Environment Systems and Decisions
https://doi.org/10.1007/s10669-023-09927-w

Safety-by-design and engineered nanomaterials: the need to move from theory to practice

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Accepted: 24 July 2023

Abstract

As the governance of engineered nanomaterials (ENMs) evolves, innovations in the prevention, mitigation, management, and transfer of risk shape discussion of how nanotechnology may mature and reach various marketplaces. Safety-by-Design (SbD) is one leading concept that, while equally philosophy as well as risk-based practice, can uniquely help address lingering uncertainties and concerns stemming from regulatory evaluation of ENM risk across worker, consumer, and environmental safety. This paper provides a discussion on the SbD concept across different disciplines aiming to identify different approaches and needs to meet regulatory requirements—ultimately, we argue that SbD is evolving both to meet the needs and discourse of various disciplines, and to apply within differing marketplaces and national regulatory structures. Understanding how SbD has evolved within ENM can yield a more practical application and development of SbD, and help guide or unify national and international ENM governance around a core set of safety-driven principles.

Keywords Safety-by-design · Nanomaterial · Risk governance

1 Introduction

Safety-by-Design[1] (SbD) as a longstanding concept in the scientific literature for emerging technologies, yet a singular definition or universal approach has been agreed upon in scientific discourse or technology development practice. Implied within the term includes the desire to 'engineer out' harmful components of materials that yield hazard at the earliest stages of development, and to improve the cost-effectiveness of material development by limiting the potential for hazardous products to reach the marketplace (EU-funded project on "Safety-by-design Of nanoMaterials - From Lab Manufacture to Governance and Communication: Progressing Up the TRL Ladder"; Trump et al. 2018; Kelty 2009; Hjorth et al. 2017). Over the past decade, SbD has been deployed as a philosophical construct or as an operational tool to guide the research, manufacturing, and commercialization of various engineered

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[1] Many permutations of this idea have gained traction in literature and policy, including examples such as 'safety-by-design', 'safe-by-design', 'prevention-through-design'. While the definitions of each are near-synonymous (albeit with some distinctions in implementation), and the literature searches yield similar results, we utilize 'safety-by-design' except where explicitly mentioned.

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nanomaterials (ENM) around the globe. Despite such advancement, however, there has been little synthesis regarding the term's usage and deployment across various disciplines and practitioners, either to streamline its academic discourse or to standardize its usage among interested parties in industry.

There are many causes for this lack of standardization or common diction regarding SbD for ENM. Social science work (ethical, legal, social implications, economics, consumer product safety, downstream environmental health and safety, workplace safety, etc.) has remained an ongoing dilemma in regard to ENMs as it did not develop into a defined scholarly field until the mid-2000s (Trump et al. 2018; Mohan et al. 2012). This juxtaposes years of basic and applied sciences (research and development of ENMs in tabletop sciences) upon fullerenes (since 1985) and carbon nanotubes (since 1991). Similarly, the notion of SbD lacks cohesive structure or intention, either as a risk analysis tool or as a (regulatory) risk management strategy, ranging from philosophical governing practice (ethics and belief-system driven) to operational guidance (methods driven) to facilitate commercial product development (Kelty 2009; Hjorth et al. 2017). As such, multiple disciplines and pedagogies make use of similar SbD principles, but often use discordant language or framing to describe and operationalize the term. In turn, this has led to an unharmonized governing practice for ENM.

ENM lacks a standardized diction for SbD, presenting a significant loss for nanotechnology governance. As broader nanotechnology edges further toward common commercial applications, a handful of questions will separate the further sustainable development of ENM with respect to whether they can fulfill their potential as a lucrative industrial sector. Can such ENMs be adequately assessed for risk? Can their developers and commodifiers guarantee compliance with regulatory requirements and institutional best practices? Can key stakeholders address core ethical challenges about shared economic opportunities on one hand, and reduce social inequities of exposure to material risk on the other? These and other social challenges present critical roadblocks that, if ignored, could stymie the commercialization of ENM in many industrial sectors and even certain countries.

The purpose of this paper is to characterize how SbD is defined or mentioned in scientific literature, to categorize these definitions, and understand to whom these definitions are targeted to and how the field may evolve. Ultimately, while the ENM SbD field will continue to develop across various countries, a fusion of these disciplinary approaches and ideas is necessary to further SbD into an established and trusted governance practice. Critical to this fusion is a blending of SbD as both a guiding philosophy and a methodological practice—through differing disciplinary lenses, SbD is often framed as one or the other, with no resolution on how it could be adopted by governance institutions.

