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Safe and sustainable by design (SSbD) for nanotechnology: scientific foundations, global policy perspectives, and industrial practice

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Abstract
Safe and Sustainable by Design (SSbD) is emerging as a transformative framework for integrating safety and sustainability with functionality in nanotechnology. This review provides a unified perspective on SSbD, bridging its scientific foundations, global policy developments, and industrial implementation. We highlight how advances in mechanistic understanding of nanomaterial–biological interactions enable earlier and more predictive safety assessment, supporting informed material design. At the policy level, evolving regulatory and governance approaches across regions are shaping the integration of sustainability and safety requirements. From an industrial perspective, SSbD is driving innovation in material substitution, process optimization, and lifecycle-oriented design. Despite this progress, challenges remain in standardization, data integration, and alignment between regulatory frameworks and industrial practice. This work positions SSbD as a central paradigm for enabling responsible innovation and accelerating the transition toward safer and more sustainable nanotechnologies.

Keywords Safe and sustainable by design, Nanomaterials, Nanosafety, Sustainability, Life cycle assessment, Regulatory policy, Industrial practice, Risk assessment

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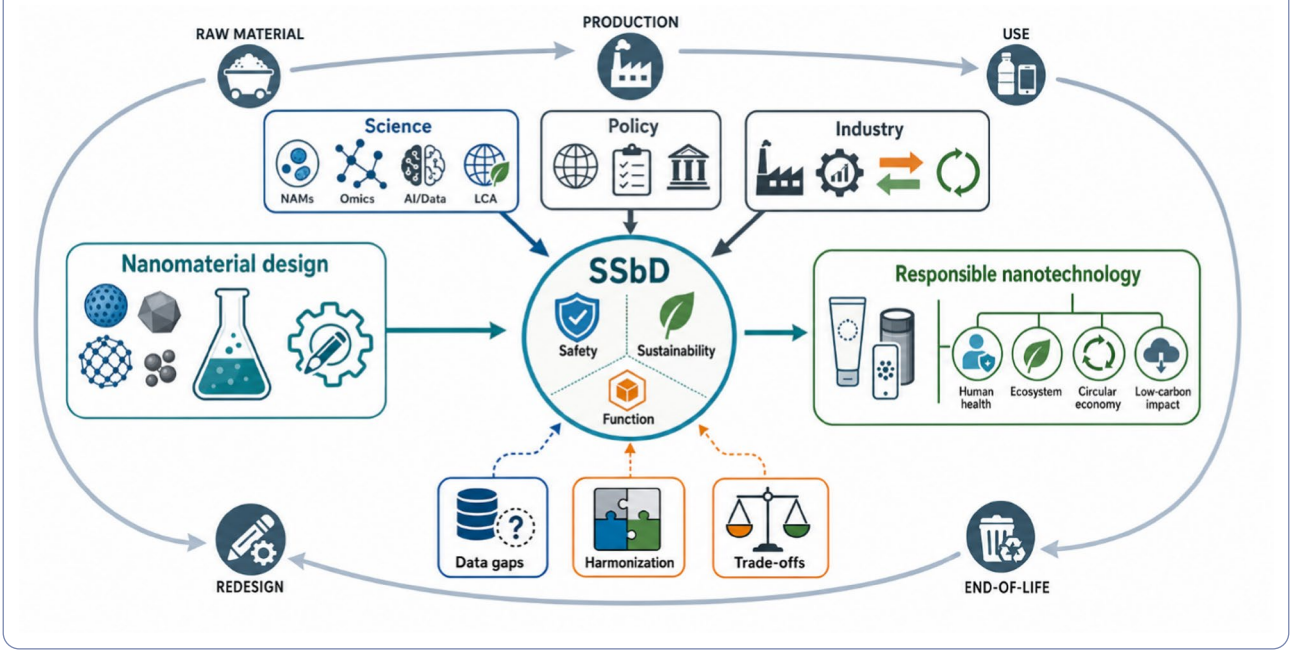
Graphical abstract



1 Safe and sustainable by design (SSbD)–concept, evolution, and relevance to nanomaterials

1.1 Background and motivation

Addressing escalating concerns over pollution and chemical safety, the concept of Safe and Sustainable by Design (SSbD) represents a paradigm shift. This holistic approach proactively embeds human and environmental safety, as well as environmental, economic, and social sustainability, into the design phase of chemicals, materials, and technologies [1]. This concept represents a paradigm shift from traditional reactive measures to a preventive strategy that addresses chemical risks and pollution during the design phase [2]. Scientific and policy consensus is fueling a global shift toward SSbD, moving the focus to "designing out" harms before they reach the market [1, 2]. Through initiatives such as the European Chemicals Strategy for Sustainability (CSS), Organisation for Economic Co-operation and Development (OECD) innovation frameworks, and emerging national sustainable chemistry programs, SSbD principles are increasingly being incorporated into international policy and research agendas [1, 3]. Importantly, these developments signal a broader transformation in innovation governance in which safety and sustainability are increasingly treated not merely as post-market regulatory obligations, but as core design requirements for responsible innovation [4]. Globally, these developments are increasingly converging with broader initiatives in green chemistry, sustainable chemistry, circular economy strategies, and anticipatory governance promoted by organizations such as the United Nations Environment Programme (UNEP), the OECD, and national innovation programs. In particular, UNEP's Green and Sustainable Chemistry framework emphasizes the integration of environmental protection, resource efficiency, and human health considerations throughout the chemical and material innovation process, reinforcing the growing international consensus that safety and sustainability must be incorporated as intrinsic components of technological development rather than addressed retrospectively.

Parallel advances in mechanistic toxicology, predictive modeling, high-throughput screening, life cycle assessment (LCA), data science, artificial intelligence, and new approach methodologies (NAMs) have further accelerated efforts to integrate safety considerations directly into material and chemical innovation pipelines. Together, these developments are enabling SSbD to evolve from a conceptual governance framework into an increasingly operational and data-driven paradigm capable of guiding innovation under conditions of scientific uncertainty. Rather than functioning solely as a regulatory concept, SSbD is emerging as an integrated decision-making architecture that connects scientific assessment, sustainability evaluation, industrial implementation, and anticipatory governance throughout the material life cycle. This transition from conventional reactive risk management toward integrated and operational SSbD implementation is summarized in Fig. 1.

1.2 Definition and key principles of SSbD

SSbD is broadly defined as an approach that integrates safety and sustainability aspects into the earliest stages of chemical, material, or technological development, with the explicit goal of preventing harm rather than managing it retrospectively [5, 6]. In contrast to conventional risk management paradigms that evaluate hazard and exposure after a product has been developed, SSbD embeds these considerations as design constraints from the outset, ensuring that safety and sustainability are intrinsic to the final product [7].

At its conceptual core, SSbD rests on several broadly shared principles. First, it adopts a life cycle perspective, requiring that potential impacts on human health, ecosystems, and the material extraction to end-of-life disposal [4, 6]. Second, it emphasizes the consideration of intrinsic properties, exposure and process-related risks, highlighting a proactive and innovation-driven approach in which safer and more sustainable materials are preferred even under conditions of uncertainty [2, 5, 8]. Third, SSbD emphasizes the preservation of functionality, recognizing that safer and more sustainable alternatives must remain technically viable and economically competitive to achieve real-world adoption. Finally, it incorporates a multi-dimensional sustainability framework encompassing environmental, economic, and social dimensions, moving beyond purely toxicological endpoints toward a more holistic assessment of impact. As a result, SSbD increasingly represents the convergence of sustainable chemistry, predictive toxicology, lifecycle-based assessment, and innovation governance into a more integrated framework for responsible materials development. The conceptual distinctions between SSbD and related design and governance paradigms relevant to nanomaterials are summarized in Table 1.

Importantly, SSbD is designed to operate under conditions of scientific uncertainty, which is precisely why precautionary, design-phase intervention is preferable to awaiting definitive hazard data. This precautionary logic underpins the "no regret" principle and reflects a broader shift in risk governance toward anticipatory rather than reactive decision-making [2, 4]. Furthermore, while SSbD places particular emphasis on the design phase, its principles are intended to be iteratively applied and revisited throughout the full innovation cycle — from early-stage research and development through scale-up, commercialization, and end-of-life management—allowing for continuous improvement as new scientific evidence, stakeholder priorities, and technological advances emerge over time. This iterative structure is central to the operationalization of SSbD and supports more adaptive and evidence-informed decision-making throughout the innovation process [3, 5]. SSbD also emphasizes multi-stakeholder integration, unlike purely technical risk assessment frameworks, SSbD requires the active involvement of industry, regulators, researchers, and civil society throughout the innovation process, ensuring that safety and sustainability objectives are co-developed and practically implementable across the value chain [1, 6].

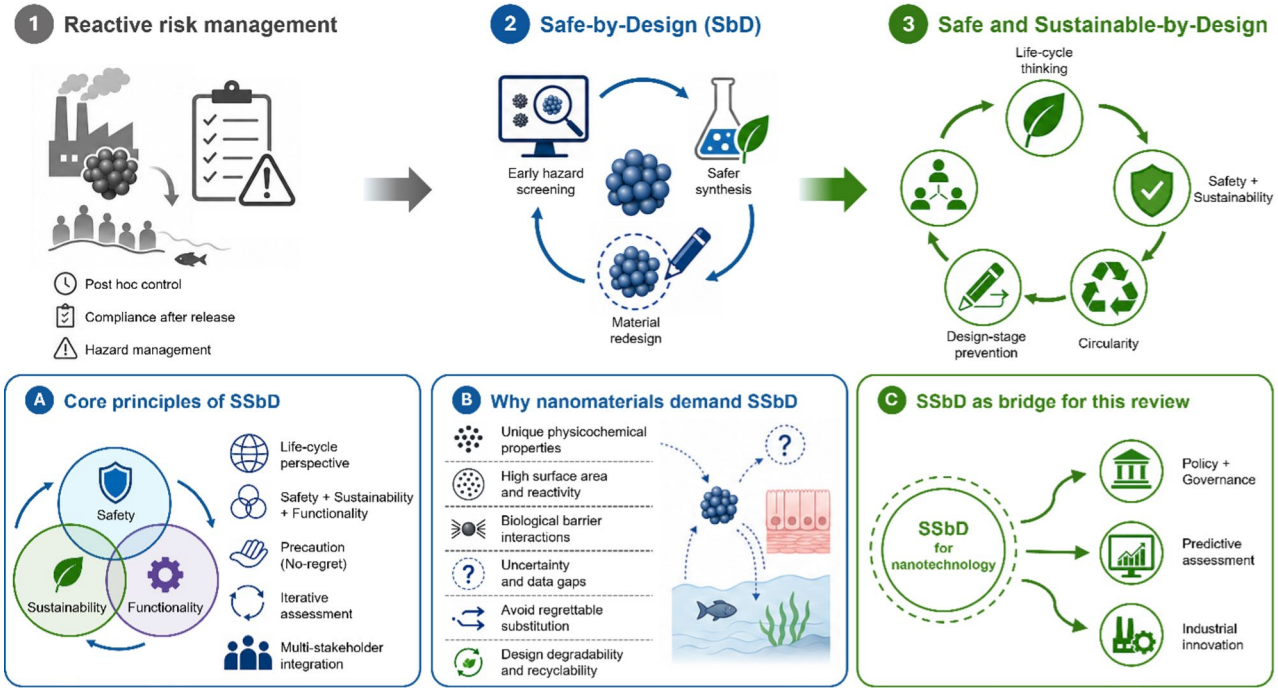


Fig. 1 Strategic framework and operational roadmap for safe and sustainable by design (SSbD) in nanotechnology

Table 1 Conceptual positioning of SSbD relative to related design and governance approaches relevant to nanomaterials

Approach	Core logic and primary aim	Dominant scope	Relevance to nanomaterials	Main limitation	References
Conventional risk management	Post hoc identification and control of hazard and exposure once a substance or product is largely defined	Safety and regulatory compliance; limited integration of functionality and sustainability	Provides the regulatory baseline for hazard, exposure, and compliance assessment	Reactive; offers limited opportunity for redesign once nano-specific concerns emerge	[2, 5, 6]
Green chemistry	Prevent pollution and reduce hazard through safer synthesis, solvent choice, atom economy, and energy-efficient processing	Process/resource efficiency; partial life-cycle perspective	Useful for cleaner synthesis and lower-burden manufacturing of nanomaterials	Does not by itself address nano-specific release, use-phase behavior, or end-of-life fate	[3, 8]
Benign-by-design	Tune material composition and structure to lower intrinsic hazard, persistence, or bioavailability while retaining function	Structure–property–hazard optimization; variable life-cycle coverage	Directly applicable to tuning size, coating, dissolution, and surface reactivity	Often underrepresents exposure context, scale-up constraints, and broader sustainability trade-offs	[3, 8]
Safe-by-Design (SbD)	Integrate safety considerations at the earliest possible stage of R&D and iteratively redesign materials and processes	Hazard minimization, exposure prevention, and safer product/process design	Particularly suited to nanotechnology, where uncertainty and data gaps are high and redesign is most effective early	Primarily safety-centered; sustainability dimensions are not always systematically integrated	[2, 3, 9]
Safe and Sustainable by Design (SSbD)	Simultaneously optimize safety, environmental sustainability, socioeconomic viability, and functionality across the innovation life cycle	Full life-cycle, multi-stakeholder, iterative assessment	Most comprehensive approach for nanomaterials, helping avoid regrettable substitution and downstream sustainability burdens	Data- and expertise-intensive; metrics and decision criteria remain under harmonization	[1, 2, 4–6]

1.3 Historical evolution: from SbD to SSbD

SSbD is an evolution of Safe-by-Design (SbD), a concept intensely progressed by the nanotechnology community to address the unique uncertainties of nano-scale materials [9]. While SbD sought to proactively "design out" risks during early development, its efficacy was often limited by significant data gaps regarding hazard and exposure. Recognizing that safety cannot be evaluated as an isolated metric, the framework has since expanded into the more holistic SSbD paradigm [10]. This transition integrates broader sustainability criteria—such as resource efficiency, energy demand, and life cycle impact with traditional toxicological safety protocols. By integrating the proactive philosophy of SbD with concepts from green chemistry, sustainable chemistry, green toxicology, life cycle assessment, sustainable engineering, and circular economy strategies, SSbD has evolved into a broader framework aimed at optimizing the overall safety and sustainability performance of materials and technologies throughout their entire life cycle. It ensures that new materials are not only low-risk but also environmentally and socially responsible throughout their entire life cycle [8]. Importantly, the evolution from SbD to SSbD has also coincided with advances in mechanistic toxicology, computational modeling, FAIR data infrastructures, and NAMs, transforming SSbD from a largely conceptual aspiration into an increasingly operational, predictive, and data-driven framework for materials innovation. In this context, nanotechnology has served not only as a driver of SSbD development, but also as a testbed for broader next-generation approaches to sustainable materials governance.

