product domain (biocides, cosmetics, etc.) and exposure route (dermal, oral or inhalation), which population (consumer, environment, general population, or worker), and type of output (qualitative, quantitative, or semi-quantitative)
(Sørensen et al., 2019)	Yes		38	Quantitative: models and tools scored on applicability, resource demands, and outcome parameters	Yes, development of a scoring scheme to assess fitness at each innovation stage	Yes, to determine relevant needs from tools/models	- Funded under caLIBRAte - Regulators, Industry Associations, Large Enterprises, Consultants, SMEs, and Research Organizations were stakeholders - Environmental Risk Assessment (ERA) Models considered: Material Flow, Fate and Transport, Hazard Assessment, Uptake or Bioavailability, and Risk Assessment Models

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Reference	Safety Category		Number of Tools	Nature of Review	Consideration of Stage-gate	Incorporating Stakeholder Input	Additional Notes
	Environmental	Human					
							- Some relevant scoring criteria include time/cost to parameterize and run models, level of required expertise, approval status, availability of guidance, etc.
(Franken et al., 2020)		Yes	17	Quantitative: models were evaluated against relevant compliance criteria established by stakeholders	Yes, assessed tools coupled with idea-to-launch innovation funnel model	Yes, to establish 24-compliance criteria for models at different innovation stages	- Funded under caLIBRAte - Study limited to Human Risk Assessment (HRA) tools and assess - 19 (including regulators, industry associations, large industries, SMEs, consultants, and research organizations) out of 45 stakeholders provided inputs to this study - Evaluation of models against the following criteria: cost to run the model; maximal duration; market readiness and its validation level; availability of guidance; chemical and toxicological expertise required; etc.
(Nymark et al., 2020)		Yes	50	Qualitative: NAMS have been evaluated in detail against the defined criteria to assess their applicability along stage-gate; however, no scoring has been applied	Yes, "where and how" to apply a NAM along the innovation funnel evaluated	Yes, to establish assessment criteria	- Funded under caLIBRAte, Gov4Nano, NanoSolveIT, etc. - 8 NAM categories defined: 1. Searchable databases for grouping and read across purposes; 2. Exposure assessment and modeling; 3. In silico modeling of physicochemical structure and hazard data; 4. In vitro high-throughput and high-content screening assays; 5. Dose-response assessments and modeling; 6. Analyses of biological processes and toxicity pathways; 7. Kinetics and dose extrapolation; 8. Consideration of relevant exposure levels and biomarker endpoints - Assessed NAMS for HRA that address exposure (7), hazard (24), kinetics (4), and risk (15)

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Reference	Safety Category		Number of Tools	Nature of Review	Consideration of Stage-gate	Incorporating Stakeholder Input	Additional Notes
	Environmental	Human					
							- Relevant assessment criteria for NAMs: availability of data, expertise required, quality assessment, etc.
(OECD, 2020)	Yes	Yes	Around 40	Qualitative: descriptions of all relevant tools and their classification based on respective applications in SbD pillars	Mentioned in the document but the tools are not categorized as per Stage-gate	Yes, to identify barriers to SbD	- Report from the OECD proposing the Safe(r) Innovation Approach (SIA) - SbD goes beyond classical RA and aims to achieve safer material with physicochemical structures designed to minimize hazard - Safe material, safer production, safe use, and safe End-of-Life (EoL) are to be considered pillars of SbD, and the evaluated tools have been classified within these pillars - Barriers to SbD based on stakeholder interactions: resources and costs, lack of knowledge, lack of guidance and tools, inadequate regulation, insufficient communication, and challenges to SMEs
(Shandilya & Franken, 2020)	Yes	Yes	160 (93 for nanomaterials, 36 for conventional materials, and remaining for both)	Qualitative: inventory of many nonspecific and other tools that have been mapped and classified based on different criteria; no scoring based on criteria undertaken	Partially applied through the lifecycle model including R&D, development, and use	No	- Gov4Nano deliverable 4.1 - Types (and number) of tools: control banding (5), risk screening (16), life cycle assessment (10), risk evaluation frameworks (19), numerical estimations (50), guidance documents (52), and guidance tools (8) - Evaluation criteria developed: identity, applicability, development state, and regulatory readiness Most of the tools in the inventory are quantitative and applicable mostly to chemicals - Numerous tools that consider exposure to industrial workers due to its relevance in the regulatory phase of the innovation value chain

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Reference	Safety Category		Number of Tools	Nature of Review	Consideration of Stage-gate	Incorporating Stakeholder Input	Additional Notes
	Environmental	Human					
(Falk et al., 2021)	Yes	Yes	28	Qualitative: working descriptions of projects funded under the NanoSafetyCluster (NSC) and Horizon 2020 (NMBP-15 and NMBP-16)	No	Yes, document was created with the voluntary contributions of the project coordinators	- SbD and EU-funded NanoSafety projects document by the NSC - List of relevant policies, standards, labelling schemes, etc. to SbD and nanosafety - List of outcomes (including case studies) from EU projects that support SbD framework
(European Commission et al., 2021)	Yes	Yes	269	Qualitative: summaries of and links to all Horizon 2020 (H2020) projects funded between 2014-2020	No	No	- European research on environment and health: Projects funded by Horizon 2020 (2014-2020) - Working descriptions of all H2020 projects carrying out diverse research: chemical safety and human health; nanosafety and health; air quality and health; urban health; climate change and health; biological safety; environmental and health policymaking; environmental risk factors of health and disease; pollution monitoring and mitigation
(Krans et al., 2021)	Yes	Yes	74	Qualitative: inventory of SbD projects from H2020 funding in Nanotechnology between 2013-2020	No	No	- RIVM's report on H2020 projects on Nanotechnology and SbD - 74 studies subdivided into following themes: research, education, industry, and policy - The description of SbD by the Dutch Ministry of Infrastructure and Water Management used to select relevant projects - List of projects along with their factsheets and links to project outcomes are available
(Joint Research Centre, 2021)	Yes	Yes	Unspecified	Qualitative: repository of all guidance documents, experimental protocols, models, reports, decision	No	No	- NANoREG toolbox published as an excel sheet - Regulatory status of tools assessed and defined as: regulatory document, standardized, research product, harmonized or validated

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Reference	Safety Category		Number of Tools	Nature of Review	Consideration of Stage-gate	Incorporating Stakeholder Input	Additional Notes
	Environmental	Human					
				support tools, and data management tools along with their descriptions, documented applications, and publications			- Extensive repository of tools for nanomaterials: • 61 particle size distribution tools • 40 tools on chemical compositions, size, shape, and surface treatment of nanomaterials • 106 tools producing physicochemical, toxicological, ecotoxicological, and environmental fate data required for REACH and chemical safety assessment • 65 in vitro testing, (Q)SARs, Weight of Evidence, grouping, and read-across tools producing data for REACH registration without reliance on animal testing • 20 tools related to identifying the hazards, deriving the DNEL and PNEC values and performing the PBT/vPvB assessment of a nanomaterial according to REACH requirements, and determining the hazard classification and labelling for a nanomaterial according to CLP requirements • 106 tools related to assessing human and environmental exposure to nanomaterials and determining appropriate risk management measures to limit exposures to an acceptable level

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Reference	Safety Category		Number of Tools	Nature of Review	Consideration of Stage-gate	Incorporating Stakeholder Input	Additional Notes
	Environmental	Human					
							• 27 tools related to characterizing or managing the risk(s) of nanomaterials according to the REACH procedure or within the REACH regime • 19 tools related to the nonspecific prioritization and risk assessment approach developed in NANoREG, as well as other risk assessment approaches and strategies for nanomaterials that do not necessarily operate within the current REACH regime • 16 tools related to managing the risks of nanomaterials by applying the Safe-by-design approach at the research and development stage of nanomaterials and products containing them • 6 tools related to applying the Life Cycle Assessment approach when assessing the risks posed by nanomaterials • 18 tools that help to screen, rank, prioritize, and categorize the risks of nanomaterials and to apply control banding to manage those risks based on minimal information, thus addressing practical (rather than regulatory) risk assessment or management needs - List of all relevant chemical bodies and organizations provided

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Reference	Safety Category		Number of Tools	Nature of Review	Consideration of Stage-gate	Incorporating Stakeholder Input	Additional Notes
	Environmental	Human					
(Shandilya et al., 2021, 2023)	Yes	Yes	14	Quantitative: Transparency, Reliability, Accessibility, Applicability, and Completeness (TRAAC) assessment framework applied to tools	Partially incorporated through scoring in the "applicable lifecycle stages" criteria under the Applicability pillar; direct reference to stage-gate absent	Yes, through a workshop to present the TRAAC framework also refine it	- TRAAC framework (preprint) funded under Gov4Nano - Aim is to assess regulatory acceptance, downstream use by different stakeholders, and hindrances to the same - Workshop stakeholders included researchers, academics, industry, regulators, consultants, and government from the EU - Five TRAAC Pillars: 1. Transparency: Ownership, clear communication about development, methods, strengths, and limitations (i.e. boundary of use); 2. Reliability: Quality, correctness, and consistency of output; 3. Accessibility: Usability, findability, and user experience evaluation; 4. Applicability: Applicability domain and adequacy to address user need(s); 5. Completeness: Comprehensiveness regarding EU regulatory frameworks and requirements for MNMs.
(European Commission, Joint Research Centre, Caldeira, Farcal, Garmendia Aguirre, et al., 2022; European Commission, Joint Research Centre, Caldeira, Farcal, Moretti, et al., 2022)	Yes	Yes	119 frameworks reviewed	Qualitative: compilation of all relevant literature pertinent to Safe- and Sustainable-by-Design (SSbD) including industry standards, compliance documents, methods, models, tools, etc.	Both lifecycle and stage-gate are central to SSbD but the proposed frameworks have only been partially assessed for the same	Planned incorporation in future reports (Case Study reports)	- SSbD reports from JRC including the framework, along with the review methods, indicators, and tools - Sectors considered: Chemicals, Products (cosmetics, electronics, etc.), Materials (nanomaterials, plastics, textiles, etc.), and Services - Origin of the frameworks could be from Academia, Industry, NGOs, Legislation or proposals, international organizations, and Certification bodies