2 A primer on safety-by-design

Before reviewing SbD discussion for ENM, we first frame SbD as an expansive subject with extensive application in other fields. Safety-by-design, also referred to as prevention through design (PtD), is an approach that seeks to mitigate potential risks in systems, processes, and products right at the design stage (Manuele 2008). Though the conceptual origins of SbD can be traced back to several centuries when builders, engineers, and architects implicitly integrated safety considerations into their creations, its formal recognition and practice is largely a development of the twentieth century (Renshaw 2019; Alexander 2014). Post World War II industrial advancements, alongside increasing complexities in products and processes, called for a conscious, systematic incorporation of safety measures into the design phase. This necessity was particularly apparent in high-risk sectors such as nuclear power and aerospace, where the cost of failure was potentially catastrophic (Carelli et al. 2008; Foster and Foster 1980).

The term 'Inherent Safety', a key principle of SbD, was coined by the British chemist Trevor Kletz in the late 1970s (Kletz 1996, 1980). Kletz's work in the chemical industry led him to advocate for the elimination or reduction of hazards instead of controlling them with safety devices. His work laid the foundation for a holistic approach to safety, moving beyond the mere addition of safety features after a product or process was created. Kletz's principles revolutionized the chemical and process industries and gradually diffused into other fields, marking a critical point in the evolution of safety-by-design (Li et al. 2020).

The 1990s and early 2000s saw increased recognition of the SbD principle in various sectors outside of emerging and advanced materials, including construction, manufacturing, software engineering, and healthcare. Notably, in the U.S., the National Institute for Occupational Safety and Health (NIOSH) initiated the Prevention Through Design program in 2007, highlighting the importance of eliminating hazards and controlling risks at the design stage in occupational settings (Schulte et al. 2008). This program acknowledged the efficacy of early hazard control, positioning SbD as a comprehensive risk management strategy.

By the 2010s, the SbD concept had also extended to privacy and cybersecurity, propelled by the surge in digital technologies and data-intensive applications. The European Union's General Data Protection Regulation (GDPR), enacted in 2016, specifically called for "Data Protection by Design and by Default," underscoring the urgency for proactive measures to ensure data safety (Jasmontaite et al. 2018). Likewise, the Australian government has introduced the SbD initiative for online safety. This initiative, led by the Office of the eSafety Commissioner, promotes proactive incorporation of user safety measures in the development and deployment of online products, services, and platforms (eSafety Commissioner (Australian Government) 2019).

Eclipsing 2020, ENM/advanced materials scholarship embraced SbD principles through multiple angles, and sought to identify avenues for how to integrate ENM SbD into various technology governance platforms. From 2016 to 2019, the NanoReg2 EU Horizon 2020 project focused on providing regulatory guidelines for ENM, emphasizing a proactive safety approach to reduce or eliminate potential hazards in design stages known as 'Safe-by-Design.' This proactive approach toward nanosafety aimed to promote innovation while ensuring protection for workers, consumers, and the environment (Dekkers et al. 2020). Multiple following projects, including Gov4Nano, RiskGONE, and NanoRIGO explored risk governance considerations of ENM and advanced materials, while the PRISMA project delved into safety and prevention-related concerns via responsible research and innovation (RRI) platforms. Collectively, these projects illustrate a concerted, ongoing effort to navigate the unique challenges posed by nanotechnologies, integrating SbD and governance frameworks to ensure that the benefits of these technologies can be safely realized.

2.1 Methods

We used a topic-driven literature review to survey scholarly literature with direct relevance to both (a) ENM and (b) SbD. To accomplish this task, however, a more precise literature search methodology is required to limit discussion that is tangentially relevant, or not at all.

The initial search for this topic is unconventional, particularly due to the specified nature of (a) focusing upon a core concept of governance within engineered nanomaterials and emerging nanotechnologies, and (b) aligning closely with the core principles of safety-by-design, without running the risk of considerable noise when searching core technology governance literature. The highly specified intent of this literature review was driven by a mixture of terms (e.g., nanotechnology and safety-by-design) that separately would generate significant and highly unrelated noise that would reduce project efficiency and likely contribute to an incomplete or inaccurate understanding of the broader field. To address such concerns, this literature review prioritizes accuracy and validity of our research results over maximal inclusiveness of tangentially related scholarly publications. Though such a review cannot be claimed as exhaustive, it does increase the internal validity of our analysis by focusing only upon those papers with a clear connection to both the principles safety-by-design as well as engineered nanomaterials.

Given the highly specified nature of this question, we conducted a two-part review. First, we conducted a highly specified Google Scholar search around a single query for peer-reviewed literature ("Safety-by-design" nanotechnology), including a range from 2001 to 2022. These dates were chosen to include major developments in the field (e.g., the funding and operation of the US National Nanotechnology Initiative in 2000, the implementation of many EU H2020 Projects). Additionally, this time period captures the bulk of social sciences discussion within broader nanotechnology—a critical inclusion to ensure validity and relevance of safety-by-design of engineered nanomaterials (Shapira et al. 2010; Trump et al. 2018).