1.4 Why nanomaterials demand SSbD

Nanomaterials (NMs) are central to the SSbD paradigm, representing both a frontier for sustainable innovation and a challenge for traditional risk assessment. While NMs enable breakthroughs in medicine, energy, and environmental remediation, their unique physicochemical properties—such as high reactivity, high surface-area-to-volume ratios, and the ability to traverse biological barriers—introduce unforeseen toxicity and persistence risks. Consequently, the "design it right from the start" philosophy of SbD originated within the nanotechnology sector to mitigate these inherent uncertainties. SSbD expands this mandate by ensuring that the functional benefits of NMs are not offset by "regrettable substitutions" or life cycle sustainability pitfalls. By integrating criteria such as degradability and recyclability into the design stage, SSbD harmonizes the transformative economic potential of NMs with the global need for environmental and human health protection. At the same time, nanotechnology increasingly serves as a model system for addressing broader challenges associated with

advanced materials innovation. Many of the scientific, regulatory, and sustainability challenges first encountered in nanomaterials—including complex structure–activity relationships, limited hazard predictability, data gaps, and lifecycle uncertainty—are now emerging across a wider range of advanced and multi-component material systems. Consequently, lessons learned from SSbD implementation in nanotechnology are increasingly informing broader frameworks for sustainable materials governance.

The growing institutionalization of SSbD through initiatives such as the European Green Deal, the CSS, UNEP sustainable chemistry initiatives, OECD frameworks, and emerging national programs reflects the increasing recognition that advanced materials innovation must be aligned with long-term societal and environmental objectives. Importantly, the European Union has emerged as one of the most active institutional drivers of SSbD implementation, particularly through coordinated policy frameworks and research infrastructures. However, related activities in sustainable chemistry, green toxicology, predictive toxicology, and safer materials innovation are also expanding rapidly in the United States and Asia, highlighting the increasingly global nature of the transition toward sustainability-integrated innovation systems.

Despite this momentum, significant challenges remain in operationalizing SSbD for nanomaterials and advanced material systems. Predicting long-term ecotoxicity, persistence, transformation behavior, and end-of-life sustainability profiles remains difficult due to persistent methodological limitations and data gaps. Furthermore, the multidimensional nature of SSbD introduces complex trade-offs among safety, technical performance, climate impacts, resource efficiency, and economic feasibility. As a result, one of the central challenges facing the field is the development of integrated decision-support systems capable of translating diverse safety and sustainability metrics into practical innovation guidance during early-stage material development.

To address these challenges, current research increasingly focuses on the integration of mechanistic toxicology, NAMs, high-throughput screening, computational modeling, artificial intelligence, FAIR data infrastructures, and life cycle assessment into unified assessment ecosystems. Ultimately, transitioning SSbD from theory to practice requires integrated decision-support systems, interoperable digital infrastructures, open-access data ecosystems, and user-friendly tools capable of translating diverse safety and sustainability metrics into practical innovation guidance for researchers, industry stakeholders, and regulators alike.

1.5 Scope and objective of this review

Building upon these developments, this review examines how SSbD is evolving from a conceptual governance framework into an operational paradigm for nanotechnology and nanomaterials innovation. While the primary focus of this review is SSbD in nanotechnology and nanomaterials development, the discussion also extends to broader advanced material systems where similar challenges related to predictive safety assessment, sustainability evaluation, and lifecycle governance are increasingly emerging. In particular, this review highlights the role of global policy perspectives, examining how regulatory frameworks and governance strategies across regions (e.g., EU, Americas, and Asia) are shaping the development, harmonization, and implementation of SSbD in nanotechnology. Particular attention is given to the growing convergence between SSbD, sustainable chemistry, green toxicology, circular economy strategies, and predictive toxicological sciences at the international level. The following sections will delve deeper into the scientific foundations of SSbD (examining how safety and sustainability metrics can be integrated into NM design), survey the evolving policy landscape and global frameworks promoting SSbD, and discuss case studies where SSbD is being implemented across nanotechnology applications and value chains. In particular, this review emphasizes how SSbD can be operationalized in nanotechnology through the integration of mechanistic nanosafety science, advanced analytical tools, new approach methodologies (NAMs), life cycle assessment, and computational modeling. By synthesizing insights from these domains, the review aims to provide an accessible, interdisciplinary overview of SSbD for NMs – explaining why SSbD has become a focal point for innovation policy, what scientific progress is enabling its implementation, and how it is influencing the development of next-generation materials and technologies. Furthermore, the discussion extends toward advanced material and multi-component systems, highlighting how increasing material complexity requires the evolution of SSbD toward more data-driven, systems-level, and predictive frameworks. Rather than presenting SSbD solely as a collection of individual projects, frameworks, or regulatory initiatives, this review emphasizes the broader convergence of nanosafety science, sustainability assessment, data-driven methodologies, and anticipatory governance into an integrated innovation ecosystem for advanced materials development. Ultimately, this review aims to highlight both the opportunities and remaining challenges associated with transitioning from conceptual SSbD frameworks toward globally harmonized, operational, and predictive systems for responsible materials innovation. As we explore in this review, realizing this vision for NMs will require bridging knowledge gaps, fostering collaboration, and

committing to the principle that the best way to manage risks and sustainability challenges is to design them out before they arise [11]. This approach promises not only safer nanotechnologies but also represents a model for achieving sustainability and safety across the broader spectrum of materials science and engineering.

2 Global policy landscapes for SSbD

Although the operationalization of SSbD has been most actively advanced within the European Union, broader international policy initiatives have also contributed to shaping the global governance context surrounding safe and sustainable innovation. In particular, the United Nations Environment Programme (UNEP) introduced the Green and Sustainable Chemistry: Framework Manual (2020) [12], which established a global conceptual framework for advancing chemistry innovation in alignment with the Sustainable Development Goals (SDGs) and the sound management of chemicals and waste. The framework emphasizes principles closely aligned with SSbD, including hazard minimization, avoidance of regrettable substitution, sustainable sourcing of feedstocks, life cycle thinking, non-toxic circularity, and systems-level innovation across value chains. Furthermore, UNEP highlights the importance of multi-stakeholder governance, sustainable supply chains, sustainability metrics, and roadmap-based implementation strategies, thereby providing an international policy foundation that complements region-specific SSbD frameworks and regulatory initiatives. Major regional policy paradigms and governance approach relevant to SSbD implementation are summarized in Fig. 2.

2.1 European union: established frameworks and the chemicals strategy for sustainability (CSS)

2.1.1 European commission SSbD framework

The SSbD framework was first introduced by the European Commission (EC) in 2022 by a series of guidance reports published by the EC Joint Research Centre (JRC) [5, 6]. After a dedicated period of testing and stakeholder feedback, the framework was revised in 2025 [8], followed by the revised EC recommendation adopting the updated framework [13]. Together with these implementing documents, the EC has developed the most operationally mature and policy-integrated SSbD framework to date, providing a structured methodology for assessing and guiding the development of chemicals and materials in alignment with the CSS [14]. Conceived as a practical tool for both regulators and innovators, the EC SSbD framework translates the broad principles of SSbD into a systematic, iterative, and explicitly life cycle–oriented guidance and assessment procedure that can be applied across the chemicals and materials innovation pipeline.

The revised EC SSbD framework is organized as a circular iterative process that begins with defining the innovation goal, followed by the identification of objectives

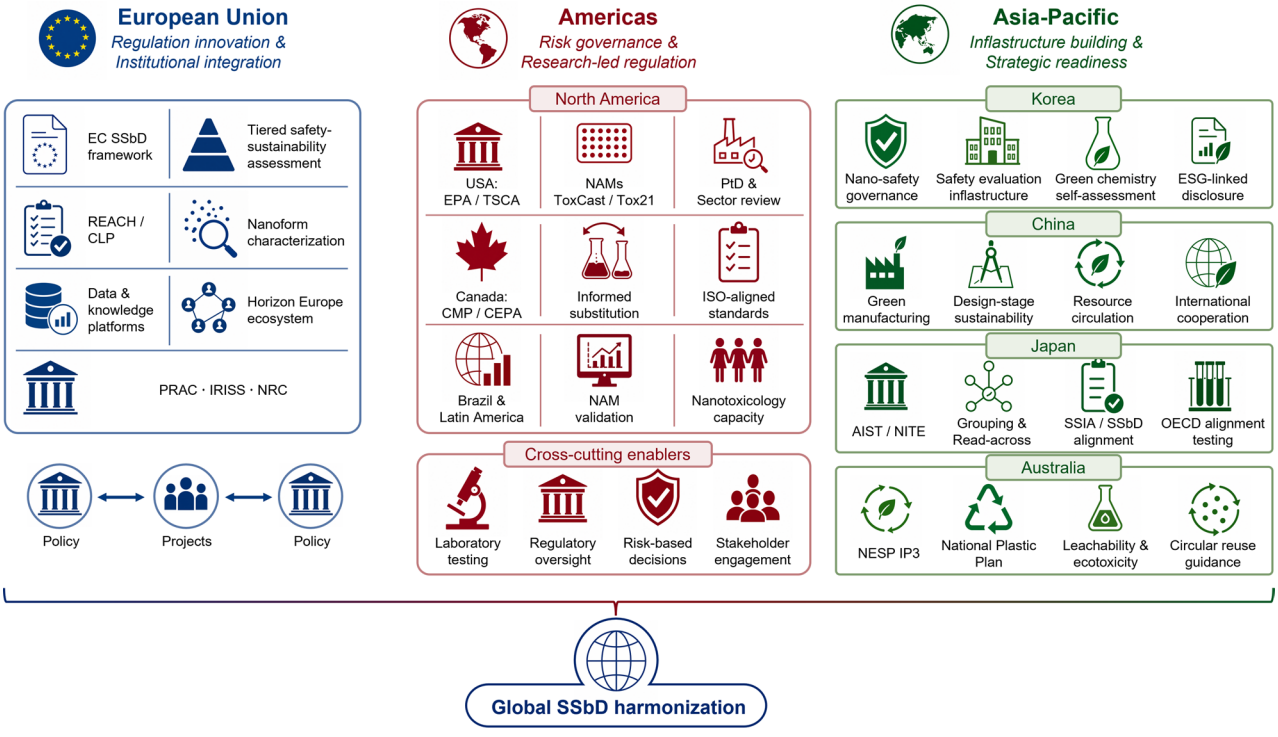


Fig. 2 Global landscape and regional paradigms of SSbD policy

and system boundaries of the innovation through the scoping analysis process, which formulates the corresponding SSbD scenario, and then proceeds to a holistic assessment of the safety and sustainability aspects of a chemical, material, or technological process. The structure concludes with evaluating the assessment results and documenting all actions undertaken and results obtained. The assessment process, in its current formulation, is structured into two main parts, the safety and sustainability assessment parts. The first part, safety, encompasses human health, environmental and process safety related to uses of chemical or material across the entire life cycle. The sustainability part consists of two dimensions: environmental and socioeconomic sustainability. Environmental sustainability evaluates resource efficiency, carbon footprint, and ecosystem impacts, typically using life cycle assessment (LCA) approaches. Socioeconomic sustainability considers cost-effectiveness, market viability, and the broader economic implications of design choices across the value chain, while also addressing societal impacts including occupational health, supply chain ethics, and community-level considerations [6]. A defining structural feature of the EC SSbD framework is its tiered assessment approach, which allows the depth of evaluation to be calibrated to the stage of innovation and the availability of data [8]. This tiered structure is particularly valuable in a nanotechnology context, where data availability is even more limited in early development stages and full characterization is resource-intensive. In this way, the framework can support early-stage design choices while still offering a pathway toward more comprehensive assessment as information accumulates.

Despite its comprehensive scope, the EC SSbD framework faces several practical challenges. The data requirements for full multi-criteria assessment, particularly at advanced tiers, can be substantial and may present barriers for small and medium-sized enterprises (SMEs) and early-stage innovators. Furthermore, the application of the framework to advanced materials such as NMs requires adaptation, as standard hazard assessment methodologies were not originally developed with the unique physicochemical complexity of NMs in mind [2, 4]. Additional issues include the need for harmonised metrics and indicators across safety and sustainability dimensions, and the integration of emerging data sources (e.g., NAMs and digital tools) into the assessment logic in a way that is both scientifically robust and acceptable for regulators. These limitations underscore the need for continued framework development and the generation of appropriate data to support SSbD implementation across diverse material classes.