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Reference	Safety Category		Number of Tools	Nature of Review	Consideration of Stage-gate	Incorporating Stakeholder Input	Additional Notes
	Environmental	Human					
							- Hierarchical and scoring methods for SSbD evaluation described
(Guinée et al., 2022)	Yes	Yes	19	Qualitative review of SbD and SSbD literature to assess consistency in the definition of lifecycles	No, but lifecycle is a central theme	No	- SbD and lifecycles review - Assesses the consistency in the definitions and terms used by SbD literature - Focus on distinguishing definitions and lifecycles of products, materials, and chemicals - Identifies the following 3 relevant lifecycles: 1. Product lifecycle 2. Chemical lifecycle in a specific product or material 3. Chemical lifecycle in all possible product or material applications
(Furxhi, Costa, et al., 2023)				Qualitative review of 11 relevant EU projects and how they meet SSbD requirements foreseen by stakeholders	No	Yes, reports the answers and opinions from stakeholder workshops	- Funded under DIAGONAL, HARMLESS, SUNSHINE, NanoFabNet, ASINA, SAbyNA, RiskGone, SbD4Nano, SABYDOMA, and IRISS - Highlights the relevant industrial topics along with technical and organizational challenges to SSbD - Discussion on key feedback from stakeholders relating to: Industrial targeted sectors, SSbD framework, lifecycles, FAIR data, business models, missing knowledge, certifications, challenges, and future goals
(Ruijter et al., 2023)		Yes	20	Qualitative: in vitro assays for hazard testing have been evaluated against specific criteria to understand suitability for SbD	Partially, as the methods have been assessed on the basis of their prediction accuracy for early hazard warning; so the early-phase 'by-design' concept has	No	- Funded under SAbyNA - Hazard testing assays (and number) evaluated: Cytotoxicity (5), dissolution (3), oxidative potential (4), inflammation (4), and genotoxicity (4) - Evaluation criteria for assays: predictive, simple, and cost-effective, robust, compatible, and readiness

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Reference	Safety Category		Number of Tools	Nature of Review	Consideration of Stage-gate	Incorporating Stakeholder Input	Additional Notes
	Environmental	Human					
					been adhered to strongly		- Challenges posed by in Vitro Testing NMs for SbD Applicability identified: Influence of Medium Components; Determining Dose Delivered to Cells; SbD Hazard Testing of NMs Released during the Life Cycle; Feasibility and Relevance
(Subramanian et al., 2023)	Yes	Yes	12	Qualitative: review of literature presenting approaches to combine Lifecycle Assessment (LCA) and RA approaches at lower Technology Readiness Levels (TRLs) and describes them against defined criteria	Yes, the assessment particularly focuses on and attempts to reconcile the TRL and stage-gate models to see the applicability of proposed LCA+RA approaches	No	- Funded by the Dutch Ministry of Infrastructure and Water Management and under BALIHT - Criteria used to describe LCA+RA approaches: TRL, application domain, SbD focus, RA approach, LC approach, Technology System, and System Boundaries - Advantages and disadvantages in the context of product design have also been evaluated
(NanoSolveIT, 2023)	Yes	Yes	7	Qualitative: compilation of tools developed in NanoSolveIT project	No	No	- Funded under NanoSolveIT - In silico Integrated Approach to Testing and Assessment (IATA) for the environmental health and safety of nanomaterials (ENM), implemented through a decision support system packaged as both stand-alone open software and via a Cloud platform - Compilation of tools capable of: omics data preprocessing, zeta potential calculation, cytotoxicity prediction, prediction of exposure effects on Daphnia Magna, visualization for IATA, and organizing gene annotations in experiments
(caLIBRATE & Gov4Nano, 2023;	Yes	Yes	35 (including regulations, guidance	Qualitative: repository of nano-risk governance tools	Yes, the objective is to provide a stage-gate nano-risk	Compilation of tools developed by internal	- caLIBRAte x Gov4Nano Nano-Risk Governance Platform (under development)

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Reference	Safety Category		Number of Tools	Nature of Review	Consideration of Stage-gate	Incorporating Stakeholder Input	Additional Notes
	Environmental	Human					
RiskGONE et al., 2023)			documents, etc.)	compiled into a platform of tools	governance guidance approach	project stakeholders	- Library containing information on nanotechnology, relevant regulations (4), guidance documents (8), tools (20), and data libraries (3) - Domains covered: governance, risk scoping, data, worker, consumer, exposure, environment, characterization, toxicological testing, SbD, and sustainability - Description of nano-risk governance framework as per ISO 21505

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Annex S3 - Sbd Case Studies

Table S 3 Details about case studies assessed here in this study; ; the S. No. indexed according to Table S 1

S. No.	Reference	Description	Application Sector	Focus	Framework or Project	Type of Case Study	Scope of Case Study
5	(Salieri et al., 2021)	Combining RA and LCA approach to select the nanomaterial for use in Li-ion battery and ensure implementation of safe- and sustainable-by-design	Energy Storage	Nanomaterials	NanoReg2	Safe-by-Selection	Multiple
6	(Marques et al., 2020)	Expresses challenges encountered when implementing the SbD concept to polymeric drugs based on chitosan	Pharmaceutical	Nanomaterials	GoNanoBioMat	Literature Review	Single
8	(Le et al., 2016)	45 types of ZnO nanoparticles with varying particle size, aspect ratio, doping type, doping concentration, and surface coating is synthesized, and their biological effects measured to assess the impacts of physicochemical modifications on toxicity ZnO nanoparticles	Not Specified	Nanomaterials		Safe-by-Selection	Multiple
10	(Janko et al., 2017)	Improving biocompatibility of superparamagnetic FeO nanoparticles (SPION) by an artificial protein corona consisting of serum albumin	Nanomedicine	Nanomaterials		Safe-by-Redesign	Single
12	(Naatz et al., 2017)	Reducing dissolution properties of CuO nanoparticles by doping with Fe results in lower cytotoxicity as observed in tissue culture cell lines and zebrafish embryos	Not Specified	Nanomaterials		Safe-by-Redesign	Multiple
13	(Guo et al., 2021)	Review of surface functionalization (both intentional and unintentional), uptake mechanisms, and computational tools relevant to the nanotoxicity of Graphene-based materials (GBMs)	Not Specified	Nanomaterials	NanoSolveIT, RiskGone, and NanoCommons	Literature Review	Multiple

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S. No.	Reference	Description	Application Sector	Focus	Framework or Project	Type of Case Study	Scope of Case Study
15	(Bae et al., 2019)	Toxicity assessment of Pb species released from perovskite solar cells (PSCs)	Energy Production	Chemicals		Toxicity Analysis	Multiple
16	(Tavernaro et al., 2021)	Literature based case study linked to stage-gate model described to illustrate NanoReg2 framework	Multiple	Nanomaterials	NanoReg2	Literature Review	Multiple
18	(Sánchez Jiménez et al., 2020)	6 separate industrial case studies illustrating safe-by-redesign principle (applied to individual materials and processes both) to reduce toxicity, exposure, and environmental impact of specific nanomaterials for various applications	Multiple	Nanomaterials	NanoReg2	Safe-by-Redesign	Single
20	(Soeteman-Hernández et al., 2020)	4 separate academic case studies illustrating safe-by-redesign principle (applied to individual materials and processes both) to reduce toxicity, exposure, and environmental impact of specific nanomaterials for various applications	Multiple	Nanomaterials	Risk Analysis and Technology Assessment (RATA) under NanoReg2	Safe-by-Redesign	Single
24	(Cazzagon, Giubilato, Bonetto, et al., 2022)	Mechanical strength, antibacterial effect, leaching of Ag defined as SbD criteria and best of 5 Nano-Ag based wound dressing selected	Medical	Product	Biorima	Safe-by-Selection	Multiple
25	(Varsou et al., 2019)	Prediction of biological and toxicological profile of multi-walled carbon nanotubes (done for each surface molecule)	Not Specified	Nanomaterials	Enalos Nanoinformatics Cloud platform	Safe-by-Modelling	Multiple
26	(Som et al., 2013)	Review of different methodologies and cases studies applied to assess safety aspects of nanomaterials	Not Specified	Nanomaterials	FP7	Literature Review	Multiple

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S. No.	Reference	Description	Application Sector	Focus	Framework or Project	Type of Case Study	Scope of Case Study
27	(Rybińska-Fryca et al., 2020)	The Structure–Activity Prediction Network (SAPNet) applied to predict the functionality and toxicity to TiO2	Not Specified	Nanomaterials	NanoSolveIT	Safe-by-Modelling	Single
28	(Halappanavar et al., 2020)	A review and network creation of Adverse Outcome Pathway (AOP) framework to assess toxicity of nanomaterials	Not Specific	Nanomaterials	SmartNanoTox and PATROLS	Literature Review	Multiple
36	(Rodrigues et al., 2020)	Correlation study between pulmonary toxicity and GO size	Not Specific	Nanomaterials	Graphene Flagship	Safe-by-Selection	Multiple
37	(Donaldson et al., 2010)	Review of toxicity of High aspect ratio, or fiber-shaped, nanoparticles (HARNs) including rods, wires, and fibers	Not Specific	Nanomaterials		Literature Review	Multiple
39	(Semenzin et al., 2019)	Hypothetical case study showing application of framework similar to one proposed by JRC	Art Conservation	Nanomaterials	NANORESTART	Safe-by-Selection	Single
40	(Gautam et al., 2019)	In vitro & in vivo toxicity assays of Cu-Te nanoparticles	Antibacterial Coating	Nanomaterials		Toxicity Analysis	Single
41	(Azmi et al., 2016)	Library of 8 colloidally stable aqueous and hemocompatible nanodispersions of diverse nanoarchitectures ISAsomes (internal self-assembled nanostructures) developed	Nano medicine	Nanomaterials		Safe-by-Redesign	Multiple
42	(Movia et al., 2014)	2 proprietary gold nanoboxes (AuNBs) as carriers synthesized with tiered SbD approach	Nano medicine	Nanomaterials	EU FP7	Safe-by-Redesign	Multiple
43	(Miao et al., 2020)	High-efficiency exfoliation of niobium diselenide nanosheets (NbSe2 NSs) to improve biocomplatibility	Nano medicine	Nanomaterials		Safe-by-Redesign	Single
44	(Motta et al., 2023)	2 safe-by-design (SbD) Ag NPs coated with hydroxyethyl cellulose (HEC) show lower toxicity	Not Specific	Nanomaterials	ASINA	Safe-by-Redesign	Multiple

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S. No.	Reference	Description	Application Sector	Focus	Framework or Project	Type of Case Study	Scope of Case Study
		than conventional Ag NPs as per the AOP approach					
45	(Remzova et al., 2019)	Toxicity of TiO_2, ZnO, SiO_2 and coated SiO_2 NPs compared for application in weathered construction materials	Construction	Nanomaterials		Safe-by-Redesign	Multiple
46	(Karayannis et al., 2019)	A detailed strategy for Safe-by-Design (SbD) 3D-printed lab-on-a-chip (LOC) device manufacturing provided	Electronics	Product	MEDLOC	General guidance	Single
47	(Mantecca et al., 2017)	Both toxicity of and exposure to ZnO and CuO applied in textiles for antibacterial action were studied as alternatives to Ag	Textiles	Nanomaterials	PROTECT	Safe-by-Selection	Multiple
48	(Wolska-Pietkiewicz et al., 2018)	High-quality, nontoxic, ligand coated ZnO nanocrystals were obtained	Nano medicine	Nanomaterials		Safe-by-Redesign	Single
49	(Fiandra et al., 2020)	Toxicity of CuO and ZnO NPs on non-target cells reduced with the polymer’s poly (ethylene imine) coating	Not Specific	Nanomaterials	PROTECT	Safe-by-Redesign	Multiple
50	(Furxhi, Bengalli, et al., 2023)	Hazard prediction of Ag NPs using model relying on both system and non-system NP features and rules derived from Bayesian networks and reasoning	Textiles and Cosmetics	Nanomaterials	ASINA	Safe-by-Modelling	Multiple
52	(Park et al., 2019)	Biocompatibility and antimicrobial activity balanced for Te NPs by altering ratio of Ag- and Cu-doping	Antimicrobial Coating	Nanomaterials		Safe-by-Redesign	Multiple
53	(Boulanger et al., 2013)	Updated production and embedding of CNTs to lower risk	Not Specific	Nanomaterials	SAPHIR	Safe-by-Redesign	Single