This query included two backup searches for search term validity to ensure that no directly related material was accidentally left out (e.g., "prevention through design" nanotechnology; "safety-by-design" nanotechnology). Within this search, 938 results were returned, all of which were individually reviewed based on their title, abstract, and keywords to determine their overall relevancy and accessibility. At this stage, we also conducted a 'relevancy' test, whereby all articles were reviewed to determine their application to BOTH engineered nanomaterials AND safety-by design (articles that mention both words tangentially, but do not structure discourse around these topics, were excluded from further analysis). From the initial return, 565 results were found to pass the initial relevancy screening, and were passed for further review. Subsequently, articles that (a) were irretrievable, including conference proceedings whose public-facing discussion has been removed, and (b) a filter for non-English language peer-reviewed literature, although this was a very minor screening mechanism. At the end of this two-stage filtering process, 490 articles were selected for refined analysis.

As a second and more targeted review process, we sought to make sure that pertinent gray literature (e.g., core government policy documents stating government opinion between 1990 and 2021) were included. As a more targeted search, primary governmental and policy activity within engineered nanomaterials and safety-by-design were reviewed, resulting in six directly relevant hits to this overall subject. To satisfy the needs of this project, we made sure to include contributions from the People's Republic of China, the European Union, and the United States. The intent of this gray literature search was not necessarily to be exhaustive, but to make sure that core documents of opinion, policy needs, and future goals related to safety-by-design may be integrated into near term or long-term nanotechnology development, commodification, and overall practice (Fig. 1).

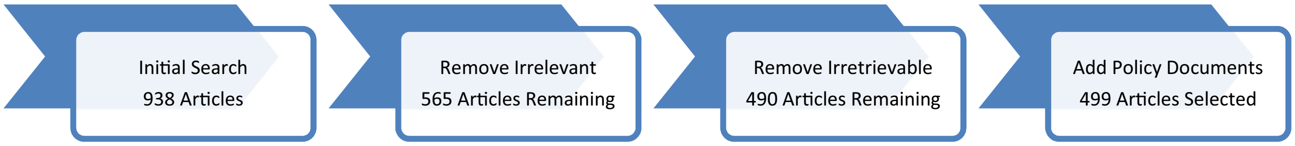
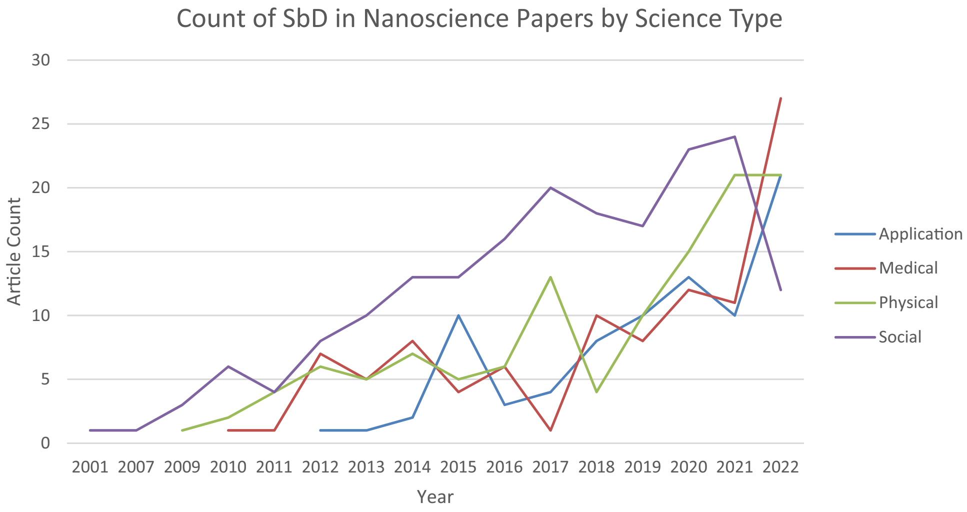


Fig. 1 Literature search and filtering process (2001–2022)

Fig. 2 Time-series (2001–2022) of safety-by-design scholarly literature



With the resulting 496 articles, additional descriptive statistics were levied regarding article age, citation counts, common publication cites (e.g., specific journals), and other basic information provided by publishers. This was complemented by a more interpretive analysis where each article was coded by team members as falling into one of four categories: (i) basic/physical sciences, (ii) non-medical application, (iii) medical application, and (iv) social sciences. Category I includes articles that cover research related to core physical and life sciences exploration of engineered nanomaterials, but largely outside of the context of a specific product line. Category II includes similar core bench sciences, but within the context of a non-medical product application. Likewise, Category III includes discussion of applied bench sciences for medical/pharmaceutical research. Lastly, Category IV includes broader social inquiry, including discussion of risk assessment, regulation and governance, ethics, law, and social implications, among similar subjects.