2.1.2 REACH amendments and nanoforms

Within the EU, NM-specific regulatory obligations have been embedded within the general REACH and CLP architecture, under which NMs have been covered as chemical substances, while explicit nanoform requirements have been introduced under REACH [15–17]. Under Commission Regulation (EU) 2018/1881, REACH Annexes I, III and VI to XII were amended to address nanoforms, and application of those amended requirements has been required since 1 January 2020 [18, 19].

In ECHA's updated guidance for registering substances in nanoform, the term nanoform has been defined, advice on building and justifying sets of nanoforms has been provided, and the characterization information to be reported has been specified [20]. Differences in size distribution, shape, and surface chemistry or surface treatment have been identified as determinants by which distinct nanoforms may be distinguished. Proper characterization of the test nanoform has been described as requiring information on size distribution, shape and aspect ratio, surface treatment, and specific surface area [21].

In Regulation (EU) 2020/878 [22], the introduction of nanoform-specific requirements under Regulation (EU) 2018/1881 [18] has been explicitly cited as a reason for revising REACH Annex II on safety data sheets, and related information has been required to be included in safety data sheets [20, 21].

Although a full SSbD determination has not been performed through REACH alone, a clearer regulatory starting point for nanoform differentiation, dossier preparation, and supply-chain communication has been established, and that foundation has been of direct relevance to European SSbD implementation for NMs [8, 10].

2.1.3 EU research projects and policy integration

Operationalization of the EU SSbD agenda in nanotechnology has proceeded through a policy-to-project-to-policy feedback loop linking the Commission Recommendation establishing the EU framework for SSbD chemicals and materials with successive Horizon 2020 and Horizon Europe research portfolios [5, 6, 8, 10, 13, 23, 24]. A first wave of Horizon 2020 projects translated safe-by-design and SSbD principles into operational tools for NMs and nano-enabled products, including ASINA with a data-driven safe-by-design management methodology [3, 25], as well as SAbyNA which developed an integrative web-based guidance platform for safer nanoforms, nano-enabled products, and nano-processes [26]. SUNSHINE, HARMLESS, and DIAGONAL operationalized SSbD strategies for multicomponent and high-aspect-ratio NMs through tiered tool suites and

decision-support systems for both industrial innovation and regulatory preparedness [27–31].

From late 2023 onward, a second wave of Horizon Europe projects extended SSbD operationalization beyond the core nanosafety portfolio to include computational integration, such as PINK [32], mechanistic pathway modelling, including projects like INSIGHT [32], new approach methodologies (NAMs), such as CHIASMA [33], and sectoral demonstrators, such as DESIDERATA [34]. At ecosystem level, translation of project outputs into practice was institutionalized through PARC [35, 36], IRISS [37], the Network for Safety and sustainability of Chemicals and materials (NSC) [28, 38], and related SSbD community infrastructures. Taken together, the project landscape has produced an increasingly interconnected implementation ecosystem in which policy criteria, digital infrastructures, methodological guidance, sectoral demonstrators, and regulatory learning are being progressively aligned to support nanotechnology-oriented SSbD.

2.2 The Americas: risk-based regulatory approaches and sustainable chemistry initiatives

2.2.1 United States (US)

In the United States, the regulatory efforts addressing NMs are led by the United States Environmental Protection Agency (US-EPA), which has been developing nanospecific provisions under the Toxic Substances Control Act (TSCA), with a marked emphasis on environmental protection and human health. However, the U.S. approach to NMs should not be described only as a nano-specific regulatory framework. Recent federal documents indicate that NM governance is increasingly embedded within a broader sustainable chemistry and advanced-materials R&D ecosystem that connects chemical safety, sustainable design, life-cycle thinking, standards and metrics, data infrastructure, alternatives assessment, and commercialization support [39, 40]. When considering occupational risks, the framework is guided by the National Institute for Occupational Safety and Health (NIOSH), which promotes approaches such as Prevention through Design (PtD). These initiatives together support the advancement of sustainable chemistry and anticipatory risk management [41].

This broader framing is based on the 2023 Sustainable Chemistry Report: Framing the Federal Landscape, which proposed a federal consensus definition of sustainable chemistry covering the intentional design, manufacture, use, and end-of-life management of chemicals, materials, and products across their life cycle. The report emphasizes renewable inputs, optimal efficiency, avoidance of adverse human-health and environmental impacts, circularity, societal needs, economic resilience, and avoidance of resource depletion or waste accumulation [40]. It also identifies standards and metrics development, data sharing, life-cycle assessment/modular design, incentives, education, resource access, alternatives, circularity, and novel hazard-assessment methods as strategic areas relevant to sustainable chemistry and advanced materials [40]. For NMs and nano-enabled products, this implies that safety assessment should be connected not only to intrinsic hazard, but also to functional performance, exposure potential, resource use, circularity, and end-of-life behavior. The 2024 Federal Sustainable Chemistry Strategic Plan further translates this landscape into four goals: discovering more sustainable chemistry, bridging discovery to commercialization, promoting adoption in business and subnational government, and creating a 21st-century federal service for sustainable chemistry [39]. The plan also highlights crosscutting themes such as federal investment, circular economy, data sharing and AI, environmental justice and equity, and education/community engagement, which are relevant to SSbD-oriented development of NMs and advanced materials.

Additionally, the US-EPA has been implementing high-throughput screening platforms, such as ToxCast and Tox21, to evaluate the biological activity of chemicals across multiple pathways, integrated with computational approaches. Furthermore, NAMs are strongly encouraged as alternatives to reduce reliance on animal testing [42].

The U.S. Food and Drug Administration (FDA) has established a nanotechnology task force involving multiple centers and offices, addressing the application of nanotechnology across a range of sectors, including cosmetic products, food, pharmaceuticals, and medical devices. Accordingly, the FDA then evaluates nanotechnology-enabled products on a case-by-case basis, with regulatory decisions guided by the specific application and other relevant factors. In addition, its guidance documents highlight the importance of thorough physicochemical characterization as part of the premarket approval process to ensure the safety, quality, and performance of these products [43].

The U.S. also have several organizations involved in nanotechnology standardization. For example, the American National Standards Institute (ANSI) plays a central role as the national standardization body, and American Society for Testing and Materials (ASTM) International established Committee E56 on Nanotechnology, which has been responsible for developing nanotechnology-related standards since 2005 [44]. The recent sustainable chemistry framework broadens this standardization discussion beyond nano-specific terminology and test methods by emphasizing interoperable data, decision models, measurement science, life-cycle assessment, and sustainability metrics, with agencies such as NIST, EPA, NSF, DOE, FDA, and USDA contributing to the

broader federal ecosystem [39, 40]. At the same time, this framework should be distinguished from TSCA: TSCA remains the binding chemical risk-management statute, whereas the sustainable chemistry framework primarily supports coordinated R&D, data development, standards, commercialization, education, and market facilitation rather than creating a new binding nano-specific regulatory regime [39, 40].

Taken together, the U.S. approach reflects a distributed but highly innovation-oriented model for sustainable materials governance, in which sustainable chemistry, computational toxicology, high-throughput screening, standards development, and commercialization support collectively contribute to the operationalization of anticipatory and sustainability-oriented innovation principles closely aligned with SSbD.

2.2.2 Canada

Canada has a well-developed chemical management infrastructure that is currently evolving to incorporate more preventive, sustainable, and socially equitable standards [45].

The Chemicals Management Plan (CMP), jointly administered by Health Canada and Environment and Climate Change Canada (ECCC), systematically assesses and manages toxic substances under the Canadian Environmental Protection Act, 1999 (CEPA) [46].

The recent passage of Bill S-5 (Strengthening Environmental Protection for a Healthier Canada Act) represents a significant shift in Canadian chemical regulation. The amended CEPA now formally recognizes the right to a healthy environment, mandates the development of strategies to replace vertebrate animal testing with NAMs, and requires consideration of cumulative effects as well as the protection of vulnerable populations [47]. These developments are further supported by Canadian initiatives such as the Canadian Centre for Alternatives to Animal Methods (CCAAM), which promotes the development and implementation of alternative testing approaches relevant to predictive toxicology and sustainable chemical assessment.

At the same time, there is growing momentum toward "Informed Substitution" and Alternatives Assessment (AA). This approach seeks to avoid "regrettable substitutions" by evaluating alternatives in terms of hazard, performance, and economic feasibility, thereby moving Canada's strategy beyond exposure control toward the active replacement of toxic chemicals with safer alternatives [45].

2.2.3 Brazil and other South American nations

In Brazil, significant progress in nanotechnology governance has been driven by the Ministry of Science, Technology and Innovation (MCTI), which has promoted national strategies for nanotechnology and advanced materials development. At the regulatory level, the National Health Surveillance Agency (ANVISA), together with agencies such as the Brazilian Institute of Environment and Renewable Natural Resources (IBAMA) and the National Institute of Metrology, Quality and Technology (INMETRO), oversees the safety evaluation and approval of nanotechnology-enabled products. In light of this, before entering the Brazilian market manufacturers need to ensure both the efficacy and the safety of their products. Despite the absence of a specific regulatory framework explicitly addressing NMs, project law still being considered in the Federal Senate (PL No. 880/2019) aims to establish a legal basis for nanotechnology and advanced material; promoting innovation and safeguarding human, animal, and environmental health [48].

To strengthen technical capacity and regulatory harmonization, Brazil has developed national infrastructures for nanotechnology standardization and safety assessment. INMETRO, in collaboration with the Brazilian National System of Laboratories on Nanotechnologies (SisNANO/MCTI), supports the development of technical procedures, reference materials, and nanosafety-related methodologies. In parallel, the Brazilian Association of Technical Standards (ABNT) participates in ISO/TC 229 nanotechnology standardization activities, contributing to alignment with international best practices. Brazil has also engaged in international nanosafety collaborations, including NANoREG, the European NanoSafety Cluster, NanoCommons KB, CompSafeNano, and INSIGHT, supporting the development of internationally harmonized approaches to nanosafety assessment and SSbD-related research [41].

Brazil has additionally expanded its activities in NAMs as alternatives to animal testing. The principles of the 3Rs (Replacement, Reduction, and Refinement) are incorporated into national legislation through the Arouca Law, while initiatives such as the Brazilian Network for Alternative Methods (RENAMA), the Brazilian Center for the Validation of Alternative Methods (BraCVAM), and the Mercosur Platform for Alternative Methods (PREMASUL) support the development, validation, and regional dissemination of alternative testing approaches across Latin America [49]. An important recent milestone was the approval of the Brazilian Chemical Management Law (Law No. 15,022) in 2024, which introduces a national chemical registration system inspired by the European REACH framework. Under this regulation, chemical substances manufactured or imported above defined thresholds must be registered together with hazard, use, and production information aligned with the Globally Harmonized System (GHS) for classification and labeling [44, 50]. Beyond Brazil, several Latin American countries, including Mexico, Argentina, Colombia,

and Costa Rica, have increasingly engaged in nanotechnology governance, nanosafety initiatives, and international standardization activities aligned with OECD and ISO frameworks. Although dedicated SSbD regulatory systems remain limited across the region, growing participation in international harmonization efforts, alternatives assessment initiatives, and NAM-related collaborations suggests that Latin America is progressively building foundational capacities relevant to future SSbD implementation.

2.3 Asia-Pacific: national infrastructures and international standard alignment

2.3.1 Korea: green chemistry initiative

In Korea, policy developments relevant to SSbD remain centered on nano-safety governance rather than a unified national SSbD framework. The 5th Korea Nanotechnology Initiative (2021–2030), implemented across nine ministries, identifies nano-safety and standardization as core policy pillars [51, 52]. This emphasis is reflected in the Ministry of Environment's nano-safety management program and the 3rd master plan (2022–2026), which covers environmental and product monitoring, exposure assessment, physicochemical characterization, and risk assessment [53]. The National Institute of Environmental Research is also applying new approach methodologies, including air–liquid interface systems, to nanoparticle toxicity studies [53].

Korea's governance base is complemented by product- and industry-oriented support. The Ministry of Trade, Industry and Energy has funded inhalation-toxicity studies to support ISO methods, while a safety evaluation support center launched in 2023 provides industry-facing characterization and GLP-aligned testing services. In parallel, the Ministry of Food and Drug Safety has advanced immunotoxicity research on nanomaterials used in food and drug products. Korea Research Institute of Standards and Science (KRISS) further strengthens this system through nanosafety metrology and active participation in ISO and OECD standardization activities [54–56].

Korea is recently promoting a green chemistry initiative. In September 2025, the Ministry of Climate, Energy and Environment launched a pilot program to develop a national 'Green Chemistry Self-Assessment Guideline,' running through June 2026 [57]. This program also supports the alignment between chemical safety performance and ESG disclosure. Ultimately, its goal is to protect human health and the environment while enhancing industrial competitiveness. The draft guidelines provided by this program are structured around two main pillars. First, the Green Chemistry Self-Assessment Framework. This is a structured, stepwise self-audit. Second, Methodology for Evaluating Green Chemistry Substances. This is meant to avoid so-called 'regrettable substitution,' where one dangerous chemical is simply replaced by another that turns out to be equally harmful. Although not nanomaterial-specific, it suggests that Korea is building an enabling foundation for future SSbD implementation.

2.3.2 China: emerging policy signals

China holds a leading technological position in the field of nanotechnology, accounting for 43% of global patents [58]. By 2025, China's nanotechnology industry market size and number of companies have grown explosively, and in step with this, the system for evaluating the safety and sustainability of NMs at the design stage has also become more sophisticated. The National Center for Nanoscience and Technology (NCNST) and the National Medical Products Administration (NMPA) in China are continuously updating guidelines for safety assessments of medical devices, cosmetics, and new materials containing NMs [59].