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S. No.	Reference	Description	Application Sector	Focus	Framework or Project	Type of Case Study	Scope of Case Study
55	(Micheletti et al., 2017)	3 case studies showing early-stage adoption of NANoReg	Multiple	Nanomaterials	NANoREG	General guidance	Multiple
56	(Tedesco et al., 2015)	Toxicity and exposure tests of commercially available nanoparticle-based consolidants SiO_2, silanized SiO_2 and $Ca(OH)_2$ to select best alternative	Art Conservation	Nanomaterials		Safe-by-Selection	Multiple
57	(Herva et al., 2011)	Combination of LCA and RCA to compare children's shoes	Footwear	Product		Safe-by-Selection	Multiple
59	(Chang et al., 2016)	Crystallization strategy developed to minimize toxicity due Pb dissolution	Not specific	Nanomaterials		Safe-by-Redesign	Single
60	(López De Ipina et al., 2017)	Discusses nanosafety aspects in PPL design to comply with Essential Health and Safety Requirements (EHSRs)	Pilot Production Lines (PPLs)	Nanomaterials	PLATFORM	General guidance	Multiple
61	(Dzhemileva et al., 2021)	Large-scale study on the mechanisms of the cytotoxic action of various classes of ionic liquids	Ionic Liquids	Chemicals		Toxicity Analysis	Multiple
64	(van Harmelen et al., 2016)	Limited specificities of safety; the LICARA nanoSCAN looks at the necessity & benefits of nanomaterial application	Multiple	Nanomaterials	LICARA nanoSCAN	General guidance	Multiple
83	(Hong et al., 2023)	Focuses on the functional, health and environmental benefits of nanomaterials	Textile	Nanomaterials	BAM	General guidance	Single
84	(Hristozov et al., 2018)	Risk assessment of CuO and basic copper carbonate (Cu2(OH)2CO3) in wood preservatives	Wood Preservatives	Nanomaterials	EU FP7	Risk Assessment	Multiple
85	(Cazzagon, Giubilato, Pizzol, et al., 2022)	assessing the occupational risks of magnetite (Fe3O4) nanoparticles coated with PLGA-b-PEG-COOH used as contrast agent in magnetic resonance imaging (MRI)	Nano medicine	Nanomaterials	BIORIMA	Risk Assessment	Single

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S. No.	Reference	Description	Application Sector	Focus	Framework or Project	Type of Case Study	Scope of Case Study
86	(A. J. Koivisto et al., 2015)	Investigate how well the NF/FF model predicts PM concentration levels in a paint factory	Paint	Particulate Matter	NanoValid	Exposure Assessment	Single
87	(Antti Joonas Koivisto et al., 2018)	Halloysite nanotubes (HNTs) exposure studies	Not Specific	Nanomaterials		Exposure Assessment	Single
88	(van Dijk et al., 2022)	Over 6.3 million alternative structures of triisobutylphosphate (TiBP) were created in silico and filtered based on QSAR outputs to remove potentially non-readily biodegradable structures	Flame Retardants	Chemicals		Safe-by-Modelling	High throughput
89	(Caldeira et al., 2023)	JRC's case study showing implementation of the proposed SSbD framework for the case of plasticizers	Plastics	Chemicals	JRC's SSbD Framework	Safe-by-Selection	Multiple

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Annex S4 – SbD Survey

'Safe-by-design' concepts are understood as per: the definition of safe by design concepts in the nano-field and adopted in EU projects; the second refers to the adoption of design criteria and safety assessment practices described in the JRC's SSbD report.

1. Have you applied the SbD tools developed/proposed by EU projects in you work?

No, we have never used SbD concepts propoed by EU-projects.

Yes, the EU project and the specific use-case is listed out in the following table:

EU Projects	Use (y/n)	Specific Use Case or Example	Relevant Links/References
Gov4Nano			
NanoReg2			
SbD4Nano			
CALIBRATE			
MARINA			
SAFERA			
NANOMET			
PROSAFE			
NANORIGO			
OpenRiskNet			
Others not mentioned above			

2. Do you perform hazard assessments for new materials and chemicals applied in your product?

No, we do not assess the hazard of materials

Yes, we assess the material hazard using one or more of the following frameworks:

Framework or Tools	Hazard Level	Specific Use or Case Example	Relevant Links/References
REACH	Criteria H1: substances of very high concern (SVHC)		
Chemical Strategy for Sustainability (CSS)	Criteria H2: Substances of concern		
JRC's SSBD Framework	Criteria H3: Other Hazards		

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Novel Assessment Methods	Any		
Others not mentioned above			

3. Do you consider occupational health and safety factors, human health and environmental risk <u>during the manufacturing or use-phase</u> of materials and chemicals?

No, we do not assess the hazard of materials

Yes, we assess the material hazard using one or more of the following frameworks:

Tool	**Occupational Health and Safety (OHS)**	**Human Health Risk Assessment**	**Environmental Risk Assessment**	**Notes and Comments**
COSHH Essentials by British Institute of Occupational Safety (Health and Safety Executive, HSE)				
International Labor Organization (ILO) Model				
German Hazardous Substances (GHS) Column Model				
Easy-to-use Workplace Control Scheme for Hazardous Substances (EMKG) Tool				
Dutch Stoffenmanager Model				
Belgian REGETOX Model				
Targeted Risk Assessment (TRA) tool by ECETOC				
Chesar by ECHA				
EUSES2.1				
ProScale 1.5				

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USEtox				
Others not mentioned above				