Ultimately, though this literature review is likely not exhaustive, its results are more closely specified to the conjoint topics of safety-by-design AND engineered nanomaterials than would have been observed from a less restrictive set of search parameters. Our intention is not to be exhaustive, but to present a sizeable body of directly relevant scholarly papers by which we can (a) analyze core publication trends and descriptive statistics for the literature, and (b) comparatively evaluate discussion via discourse analysis. Results of this approach are presented below.

Table 1 SbD papers by science type with citation counts from 2001 to 2022

Science Type	Papers	Citations	Average Citations	Median Citations
Application	84	1230	14.6	4
Medical	101	2290	22.7	4
Physical	120	3290	27.4	4
Social	189	3498	18.5	4
Grand Total	494	10,308	20.9	4

Citation analysis conducted 2 January, 2023

3 Results

Collectively, the field grew slowly from 2001 to 2011, yet grew substantially in the years that followed (Fig. 2). The plurality of articles is concentrated within various areas of the social sciences, with the other three broad categories of research generally increasing in publication rates over time as well. Though the four disciplinary areas express similar median citation rates, the averages for physical and medical/applied papers are disproportionately larger than social and nonmedical/applied, suggesting through these differential rates that the individual fields coalesce around specific developments or ideas (Table 1).

Table 1 illustrates the volume of social science-related papers that were published in comparison to other science types. While social science papers predominated SbD publications for nanomaterials for the past decade, the previous year witnessed an uptick of application and medical-related papers, surpassing social science papers. Physical papers, or those papers discussing biological, chemical, or physics principles of nanomaterials, underwent relatively steady growth since 2018 and were the most popular with average citations just over 27 per paper. If trends continue, the bulk of SbD in nanoresearch papers will likely gravitate to application, medical, or physical papers as opposed to social science-related research. Of all 494 papers analyzed in this review, the average citations per paper seen in Table 1 is just under 21 and median citations for each science type were far less. Thus, for each science type, a few papers largely overtake the calculation for average, indicating that each science type has sparked few to several heavily cited papers.

4 Discussion

Initially, in the early 2000s, the number of publications on SbD for ENM was relatively limited as the field of nanotechnology was still in its nascent stages. However, as the potential health and environmental impacts of nanomaterials became more evident, researchers and regulatory bodies began to emphasize the significance of incorporating safety measures from the early stages of nanomaterial design. This shift in perspective led to a significant surge in the number of scientific publications dedicated to SbD for ENM, with researchers striving to understand the underlying principles and develop strategies to engineer nanomaterials with improved safety profiles. These publication trends have contributed to a divergence in how SbD for ENM is applied by various practitioners, the increased interest in moving from SbD as a guiding philosophy toward a more quantifiable and benchmarkable tool, and how this all contributes to ENM governance strategy. Highlights from selected articles are noted below.

4.1 Unpacking SbD perspectives by practitioner

Physical literature (chemical, biological, and physical properties) discusses safety-by-design for nanomaterials from reviewing nanomaterial properties. SbD has been referred in this literature as, “benign-by-design,” inferring that the goal of physical research is to design nanomaterials that minimizes risk (Crawford et al. 2017). Furthermore, SbD has been referred to metaphorically in this field as a method to ensure, “the baby is not thrown out with the bathwater” (Bhattacharya et al. 2016). In other words, safety-by-design defines and predicts nanomaterial interactions with the host subject to maximize the potential of the application’s benefits (Mahmoudi et al. 2011). However, since physical-based research tends to be property-driven, safety is narrowed in scope for several papers by focusing on a few aspects of safety (Glazer and Curley 2011; Lehman et al. 2016a; Silva et al. 2013; Tilton et al. 2014). This allows for components of safety to be highlighted, building safety from a ground-up approach.

Social science literature combines safe-by-design principles into a subset of larger concepts. Lynch et al. (Lynch et al. 2014) highlights safety-by-design as strategically minimizing the harmful aspects of a nanomaterial and either avoiding or minimizing the hazards for biological systems. Through this hazard reduction, the lifecycle of nanomaterials can be extended, producing more robust nanomaterials that operate from cradle-to-grave (Reijnders 2009). Governance, ethics, risk assessment, risk management, and safety all incorporate elements of safety-by-design by discussing the avoidance or minimization of hazards (Castranova et al. 2013; Grieger et al. 2010; Melagraki and Afantitis 2015; Roco et al. 2011; Linkov et al. 2013). In this regard, safety-by-design serves as a proxy for these subfields to encourage more design and implementation of nanomaterials.