China has explicitly designated the green and low-carbon transition and green manufacturing as core pillars of its national development strategy through the 14th Five-Year Plan and related policy documents. In high-value-added manufacturing and AdMa sectors, measures are being strengthened to achieve improved energy efficiency, reduced pollution emissions, and resource circulation. This signifies a shift beyond post-pollution management toward a systematic approach that manages environmental performance and safety throughout the life cycle of products and processes.

Research on China's green manufacturing identifies green design, green processes, green equipment, remanufacturing, and resource recovery as an integrated system and emphasizes evaluating environmental impact and resource efficiency from the initial design stage. In parallel, nanotechnology researchers have stressed that maintaining competitiveness requires exposure studies, toxicity research, and SbD. Consequently, a mindset corresponding to SSbD—integrating safety and sustainability elements in the early stages of design and manufacturing—is gradually being shared among researchers within China [60].

2.3.3 Japan: OECD-aligned SSbD/SSIA frameworks

In Japan, establishing a NM safety assessment system has been recognized as a national-level task from a relatively early stage, with public research and evaluation institutions such as Advanced Industrial Science and Technology (AIST) and National Institute of Technology and Evaluation (NITE) at its core. Since the early 2000s, NITE has positioned itself as a national agency performing chemical and product safety assessments, testing and certification, and standardization work, providing testing infrastructure to support safety verification for various

industrial products, including NMs. Japan recognized early the need to develop a more sophisticated testing and evaluation system capable of characterizing NMs and assessing their hazards to respond to the expanding industrial application of nanotechnology [61].

Based on this awareness, the Ministry of Economy, Trade and Industry (METI) organized the production and usage status of major NMs in Japan through the "Expert Committee on Nanomaterial Safety Measures" in the late 2000s and proposed directions for developing exposure, toxicity, and risk assessment technologies. The report proposed advancing physical property evaluation, toxicity testing, exposure scenario setting, and risk management measures for representative industrial NMs such as titanium dioxide and carbon nanotubes, with compatibility to OECD test guidelines.

Throughout this process, AIST functioned as the core implementing agency for nanosafety research, developing methodologies linking particle characteristics (size, surface area, surface chemistry, etc.) with toxicity and kinetic (TK) data, grouping approaches, and read-across methodologies, linking these to international discussions. AIST also participated in the OECD NMs Sponsorship Program and project results were shared at meetings of OECD expert committees [62]. Recently, these activities have also been connected to broader advanced/nanomaterial policies and SSbD/SSIA discussions. The latest report from the international organization suggests Japan is seeking alignment with international SSIA/SSbD frameworks based on its domestic nano-safety infrastructure. Summarizing these trends, Japan has built a robust nano-safety testing infrastructure centered on AIST and NITE. Using this as a foundation, it is advancing the safe and sustainable design of NMs and advanced material from both institutional and technological perspectives, aligning with international discussions, including those within the OECD [53].

2.3.4 Australia: emerging SSbD-adjacent infrastructure

In Australia, policy and research activities relevant to SSbD remain distributed across chemicals management, plastics circularity, hazardous waste, and nanosafety rather than consolidated into a single national SSbD framework [23, 63–67]. However, several recent initiatives indicate a clear movement toward SSbD-adjacent infrastructure building, particularly through the National Environmental Science Program's Impact Priority 3 (IP3), the National Plastics Plan, and broader research efforts related to waste safety, circular economy implementation, and safer material reuse [63, 66–69]. The strongest national-level example is IP3 under the NESP Sustainable Communities and Waste Hub, which focuses on the management of hazardous waste, substances, and pollutants [67, 70]. IP3 aims to improve the safe recovery and reuse of resources from wastes by generating high-quality data on chemicals of potential concern, validating sampling and analytical methods, assessing leachability and ecotoxicological risk, and developing guidance for the safe reuse of recovered materials [67, 70]. In practice, this positions IP3 as an important enabling initiative for circular-economy implementation and safer material recovery, especially for complex waste streams such as end-of-life tyres and e-waste [67, 69–71]. The program also seeks to establish transferable methodologies for emerging waste streams, including batteries, photovoltaic cells, textiles, and organics, thereby contributing to broader national capability development for risk-based waste reuse and resource recovery [70].

Australia's National Plastics Plan also reinforces this direction by emphasizing plastic waste reduction, improved recyclability, reuse, recycled content, and leakage prevention across the plastics life cycle [66]. Although the plan is not framed as an SSbD policy, it shares the same logic of upstream design and downstream risk reduction by encouraging better material choices, more recyclable product design, and the phase-out of problematic plastics [23, 66]. The plan explicitly identifies product design as a critical intervention point for reducing environmental impacts and promoting reusable and recyclable materials. Taken together with IP3, this suggests that Australia's policy base is progressively building the technical, analytical, and governance foundations needed for future SSbD adoption [63, 66–68, 70]. At the research level, Australia has also been expanding capabilities relevant to safer material innovation and environmental risk assessment [68–71]. In particular, CSIRO-led and university-linked work under IP3 develops analytical, leaching, and ecotoxicological assessment methodologies that are intended to support evidence-based risk management of hazardous and complex waste streams [70, 71]. The project further aims to establish nationally transferable approaches for waste characterization, safe reuse assessment, and environmental exposure evaluation, which are conceptually aligned with several SSbD principles, including anticipatory risk assessment and safer lifecycle management [23, 69, 70].

Overall, Australia is best described as being in an early capability-building phase for SSbD-related governance [23, 63, 67, 68, 70]. While the country has not yet established a unified national SSbD framework, initiatives such as the National Plastics Plan and NESP IP3 are progressively developing the technical, analytical, and governance foundations needed for safer material recovery, circular resource use, and evidence-based risk assessment. These efforts collectively indicate a gradual transition toward more preventive and sustainability-oriented approaches to chemicals and materials management [23, 63, 64, 68, 69].

2.4 Towards global convergence: overcoming challenges in international policy harmonization

Despite significant regional differences in regulatory structures, innovation priorities, and industrial ecosystems, the global policy landscape for SSbD in nanotechnology reveals several complementary strengths that could support more coordinated international implementation. The European Union has established the most operationally mature SSbD framework, integrating life cycle thinking, tiered assessment, and sustainability criteria into regulatory and innovation policy. In contrast, the United States has developed strong capabilities in sustainable chemistry, computational toxicology, high-throughput screening, and data-driven innovation ecosystems. Asian countries, including Japan, Korea, and China, have advanced nano-safety infrastructure, industrial scale-up capacity, standardization activities, and strategic manufacturing initiatives, while emerging economies in Latin America are increasingly contributing through international harmonization efforts, alternatives assessment initiatives, and adoption of OECD-aligned methodologies. At the same time, important limitations remain across all regions. These include fragmented regulatory definitions, inconsistent assessment metrics, limited interoperability of datasets, insufficient life cycle data, and challenges associated with evaluating advanced and multicomponent nanomaterials. In particular, the absence of globally harmonized criteria for integrating safety, sustainability, functionality, and socioeconomic dimensions remains a major barrier to scalable SSbD implementation.

These challenges highlight the need for a global collaboration strategy for SSbD in nanotechnology. Such a strategy could include harmonization of terminology and assessment criteria, development of interoperable FAIR data infrastructures, expansion of OECD-compatible NAMs, shared reference materials and testing protocols, and coordinated international platforms for nanosafety and sustainability assessment. Furthermore, stronger collaboration between regulatory agencies, research infrastructures, industry, and standardization bodies will be essential to support globally consistent yet regionally adaptable SSbD implementation across nanotechnology value chains. Ultimately, international collaboration may enable SSbD to evolve from a collection of regional initiatives into a globally coordinated framework for the safe, sustainable, and responsible development of nanotechnology and advanced materials.

3 Methodological frameworks for implementing SSbD

3.1 Mechanistic insight for safer nanomaterials: toxicogenomics and adverse outcome pathways (AOPs) in design

The diversity, dynamic behavior, and context-dependent biological interactions of nanomaterials challenge traditional hazard assessment paradigms that rely on apical endpoints and late-stage testing. Within the SSbD framework, safety must instead be anticipated early, requiring approaches that explain why and how materials induce adverse effects rather than merely describing what outcomes occur. Mechanistic strategies are therefore essential to translate molecular perturbations into predictive knowledge that can guide material design, enable read-across, and support regulatory decision-making under uncertainty. In this context, integrating mechanistic toxicogenomics with systems-level and multi-omics approaches provides the necessary foundation to link physicochemical properties to biologically meaningful pathways, capture system-specific responses, and distinguish adaptive from adverse trajectories across biological scales. The integration of predictive assessment tools, mechanistic toxicology, digital infrastructures, and SSbD-oriented R&D workflows is illustrated in Fig. 3.

3.1.1 Mechanistic and multiscale hazard assessment of nanomaterials using toxicogenomics and adverse outcome pathways

Traditional toxicity testing, focused on apical endpoints (e.g. organ pathology), provides limited insights into the molecular mechanistic underlying toxicity, creating a gap that the SSbD framework seeks to bridge. SSbD requires an understanding of how materials cause harm, driving the need for NAMs and mechanistic insights from the initial stages of development [72]. Furthermore, understanding the molecular background, they can detect lower levels of alterations even in the absence of phenotypic disruptions.

Toxicogenomics (TgX) has emerged as a key methodology capable of filling this mechanistic gap by capturing genome-wide molecular responses that precede, and often predict, higher-level toxicological outcomes. TgX is particularly powerful for engineered nanomaterials (ENMs), where biological interactions depend on dose and dynamic physicochemical properties such as size, shape, dissolution, and surface chemistry. Previous studies demonstrated that TgX can identify molecular drivers of adverse outcomes, including fibrosis, immune modulation, and conserved transcriptomic responses across diverse ENMs and biological systems [73–76]. Together, these findings highlight how TgX can disentangle ENM-specific modes of action (MoA), supporting robust grouping, read-across, and early hazard flagging.

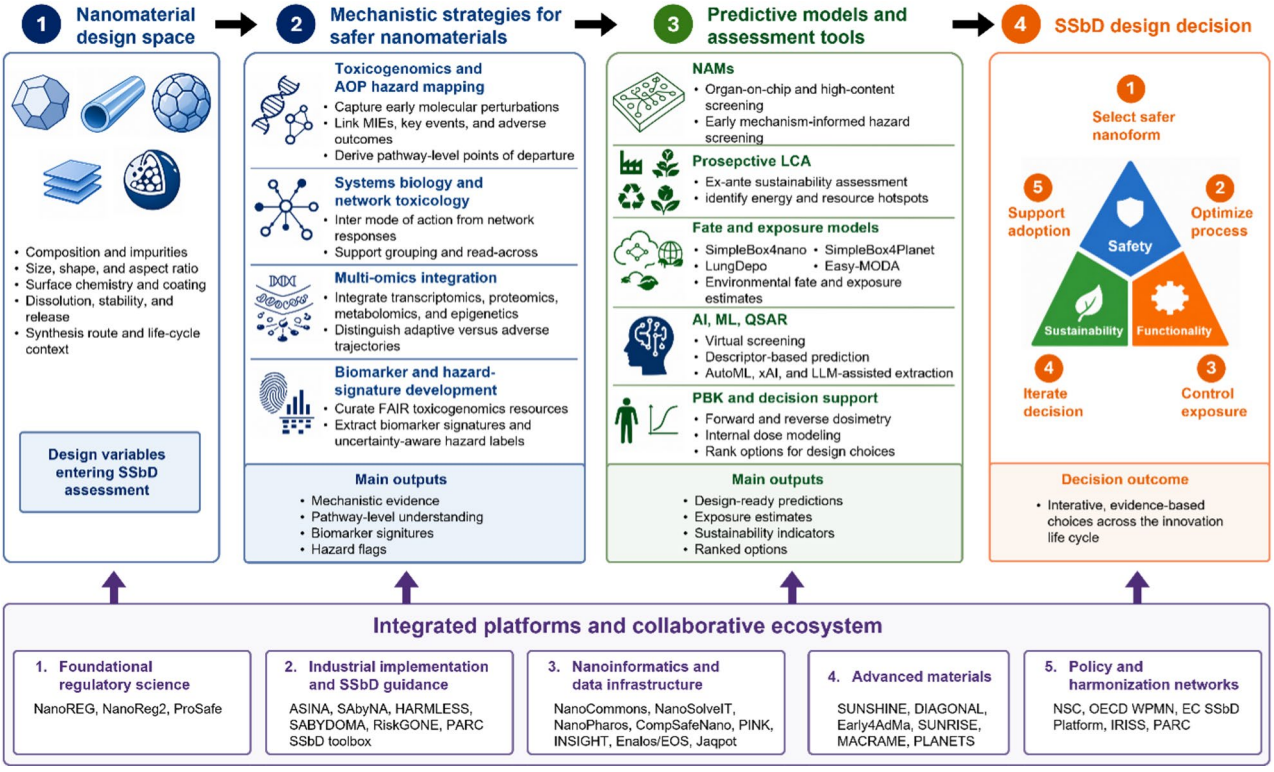


Fig. 3 Integration of SSbD principles into research and development (R&D) workflows

However, molecular responses cannot be interpreted in isolation from the biological system in which they arise [77]. Different species, tissues, and even cell populations display distinct regulatory architectures, meaning that the same ENM can trigger divergent transcriptomic responses depending on the system's intrinsic properties. This system effect is particularly important for ENMs, whose heterogeneity and dynamic behavior make them poorly suited to "one-chemical–one-assay" frameworks. Contextualizing molecular alterations by considering cell-type composition, gene-regulatory programs, and epigenetic state is therefore essential for mechanistically meaningful interpretation. Recognizing toxicity as an emergent response of a system's internal molecular machinery aligns naturally with the One Health concept and highlights the need to contextualize transcriptomic changes within each system's genetic, epigenetic, and cellular landscape [78].