Digital Appendix

S.No.	Reference	Year	Funding	Title	SbD Keyword				Applicability					Safety Category		Tool				New Tool	Existing Tool	Adapted Tool	Case Study	Guidance	Review	Commentary	Stakeholder or Feedback	Stage-gate or Early-stage	Excerpt from Abstract	Link
					Title	Keyword	Abstract	Other	Chemicals	Nano/Advanced Materials	Conventional Materials	Products	Others	Environment	Human	Toxicity or Hazard	Exposure or Transportation	Risk	Other											
1	(van de Poel & Robaey, 2017)	2017	Netherlands	Safe-by-Design: from Safety to Responsibility	yes	yes	yes																			yes			Limitations of SbD appraoch and concepts highlighted	Safe-by-Design: from Safety to Responsibility | SpringerLink
2	(Yan et al., 2019)	2019	China	A Safe-by-Design Strategy towards Safer Nanomaterials in Nanomedicines	yes	yes	yes			yes						yes								yes				Early Stage	Categories of nanomaterials with clinical potential and their toxicological mechanisms are summarized; an overview of the principles in developing safe-by-design nanomaterials for medical applications and of the recent progress in this field is provided	A Safe-by-Design Strategy towards Safer Nanomaterials in Nanomedicines - Yan - 2019 - Advanced Materials - Wiley Online Library
3	(Schmutz et al., 2020)	2020	EU (GoNanoBioMat)	A Methodological Safe-by-Design Approach for the Development of Nanomedicines	yes		yes			yes				yes	yes			yes						yes				Early Stage	GoNanoBioMat SbD approach presented, which allows identifying and addressing the relevant safety aspects to address when developing polymeric NBMs during design, characterization, assessment of human health and environmental risk, manufacturing and handling, and combines the nanoscale and medicine field under one approach. Furthermore, regulatory requirements are integrated into the innovation process.	Frontiers | A Methodological Safe-by-Design Approach for the Development of Nanomedicines (frontiersin.org)
4	(Kraegeloh et al., 2018)	2018	EU (NanoReg, NanoReg2, ProSafe)	Implementation of Safe-by-Design for Nanomaterial Development and Safe Innovation: Why We Need a Comprehensive Approach	yes	yes	yes			yes														yes	yes	yes		Stage-gate	allow for cost effective industrial innovation, and an exchange of key information between regulators and innovators. Regulators are thus informed about incoming innovations in good time, supporting a proactive regulatory action. The final goal is to contribute to the nanotechnology governance, having faster, cheaper, effective, and safer nano-products on the market. The NANoREG SbD Concept is explained here	Nanomaterials | Free Full-Text | Implementation of Safe-by-Design for Nanomaterial Development and Safe Innovation: Why We Need a Comprehensive Approach (mdpi.com)
5	(Salieri et al., 2021)	2021	EU (NanoReg2, Porous4App)	Integrative approach in a safe by design context combining risk, life cycle and socio-economic assessment for safer and sustainable nanomaterials	yes	yes	yes			yes				yes	yes			yes	LCA			yes	yes	yes				Stage-gate	integration of human and environmental risk assessment, life cycle assessment as well as an assessment of the economic viability	Integrative approach in a safe by design context combining risk, life cycle and socio-economic assessment for safer and sustainable nanomaterials - ScienceDirect
6	(Marques et al., 2020)	2020	EU (GoNano-BioMat)	How the Lack of Chitosan Characterization Precludes Implementation of the Safe-by-Design Concept	yes	yes	yes			yes													yes		yes				This review shows that the characterization of chitosan is frequently missing in scientific reports, which complicates the translation into a SbD driven approach. Since the term chitosan is applied to a large group of polymers, the biological effects can be different and dependent on the degree of deacetylation and molecular weight of the polymer used on the study.	Frontiers | How the Lack of Chitosan Characterization Precludes Implementation of the Safe-by-Design Concept (frontiersin.org)
7	(Robaey, 2018)	2018	Netherlands	Dealing with risks of biotechnology: understanding the potential of Safe-by-Design	yes								Biotechnology												yes	yes	yes		The goal of this report is to provide an accessible summary of recent advances in biotechnology with regard to Safe-by-Design, a new way to deal with risks of biotechnology. The information presented is the result of literature review and ten expert interviews.	Potential_of_SbD_in_Biotech_Robaey-libre.pdf (d1wqtxts1xzle7.cloudfront.net)
8	(Le et al., 2016)	2016	Australia and	An Experimental and Computational Approach to the Development of ZnO Nanoparticles that are Safe by Design	yes					yes					yes	yes				yes			yes						A library of 45 types of ZnO nanoparticles with varying particle size, aspect ratio, doping type, doping concentration, and surface coating is synthesized, and their biological effects measured. Three biological assays measuring cell damage or stress are used to study the responses of human umbilical vein endothelial cells (HUVECs) or human hepatocellular liver carcinoma cells (HepG2) to the nanoparticles. These experimental data are used to develop quantitative and predictive computational models linking nanoparticle properties to cell viability, membrane integrity, and oxidative stress.	An Experimental and Computational Approach to the Development of ZnO Nanoparticles that are Safe by Design - Le - 2016 - Small - Wiley Online Library
9	(Damasco et al., 2020)	2020	USA	Understanding Nanoparticle Toxicity to Direct a Safe-by-Design Approach in Cancer Nanomedicine	yes					yes					yes	yes								yes	yes				This review covers preclinical and clinical inorganic-nanoparticle based nanomaterial utilized for cancer imaging and therapeutics. A special emphasis is put on the rational design to develop non-toxic/safe inorganic nanoparticle constructs to increase their viability as translatable nanomedicine for cancer therapies.	Nanomaterials | Free Full-Text | Understanding Nanoparticle Toxicity to Direct a Safe-by-Design Approach in Cancer Nanomedicine (mdpi.com)
10	(Janko et al., 2017)	2017	Germany	Strategies to optimize the biocompatibility of iron oxide nanoparticles – "SPIONs safe by design"		yes	yes			yes					yes	yes				yes			yes						Based on combined toxicological data, we follow a "safe-by design" strategy for our superparamagnetic iron oxide nanoparticles (SPION). Using complementary interference-free toxicological assay systems, we initially identified agglomeration tendencies in physiological fluids, strong uptake by cells and improvable biocompatibility of lauric acid (LA)-coated SPIONs (SPIONLA). Thus, we decided to further stabilize those particles by an artificial protein corona consisting of serum albumin.	Strategies to optimize the biocompatibility of iron oxide nanoparticles – "SPIONs safe by design" - ScienceDirect
11	(Lynch et al., 2014)	2014	EU (NanoMIL	A strategy for grouping of nanomaterials based on key physico-chemical descriptors as a basis for safer-by-design NMs	yes					yes					yes	yes				yes						yes			A novel approach to identify interlinked physicochemical properties, and on this basis identify overarching descriptors (axes or principle components) which can be used to correlate with toxicity is proposed (ONARs)	A strategy for grouping of nanomaterials based on key physico-chemical descriptors as a basis for safer-by-design NMs - ScienceDirect
12	(Naatz et al., 2017)	2017	USA	Safe-by-Design CuO Nanoparticles via Fe-Doping, Cu–O Bond Length Variation, and Biological Assessment in Cells and Zebrafish Embryos	yes	yes				yes				yes	yes	yes				yes			yes						Adapted CuO nanoparticles. Hazard screening was performed in tissue culture cell lines and zebrafish embryos to discern the change in the hazardous effects of doped vs nondoped particles. This demonstrated that with increased levels of doping there was a progressive decrease in cytotoxicity in BEAS-2B and THP-1 cells, as well as an incremental decrease in the rate of hatching interference in zebrafish embryos.	Safe-by-Design CuO Nanoparticles via Fe-Doping, Cu–O Bond Length Variation, and Biological Assessment in Cells and Zebrafish Embryos | ACS Nano
13	(Guo et al., 2021)	2021	EU (NanoSolv	Surface Functionalization of Graphene-Based Materials: Biological Behavior, Toxicology, and Safe-By-Design Aspects	yes	yes				yes				yes	yes	yes							yes		yes				Surface functionalization of GBMs, including those intentionally designed for specific applications, as well as those unintentionally acquired (e.g., protein corona formation) from the environment and biota, are reviewed through the lenses of nanotoxicity and design of safe materials (safe-by-design). Uptake and toxicity of functionalized GBMs and the underlying mechanisms are discussed and linked with the surface functionalization. Computational tools that can predict the interaction of GBMs behavior with their toxicity are discussed.	Surface Functionalization of Graphene-Based Materials: Biological Behavior, Toxicology, and Safe-By-Design Aspects - Guo - 2021 - Advanced Biology - Wiley Online Library
14	(Dekkers et al., 2020)	2020	EU (NanoReg	Safe-by-Design part I: Proposal for nanospecific human health safety aspects needed along the innovation process	yes	yes	yes			yes					yes	yes	yes	yes		yes				yes			yes	Stage-gate	This paper provides sets of questions that can help innovators to assess nanospecific human health safety aspects of their product or material along the various stages of the innovation process	Safe-by-Design part I: Proposal for nanospecific human health safety aspects needed along the innovation process - ScienceDirect
15	(Bae et al., 2019)	2019	South Korea	Hazard potential of perovskite solar cell technology for potential implementation of "safe-by-design" approach	yes	yes	yes		yes					yes	yes	yes					yes		yes					Early Stage	In this study, the potential hazards of the PSC were investigated with consideration of Pb species released from PSC using an ecotoxicity, cytotoxicity, chronic toxicity, and genotoxicity battery assay. PSC and its degradation products can cause significant toxicity, with PSC being more toxic than the individual degradation products. The order of ecotoxicity and cytotoxicity was found to be Pb2+ > PSC > PbI2 = PbO.	Hazard potential of perovskite solar cell technology for potential implementation of "safe-by-design" approach | Scientific Reports (nature.com)
16	(Tavernaro et al., 2021)	2021	EU (NanoReg2	Safe-by-Design part II: A strategy for balancing safety and functionality in the different stages of the innovation process	yes	yes	yes		yes	yes	yes	yes							Decision Support				yes	yes				Stage-gate	In this paper a first proposal for a strategy is presented to link the functionality of nanomaterials with safety aspects. This strategy first combines information on the functionality and safety early during the innovation process and onwards, and then identifies Safe-by-Design (SbD) actions that allow for optimisation of both aspects throughout the innovation process. The strategy encompasses suggestions for the type of information needed to balance functionality and safety to support decision making in the innovation process	Safe-by-Design part II: A strategy for balancing safety and functionality in the different stages of the innovation process - ScienceDirect
17	(Sánchez Jiménez et al., 2022)	2022	EU (NanoReg2	Safe(r) by design guidelines for the nanotechnology industry	yes	yes	yes		yes	yes	yes	yes		yes	yes			yes	LCA					yes	yes			Stage-gate	The SbD approach foresees the identification, estimation, and reduction of human and environmental risks as early as possible in the development of a NM or NEP, and it is based on three pillars: (i) safer NMs and NEP; (ii) safer use and end of life and (iii) safer industrial production. The presented guidelines include a set of information and tools that will help deciding at each step of the innovation process whether to continue, apply SbD measures or carry out further tests to reduce uncertainty.	Safe(r) by design guidelines for the nanotechnology industry - ScienceDirect