Application-based literature varies its definition of safety-by-design depending on the subject of the application. However, since applications discuss the use of nanomaterials, it is incumbent for safety research to focus on toxicity toward humans and animals for various products (Stamm et al. 2012). For the environment, safety-by-design in literature is geared toward mitigating the effect that engineered nanomaterials could place on air quality and surface waters, known as nanoremediation (Blasco and Corsi 2019; Heggelund et al. 2015; Karn et al. 2009; Riego Sintes 2020). In the food and agricultural industries, safety-by-design has been mentioned as an uncertainty that still must be addressed and that methods to minimize ecotoxicity in these fields are required (Rhodes 2014). Since this call-to-action, researchers investigated how foods containing nanomaterials can be made safer, but can also enhance the nutritional quality of life for humans (Bi et al. 2018; McClements 2019; Tentschert et al. 2014; Wrona and Nerín 2020). Safety-by-design is mentioned in research involving asbestos-like nanomaterials as a requirement, qualifying SBD as a guiding principle to encourage more research on these nanomaterials (Lee et al. 2018; Skuland et al. 2020; Tian et al. 2013). For workforce applications, safety-by-design is defined as the methods in the nascent stages of a product’s lifecycle that are meant to minimize hazards at health and safety’s benefit (Barata et al. 2019a; Brown et al. 2018; Bugnicourt 2018). This definition encapsulates the majority of application-based research for safety-by-design.

Safety-by-design is proliferating in the applied, medical research in the last decade. The literature review of applied, medical papers revealed that research involving the risks of inhalation of nanomaterials maintained the most consistent definition of safety-by-design: facilitating the design and assessing the hazards of nanomaterials early in the industrial innovation process in order to reduce toxicity but maintain usefulness (Farrera and Fadeel 2015; Singh et al. 2019). Many papers in the literature review discuss the risk of malignancies due to inhalation of nanoparticles (Demokritou et al. 2013; Donaldson and Poland 2012; Geiser 2010; Hussain et al. 2014; Schinwald et al. 2012). Several of the papers mention the opportunity for safety-by-design to be incorporated into future research to reduce the risk of airborne nanoparticles from being inhaled or ingested (Demokritou et al. 2013; Donaldson and Poland 2012; Kermanizadeh et al. 2016). Others discussed the production and distribution of pharmaceuticals and medical devices, particularly in the fight against the COVID-19 pandemic (Golan et al. 2021). Aspects of safety-by-design were also mentioned in oncological research involving nanomaterials, yet the actual definitions of SBD in these studies were sparse (Farrera and Fadeel 2015; Narang et al. 2018; Samykutty et al. 2018; Torres Andón and Alonso 2015).

4.2 SbD as an operational tool and a guiding philosophy

Conceptually through the social sciences, SbD's emergence was philosophically driven. Emphasis was placed upon incentivizing the "engineering-out" of material hazard at the earliest stages of development, yet rarely outlined benchmarks or standards of how to do so. This is reasonable—in the early 2000s, significant uncertainties characterized extant knowledge of ENM risk. Over time, the physical and applied sciences have explored avenues of how to apply the philosophical aims of SbD into a quantifiable or semi-quantifiable practice.

Physical-based papers discuss the characteristics of safe ENMs as a philosophy. While safety was not the main subject in many of these papers, safety was broached by, "what is preventing safer ENMs" (Cialla-May et al. 2017; Gasser et al. 2012; Ma et al. 2014), or, "how could this ENM impact its subject" (Glazer and Curley 2011; Fubini et al. 2011; Sager et al. 2014). In this regard, principles of safety, which support safe-by-design ENMs, are implemented as a system that can be improved through research (Bhattacharya et al. 2016; Mahmoudi et al. 2011). Web applications have been developed and are available within a SbD framework in the physical-based realm that can contribute to the reduction of in vivo experiments through replacement by in vitro and, in due course, through in silico experiments (Varsou et al. 2019). In silico approaches can substantially reduce the effort and time needed for the design, production and evaluation (e.g., regulatory dossiers) of stable and safe ENM.

In the social science literature, safety is often described as a philosophy or goal, whereas SbD is a tool. Safety is discussed broadly throughout the social science literature through various subtopics and applications (Castranova et al. 2013; Ahonen et al. 2017; Hofmann-Amtenbrink et al. 2015; Nyström and Fadeel 2012; McCarthy and Kelty 2010). SbD is one of these subtopics of safety research, with several examples throughout the review that illustrate SbD as a tool to safer ENMs (Lynch et al. 2014; Donaldson et al. 2010; Lehman et al. 2016b; Kraegeloh et al. 2018; Poel and Robaey 2017). However, both safety and SbD face a litany of challenges for ENMs to become commonplace (Nyström and Fadeel 2012), perching SbD with an opportunity to address these challenges to arrive at safer ENMs.