Current integrative frameworks increasingly couple TgX with Adverse Outcome Pathways (AOPs) to link molecular perturbations to higher-level effects through causally connected key events [79]. Recent applications show how transcriptomic responses can be anchored to AOP components through nano-Quantitative Structure Activity Relationship (QSAR) approaches for lung inflammation [80], molecular AOP annotation that links genes to causal key events [81], and benchmark-dose modeling that translates molecular data into gene-level or pathway-level points of departure [82]. Such integration enhances the interpretability of toxicological effects and strengthens the regulatory relevance of TgX within SSbD.

While these mechanistic and AOP-anchored based modeling approaches highlight the analytical power of TgX, their reliability fundamentally depends on the availability of high-quality datasets with well-annotated experimental design [83]. A notable effort to address the need of harmonized resources is the large-scale ENM TgX resource assembled by Saarimäki et al. [84], which consolidates and standardizes 101 high-quality TGx datasets across species, platforms, and nanoforms, covering more than 500 ENM-versus-control comparisons across diverse in vitro and in vivo systems. These datasets span multiple ENM compositions, nanoforms, dose–time designs, and biological models, providing the nanosafety community with an unprecedented resource for predictive toxicology. Standardized and fully documented preprocessing workflows [85], including quality evaluation, normalization, batch-structure assessment, correction of technical variation, and gene annotation, were then applied to produce harmonized expression matrices and differential expression results suitable for robust cross-study comparison and integrative modeling. Importantly, the curation process highlighted that usability, rather than discoverability, often represents the major barrier to data reuse. Ensuring both technical

and scientific FAIRness is therefore essential for reproducible pathway analysis, read-across, AOP development, and ML-driven hazard prediction [86]. Resources that integrate FAIR accessibility with rigorous metadata and preprocessing, unlock the full analytical potential of TgX [84, 85, 87, 88]. By doing so, differentially expressed genes can be linked to specific biological processes and to critical physicochemical features such as size, coating, or impurity content, generating hypotheses about structure–activity relationships and guiding safer-by-design modifications.

Building on this foundation, the availability of harmonized, and high-quality TGx datasets enable advanced applications such as biomarker detection and toxicity assessment, addressing the limitations of classical toxicology approaches [89, 90]. Therefore, integrating TgX with advanced computational frameworks has become an essential avenue to enhance mechanistic interpretability and predictive capacity [91]. As an example, Fortino et al. showcase the potential of integrated multi-omics models to derive predictive biomarker signatures for 31 ENMs, linking transcriptomic perturbations with early mechanistic programs related to lipid metabolism, innate immunity, fibrotic responses, and cytoskeletal remodeling [92]. Importantly, the predictive models generalized to external transcriptomics datasets, even for ENMs outside the training set, reinforcing the biological stability of these mechanistic signatures.

Even with well-curated TGx datasets, predictive toxicology requires accurate outcome annotations to train models capable of generalization across nanoforms. Developing reliable toxicity classifiers for ENMs is often limited not by transcriptomic data availability but by the scarcity and inconsistency of high-quality hazard labels. To address this, Saarimäki & Fratello et al. [93] introduced a Bayesian wisdom-of-crowds framework that aggregates expert knowledge into probabilistic hazard scores across multiple toxicological endpoints, enabling uncertainty-aware assessment of nanomaterial risks. By integrating these scores with transcriptomic and physicochemical data, the approach identifies key molecular mechanisms underlying toxicity, such as oxidative stress, immune response, and Deoxyribonucleic acid (DNA) repair. This approach shows how a combination of structured expert inference and transcriptomic analysis can serve as a powerful tool for data gap filling, enabling early mechanistic hazard prediction even in data-sparse regimes.

Beyond describing mechanisms, these frameworks facilitate grouping and read-across efforts by identifying mechanistic similarities and divergence across nanoforms [72].

This approach is essential to manage the diversity of ENMs and accelerate safety assessment. For example, Torres Maia et al. used the collection from Saarimäki et al., to investigate pairwise similarities among a variety of transcriptomic NM exposure data through clustering analysis, gradient boosting based machine learning (ML), and explainable artificial intelligence (AI) approaches (SHapley Additive exPlanations) [94].

According to this study, transcriptomic similarity depends on multiple descriptors, including size, chemical composition, surface properties, and exposure duration, and that nanoforms sharing the same core composition are not necessarily toxicologically equivalent [94, 95].

These NAM approaches support data gap filling through read across for novel NMs, contribute to reducing animal testing, and encourage the reuse of existing data, in alignment with the hazard assessment principles within the SSbD framework [72].

The shift from descriptive toxicology to genuinely mechanistic interpretation requires analytical frameworks capable of capturing the complexity of the responses of biological systems. TgX provides the molecular resolution needed for early hazard identification, but gene-level signatures alone cannot fully explain how their interactions produce higher-level effects. Systems biology offers a valuable perspective, interpreting toxicity not as a linear sequence of deregulated genes but as an emergent phenotype arising from coordinated disturbances across multiple biological scales. Recent developments in network toxicology illustrate how molecular responses to ENMs can be interpreted directly as chains of functionally connected events. Instead of viewing toxicogenomic data as isolated signatures, network-based models infer co-regulatory structures, representing the coordinated patterns of gene activity that characterize a material's MoA [96]. Using transcriptomic datasets across dozens of ENMs and across in vitro and in vivo systems, we showed how these patterns can be mapped as network modules and traced along mechanistic pathways, enabling the direct translation of omics perturbations into event chains on the AOP framework [97]. These approaches improve interpretability, support the prediction of multiple adverse outcomes, and better capture the system-specific context of ENM responses [97]. This ability to integrate system-specific context marks an important departure from chemocentric or assay-centric approaches, aligning mechanistic toxicology more closely with the multiscale thinking [97]. Together, these developments demonstrate that TgX provides a mechanistically rich and increasingly mature foundation for the safe and sustainable assessment of ENMs. By combining high-quality curated datasets, multiscale omics readouts, AOP-anchored mechanistic modeling, expert-informed hazard labels, and computational tools for grouping and prediction, the field is rapidly moving beyond descriptive toxicology toward integrative, anticipatory, and

regulatory-ready approaches. Continued investment in data quality, mechanistic frameworks, and interoperable resources will be essential to fully realize the promise of TgX in supporting SSbD and enabling early, mechanism-based design of safer NMs.

Importantly, these mechanistic insights provide direct guidance for SSbD by linking specific physicochemical properties to adverse biological pathways. For example, identifying ion-driven oxidative stress or inflammatory signaling pathways can inform the selection of surface coatings or material compositions that suppress these effects, enabling mechanism-informed material design.

3.1.2 From transcriptional signatures to multi-omics integration

Although transcriptomics is now a major cornerstone of mechanistic toxicology, relying solely on mRNA levels leaves a significant gap in our understanding of a cell's actual functional state. The reality is that transcriptional changes do not always correlate with protein abundance or metabolic activity due to varying translation rates, post-translational modifications (PTMs), and protein degradation kinetics, which are the ultimate effectors of the cellular response [98]. To address these limitations, modern TgX has shifted toward vertical multi-omic integration, combining transcriptomics with proteomics and metabolomics to capture the dynamic flow of biological information. While the transcriptome reflects the potential for a cellular response, metabolomics provides the necessary phenotypic anchoring, linking molecular alterations to measurable functional changes in the physiological state [99].

In the context of AOPs, multi-omics integration is crucial for the precise identification of MIEs. Many MIEs, such as enzyme inhibition or receptor activation, occur at the protein level and may not trigger a proportional transcriptional signal immediately. By incorporating proteomics, researchers can detect these direct molecular interactions, while metabolomics connects molecular perturbations to measurable changes in the physiological state [100]. This systemic perspective is vital for distinguishing between reversible adaptive responses, where the cell adjusts to stress without permanent damage, and adverse trajectories that lead to irreversible organ toxicity.

Furthermore, while multi-omics approaches have become increasingly standardized in fields such as precision oncology and personalized medicine to identify therapeutic targets and biomarkers [101–103], their full integration into TgX is still an evolving frontier. The primary challenge lies in transitioning from descriptive molecular profiling to the construction of quantitative, predictive models (qAOPs) that can account for chemical dose-response and temporal dynamics [104]. Integrated datasets serve as the primary input to define the precise points at which a chemical insult causes a biological system to transition from a homeostatic state into a state of disease [105]. By integrating these multi-omics layers through computational modeling, Systems Toxicology can trace the flow of molecular events, transforming correlative data into a causal map of Pathways of Toxicity (PoT), and enabling the establishment of mechanistic causality [106].

Beyond these rapid molecular changes, epigenetics emerging as a powerful source to investigate more stable long term cellular responses [107]. Cells subjected to persistent environmental stress, including ENMs exposures, rewire their regulatory landscape through DNA methylation, histone modifications, and transcription factor redistribution [108, 109]. This epigenetic reprogramming allows organisms to adjust their sensitivity and maintain functionality under prolonged exposure. Because epigenomic features tend to be more stable and evolutionarily conserved than expression profiles, they offer a robust framework for comparing responses across systems and species, providing a mechanistic bridge that naturally supports the One Health vision of cross-species relevance. For example, epigenetic responses to NMs successfully uncovered an ancestral molecular adaptation mediated by the conserved family of C_2H_2-ZNF transcription factors across species [87]. This discovery highlights a mechanism that shapes long-term cellular behavior and modulates immune responses to nanoparticles with diverse chemistries. Importantly, these alterations influence how future exposures are handled, priming or conferring resistance to subsequent responses [87]. This perspective reframes toxicity as an emergent property arising from the interplay between stimulus reactivity and biological system robustness. Interpreting toxicity through the lens of epigenetics emphasizes that adverse effects emerge from disruptions occurring across interconnected molecular, cellular, and physiological layers [110]. Integrating these adaptive epigenetic modifications and regulatory compensation enhances the mechanistic interpretability of toxicogenomic findings but also brings toxicology closer to a transdisciplinary, One-Health-aligned understanding of how environmental agents affect biological systems across species and life stages [87].

Finally, the regulatory acceptance of these high-dimensional datasets represents a critical milestone in modern risk assessment. While TgX has reached a level of technical maturity that allows for the derivation of molecular Points of Departure (PODs) [111], the field is moving toward a more holistic integration to support Next-Generation Risk Assessment (NGRA) [112]. This evolution is supported by the rapid advancements in multi-omics integration strategies which are essential for capturing

the complexity of biological systems across different layers. Ultimately, the convergence of high-quality multi-omics data with mechanistic biological understanding offers unprecedented potential for improving the predictive accuracy of chemical safety assessment and becoming the new regulatory standard.

From an SSbD perspective, multi-omics integration enables a more precise identification of critical biological thresholds and transition points between adaptive and adverse responses, thereby supporting the design of materials that remain within safe biological operating ranges.

3.2 Predictive assessment: integration of advanced modeling and life cycle assessment

While Sect. 3.1 focuses on mechanistic understanding of nanomaterial–biological interactions, this section addresses how such knowledge is translated into predictive models and decision-support tools for SSbD implementation.

3.2.1 New approach methodologies (NAMs) for early hazards screening

Operationalizing SSbD requires moving away from slow, expensive animal testing towards high-throughput, predictive methodologies [113]. NAMs represent a suite of in vitro and in silico tools designed to replace in vivo experimentation [114]. In the context of NMs, these approaches are particularly valuable because they enable rapid, mechanism-informed evaluation of hazard at early stages of material development, when redesign is still feasible. Among the most promising NAMs are organ-on-chip models and high-content screening (HCS) platforms allowing for the rapid assessment of multiple toxicity endpoints (e.g., cytotoxicity, genotoxicity) under physiologically relevant conditions [106, 107, 115, 116]. By generating early biological signals before full-scale development, these platforms function as practical tools that are essential for the "early-warning" systems within the SSbD design phase, providing immediate feedback to material scientists and helping prioritize safer candidate materials [117].

3.2.2 Prospective life cycle assessment (LCA) and sustainability assessment

While hazard screening is essential, SSbD also requires early evaluation of environmental sustainability. Traditional LCA is often retrospective, performed only after the industrial process is established [118]. In contrast, SSbD calls for "prospective" or "ex-ante" LCA, which estimates environmental impacts at the laboratory or pilot scale using simulation data and early process assumptions [119, 120]. This approach allows researchers to identify energy hotspots—such as high-temperature calcination steps—and substitute them with milder, green synthesis routes early in the development cycle [121, 122].

Modelling approaches supporting "prospective" LCA within the SSbD framework include multimedia environmental fate models, exposure models, and decision-support tools for sustainable material design. For instance, multimedia fate models such as SimpleBox4nano [123] and SimpleBox4Planet [124] enable the estimation of NM and chemical distribution across environmental compartments, respectively, supporting the derivation of fate-related indicators for impact assessment. Exposure models, such as LungDepo [125], allow the quantification of inhalation exposure and regional particle deposition within the human respiratory system, thereby linking environmental concentrations to internal dose metrics. In parallel, frameworks such as Easy-MODA [126] support the standardized documentation and transparent reporting of modelling approaches and generated data, thereby enhancing reproducibility and facilitating their integration into SSbD-oriented assessment workflows. These modelling approaches contribute to the generation of simulation-derived data that can support early-stage sustainability assessment and informed decision-making.