18	(Sánchez Jiménez et al., 2020)	2020	EU (NanoReg	Safe(r) by design implementation in the nanotechnology industry	yes	yes	yes			yes				yes	yes	yes		yes	LCA				yes						SbD was implemented in six industrial companies where SbD measures were applied to NMs, nano-enabled products (NEPs) and NM/NEP manufacturing processes. The approach considers human and environmental risks, functionality of the NM/NEP and costs as early as possible in the innovation process, continuing throughout the innovation progresses. Based on the results of the evaluation, a decision has to be made on whether to continue, stop or re-design the NM/NEP/process or to carry out further tests/obtain further data in cases where the uncertainty of the human and environmental risks is too large. However, SbD can also be implemented at later stages when there is already a prototype product or process available, as demonstrated in some of the cases.	Safe(r) by design implementation in the nanotechnology industry - ScienceDirect
19	(Giusti et al., 2019)	2019	EU (NanoReg	Nanomaterial grouping: Existing approaches and future recommendations						yes				yes	yes	yes	yes	yes		yes	yes	yes		yes	yes				This paper compares existing concepts for NM grouping, considering their underlying basic principles and criteria as well as their applicability for regulatory and other purposes.	Nanomaterial grouping: Existing approaches and future recommendations - ScienceDirect
20	(Soeteman-Hernández et al., 20	2020	EU (NanoReg	Challenges of implementing nano-specific safety and safe-by-design principles in academia	yes	yes	yes			yes				yes	yes	yes	yes	yes					yes	yes			yes	Early Stage	This perspective tries to get a better understanding on the role of safe-by-design within engineered nanomaterial research to create awareness on the importance on assessing the safety early in research. A method was developed that integrates SbD with a set of questions to aid material scientists assess the safety of their materials (nano-specific safety aspects) and Risk Analysis and Technology Assessment (RATA).	Challenges of implementing nano-specific safety and safe-by-design principles in academia - ScienceDirect
21	(Marcoulaki et al., 2021)	2021	EU (EC4SafeN	Blueprint for a self-sustained European Centre for service provision in safe and sustainable innovation for nanotechnology		yes	yes																	yes	yes	yes			This paper summarises the work undertaken to develop a blueprint for the deployment and operation of a permanent European Centre of collaborating laboratories and research organisations supporting safe innovation in nanotechnologies. The proposed entity, referred to as "the Centre", will establish a 'one-stop shop' for nanosafety-related services and a central contact point for addressing stakeholder questions about nanosafety. Its operation will rely on significant business, legal and market knowledge, as well as other tools developed and acquired through the EU-funded EC4SafeNano project and subsequent ongoing activities.	Blueprint for a self-sustained European Centre for service provision in safe and sustainable innovation for nanotechnology - ScienceDirect
22	(Cummings et al., 2021)	2021	USA	Barriers to responsible innovation of nanotechnology applications in food and agriculture: A study of US experts and developers			yes			yes															yes	yes	yes		Builds the first typology of barriers to responsible innovation as perceived by researchers and product developers working in nano-agrifood sectors in the United States.	Barriers to responsible innovation of nanotechnology applications in food and agriculture: A study of US experts and developers - ScienceDirect
23	(Soeteman-Hernández et al., 20	2021	EU (NanoReg	Modernizing innovation governance to meet policy ambitions through trusted environments			yes			yes														yes		yes	yes		A vision for modernization of nanotechnology innovation governance is a Safe Innovation Approach (SIA). SIA combines two concepts: Safe-by-Design (SbD) and Regulatory Preparedness (RP). SbD aims to motivate industry to integrate safety considerations early in the innovation process and onwards. RP aspires to improve the anticipation capabilities of regulators and develop legislation that can keep pace with innovations.	Modernizing innovation governance to meet policy ambitions through trusted environments - ScienceDirect
24	(Cazzagon et al., 2022)	2022	EU (BIORIMA	Identification of the safe(r) by design alternatives for nanosilver-enabled wound dressings	yes		yes			yes		yes		yes		yes	yes				yes	yes	yes	yes					a Safe-by-Design procedure has been developed to reduce potential environmental risks while optimizing functionality and costs of wound dressings containing Ag NPs. The SbD procedure is based on ad-hoc criteria (e.g., mechanical strength, antibacterial effect, leaching of Ag from the product immersed in environmental media) and permits to identify the best one among five pre-market alternatives. A ranking of the SbD alternatives was obtained and the safer solution was selected based on the selected SbD criteria.	Frontiers | Identification of the safe(r) by design alternatives for nanosilver-enabled wound dressings (frontiersin.org)
25	(Varsou et al., 2019)	2019	EU (NANOGE	A safe-by-design tool for functionalised nanomaterials through the Enalos Nanoinformatics Cloud platform	yes		yes		yes	yes						yes						yes	yes						Computational methods and techniques, previously applied in the area of cheminformatics for the prediction of adverse effects of chemicals, can also be applied in the case of nanomaterials (NMs), in an effort to reduce expensive and time consuming experimental procedures. In this context, a validated and predictive nanoinformatics model has been developed for the accurate prediction of the biological and toxicological profile of decorated multi-walled carbon nanotubes. The nanoinformatics workflow was fully validated according to the OECD principles before it was released online via the Enalos Cloud platform.	A safe-by-design tool for functionalised nanomaterials through the Enalos Nanoinformatics Cloud platform - Nanoscale Advances (RSC Publishing)
26	(Som et al., 2013)	2013	EU (NanoHou	Toward the Development of Decision Supporting Tools That Can Be Used for Safe Production and Use of Nanomaterials						yes	yes							yes			yes		yes	yes				Early Stage		Toward the Development of Decision Supporting Tools That Can Be Used for Safe Production and Use of Nanomaterials | Accounts of Chemical Research (acs.org)
27	(Rybińska-Fryca et al., 2020)	2020	EU (NanoSolv	Structure–activity prediction networks (SAPNets): a step beyond Nano-QSAR for effective implementation of the safe-by-design concept† Check for updates	yes	yes	yes			yes						yes	yes			yes			yes						Nano-QSAR has a number of important limitations. For example, it is not clear which descriptors that describe the nanoparticle physicochemical and structural properties are essential and can be adjusted to alter the target properties. This limitation can be overcome with the use of the Structure–Activity Prediction Network (SAPNet) presented in this paper. There are three main phases of building the SAPNet. First, information about the structural characterization of a nanomaterial, its physical and chemical properties and toxicity is compiled. Then, the most relevant properties (intrinsic/extrinsic) likely to influence the ENM toxicity are identified by developing "meta-models". Finally, these "meta-models" describing the dependencies between the most relevant properties of the ENMs and their adverse biological properties are developed	Structure–activity prediction networks (SAPNets): a step beyond Nano-QSAR for effective implementation of the safe-by-design concept - Nanoscale (RSC Publishing)
28	(Halappanavar et al., 2020)	2020	EU (SmartNar	Adverse outcome pathways as a tool for the design of testing strategies to support the safety assessment of emerging advanced materials at the nanoscale						yes					yes	yes							yes		yes				The review also presents a network of AOPs derived from connecting all AOPs, which shows that several adverse outcomes induced by nanomaterials originate from a molecular initiating event that describes the interaction of nanomaterials with lung cells and involve similar intermediate key events. Finally, using the example of an established AOP for lung fibrosis, the review will discuss various in vitro tests available for assessing lung fibrosis and how the information can be used to support a tiered testing strategy for lung fibrosis.	Adverse outcome pathways as a tool for the design of testing strategies to support the safety assessment of emerging advanced materials at the nanoscale | Particle and Fibre Toxicology | Full Text (biomedcentral.com)
29	(Stone et al., 2020)	2020	EU (GRACIOU	A framework for grouping and read-across of nanomaterials- supporting innovation and risk assessment		yes				yes						yes	yes			yes		yes		yes				Stage-gate	The GRACIOUS Framework aims to facilitate the application of grouping of nanomaterials or nanoforms (NFs), in a regulatory context and to support innovation. This includes using grouping to enable read-across from (a) source(s), for which data and information exist, to a similar target NF where information is lacking.	A framework for grouping and read-across of nanomaterials- supporting innovation and risk assessment - ScienceDirect
30	(Afantitis et al., 2020)	2020	EU (NanoSolv	NanoSolveIT Project: Driving nanoinformatics research to develop innovative and integrated tools for in silico nanosafety assessment		yes	yes			yes				yes	yes	yes	yes	yes		yes					yes				These established and well-characterized NM libraries (e.g. NanoMILE, NanoSolutions, NANoREG, NanoFASE, caLIBRAte, NanoTEST and the Nanomaterial Registry (>2000 NMs)) contain physicochemical characterization data as well as data for several relevant biological endpoints, assessed in part using harmonized Organisation for Economic Co-operation and Development (OECD) methods and test guidelines. Integration of such extensive NM information sources with the latest nanoinformatics methods will allow NanoSolveIT to model the relationships between NM structure (morphology), properties and their adverse effects and to predict the effects of other NMs for which less data	NanoSolveIT Project: Driving nanoinformatics research to develop innovative and integrated tools for in silico nanosafety assessment - ScienceDirect
31	(Choi et al., 2018)	2018	South Korea	Towards a generalized toxicity prediction model for oxide nanomaterials using integrated data from different sources						yes						yes				yes									As the presented model can predict the toxicity of the nanomaterials in consideration of various experimental conditions, it has the advantage of having a broader and more general applicability domain than the existing quantitative structure-activity relationship model.	Towards a generalized toxicity prediction model for oxide nanomaterials using integrated data from different sources | Scientific Reports (nature.com)

32	(Himly et al., 2020)	2020	EU (NANORIG	When Would Immunologists Consider a Nanomaterial to be Safe? Recommendations for Planning Studies on Nanosafety						yes					yes	yes					yes				yes				The state of research into taking the immune system into account in nanosafety studies is reviewed and three aspects in which further improvements are desirable are identified: 1) Due to technical limitations, more stringent testing for endotoxin contamination should be made. 2) Since under overdose conditions immunity shows unphysiological responses, all doses used should be justified by being equivalent to tissue-delivered doses. 3) When markers of acute inflammation or cell stress are observed, functional assays are necessary to distinguish between homeostatic fluctuation and genuine defensive or tolerogenic responses.	When Would Immunologists Consider a Nanomaterial to be Safe? Recommendations for Planning Studies on Nanosafety - Himly - 2020 - Small - Wiley Online Library
33	(Labouta et al., 2019)	2019	Canada	Meta-Analysis of Nanoparticle Cytotoxicity via Data-Mining the Literature			yes			yes					yes	yes				yes									Developed a rigorous approach for assembling published evidence on cytotoxicity of several organic and inorganic nanoparticles and unraveled hidden relationships that were not targeted in the original publications. We used a machine learning approach that employs decision trees together with feature selection algorithms (e.g., Gain ratio) to analyze a set of published nanoparticle cytotoxicity sample data (2896 samples). The specific studies were selected because they specified nanoparticle-, cell-, and screening method-related attributes.	Meta-Analysis of Nanoparticle Cytotoxicity via Data-Mining the Literature | ACS Nano
34	(Papadiamantis et al., 2020)	2020	EU (NanoSolv	Predicting Cytotoxicity of Metal Oxide Nanoparticles Using Isalos Analytics Platform						yes					yes	yes				yes		yes			yes				A literature curated dataset containing 24 distinct metal oxide (MexOy) nanoparticles (NPs), including 15 physicochemical, structural and assay-related descriptors, was enriched with 62 atomistic computational descriptors and exploited to produce a robust and validated in silico model for prediction of NP cytotoxicity. The model can be used to predict the cytotoxicity (cell viability) of MexOy NPs based on the colorimetric lactate dehydrogenase (LDH) assay and the luminometric adenosine triphosphate (ATP) assay, both of which quantify irreversible cell membrane damage	Nanomaterials | Free Full-Text | Predicting Cytotoxicity of Metal Oxide Nanoparticles Using Isalos Analytics Platform (mdpi.com)
35	(Saarimäki et al., 2021)	2021	EU (Nano-Sol	Manually curated transcriptomics data collection for toxicogenomic assessment of engineered nanomaterials						yes					yes	yes									yes				Toxicogenomics (TGx) approaches are increasingly applied to gain insight into the possible toxicity mechanisms of engineered nanomaterials (ENMs). Omics data can be valuable to elucidate the mechanism of action of chemicals and develop predictive models in toxicology. While vast amounts of transcriptomics data from ENM exposures have already been accumulated, a unified, easily accessible and reusable collection of transcriptomics data for ENMs is currently lacking. In an attempt to improve the FAIRness of already existing transcriptomics data for nanomaterials, we curated a collection of homogenized transcriptomics data from human, mouse and rat ENM exposures in vitro and in vivo.	Manually curated transcriptomics data collection for toxicogenomic assessment of engineered nanomaterials | Zenodo
36	(Rodrigues et al., 2020)	2020	EU (Graphene	Size-Dependent Pulmonary Impact of Thin Graphene Oxide Sheets in Mice: Toward Safe-by-Design	yes		yes			yes					yes	yes					yes		yes						Here, the effects of lateral dimensions of GO sheets in acute and chronic pulmonary responses after single intranasal instillation in mice are compared. Micrometer-sized GO induces stronger pulmonary inflammation than nanometer-sized GO, despite reduced translocation to the lungs. Genome-wide RNA sequencing also reveals distinct size-dependent effects of GO, in agreement with the histopathological results.	Size-Dependent Pulmonary Impact of Thin Graphene Oxide Sheets in Mice: Toward Safe-by-Design - Rodrigues - 2020 - Advanced Science - Wiley Online Library
37	(Donaldson et al., 2010)	2010	UK	Identifying the pulmonary hazard of high aspect ratio nanoparticles to enable their safety-by-design	yes					yes	yes				yes	yes							yes		yes				In this article we describe the unusual hazard associated with fibers, with special reference to asbestos, and address the features of fibers that dictate their pathogenicity as developed in the fiber pathogenicity paradigm. This paradigm is a robust structure:toxicity model that identifies thin, long, biopersistent fibers as the effective dose for fiber-type pathogenic effects.	Identifying the pulmonary hazard of high aspect ratio nanoparticles to enable their safety-by-design | Nanomedicine (futuremedicine.com)
38	(Bouchaut & Asveld, 2020)	2020	Netherlands	Safe-by-Design: Stakeholders' Perceptions and Expectations of How to Deal with Uncertain Risks of Emerging Biotechnologies in the Netherlands	yes		yes						Biotechnology													yes	yes		To explore the possibilities of SbD for future governance of biotechnology, we should gain insight in how various stakeholders perceive notions of risk, safety, and inherent safety, and what this implies for the applicability of SbD for risk governance concerning industrial biotechnology. Our empirical research reveals three main themes: (1) diverging expectations with regard to safety and risks, and to establish an acceptable level of risk; (2) different applications of SbD and inherent safety, namely, product- and process-wise; and (3) unclarity in allocating responsibilities to stakeholders in the development process of a biotechnology and within society	Safe-by-Design: Stakeholders' Perceptions and Expectations of How to Deal with Uncertain Risks of Emerging Biotechnologies in the Netherlands - Bouchaut - 2020 - Risk Analysis - Wiley Online Library
39	(Semenzin et al., 2019)	2019	EU (NANORES	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	yes		yes		yes	yes	yes			yes	yes	yes					yes		yes	yes				Stage-gate	we propose a sustainability framework implementing the Safe by Design concept to support product developers in the early steps of product development, with the aim to provide safer nano-formulations for conservation, while retaining their functionality. In addition, this framework can support the assessment of sustainability of new products and their comparison to their conventional chemical counterparts if any. The goal is to promote the selection and use of safer and more sustainable nano-based products in different conservation contexts.	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 | SpringerLink
40	(Gautam et al., 2019)	2019	South Korea	Plug-In Safe-by-Design Nanoinorganic Antibacterials	yes	yes	yes			yes				yes	yes	yes					yes		yes						we developed a plug-in system comprising a spark plasma reactor and a flow heater under nitrogen gas flow to supply precursor inorganic nanoparticles (Cu–Te configuration) that can be modulated in-flight at different temperatures. From antibacterial and toxicological assays in both in vitro and in vivo models, bactericidal and toxicological profiles showed that the plug-in system-based platform can be used to identify key parameters for producing safe-by-design agents with antibacterial activity [>88% (in vitro) and >80% (in vivo) in antibacterial efficiency] and safety (>65% in in vitro viability and >60% in in vivo survival rate)	Plug-In Safe-by-Design Nanoinorganic Antibacterials | ACS Nano
41	(Azmi et al., 2016)	2016	Denmark	A structurally diverse library of safe-by-design citrem-phospholipid lamellar and non-lamellar liquid crystalline nano-assemblies	yes					yes					yes	yes							yes						Reducing immunotoxicity with surfece treatment.	A structurally diverse library of safe-by-design citrem-phospholipid lamellar and non-lamellar liquid crystalline nano-assemblies - ScienceDirect
42	(Movia et al., 2014)	2014	EU (NAMDIAT	A safe-by-design approach to the development of gold nanoboxes as carriers for internalization into cancer cells	yes	yes	yes			yes					yes	yes					yes		yes					Early Stage	we investigated the potential of proprietary gold nanoboxes (AuNBs) as carriers for their perspective translation into multifunctional, pre-clinical nano-enabled systems for personalized medicine approaches against lung cancer. A safe-by-design, tiered approach, with systematic tests conducted in the early phases on uncoated AuNBs and more focused testing on the coated, drug-loaded nanomaterial toward the end, was adopted. Our results showed that uncoated AuNBs could effectively penetrate into human lung adenocarcinoma (A549) cells when in simple (mono-cultures) or complex (co- and three-dimensional-cultures) in vitro microenvironments mimicking the alveolar region of human lungs.	A safe-by-design approach to the development of gold nanoboxes as carriers for internalization into cancer cells - ScienceDirect
43	(Miao et al., 2020)	2020	China	Safe-by-Design Exfoliation of Niobium Diselenide Atomic Crystals as a Theory-Oriented 2D Nanoagent from Anti-Inflammation to Antitumor	yes		yes			yes													yes						A safe-by-design exfoliation strategy, integration of cryo-pretreatment and DNA-assisted exfoliation, is proposed for high-efficiency exfoliation of atomically thin NbSe2 NSs. Especially, computational simulation reveals that NbSe2 NSs effectively eliminate reactive oxygen and nitrogen species (RONS) via hydrogen atom transfer and redox reaction.	Safe-by-Design Exfoliation of Niobium Diselenide Atomic Crystals as a Theory-Oriented 2D Nanoagent from Anti-Inflammation to Antitumor - Miao - 2020 - Advanced Functional Materials - Wiley Online Library
44	(Motta et al., 2023)	2023	EU (ASINA)	Preliminary Toxicological Analysis in a Safe-by-Design and Adverse Outcome Pathway-Driven Approach on Different Silver Nanoparticles: Assessment of Acute Responses in A549 Cells	yes	yes	yes			yes					yes	yes					yes		yes						n the present manuscript, according to an adverse outcome pathway (AOP) approach, we tested two safe-by-design (SbD) newly developed Ag NPs coated with hydroxyethyl cellulose (HEC), namely AgHEC powder and AgHEC solution. These novel Ag NPs were compared to two reference Ag NPs (naked and coated with polyvinylpyrrolidone—PVP). Cell viability, inflammatory response, reactive oxygen species, oxidative DNA damage, cell cycle, and cell–particle interactions were analyzed in the alveolar in vitro model, A549 cells. The results show a different toxicity pattern of the novel Ag NPs compared to reference NPs and that between the two novel NPs, the AgHEC solution is the one with the lower toxicity and to be further developed within the SbD framework.	Toxics | Free Full-Text | Preliminary Toxicological Analysis in a Safe-by-Design and Adverse Outcome Pathway-Driven Approach on Different Silver Nanoparticles: Assessment of Acute Responses in A549 Cells (mdpi.com)