Applied, nonmedical research maintains SbD as a guiding approach to encourage the use of various products containing ENMs. In papers that mention SbD, the principle is referred to as a method to guide ENM research (Lee et al. 2018; Barata et al. 2019a; Bugnicourt 2018). However, the literature presented scarce results in its discussion of methods for conducting SbD practices. For some applications, safety was measured by risk classification both qualitatively and quantitatively (Stamm et al. 2012; Hristozov et al. 2018). For others, safety was addressed through a stand-alone tool procured for the specific application of certain ENMs (Hedmer et al. 2015; Mitrano and Nowack 2017; Harmelen et al. 2016). Since SbD is considered differently depending on the application, no singular guiding approach is maintained for SbD in the applied, nonmedical literature.

Applied, medical research suggests that SbD is a philosophy. Since ENMs could both positively or negatively impact human health, SbD has been paired with "bioX" terms such as biocompatibility, biodurability, and biosafety (Leso et al. 2019; Ramsey et al. 2020; Stefaniak et al. 2014). Researchers and governance stakeholders have aspired for SbD ENMs through these concepts, inferring that SbD in medicine is non-negotiable to prevent undue harm to humans (Farrera and Fadeel 2015; Demokritou et al. 2013).

Views of SbD ENM Governance Share Common Roots, but Differences are Emerging.

Emerging technologies research and development has been and will likely continue to be a fundamentally international venture. The US and China remain among the major developers and commodifiers of nanotechnology, and have developed a sizeable patent and product pipeline portfolio that will have many billions of euros of impact upon European Union consumers and economies (Wu et al. 2019). European companies, citizens, and scientists interested in engaging in basic or applied nanotechnology sciences will inevitably be working with or competing against such interests; at a minimum, EU scientists and regulatory agencies must remain knowledgeable of ongoing development trends, safety requirements, risk assessment challenges, and opportunities arising in the US, China, and elsewhere, in order to anticipate future consumer products and other processes/products warranting evaluation.

Governmental works set the tone for the respective nation's ENM future. To foster development and influence for ENM research, each country and organization calls for differing governance structures. In 2004, to address concerns of safe development of ENMs as well as environmental health, the UK Royal Society and Royal Academy Engineering called for the requirement of governance toward ENMs due to a lack of evidence on the risks that ENMs pose. While partnerships have been formed between the EU and US for ENM research, the US federal government has taken matters into their own hands, highlighting how local, state, and federal governments can collaborate to provide funding toward US based nanoresearch.

One of the more robust discussions of SbD for ENM is emerging in the European Union, with many agencies and committees charged with a duty of tying nanomaterial safety to the earliest stages of development and manufacturing. The European Chemicals Agency (ECHA) operates at the center of EU Chemicals Legislation, covering all EU Member States. ECHA helps companies comply with legislation, advance the safe use of chemicals, address chemicals of concern, and provide information on chemicals to all stakeholders including civil society. The obligations of ECHA to implement certain processes and corresponding operational practices is largely driven by legislative changes within the law-making frameworks. Risk Assessment Committee (RAC) and Socio-Economic Assessment Committee (SEAC) are two key committees in ECHA's assessment focused approach to risk governance of chemicals including ENMs.

SCCS (Scientific Committee on Consumer Safety) and SCHEER (Scientific Committee on Health, Environmental and Emerging Risks), two key European Commission committees focused on public health, are also influential in this space through their provision of expert opinions and associated oversight on important decisions at the axis of public health and ENMs. The SCCS Committee provides Opinions on questions concerning all types of health and safety risks of non-food consumer products.

As noted in Sect. 2, multiple European research projects have emphasized the importance of SbD, and offered further opportunities for refinement and adoption. This includes NanoReg2 (ending 2019), which reframed 'safety-by-design' into 'safe-by-design' out of the desire to differentiate design-based process improvements from personal protection from physical hazards. Efforts from various projects helped inform, the 'Malta Initiative' (2017), a self-organized group without legally binding status, was formed to develop and improve Test Guidelines (TGs) and Guidance Documents (GDs) to address concerns unique to engineered nanomaterials (Initiative and (n.d.)). The Malta Initiative's work, in turn, has informed legally binding initiatives, such as various EU agencies such as the ECHA's Nanomaterial Expert Group (NMEG). Overall impact includes improvements to ENM testing needs via EU REACH regulations (e.g., industrial chemicals (EU 2018)), as well as OECD Working Party on Manufactured Nanomaterials (WPMN) and the OECD Working Party of National Coordinators of the Test Guidelines Programme (WNT) (OECD 2022). A summary of various regulatory activities stemming from the Malta Initiative may be found in (Bleeker et al. 2023).