3.2.3 ML, QSAR, and decision support systems

To bridge persistent data gaps in nanosafety assessment, ML approaches are increasingly being applied to develop QSARs for NMs [127, 128]. By training on FAIR-compliant datasets, ML models can predict the biological activity and environmental fate of new NMs based solely on their structural descriptors (such as size, aspect ratio, zeta potential), enabling "virtual screening" of safe candidates before synthesis begins [129]. A notable application involves the development of high-performing classification models to identify possibly genotoxic MWCNTs. By utilizing feature selection techniques like recursive feature elimination (RFE) to train classification algorithms such as Random Forest (RF) and Logistic Regression (LR), it was shown that accurate predictions can be achieved using a highly interpretable set of structural descriptors, like length, purity and zeta average [130]. Ensemble modelling can be employed to enhance prediction's reliability, by combining different nanoinformatics models predicting the same endpoint, into a consensus scheme where individual model biases or limitations are mitigated [121–123, 131]. Nonetheless, data scarcity, fragmentation, and heterogeneity in the area of nanoinformatics remains a challenge [132, 133], raising questions on the reliability of QSAR methods applied on small datasets [134]. To address experimental data scarcity, which primarily reflects the limited number of nanomaterials with reliable endpoint annotations, complementary strategies have been developed to

maximize the utility of existing datasets. In this context, descriptor enrichment approaches—such as incorporating image-based features [135], periodic table-derived descriptors [136] and properties obtained from density functional theory (DFT) calculations [118, 130, 137, 138] can enhance the representation of nanomaterials and improve model performance when endpoint data are available. In addition, to handle the problem of imbalanced datasets, oversampling techniques are employed to generate synthetic samples and better represent minority classes, thereby improving model robustness and predictive performance [139–143].

Grouping and read-across approaches have been also proposed to deal with limited data in the field of nanoinformatics [144]. In these cases, data gap filling is based on the concept that by interpolating or extrapolating the property of one or a group of NPs (source materials), the property value of a similar NP (target material) can be estimated with satisfactory accuracy [136, 139, 140, 145–148]. Automation and optimization aspects have been explored in terms of grouping (search for the optimal grouping hypothesis and features involved in models) through mathematical programming methodologies [149–151].

To further optimize nanoinformatics ML model development, autoML approaches have been lately employed and have contributed to the efficient and optimized training, in comparison to conventional ML approaches [139, 142, 152–156]. In addition, nanoinformatics leverages the recent advances in the explainable AI (XAI) techniques in order to interpret how individual descriptors and/or experimental parameters affect the model outputs. Different model-agnostic XAI techniques such as individual conditional expectation (ICE), partial dependence plots (PDP), and Shapley additive explanations (SHAP) have been integrated so far to support model interpretability [130, 157–160]. Beyond model optimization and interpretability, recent AI-enabled workflows are also being used upstream to address the scarcity of structured nanosafety data. In particular, large language models (LLMs) can extract physicochemical descriptors, biological test conditions, and toxicity outcomes from unstructured publications—including material identity, composition, core and hydrodynamic size, cell type, assay type, exposure time and dose, and assay readouts—and transform them into harmonized, ML-ready datasets [149]. Such pipelines may facilitate the development of nanotoxicity prediction models that jointly consider material properties and exposure conditions. Finally, deep learning (DL) nanoinformatics models are already applied in the field of computational NP evaluation, leveraging other data types as input for model training. These are the cases of Karatzas et al. [161, 162], who applied two DL methods on microscopic images of *Daphnia magna* to detect regions of interest for possible abnormalities after NP exposure and then classify the severity of abnormalities based on the controls, and of Yan et al. [151]. who used convolutional neural network techniques to generate nanostructure features from NP photos and use them to predict physicochemical parameters and nano-bio interactions.

Complementing these data-driven ML approaches, Physiologically Based Kinetic (PBK) models provide a mechanistic framework for assessing the systematic internal biodistribution of NMs within the organism of various species. PBK models specifically contribute to the quantification of NM concentrations in organs that are susceptible to high accumulation of NMs, such as liver, spleen and others. Therefore, PBK models can be used either in forward dosimetry to acquire detailed concentration-time profiles of NMs after specific exposure scenarios, or in reverse dosimetry to map internal points of departure (PODs) with external exposure concentrations in risk assessment frameworks.

Building upon their mechanistic role, several PBK models have been published in literature to simulate different routes of exposure, species and NMs. For instance, a human model for inhaled carbon nanoparticles was developed to quantify the translocation of nanoparticles from lung to blood systemic circulation [163] and their distribution to the rest organs and tissues. To enhance the accuracy of the absorption, distribution, metabolism and elimination (ADME) simulations through PBK models, macrophages-mediated phagocytosis has been incorporated into the modeling as an important process of accumulation of nanoparticles in richly perfused tissues, such as liver and spleen [164]. Furthermore, the parameterization of the PBK models often requires a large number of chemical-specific parameters that are difficult to quantify experimentally and thus need to be defined through model fitting on in vivo data. Therefore, an automated workflow exploiting genetic algorithms has been proposed by Tsiros et al. [165] to manage high dimensionality and avoid possible overparameterization of complex PBK models through grouping and co-estimation of kinetic parameters, such as the permeability and partition coefficients of the nanoparticles across different organs. As demonstrated in a case study on TiO_2, such approaches secure the model's statistical robustness while maintaining representation of physiology within the PBK structure.

To synthesize these diverse assessment streams into actionable industrial guidance, advanced Decision Support Systems (DSS) are essential [166]. A prominent example is the DSS developed within the HARMLESS project by TNO, which specifically targets the SSbD development of complex, multi-component nanomaterials (MCNMs) and high-aspect ratio structures [167]. This system integrates hazard, exposure, and sustainability

data to guide users through an iterative design process. The practical utility of this approach has been demonstrated through real-world industrial case studies, such as the development of nano-enabled, per- and polyfluoroalkyl substances (PFAS)-free anti-sticking coatings for bakery molds, and the engineering of essential oil nanodroplets anchored to nanoclay surfaces encapsulated in polymeric films [168]. These cases illustrate how integrated DSS tools can successfully operationalize SSbD principles, balancing functional performance with safety in advanced material applications [28, 156, 169].

3.3 Digital infrastructure: FAIR data principles and decision-support platforms

Building on mechanistic understanding and predictive modeling approaches (Sect. 3.1–3.2), integrated platforms aim to operationalize SSbD through coordinated data infrastructures, tools, and decision-support frameworks. The operationalization of SSbD requires a coordinated ecosystem that links regulatory science, digital infrastructure, industrial implementation, and policy networks [170]. Over the past decade, this landscape has evolved from early regulatory testing initiatives toward integrated platforms that combine hazard assessment, sustainability analysis, data management, and governance [171]. These platforms play a critical role in translating scientific advances into practical guidance, enabling a shift from reactive risk assessment toward predictive, design-oriented strategies that support responsible innovation in nanotechnology. The major SSbD-related platforms and initiatives currently shaping the nanosafety and advanced materials ecosystem are summarized in Table 2.

3.3.1 From regulatory testing to industrial guidance

The foundation of SSbD platforms can be traced to early regulatory-driven initiatives aimed at establishing standardized approaches for nanosafety assessment. Projects such as NanoREG represented a major milestone by systematically organizing available tools and methodologies into structured frameworks for regulatory safety evaluation of NMs [172]. Building on this, ProSafe translated these scientific outputs into practical guidance for regulatory authorities and industry, bridging the gap between research and implementation [173]. The subsequent NanoREG2 project further advanced this effort by validating SbD principles in real-world industrial contexts, marking a transition from theoretical frameworks to applied innovation [174]. More recent initiatives have expanded this approach by embedding safety and sustainability considerations directly into early-stage material design. Projects such as RiskGONE and SAbyNA provide governance models and industry-oriented guidance platforms that support safer innovation pathways, particularly for small and medium-sized enterprises [175]. Complementing these developments, the MACRAMÉ project contributes a critical measurement and characterization backbone by harmonizing methods for detecting and quantifying advanced material across their lifecycle, thereby supporting standardization efforts within OECD and CEN/ISO frameworks [176].

As NMs become increasingly complex, advanced assessment strategies have also emerged. The HARMLESS project addresses challenges associated with multicomponent and high-aspect-ratio NMs through the development of intelligent testing strategies, including high-throughput screening, machine learning-assisted TgX, and the Advanced Materials Earliest Assessment framework [30]. Together, these initiatives illustrate the evolution of SSbD platforms from compliance-driven regulatory testing toward integrated guidance systems that enable proactive, design-phase decision-making. A parallel U.S. framing is Green Toxicology, which reaches the same design-phase objective through benign-by-design principles, "test early—produce safe," predictive in silico/in vitro tools, exposure reduction, and sustainable testing, thereby complementing EU SSbD platforms with an R&D-centered toxicology strategy [177, 178].

3.3.2 Digital infrastructure and data integration for SSbD

The advancement of SSbD is increasingly enabled by digital infrastructures that support the integration,

Table 2 Categorization of key SSbD platforms and initiatives

Category	Platforms/Projects	Primary function and focus
Foundational regulatory science	NANoREG, NanoReg2, ProSafe	Established baseline regulatory testing protocols and identified gaps in RA for nanomaterials
Industrial implementation & SSbD	ASINA, SAbyNA, HARMLESS, SABYDOMA, RiskGone, PARC SSbD toolbox	Develops practical guidance, digital twins, and decision support systems for manufacturing safer nano-enabled products
Nanoinformatics & data	NanoCommons, NanoSolveIT, NanoPharos, CompSafeNano, PINK, INSIGHT	Provides data infrastructure, ontology harmonization, and in silico predictive modeling tools
Advanced materials	SUNSHINE, DIAGONAL, Early4AdMa, SUNRISE, MACRAMÉ, PLANETS	Expands SSbD principles to complex, multi-component, and functional advanced materials (AMI2030 context)
Policy & harmonization	EU Network for Safety and sustainability of Chemicals and materials (SPG), OECD WPMN, EC SSbD Platform, IRISS, PARC	Coordinates global strategy, harmonizes test guidelines, and facilitates dialogue between science and regulation

harmonization, and analysis of diverse datasets. A central component of this transformation is the "FAIRification" of data, ensuring that information is Findable, Accessible, Interoperable, and Reusable across platforms. Initiatives such as NanoCommons have established open and interoperable infrastructures for nanosafety data management, facilitating standardized data curation and reuse within the scientific community [179, 180]. Complementary projects, including NanoSolveIT [129] and NanoPharos [181], have developed advanced nanoinformatics platforms that integrate computational modeling, cloud-based simulation, and machine learning to predict NM behavior and hazard potential.

Further bridging experimental and computational domains, CompSafeNano focuses on the integration of nanoinformatics, predictive toxicology, and computational modeling to support the design of inherently safer NMs [182]. In parallel, cloud-based infrastructures such as the Enalos and EOS platforms provide scalable environments hosting modular web services for environmental fate, exposure, and bioaccumulation modeling. These tools are increasingly implemented through interoperable architectures using application programming interfaces (APIs), enabling seamless integration of heterogeneous data and models within unified SSbD workflows. Alignment with OECD frameworks and standardized reporting principles further enhances transparency, reproducibility, and regulatory acceptance. In addition to mechanistic modelling, analytics platforms such as the Isalos Analytics Platform support statistical analysis, machine learning, and multi-objective optimization, thereby helping users balance competing criteria such as environmental impact, performance, and safety in design-stage decision-making [183, 184]. Such capabilities are particularly relevant for SSbD, where optimal design solutions require balancing trade-offs across multiple objectives under uncertainty.

Beyond data integration and modeling, a key advancement lies in the development of decision-support systems that enable the practical application of SSbD principles [32, 185]. Platforms such as the ASINA Expert System incorporate lifecycle-based performance indicators into multi-criteria decision analysis frameworks, generating quantitative SSbD profiles for nano-enabled products [25, 186]. Similarly, the PARC SSbD toolbox provides a comprehensive, interoperable framework that links models, methods, data sources, and workflows across the innovation lifecycle, supporting trade-off analysis and user-guided decision-making [185, 187]. In addition, platforms such as Jaqpot operationalize computational models by transforming them into accessible, web-based services, enabling stakeholders to interact with predictive tools without requiring advanced programming expertise [187].

Collectively, these digital infrastructures form the backbone of integrated SSbD platforms, enabling the transition from data generation to predictive modeling and ultimately to design-oriented decision-making. These infrastructures primarily support the development and integration of SSbD tools, while their practical application in industrial decision-making is discussed in Sect. 4.

3.3.3 Advanced materials and policy networks

The implementation of SSbD extends beyond technical integration to encompass coordinated policy frameworks and collaborative networks that support large-scale adoption. As the field evolves from traditional NMs toward advanced material [188], new initiatives are emerging to address the increasing complexity of multi-component and functional materials systems. Projects such as SUNSHINE and MACRAMÉ exemplify this shift, developing strategies for safe and sustainable innovation within the broader European advanced materials ecosystem, including initiatives associated with IAM4EU and the Innovative Advanced Materials Initiative (IAM-I), often in collaboration with related projects such as Early4AdMa, SUNRISE, and PLANETS [189].

At the policy level, the Network for Safety and Sustainability of Chemicals and Materials (NSC, formally known as EU NanoSafety Cluster) plays a central role in coordinating research efforts and fostering collaboration across SSbD-related projects [9]. These efforts are complemented by international initiatives such as the OECD Working Party on Manufactured Nanomaterials (WPMN), which contributes to the harmonization of testing strategies and regulatory approaches for advanced material [190–192]. In addition, the EC's SSbD policy platform provides a structured framework for integrating safety and sustainability considerations into research and innovation processes, while national initiatives such as the UK Knowledge Sharing Network support the dissemination of best practices [5, 193–195].