45	(Remzova et al., 2019)	2019	Czech Republ	Toxicity of TiO2, ZnO, and SiO2 Nanoparticles in Human Lung Cells: Safe-by-Design Development of Construction Materials	yes					yes					yes	yes					yes		yes						In this study, we compare the toxicological effects of pristine TiO2, ZnO, SiO2, and coated SiO2 nanoparticles, and evaluate their suitability as additives to consolidants of weathered construction materials. First, water soluble tetrazolium 1 (WST-1) and lactate dehydrogenase (LDH) assays were used to determine the viability of human alveolar A549 cells at various nanoparticle concentrations (0–250 μg mL−1). While the pristine TiO2 and coated SiO2 nanoparticles did not exhibit any cytotoxic effects up to the highest tested concentration, the pristine SiO2 and ZnO nanoparticles significantly reduced cell viability.	Nanomaterials | Free Full-Text | Toxicity of TiO2, ZnO, and SiO2 Nanoparticles in Human Lung Cells: Safe-by-Design Development of Construction Materials (mdpi.com)
46	(Karayannis et al., 2019)	2019	EU (MEDLOC)	3D-Printed Lab-on-a-Chip Diagnostic Systems-Developing a Safe-by-Design Manufacturing Approach	yes	yes	yes					yes			yes	yes	yes				yes		yes	yes				Early Stage	The aim of this study is to provide a detailed strategy for Safe-by-Design (SbD) 3D-printed lab-on-a-chip (LOC) device manufacturing, using Fused Filament Fabrication (FFF) technology. Furthermore, the most crucial health risks involved in FFF processes are examined, placing the focus on the examination of ultrafine particle (UFP) and Volatile Organic Compound (VOC) emission hazards. Thus, a SbD scheme for lab-on-a-chip manufacturing is provided, while also taking into account process optimization for obtaining satisfactory printed LOC quality.	Micromachines | Free Full-Text | 3D-Printed Lab-on-a-Chip Diagnostic Systems-Developing a Safe-by-Design Manufacturing Approach (mdpi.com)
47	(Mantecca et al., 2017)	2017	EU (PROTECT)	Airborne Nanoparticle Release and Toxicological Risk from Metal-Oxide-Coated Textiles: Toward a Multiscale Safe-by-Design Approach	yes		yes			yes					yes	yes	yes				yes		yes						The cytotoxic and pro-inflammatory effects of studied NPs were investigated in vitro in human alveolar epithelial A549 and macrophage-like THP1 cells. To understand the potential respiratory impact of the NPs, the coated textiles were subjected to the abrasion tests, and the released airborne particles were measured. A very small amount of the studied metal oxides NPs was released from abrasion of the textiles coated by the ethanol-based sonochemical process. The release from the water-based coating was comparably higher	Airborne Nanoparticle Release and Toxicological Risk from Metal-Oxide-Coated Textiles: Toward a Multiscale Safe-by-Design Approach | Environmental Science & Technology (acs.org)
48	(Wolska-Pietkiewicz et al., 2018	2018	Poland	Safe-by-Design Ligand-Coated ZnO Nanocrystals Engineered by an Organometallic Approach: Unique Physicochemical Properties and Low Toxicity toward Lung Cells	yes					yes					yes	yes					yes		yes						The ZnO NCs from the one-pot, self-supporting organometallic procedure exhibit unique physicochemical properties such as relatively high quantum yield (up to 28 %), ultralong photoluminescence decay (up to 2.1 μs), and EPR silence under standard conditions. The cytotoxicity of the resulting ZnO NCs toward normal (MRC-5) and cancer (A549) human lung cell lines was tested by MTT assay, which demonstrated that these brightly luminescent, quantum-sized ZnO NCs have a low negative impact on mammalian cell lines. These results substantiate that the self-supporting organometallic approach is a highly promising method to obtain high-quality, nontoxic, ligand-coated ZnO NCs with prospective biomedical applications.	Safe-by-Design Ligand-Coated ZnO Nanocrystals Engineered by an Organometallic Approach: Unique Physicochemical Properties and Low Toxicity toward Lung Cells - Wolska-Pietkiewicz - 2018 - Chemistry – A European Journal - Wiley Online Library
49	(Fiandra et al., 2020)	2020	EU (PROTECT)	Hazard assessment of polymer-capped CuO and ZnO nanocolloids: A contribution to the safe-by-design implementation of biocidal agents	yes					yes					yes	yes					yes		yes						In this work, we propose to investigate if the coating of copper and zinc oxides (CuO and ZnO) NPs with the polymers poly(ethylene imine) (PEI) or poly(ethylene glycol) (PEG) is able protect non-target cells and organisms from the toxicity of antibacterial MeOs NPs. The overall results obtained exposing lung cells and Xenopus laevis embryos to CuO-PEG, CuO-PEI, ZnO-PEG and ZnO-PEI, indicate that PEG, but not PEI coating, is able to exert a protective function against MeOs toxicity.	Hazard assessment of polymer-capped CuO and ZnO nanocolloids: A contribution to the safe-by-design implementation of biocidal agents - ScienceDirect
50	(Furxhi et al., 2023)	2023	EU (ASINA)	Data-Driven Quantitative Intrinsic Hazard Criteria for Nanoproduct Development in a Safe-by-Design Paradigm: A Case Study of Silver Nanoforms	yes	yes	yes			yes						yes				yes		yes	yes	yes			yes	Early Stage	In this study, we target the safety dimension, and we demonstrate the journey toward quantitative intrinsic hazard criteria derived from findable, accessible, interoperable, and reusable data. Data were curated and merged for the development of new approach methodologies, that is, quantitative structure–activity relationship models based on regression and classification machine learning algorithms, with the intent to predict a hazard class. This study reveals (i) quantitative intrinsic hazard criteria to be considered in the safety aspects during synthesis stage, (ii) the challenges within, and (iii) the future directions for the generation and distillation of such criteria that can feed SSbD paradigms.	Data-Driven Quantitative Intrinsic Hazard Criteria for Nanoproduct Development in a Safe-by-Design Paradigm: A Case Study of Silver Nanoforms | ACS Applied Nano Materials
51	(Robaey et al., 2018)	2018	Netherlands	The Food Warden: An Exploration of Issues in Distributing Responsibilities for Safe-by-Design Synthetic Biology Applications	yes								Biology													yes	yes		This research explores these assumptions through the use of a Group Decision Room. In this set up, anonymous and non-anonymous deliberation methods are used for different stakeholders to exchange views. During the session, a potential synthetic biology application is used as a case for investigation: the Food Warden, a biosensor contained in meat packaging for indicating the freshness of meat. Participants discuss what potential issues might arise, how responsibilities should be distributed in a forward-looking way, who is to blame if something would go wrong. They are also asked what safety and responsibility mean at different phases, and for different stakeholders. The results of the session are not generalizable, but provide valuable insights. Issues of safety cannot all be taken care of in the R&D phase.	The Food Warden: An Exploration of Issues in Distributing Responsibilities for Safe-by-Design Synthetic Biology Applications | SpringerLink
52	(Park et al., 2019)	2019	South Korea	Plug-and-play safe-by-design production of metal-doped tellurium nanoparticles with safer antimicrobial activities	yes		yes			yes				yes		yes							yes						we developed a safe-by-design plug-and-play approach for continuous gas flow production of silver (or copper)-doped tellurium (Ag- or Cu–Te) nanoparticles with safer antimicrobial activity. Using this approach, we achieved precise modulation of dopant contents (5–8% atomic Ag and Cu) in nanoparticles without using batch hydrothermal chemistry. We also suggest the use of ratios between biocompatibility and antimicrobial activity as safety indices (SIs) for evaluations of nanoparticle applications. Approximately 6% atomic Ag in Ag–Te particles exhibited an optimal SI and significantly reduced the minimum inhibitory concentration of individual Te nanoparticle	Plug-and-play safe-by-design production of metal-doped tellurium nanoparticles with safer antimicrobial activities - Environmental Science: Nano (RSC Publishing) DOI:10.1039/C9EN00372J
53	(Boulanger et al., 2013)	2013	France	Towards large scale aligned carbon nanotube composites: an industrial safe-by-design and sustainable approach	yes					yes		yes											yes						We present the main results demonstrating the feasibility of high surface (> A4 format size) semi-industrial fabrication of composites embedding VACNT in organic matrices. The process of growing VACNT exhibits several advantages regarding safety issues: integrating de facto a safe collecting procedure on the substrate, avoiding additional preparation steps and simplifying handling and protection by impregnation into a matrix. The following steps of the overall process: VACNT carpet functionalization, alignment control and impregnation, can be processed on-line in a closed and safe continuous process and lead to dramatically reduced direct nanotube exposure for workers and users. This project opens the route to a continuous, roll-to-roll, safer, cost-effective and green industrial process to manufacture composites with controlled and aligned greener "black" carbon nanotubes.	Towards large scale aligned carbon nanotube composites: an industrial safe-by-design and sustainable approach - IOPscience
54	(Jeliazkova et al., 2014)	2014	EU (eNanoMa	The first eNanoMapper prototype: A substance database to support safe-by-design	yes					yes				yes	yes	yes									yes				The EU-funded eNanoMapper project proposes a computational infrastructure for toxicological data management of engineered nanomaterials (ENMs) based on open standards, ontologies and an interoperable design to enable a more effective, integrated approach to European research in nanotechnology. eNanoMapper's goal is to support the collaborative safety assessment for ENMs by creating a modular, extensible infrastructure for transparent data sharing, data analysis, and the creation of computational toxicology models for ENMs. The eNanoMapper database solution builds on previous experience of the consortium partners in supporting diverse data through flexible data storage, semantic web technologies, open source components and web services.	The first eNanoMapper prototype: A substance database to support safe-by-design | IEEE Conference Publication | IEEE Xplore