Looking forward, the European Commission published on 2020 the Chemicals Strategy for Sustainability (CSS) as part of the EU's zero pollution ambition, which is a key commitment of the European Green Deal (Barata et al. 2019b). The Strategy considers that "the transition to chemicals that are Safe and Sustainable-by-Design (SSbD) is not only a societal urgency but also a great economic opportunity, as well as a key component of EU's recovery from the COVID-19 crisis" and that "Europe has frontrunner companies and the scientific and technical capacity to lead the transition to a safe and sustainable-by-design approach to chemicals. This transition needs stronger policy and financial support, as well as advice and assistance in particular for SMEs, and requires a concerted effort from all: authorities, businesses, investors and researchers." Ultimately, SSbD encourages manufacturers and developers to proactively mitigate potential environmental and health risks, reduce resource usage, and promote recyclability or biodegradability, among other sustainability goals. The approach underscores the importance of considering the full lifecycle of a product, from raw material extraction to end-of-life disposal or recycling.

Scientifically, SSbD is framed a proactive, interdisciplinary, and holistic approach that intertwines principles from various scientific domains, including engineering, toxicology, environmental science, and social sciences (Jantunen et al. 2021). The design process begins with an assessment of potential safety risks and environmental impacts, aiming to mitigate these concerns right from the conceptualization stage. This scientific evaluation involves understanding the physical and chemical properties of the materials used, their behavior under different conditions, and potential hazards they could present to human health and the environment. Concurrently, life cycle assessment methodologies are employed to evaluate environmental impacts over the entire product life cycle, from raw material extraction, through manufacturing and use, to disposal or recycling. Furthermore, SSbD incorporates social and ethical considerations, ensuring the alignment of technological advancements with societal values and norms (Salieri et al. 2021).

The inclusion of SSbD within the Strategy and the planned action marks a clear and far-reaching endorsement that will be reflected in Horizon Europe under Pillar 2 “Global challenges and European industrial competitiveness” and its Work Programmes. Most probably the first comment to make is about the naming, from SbD to SSBD, but also the fact that we are moving from “SbD” to a collection of “by design” concepts, as “circularity by design,” “security by design,” “privacy by design,” “cleaner, greener and more circular by design,” or “resilient by design” that overall direct us to the overarching concept and practices of Design for Values (DfV).

In the area of Key Performance Indicators (KPIs), the CEN, the European Committee for Standardization, is developing the standard “Nanotechnologies—Safe by Design concept dedicated for nano-scale materials (MNM) and products containing nanomaterials,” a soft law instrument that will help to harmonize the use of SSbD mechanisms. In addition, the possibility of advancing on an EU-SSBD Certification is on the table, and is to be noted the European Environmental Agency support for SSBD, that reinforces a horizontal institutional backing, breaking institutional silos.

China also proclaims the need for a country-wide, unified approach to nanoresearch. The Ministry of Science and Technology discusses the significant research gap of ENMs in the country, stating, “The important original innovation, application development and engineering are insufficient” due to low information exchange and poor funding sources. The Ministry goes on further to proclaim the need for local governments to set objectives, oversee development, commercialize products, boost enthusiasm, and work collaboratively with research groups and academia. Conversely, the EU calls for, “the creation and use of regional and cross-sectorial alliances and partnerships, among government, industry, the academic community and the research and development community” (NANOfutures. 2012). While some united fronts between organizations exist, such as the Nanoinformatics Roadmap (Lobaskin et al. 2018), the governmental structure for key players illustrates a portrait of individual, country-specific efforts as opposed to international collaboration.

US nanomaterial governance has a lengthy history, incorporating core philosophies of SbD but rarely bringing the term into regulatory action. Efforts of the US National Nanotechnology Initiative (NNI) outlined research areas and goals aimed at developing comprehensive principles for risk assessment and management for nanotechnology, with a major deliverable including their 2011 Environmental Health and Safety (EHS) Research Strategy (National Research Council 2012). The 2011 EHS Research Strategy identified five research needs (RAMM-1 to RAMM-5) in risk assessment and management methods (RAMM) for nanotechnology. These research needs aimed to incorporate risk characterization information, hazard identification, exposure science, and risk modeling methods into the safety evaluation of nanomaterials, understand and control workplace exposures, integrate life cycle considerations into risk assessment and management, integrate risk assessment into decision-making frameworks for risk management, and standardize risk communication within the risk management framework.