More recently, dedicated SSbD ecosystems such as the IRISS platform have emerged to strengthen stakeholder engagement and facilitate knowledge exchange across academia, industry, and regulatory bodies. Together, these policies and network-based platforms enable the alignment of scientific, regulatory, and industrial perspectives, supporting the scaling of SSbD from individual projects to coordinated innovation ecosystems. Despite these advances, challenges remain in achieving global harmonization, ensuring interoperability across platforms, and aligning diverse stakeholder priorities, highlighting the need for continued collaboration and integrated governance. In the U.S., this network perspective is complemented by federal sustainable chemistry activities that frame R&D around standards and metrics,

data sharing and AI, LCA/modular design, alternatives, circularity, and novel hazard-assessment methods, with the 2024 strategic plan further linking discovery, commercialization, adoption, and federal-service capacity [196, 197].

Although these initiatives have substantially advanced the operationalization of SSbD by providing harmonized methodologies, decision-support tools, and collaborative platforms, their broader implementation remains limited. Most frameworks currently function as guidance for research and early-stage innovation rather than as standardized procedures routinely adopted by industry or required in regulatory decision-making. Key challenges include the lack of harmonized evaluation criteria, limited interoperability among data platforms, variable regulatory acceptance of NAMs, and difficulties in balancing safety, sustainability, functionality, and economic performance within a single decision framework. Addressing these challenges will be essential to facilitate wider industrial adoption and the integration of SSbD into future regulatory practice.

3.4 Mechanistic assessment as a driver of SSbD

From an SSbD perspective, safety assessment and material design should not be treated as sequential or disconnected activities, but rather as complementary components of the same iterative innovation workflow. In this context, mechanistic toxicology becomes particularly valuable when molecular and pathway-level responses can be linked back to physicochemical descriptors and translated into actionable design guidance. Recent studies in nanotoxicology provide proof-of-concept for this approach. For example, transcriptomics-based nano-QSAR models developed for MWCNTs have demonstrated that structural descriptors such as aspect ratio and specific surface area can be quantitatively associated with benchmark-dose responses of pathways related to acute inflammation, leukocyte recruitment, and acute phase signaling, which are mechanistically anchored to key events in AOPs for lung fibrosis and related pathologies [80, 198]. In parallel, large-scale toxicogenomic analyses have identified conserved molecular response programs across diverse nanoparticle exposures and explored their relationship with physicochemical properties, highlighting the importance of thermodynamic stability and ion release, which is specific to the nano dimension of the particles and does not overlap with bulk compounds [87]. This concept is reinforced by recent AOP-based grouping studies showing that induced mechanisms and potency are influenced by chemical composition, size-dependent properties, and other biological descriptors, thereby supporting the organization of nanomaterials into biologically and toxicologically meaningful classes [94]. Consistent with these developments, descriptor-based and transcriptomics-informed predictive frameworks have shown that engineered nanomaterials can be classified and prioritized even under conditions of limited experimental evidence, while also identifying recurrent mechanistic signatures related to metal homeostasis, oxidative stress, inflammation, fibrosis, and DNA damage [93]. Such approaches enable upstream prioritization, mechanistically informed interpretation, and targeted follow-up testing under uncertainty, effectively positioning safety assessment as a prospective decision-support function rather than a purely downstream screening step [93]. Furthermore, nano-QSAR and AI/ML models can use these descriptor–mechanism relationships to virtually screen and rank candidate nanoforms before synthesis, identify the descriptors driving the predicted response, and thereby prioritize redesign options that are expected to reduce activation of AOP-relevant pathways while maintaining functionality [80, 87, 94, 198–200]. Together, these findings indicate that once specific physicochemical features are associated with early key events or pathway activation, the same testing strategies can be used not only to identify hazard, but also to guide redesign by indicating which material attributes should be modified to reduce progression toward adverse outcomes while preserving functionality. In this sense, toxicogenomics, AOPs, descriptor-based modeling, PBK-informed dosimetry and predictive integration frameworks already provide the core methodological elements required for a closed-loop SSbD workflow, in which safety assessment informs material redesign and redesigned materials can be iteratively re-evaluated. While such an end-to-end loop has not yet been fully operationalized within a single unified framework, the necessary components are now in place for safety and design to proceed hand in hand, transforming assessment methods into design-enabling tools rather than solely downstream screening instruments [80, 87, 93, 94, 198, 201, 202]. PBK modeling complements this design loop by linking material properties and exposure scenarios to internal dosimetry, tissue distribution, and persistence, thereby testing whether candidate redesigns are also expected to reduce target-organ accumulation or overall internal burden [201, 202]. The inclusion of target organ is even more essential for those chemicals, such as nanomaterials, for which some of the most relevant descriptors are linked with their capacity of interacting with biological structures (e.g., cell membranes), indicating that the biological context of the exposure directly modulates the toxicity and the impact of the physicochemical characteristic [87]. More broadly, this logic is consistent with integrated virtual-screening strategies used in other innovation domains, where computational prioritization is employed to reduce candidate space before experimental validation; in SSbD, analogous approaches can support the prioritization of safer

material variants before synthesis, scale-up, or resource-intensive testing [199].

4 SSbD in practice: industrial innovation and implementation: commercial strategies, operationalization, and product-level application

While Sect. 3 outlined the scientific foundations, digital infrastructures, and assessment platforms that enable SSbD, its true value lies in its translation into real-world industrial practices. Across the nanotechnology value chain, SSbD is increasingly being operationalized as a framework that integrates safety, sustainability, and performance into decision-making processes at multiple levels—from material design to manufacturing, and ultimately to market adoption. This section highlights how SSbD principles are implemented across sectors, emphasizing their role in guiding innovation toward scalable and responsible applications. Key pathways for the industrial operationalization and practical implementation of SSbD across material value chains are illustrated in Fig. 4.

4.1 Material substitution and product redesign

SSbD is actively shaping innovation across diverse industrial sectors, where nanomaterials play a critical role in enabling advanced functionalities. In the electronics and consumer products, SSbD approaches often emphasize material substitution—replacing hazardous nanoscale materials with safer alternatives—and product redesign to eliminate or mitigate risks while maintaining performance. This proactive strategy is motivated by concerns associated with occupational exposure to toxic NMs during manufacturing and the persistent toxicity of certain substances in products (e.g., heavy metals that can accumulate in the environment). Case studies described below highlight how material substitution and design innovation in this sector reflect SSbD principles.

A hallmark of SSbD-driven substitution is the industry-wide shift to cadmium-free quantum dots (QDs) in commercial displays. Traditional II-VI compounds like Cadmium Selenide (CdSe) offer high color purity but carry significant toxicological and regulatory liabilities [203]. The motivation for substitution was to reduce potential health hazards for both consumers and manufacturing workers and comply with environmental

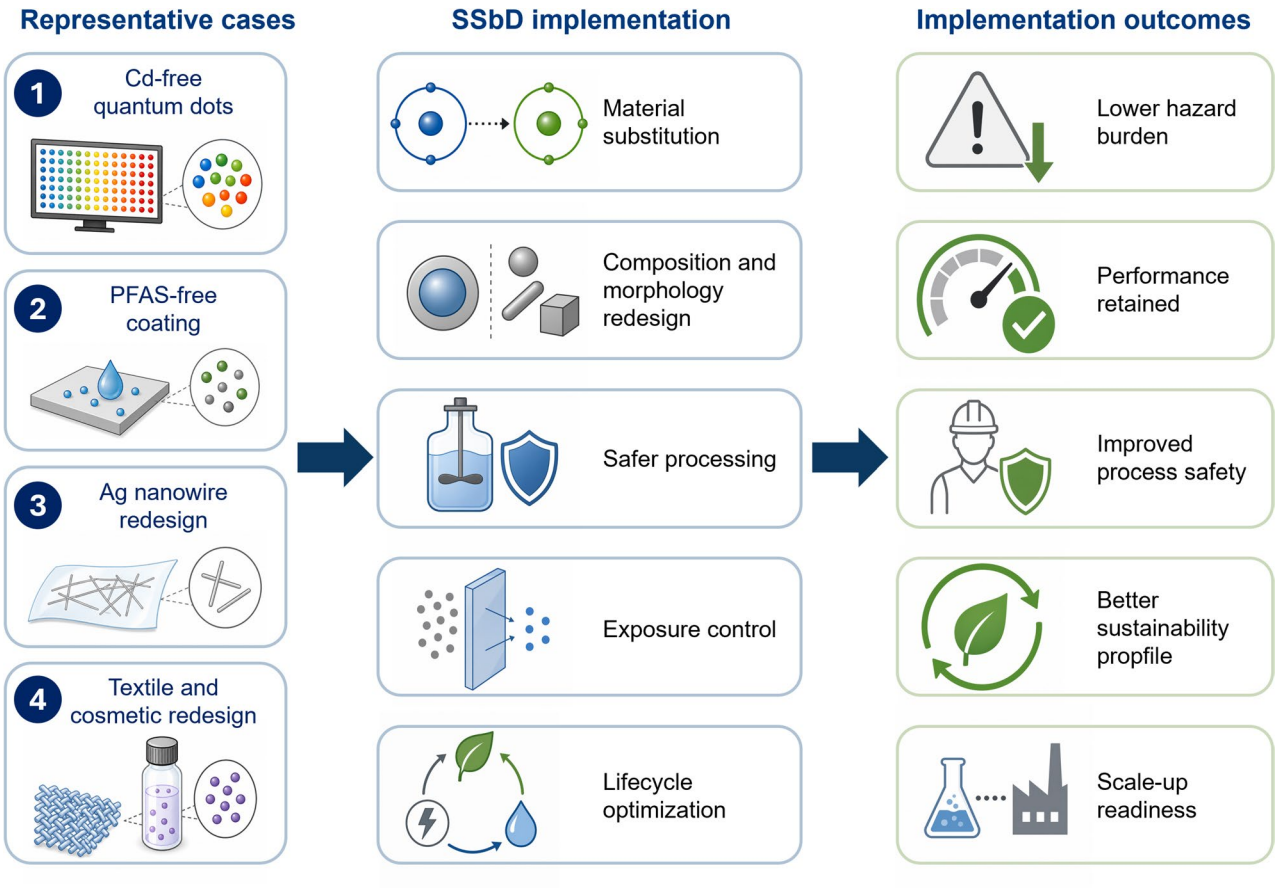


Fig. 4 Industrial operationalization and strategic implementation of SSbD in the nanotechnology value chain

regulations. Samsung and others pioneered the material redesign of quantum dots by using indium phosphide (InP)-based nanocrystals as a safer alternative to cadmium-based QDs [204]. Achieving comparable performance requires advanced surface engineering, including multi-shell InP/ZnSe/ZnS structures to enhance quantum yield and stability. This transition enabled the commercialization of high-performance Quantum Dot Light Emitting Diode (QLED) televisions that comply with the EU's RoHS directive, demonstrating that SSbD can catalyze market-leading innovation.

Comparable SSbD logic is increasingly visible in other nano-enabled consumer and industrial products. In antimicrobial textiles and nanocosmetics, the ASINA project demonstrated how product redesign can be guided by an SSbD Management Methodology that links Physical-Chemical Features (PCFs) and Key Decision Factors (KDFs) to Key Performance Indicators (KPIs), thereby enabling innovators to optimize functionality, occupational safety, and environmental impact simultaneously [25]. This approach is relevant for silver-based antimicrobial coatings and nanoencapsulated cosmetic formulations, where performance benefits must be balanced against worker exposure, release potential, and downstream environmental impacts. Rather than treating safety and sustainability as constraints assessed only after formulation, ASINA embeds them directly into the design logic of the product.

A similar strategy of material substitution and redesign has also been demonstrated for advanced coatings and flexible electronics. Within the SUNSHINE and SUNRISE context, multi-tier SSbD assessment frameworks were applied to advanced formulations, including a PFAS-free anti-sticking nanocomposite coating (SiC@TiO2) for the bakery industry, for which Social Life Cycle Assessment (S-LCA) indicated improved social sustainability performance compared to conventional Teflon-based alternatives [28]. In parallel, the DIAGONAL project showed that redesign of silver nanowires (AgNWs) for flexible electronics—through process modifications such as producing thinner wires and recycling acetone solvents—can reduce both immune cell toxicity and the overall environmental footprint while maintaining technological relevance [28]. These examples show that SSbD-driven product redesign often involves simultaneous adjustment of composition, morphology, and processing conditions, rather than simple one-to-one substitution.

Photocatalytic water splitting is considered one of the most promising long-term strategies for clean hydrogen production, and TiO_2 has become a benchmark photocatalyst because of its excellent chemical stability, low toxicity, and cost-effective synthesis [205, 206]. Cu-based modifications of TiO_2 highlight how performance enhancement can be pursued, while quantitative safety and sustainability evaluation remains indispensable for translation toward commercial viability under the SSbD framework [5, 207, 208].

Despite significant advances in nanomedicine, successful clinical translation remains challenging. Manufacturing reproducibility and scalable production are essential to ensure consistent physicochemical properties and product quality, while small variations in particle size, surface chemistry, or formulation may substantially alter biodistribution, therapeutic efficacy, and immunogenicity. In addition, long-term safety evaluation, including nanoparticle persistence, biodegradation, and repeated-dose effects, remains limited for many emerging nanomedicines. Regulatory approval also requires robust characterization, reproducible manufacturing processes, and comprehensive evidence of safety, quality, and clinical benefit. Within the SSbD framework, these challenges can be addressed by integrating safety assessment, quality-by-design principles, predictive modeling, and lifecycle considerations from the earliest stages of material development. Nevertheless, further standardization, validated predictive methodologies, and harmonized regulatory guidance are required to support broader clinical translation.