55	(Micheletti et al., 2017)	2017	EU (NanoReg	Implementation of the NANoREG Safe-by-Design approach for different nanomaterial applications	yes		yes			yes													yes	yes				Stage-gate	In order to contribute to a sustainable innovation process in the nanotechnology field by maximising both benefits and safety, the NANoREG project developed a Safe Innovation approach, based on two elements: the Safe-by-Design approach which aims at including risk assessment into all innovation stages; and the Regulatory Preparedness, focused on the dialogue with stakeholders along the innovation chain. In this work we present some examples about the implementation in our Laboratory of this approach for different MNM applications, covering different steps of the innovation chain. The case studies include: the feasibility study of a medical device including substances, for topical application; the testing of two potential nanotech solutions for the consolidation of cultural heritage artifacts; the testing of coatings already on the market for other uses, which was tested as food contact materials (FCM) to evaluate the conformity to food applications.	Implementation of the NANoREG Safe-by-Design approach for different nanomaterial applications - IOPscience
56	(Tedesco et al., 2015)	2015	Italy	Cytotoxicity and antibacterial activity of a new generation of nanoparticle-based consolidants for restoration and contribution to the safe-by-design implementation	yes	yes	yes			yes					yes	yes	yes				yes		yes						In this work, we focused our attention on potential risks posed by three commercially available nanoparticle-based consolidants: silica (SiO_2 NPs), silanized silica (silanized SiO_2 NPs) and calcium hydroxide (nanolime) nanoparticle dispersions. Occupational exposure impact was tested on three in vitro models mimicking inhalation, dermal contact and systemic routes. While no toxic effects were observed for nanolime and silanized SiO_2 NPs, bare SiO_2 NPs showed a dose- and time-dependent damage in all considered models. Corrosion test on EpiSkin® revealed no viability reduction	Cytotoxicity and antibacterial activity of a new generation of nanoparticle-based consolidants for restoration and contribution to the safe-by-design implementation - ScienceDirect
57	(Herva et al., 2011)	2011	Spain	Sustainable and safe design of footwear integrating ecological footprint and risk criteria	yes							yes			yes	yes		yes	LCA		yes		yes						Four models of children's shoes were analyzed and compared. The synthetic shoes obtained a smaller EF (6.5 gm2) when compared to the leather shoes (11.1 gm2). However, high concentrations of hazardous substances were detected in the former, even making the Hazard Quotient (HQ) and the Cancer Risk (CR) exceed the recommended safety limits for one of the synthetic models analyzed. Risk criteria were prioritized in this case and, consequently, the design proposal was discarded. For the other cases, the perspective provided by the indicators of different nature was balanced to accomplish a fairest evaluation.	Sustainable and safe design of footwear integrating ecological footprint and risk criteria - ScienceDirect
58	(Mech et al., 2022)	2022	EU	Safe- and sustainable-by-design: The case of Smart Nanomaterials. A perspective based on a European workshop	yes	yes	yes		yes	yes															yes	yes	yes		An online workshop was organised in September 2020 by the Joint Research Centre and the Directorate-General Research and Innovation of the European Commission, with participants from academia, non-governmental organisations, industry and regulatory bodies. The aims were to introduce the concept of Safe- and Sustainable-by-Design, to identify industrial and regulatory challenges in achieving safer and more sustainable Smart Nanomaterials as an example of innovative materials, and to deliver recommendations for directions and actions necessary to meet these challenges. The following needs were identified: (i) an agreed terminology, (ii) a common understanding of the principles of Safe- and Sustainable-by-Design, iii) criteria, assessment tools and incentives to achieve a transition from Safe-by-Design to Safe- and Sustainable-by-Design, and (iv) preparedness of regulators and legislation for innovative chemicals/nanomaterials.	Safe- and sustainable-by-design: The case of Smart Nanomaterials. A perspective based on a European workshop - ScienceDirect
59	(Chang et al., 2016)	2016	China	Crystallographic facet-dependent stress responses by polyhedral lead sulfide nanocrystals and the potential "safe-by-design" approach	yes		yes			yes					yes	yes					yes		yes						In this study, the toxic role of specific crystallographic facets of a series of polyhedral lead sulfide (PbS) nanocrystals, including truncated octahedrons, cuboctahedrons, truncated cubes, and cubes, was investigated in human bronchial epithelial cells (BEAS-2B) and murine alveolar macrophages (RAW 264.7) cells. (100) facets were found capable of triggering facet-dependent cellular oxidative stress and heavy metal stress responses, such as glutathione depletion, lipid peroxidation, reactive oxygen species (ROS) production, heme oxygenase-1 (HO-1) and metallothionein (MT) expression, and mitochondrial dysfunction, while (111) facets remained inert under biological conditions.	Crystallographic facet-dependent stress responses by polyhedral lead sulfide nanocrystals and the potential "safe-by-design" approach | SpringerLink
60	(López De Ipina et al., 2017)	2017	EU (PLATFORM	Implementation of a safe-by-design approach in the development of new open pilot lines for the manufacture of carbon nanotube-based nano-enabled products	yes		yes			yes			Pilot production line		yes	yes	yes	yes			yes		yes	yes					This paper discusses the methodological approach followed by the project PLATFORM to integrate all the nanosafety aspects in the design of the PPLs, in order to achieve safe designs in conformity with the relevant Essential Health and Safety Requirements (EHSRs) of the MD. Since machinery must be designed and constructed taking into account the results of the risk assessment (RA), this paper describes the systematic and iterative approach for RA and risk reduction followed to eliminate hazards as far practicable and to adequately reduce risks by the implementation of protective measures.	Implementation of a safe-by-design approach in the development of new open pilot lines for the manufacture of carbon nanotube-based nano-enabled products - IOPscience
61	(Dzhemileva et al., 2021)	2021	Russia	A large-scale study of ionic liquids employed in chemistry and energy research to reveal cytotoxicity mechanisms and to develop a safe design guide	yes				yes						yes	yes					yes		yes		yes				In this work, we carried out the first large-scale study on the mechanisms of the cytotoxic action of various classes of ionic liquids, including imidazolium, pyridinium, pyrrolidinium, ammonium, and cholinium ILs (25 in total). We determined the biological effect of these ILs in seven cell lines of various origins (HEK293 (human embryonic kidney), U937 (human myeloid leukemia), Jurkat (human T-cell leukemia), HL60 (human acute promyelocytic leukemia), K562 (human chronic myelogenous leukemia), A549 (human alveolar adenocarcinoma), and A2780 (human ovarian carcinoma)).	A large-scale study of ionic liquids employed in chemistry and energy research to reveal cytotoxicity mechanisms and to develop a safe design guide - Green Chemistry (RSC Publishing) DOI:10.1039/D1GC01520F
62	(Kramer et al., 2007)	2007		The application of discovery toxicology and pathology towards the design of safer pharmaceutical lead candidates									Pharmaceuticals		yes	yes									yes			Stage-gate	In this Review, we discuss how the early application of preclinical safety assessment — both new molecular technologies as well as more established approaches such as standard repeat-dose rodent toxicology studies — can identify predictable safety issues earlier in the testing paradigm. The earlier identification of dose-limiting toxicities will provide chemists and toxicologists the opportunity to characterize the dose-limiting toxicities, determine structure–toxicity relationships and minimize or circumvent adverse safety liabilities.	The application of discovery toxicology and pathology towards the design of safer pharmaceutical lead candidates | Nature Reviews Drug Discovery
63	(Gottardo et al., 2021)	2021	EU	Towards safe and sustainable innovation in nanotechnology: State-of-play for smart nanomaterials	yes					yes															yes	yes			This paper focuses on advanced nanomaterials that actively respond to external stimuli, also known as 'smart nanomaterials', and which are already on the market or in the research and development phase for non-medical applications such as in agriculture, food, food packaging and cosmetics. A review shows that smart nanomaterials and enabled products may present new challenges for safety and sustainability assessment due to their complexity and dynamic behaviour. Moreover, existing regulatory frameworks, in particular in the European Union, are probably not fully prepared to address them. What is missing today is a systematic and comprehensive approach that allows for considering sustainability aspects hand in hand with safety considerations very early on at the material design stage.	Towards safe and sustainable innovation in nanotechnology: State-of-play for smart nanomaterials - ScienceDirect
64	(van Harmelen et al., 2016)	2016	EU (LICARA)	LICARA nanoSCAN - A tool for the self-assessment of benefits and risks of nanoproducts						yes					yes			yes		yes			yes	yes				Early Stage	his paper introduces LICARA nanoSCAN, a modular web based tool that supports SMEs in assessing benefits and risks associated with new or existing nanoproducts. This tool is unique because it is scanning both the benefits and risks over the nanoproducts life cycle in comparison to a reference product with a similar functionality in order to enable the development of sustainable and competitive nanoproducts.	LICARA nanoSCAN - A tool for the self-assessment of benefits and risks of nanoproducts - ScienceDirect
65	(Hartmann et al., 2017)	2017	EU (ENVNANO	NanoCRED: A transparent framework to assess the regulatory adequacy of ecotoxicity data for nanomaterials – Relevance and reliability revisited						yes				yes	yes	yes								yes	yes			Early Stage	Here we propose a framework for reliability and relevance evaluation of ecotoxicity data for nanomaterials that take into account the challenges and characterisation requirements associated with testing of these substances. The nanoCRED evaluation criteria, and accompanying guidance, were developed to be used in combination with those developed through the 'Criteria for Reporting and Evaluating Ecotoxicity Data (CRED)' project.	NanoCRED: A transparent framework to assess the regulatory adequacy of ecotoxicity data for nanomaterials – Relevance and reliability revisited - ScienceDirect
66	(RIVM, 2017)	2017	EU (NanoReg	Safe Innovation Approach (SIA) Toolbox						yes				yes	yes			yes							yes					