Principles of SbD have been incorporated in the US through collaborative efforts among the NNI agencies, academia, and private sector partners. For example, NIOSH has published a state-of-the-art overview on utilizing current hazard research data and risk assessment methods for ENMs to develop and implement effective risk management guidance at the early stages of material development (NIOSH 2019). Ongoing activities have focused on using an evidence-based strategy to develop occupational exposure limits (OELs) for various ENMs, and OSHA has published a Working Safely with Nanomaterials fact sheet that addresses OELs (OSHA n.d.). Additionally, a multistakeholder workshop involving some of the NEHI agencies evaluated the potential use of alternative testing strategy data (e.g., in vitro and limited in vivo data in a tiered testing scheme) in hazard assessment and toxicity prediction of ENMs. However, while SbD is referenced frequently in US universities, these philosophies rarely invoke the term ‘SbD’ outright in policy discourse.

Life cycle considerations have been integrated into risk assessment through case studies and the development of Comprehensive Environmental Assessment (CEA) approaches, as exemplified by the EPA (Powers et al. 2012). The CEA approach integrates life cycle analysis, exposure assessment, hazard analysis, and risk characterization, and has been used in case studies on several ENMs, such as nanoscale titanium dioxide, nanoscale silver, and multiwalled carbon nanotubes (Steevens et al. 2012). In terms of integrating risk assessment into early-stage ENM development decision-making frameworks, the EPA’s CEA approach provides both a framework for systematically organizing complex risk-relevant information and a process that uses collective judgment to evaluate such information for risk management planning. NIOSH and EPA, as part of their risk assessment and risk management tool development efforts, are jointly evaluating hazard banding as a method to categorize ENMs by hazard potential.

The effect of US and Chinese attitudes and policies toward EU governments and citizens are due to the fundamental reliance of partners for international nanotechnology development (Liu et al. 2017). Many raw ENMs are frequently produced in China, worked and manufactured in the United States and other countries, and then commodified for sale within the European Union; the regulatory requirements and social framing of SbD within each respective country is framed by local unique institutional, political, and cultural expectations and requirements (Wang et al. 2019). When adopting nanotechnologies from areas beyond the home country, a heightened risk exposure to ENMs may be faced (Isigonis et al. 2020). Simultaneously, technology innovation and product development may improve SbD/SSbD capabilities in European governments as well as promote commercial innovation within Europe's nanotechnology sector.

The guiding principles related to the 'engineering out' of threat and hazard at the early stages of nanotechnology material and product development is of direct concern to each of these groups, which eases downstream regulatory and governance concerns related to risk assessment practices as diverse as consumer product safety, environmental health and safety, human health assessment, and others. As SbD gains attraction, tools that evaluate SbD/SSbD progress are under development or have recently been published, and remain a missing link toward the implementation of SbD/SSbD into national or international standards or regulatory requirements.

5 Conclusion

Despite decades of development, ENMs retain considerable challenges in their hazard and exposure characterization, as well as their use in a near-endless array of product applications. ENM governance is increasingly fragmented, with diverging perspectives on SbD emerging that reduce the term's effectiveness as a governance strategy. Governing uncertainty is never easy – governing uncertain material and technology risk stresses existing governing institutions and procedures to the limits of their capabilities.

Thankfully, however, an equally rigorous effort in the study of nanotechnology risk governance is bridging the gaps posed by the technology's fundamental risks and uncertainties (Linkov et al. 2018). Though nascent, a critical component of this includes SbD, which began with limited discussion yet has rapidly expanded to include discourse in various areas of basic and applied nanotechnology science. With pedagogical differences, SbD is entering the lexicon of nanotechnology practitioners in medicine, in industry, in academia, and government, for both the processes and products of nanotechnology. To succeed, however, governments must draw from a range of disciplinary perspectives to capture the gambit of ENM implications, as well as establish the collective philosophical and methodological requirements that would enable SbD to be implemented into law.

Significant challenges remain. Explicitly defining SbD through legal institutions and diction is a necessity—this will empower regulators to instil SbD activities, and mandate SbD practices through quantifiable and benchmark-driven research. Likewise, SbD is beginning to differentiate in its adoption and practice in different countries—this will hinder the EU's ability to foster a generalizable SbD approach, given the innately global nature of technology development and global supply chains/product distribution.

Acknowledgements This work was supported by the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No. 862296 (SABYDOMA—Safety-by-design Of nanoMaterials—From Lab Manufacture to Governance and Communication: Progressing Up the TRL Ladder).The views are by authors only and do not represent views of their respective organizations, and should not be construed as an official statement by any government agency or institution.

Author contributions The opinions represented in this paper are the author's alone, and not necessarily their host institutions. No statements or claims should be taken as formal institutional or governmental opinion.

Funding SABYDOMA project has received funding from the European Union's HORIZON 2020 Research & Innovation Programme under grant agreement no. 862296.

Declarations

Competing interests The authors declare no competing interests. Dr. Trump and Dr. Linkov are both Editorial Board members of Environment Systems and Decisions.

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