67	(Sørensen et al., 2019)	2019	EU (CaLIBRAt	Evaluating environmental risk assessment models for nanomaterials according to requirements along the product innovation Stage-Gate process		yes				yes				yes		yes	yes	yes								yes		yes	Stage-gate		
68	(Franken et al., 2020)	2020	EU (CaLIBRAt	Ranking of human risk assessment models for manufactured nanomaterials along the Cooper stage-gate innovation funnel using stakeholder criteria		yes				yes					yes			yes								yes		yes	Stage-gate		
69	(Nymark et al., 2020)	2020	EU (CaLIBRAt	Toward Rigorous Materials Production: New Approach Methodologies Have Extensive Potential to Improve Current Safety Assessment Practices		yes	yes			yes					yes	yes	yes	yes								yes		yes	Stage-gate		
70	(OECD, 2020)	2020	OECD	Moving Towards a Safe(r) Innovation Approach (SIA) for More Sustainable Nanomaterials and Nano-enabled Products						yes				yes	yes											yes		yes			
71	(Shandilya & Franken, 2020)	2020	EU (Gov4Nan	D4.1 Review of existing and near-future next generation tools and models to support the nano-risk governance council and industrial safer-by-design	yes				yes	yes				yes	yes											yes					
72	(Falk et al., 2021)	2021	EU	Safe-by-design and EU funded NanoSafety projects	yes					yes				yes	yes											yes		yes			
73	(European Commission et al., 2	2021	EU	European research on environment and health : projects funded by Horizon 2020 (2014-2020)						yes				yes	yes											yes					
74	(Krans et al., 2021)	2021	Netherlands	Nanotechnology and Safe-by-Design. Inventory of research into Safe-by-Design Horizon 2020 projects from 2013 to 2020	yes					yes				yes	yes											yes					
75	(Joint Research Centre, 2021)	2021	EU (NANoREG	NANoREG Toolbox for the Safety Assessment of Nanomaterials - Data Europa EU						yes				yes	yes	yes	yes	yes								yes					
76	(Shandilya et al., 2021)	2021	EU (Gov4Nan	TRAAC framework for regulatory acceptance and wider usability of tools and methods for safe innovation and sustainability of manufactured nanomaterials						yes				yes	yes											yes		yes			
77	(European Commission, Joint R	2022	EU	Safe and sustainable by design chemicals and materials : review of safety and sustainability dimensions, aspects, methods, indicators, and tools; Safe and sustainable by design chemicals and materials : framework for the definition of criteria and evaluation procedure for chemicals and materials	yes	yes	yes		yes	yes				yes	yes											yes			Stage-gate		
78	(Guinée et al., 2022)	2022	EU	The meaning of life ... cycles: lessons from and for safe by design studies	yes	yes	yes		yes	yes		yes														yes					
79	(Furxhi, Costa, et al., 2023)	2023	EU	Status, implications and challenges of European safe and sustainable by design paradigms applicable to nanomaterials and advanced materials	yes	yes	yes		yes	yes		yes			yes											yes		yes			
80	(Ruijter et al., 2023)	2023	EU	The State of the Art and Challenges of In Vitro Methods for Human Hazard Assessment of Nanomaterials in the Context of Safe-by-Design	yes					yes				yes	yes	yes										yes			Early stage		
81	(Subramanian et al., 2023)	2023	Netherlands	Approaches to implement safe by design in early product design through combining risk assessment and Life Cycle Assessment	yes	yes	yes		yes	yes		yes		yes	yes											yes			Stage-gate		
82	(caLIBRATE & Gov4Nano, 2023;	2023	EU (RiskGONE	Nano-Risk Governance Platform						yes				yes	yes	yes	yes									yes		yes	Stage-gate		
83	(Hong et al., 2023)	2023	EU	Development of a Benefit Assessment Matrix for Nanomaterials and Nano-enabled Products—Toward Safe and Sustainable by Design	yes	yes	yes			yes		yes								yes			yes	yes					Stage-gate	This paper describes our development of a Benefit Assessment Matrix (BAM) that focuses on the functional, health and environmental benefits of nanomaterials, nano-enabled manufacturing and nano-enabled products. The BAM is an Excel spreadsheet-based tool to help researchers and small and medium-sized enterprises assess these potential benefits throughout their product's life cycle while they are still in the early phase of the innovation process.	Sustainability | Free Full-Text | Development of a Benefit Assessment Matrix for Nanomaterials and Nano-enabled Products—Toward Safe and Sustainable by Design (mdpi.com)
84	(Hristozov et al., 2018)	2018	EU (SUN)	Quantitative human health risk assessment along the lifecycle of nano-scale copper-based wood preservatives						yes		yes			yes			yes		yes			yes	yes						we performed quantitative (probabilistic) human health risk assessment (HHRA) along the lifecycles of these formulations used in antibacterial and antifungal wood coatings and impregnations by means of the EU FP7 SUN project's Decision Support System (SUNDS, www.sunds.gd). The results from the risk analysis revealed inhalation risks from CuO in exposure scenarios involving workers handling dry powders and performing sanding operations as well as potential ingestion risks for children exposed to nano Cu2(OH)2CO3 in a scenario involving hand-to-mouth transfer of the substance released from impregnated wood.	https://www.tandfonline.com/doi/full/10.1080/17435390.2018.1472314
85	(Cazzagon, Giubilato, Pizzol, et	2022	EU (BIORIMA)	Occupational risk of nano-biomaterials: Assessment of nano-enabled magnetite contrast agent using the BIORIMA Decision Support System						yes					yes			yes		yes			yes	yes						Our goal is to contribute to increasing the knowledge in this area by assessing the occupational risks of magnetite (Fe3O4) nanoparticles coated with PLGA-b-PEG-COOH used as contrast agent in magnetic resonance imaging (MRI) by applying the software-based Decision Support System (DSS) which was developed in the EU H2020 project	Occupational risk of nano-biomaterials: Assessment of nano-enabled magnetite contrast agent using the BIORIMA Decision Support System - ScienceDirect
86	(Koivisto et al., 2014)	2014	EU (NanoVali	Testing the near field/far field model performance for prediction of particulate matter emissions in a paint factory								yes			yes		yes				yes		yes							In this study we investigate how well the NF/FF model predicts PM concentration levels in a paint factory. PM concentration levels were measured during big bag and small bag powder pouring. Rotating drum dustiness indices were determined for the specific powders used and applied in the NF/FF model to predict mass concentrations. Modeled process specific concentration levels were adjusted to be similar to the measured concentration levels by adjusting the handling energy factor.	Testing the near field/far field model performance for prediction of particulate matter emissions in a paint factory - Environmental Science: Processes & Impacts (RSC Publishing)
87	(Antti Joonas Koivisto et al., 201	2018	EU (NanoPack	Occupational exposure during handling and loading of halloysite nanotubes – A case study of counting nanofibers						yes					yes		yes				yes		yes							Here we assessed the potential inhalation exposure to HNTs in an industrial research laboratory. Due to very limited toxicological information of HNTs we recommend avoiding inhalation exposure.	Occupational exposure during handling and loading of halloysite nanotubes – A case study of counting nanofibers - ScienceDirect
88	(van Dijk et al., 2022)	2022	EU	Safe and sustainable by design: A computer-based approach to redesign chemicals for reduced environmental hazards	yes				yes					yes	yes	yes					yes		yes	yes					Early Stage	In this study, a systematic and computer-aided workflow was developed to facilitate the chemical redesign for reduced persistency. The approach includes elements of Essential Use, Alternatives Assessment and Green and Circular Chemistry and ties into goals recently formulated in the context of the EU Green Deal. The organophosphate chemical triisobutylphosphate (TiBP) was used as a case study for exploration of the approach, as its emission to the environment was expected to be inevitable when used as a flame retardant. Over 6.3 million alternative structures were created in silico and filtered based on QSAR outputs to remove potentially non-readily biodegradable structures. With a multi-criteria analysis based on predicted properties and synthesizability a top 500 of most desirable structures was identified. The target structure (di-n-butyl (2-hydroxyethyl) phosphate) was manually selected and synthesized.	Safe and sustainable by design: A computer-based approach to redesign chemicals for reduced environmental hazards - ScienceDirect
89	(Caldeira et al., 2023)	2023	EU	Safe and Sustainable by Design chemicals and materials. Application of the SSbD framework to case studies. JRC technical report for consultation. JRC131878	yes	yes	yes		yes			yes		yes	yes	yes	yes	yes	LCA		yes		yes	yes					Early Stage		