4.2 Process-level integration and risk management

For industrial stakeholders, integrating SSbD implies a shift from end-of-pipe risk management to intrinsic process safety. The NanoStreeM (Nanomaterials: Strategies for Safety Assessment in advanced Integrated Circuits Manufacturing) project - a consortium including Intel, Samsung, and IMEC-mapped NMs used throughout semiconductor fabrication [195, 203]. By identifying exposure hotspots in process steps like Chemical Mechanical Planarization (CMP), the project promoted "safe-by-design" engineering controls, such as sealed chambers and advanced filtration, ensuring the direct integration of worker safety into the fabrication protocols [209, 210]. While NanoStreeM represents an important model for exposure-aware process assessment, newer projects illustrate how SSbD can be embedded more directly into manufacturing decisions. HARMLESS extends the safety perspective by linking early warning logic to broader SSbD decision-making, thereby helping industrial actors recognize when performance gains are offset by unacceptable safety or sustainability burdens [28]. At the manufacturing stage, SABYDOMA moves even closer to intrinsic process safety by applying control engineering and online flow-through technologies to continuously screen and manufacture safer silver, CuO, and TiO_2 nanoparticles [211]. By embedding screening and control at the point of production, SABYDOMA shifts SSbD from a downstream compliance exercise

toward a production-centered strategy of prevention. Operationalizing SSbD on the factory floor adheres to the "Hierarchy of Controls," prioritizing elimination and substitution. However, when functional requirements mandate the use of hazardous NMs, strict engineering controls become the SSbD focal point. Automated handling systems and closed-loop reactors are increasingly designed to isolate the nanopowder from the operator environment. Recent emphasis is also placed on "Safety-by-Design for Process," where the synthesis method itself is modified (e.g., shifting from dry powder handling to liquid colloidal processing) to inherently reduce inhalation risks [212]. In this sense, process-integrated SSbD increasingly combines occupational hygiene, source control, stage-gate redesign, and real-time monitoring, so that risk management functions as a design variable rather than a post hoc corrective measure [28, 211].

To facilitate compliance for industries lacking extensive toxicological expertise, Control Banding (CB) tools like *Stoffenmanager Nano* and *NanoSafer* have become standard. These qualitative risk management tools group NMs into hazard bands based on available data, prescribing appropriate risk mitigation measures (RMMs). These models are crucial for bridging the gap between rigorous scientific assessment and practical, day-to-day safety management in industrial settings [213].

4.3 Digital infrastructure and decision-support systems

Digital infrastructures play a critical role in the industrial implementation of SSbD by enabling the integration of safety, sustainability, and performance considerations at early stages of the innovation process [32, 72, 214]. Rather than serving solely as analytical tools, these systems support practical decision-making workflows that guide material selection, design optimization, and development prioritization before costly synthesis and scale-up. In industrial settings, the combination of data-driven screening, predictive modeling, and NAMs allows companies to evaluate candidate materials through iterative go/no-go decisions [32, 206, 208, 215]. This integrated approach supports targeted data generation, reduces uncertainty, and enables the early identification of potential trade-offs between hazard, functionality, and lifecycle impacts. Such capabilities are particularly valuable for small and medium-sized enterprises, where resource constraints necessitate efficient prioritization and risk-informed design choices.

By linking experimental evidence, computational predictions, and lifecycle considerations within unified workflows, digital SSbD infrastructures facilitate a shift from sequential testing toward parallel and anticipatory evaluation strategies. In this context, digital systems function as decision-enabling frameworks that connect the technical capabilities described in Sect. 3 with the real-world implementation of SSbD in industrial environments.

A fundamental challenge in SSbD implementation is that design decisions rarely optimize a single objective. Improving safety may reduce material performance, environmentally preferable materials may increase manufacturing costs, and process modifications that enhance sustainability may affect scalability or product functionality. Consequently, SSbD should be viewed as a multi-objective decision-making framework that balances safety, sustainability, technical performance, manufacturability, and economic feasibility according to the intended application and lifecycle stage. Decision-support platforms and multi-criteria assessment tools therefore play an important role by making these trade-offs transparent, allowing stakeholders to identify solutions that achieve an appropriate balance rather than optimizing a single design objective.

4.4 Strategic enablers: policy, environmental, social, and governance (ESG) alignment, and market

The industrial adoption of SSbD is increasingly driven by a combination of market incentives, regulatory pressures, and evolving sustainability expectations. While SSbD provides a scientifically robust framework for integrating safety and sustainability into material design, its implementation is shaped by both enabling factors and structural barriers across the industrial landscape. SMEs, which constitute a significant portion of the nanotech innovation ecosystem, face distinct barriers in adopting SSbD. The primary hurdles include the high cost of toxicological testing and the "Data Gap" the lack of accessible, high-quality safety data for novel materials. Unlike multinational corporations, SMEs often lack in-house EHS (Environment, Health, and Safety) departments, making the complex, multi-criteria decision analysis required by SSbD frameworks resource-prohibitive [2].

Environmental, social, and governance (ESG) criteria have emerged as critical determinants of investment decisions in global capital markets [216]. Within this evolving context, the SSbD framework provides verifiable sustainability performance metrics directly aligned with the Environmental (E) and Social (S) pillars of ESG [217]. In the chemical and advanced NMs industries, proactive adoption of SSbD has become a major indicator of corporate resilience and long-term risk minimization [218]. Increasingly, green venture capital and institutional investors evaluate SSbD compliance as a proxy for assessing potential liabilities, including environmental remediation and health-related litigation [219]. Capital markets are now transitioning from traditional sustainability standards such as the Sustainability Accounting Standards Board (SASB) and Global Reporting Initiative (GRI) toward more material, science-based

performance indicators [220]. The Chemical Footprint Project, for instance, quantifies the total mass of hazardous substances used and emitted throughout a product's life cycle [219]. The chemical footprint reflects the intrinsic toxicity burden associated with a company's value chain [219]. SSbD complements this metric by offering a design-oriented approach that integrates LCA and promotes early substitution of hazardous substances [221]. Through these mechanisms, SSbD enables quantifiable reduction of chemical footprints and enhances transparency for investors seeking evidence-based sustainability credentials [10].

Global chemical, semiconductor, and consumer-facing companies are increasingly operationalizing SSbD and advanced chemical footprint management as core components of their business and valuation strategies [218]. BASF's "Sustainable Solution Steering" framework exemplifies this shift by systematically classifying and managing tens of thousands of product applications against sustainability criteria, enabling portfolio steering toward safer and more sustainable solutions and providing quantitative evidence of this transition in its public reporting to investors [222]. In parallel, SSbD concepts are being embedded in semiconductor and nanomanufacturing through process-level eco-design measures that minimize high-risk precursors and cleaning gases while integrating capture and abatement systems for process exhaust [223]. Ongoing technology developments further focus on substituting high-GWP fluorinated gases with lower-risk alternatives and optimizing process recipes, which has yielded documented double-digit reductions in fluorinated greenhouse gas and overall carbon footprints without compromising yield, thereby supporting net-zero strategies in energy-intensive fabs [224, 225]. In the consumer goods and retail sectors, initiatives such as Walmart's participation in chemical footprinting and its targets to reduce priority chemicals across its supply chain illustrate how data-driven chemical footprint reduction and transparent disclosure strengthen investor confidence, consumer trust, and long-term brand resilience [226]. Building on these developments, investor-led guidance such as IEHN's Safer Chemical Management Roadmap and related roadmaps for beauty and personal care brands promote comprehensive chemical inventories, disclosure of chemical footprints, and hazard-based substitution strategies for substances of concern such as PFAS, phthalates, and BPA, enabling companies to reduce liability and reputational risks while capturing growing demand for "clean" and low-toxicity product lines and thereby enhancing ESG performance and financial value [227]. The integrated application of SSbD and chemical footprint frameworks across the chemicals, semiconductor, and consumer goods sectors establishes SSbD as a systemic strategy for advancing both environmental toxicity reduction (E) and health equity (S) [217]. Beyond regulatory compliance, SSbD functions as a science-driven platform for sustainable innovation, supporting the co-creation of economic and societal value [217]. Through its alignment with investor expectations and policy-driven sustainability targets, SSbD is emerging as a cornerstone for industrial transformation toward green growth and responsible innovation [193].

To overcome market fragmentation, there is a growing trend towards standardized "Nano-labeling" and SSbD certification schemes. Future enablers include the development of harmonized ISO standards (e.g., via ISO/TC 229) that define clear pass/fail criteria for SSbD compliance. Furthermore, digital product passports, as mandated by the EU's Ecodesign for Sustainable Products Regulation, will likely require embedded SSbD data, ensuring transparency throughout the value chain and incentivizing early adoption [9]. At the pre-regulatory level, the Early4AdMa framework also points to an important future enabler by providing a tiered scoring system to identify potential human health, environmental, and sustainability concerns associated with advanced materials before formal regulatory requirements are fully defined [228]. Although such tools do not replace regulation, they strengthen anticipatory governance and help industry align innovation trajectories with future compliance expectations.

Although SSbD principles are broadly applicable across nanotechnology sectors, their implementation priorities differ considerably depending on the intended application. In nanomedicine, design is primarily driven by clinical safety, biocompatibility, therapeutic efficacy, and regulatory approval, while translation is often limited by stringent clinical validation requirements and lengthy approval processes. Agricultural applications place greater emphasis on environmental fate, long-term ecological impacts, and controlled release under field conditions, where uncertainty regarding environmental exposure and ecosystem effects remains a major challenge. In water treatment, durability, regeneration, contaminant removal efficiency, and prevention of secondary nanoparticle release are critical design considerations, but large-scale deployment is constrained by material recovery and lifecycle management. For energy applications, the main challenges involve balancing material performance, scalability, resource efficiency, and end-of-life sustainability while maintaining economic competitiveness. These differences indicate that successful SSbD implementation requires application-specific decision frameworks that account for distinct safety, performance, manufacturing, and regulatory requirements rather than relying on a universal assessment strategy.

5 Future perspectives, current challenges, and concluding remarks

The versatility of the SSbD framework allows its extension into cutting-edge nanotech sectors where safety and sustainability are critical for market acceptance. However, despite substantial progress in framework development and policy integration, the practical implementation of SSbD remains constrained by several scientific, technical, and systemic challenges. These limitations are particularly pronounced in nanotechnology, where complex nano–bio interactions, dynamic material transformations, and multi-scale effects complicate both hazard assessment and life cycle evaluation.

This section first outlines the key limitations of SSbD implementation and then explores its prospective applications in critical sectors, including energy systems, advanced nanomedicine, agriculture, water reclamation, and data-driven approaches. Together, these domains illustrate how SSbD is evolving from a conceptual framework into a core design paradigm for next-generation nanotechnology.

5.1 Future horizons: applying SSbD to emerging nanotechnology frontiers

5.1.1 Nanomedicine: biodegradable design for RNA therapeutics and targeted delivery

The scalability of next-generation nanomedicine critically depends on the integration of SSbD principles to ensure reproducible control of drug substance properties, structural integrity, physical stability, and biological safety [229]. This necessity is particularly apparent in mRNA-based therapeutics, where the safety and long-term biocompatibility of nanocarriers remain a focal point of global scrutiny [230]. mRNA is a large, negatively charged macromolecule highly susceptible to enzymatic degradation and unable to cross lipid membranes without assistance [231]. Lipid nanoparticles (LNPs) have thus emerged as indispensable delivery systems composed of ionizable cationic lipids, helper phospholipids (e.g., DSPC), cholesterol, and PEG-lipids [232].However, synthetic LNPs can still elicit cytotoxicity, systemic reactogenicity, and immunogenicity [233], and SSbD-oriented research increasingly focuses on molecular biodegradability to ensure safe in vivo clearance [234]. A promising strategy involves designing novel ionizable lipids incorporating biodegradable ester bonds in their hydrophobic tails [234]. These "safety-by-degradation" structures maintain stability during systemic circulation yet undergo controlled enzymatic hydrolysis into non-toxic metabolites post-delivery, preventing hepatic accumulation and inflammation [235]. Structural refinements using specific stereoisomers, cyclic disulfide linkages, or ortho-substituted hydrophobic moieties further enhance degradation kinetics and reduce bioaccumulation [236].

5.1.2 Smart agriculture: stimuli-responsive systems and ecotoxicity mitigation

The agri-food sector faces a dual challenge: increasing food production to meet global demand while mitigating environmental degradation and climate impacts caused by conventional agriculture [237]. Nanotechnology offers a powerful solution through precision agrochemicals and smart packaging systems but simultaneously raises concerns about ecotoxicity and environmental accumulation [238]. To reconcile these opposing outcomes, the SSbD framework guides the development of sustainable, low-risk NMs that ensure both agricultural efficiency and ecosystem safety [239]. Traditional pesticide formulations—such as emulsifiable concentrates or coarse suspensions—exhibit low target efficiency, as most active ingredients are lost through volatilization, runoff, or soil adsorption [240]. In contrast, SSbD-driven nanoformulations, including polymeric nanoparticles, solid lipid carriers, and bio-based nanoemulsions, enable controlled release and prolonged leaf adherence [241]. These systems reduce chemical loading and minimize off-target contamination, representing a paradigm shift toward sustainable crop protection [242]. Among emerging innovations, stimuli-responsive nanocapsules are particularly transformative [243, 244]. Engineered to respond to specific environmental or biological triggers—such as pH changes in pest guts—they release pesticides only at the intended site [245, 246]. For example, alginate- or chitosan-based capsules encapsulating avermectin remain stable on plant surfaces but degrade rapidly in an alkaline digestive environment, achieving high target specificity while preventing harm to pollinators and soil microbiota. Such designs exemplify SSbD's emphasis on functional selectivity and degradability [247–250]. Photo-responsive nanosystems provide further precision by releasing active molecules under specific light wavelengths [251]. These systems synchronize agrochemical release with crop cycles while relying on biodegradable polymers such as chitosan, starch, or ethylcellulose to ensure safe environmental assimilation and prevent microplastic accumulation [251].

5.1.3 Water reclamation: sustainable deployment of nanomaterials

Water reclamation is becoming an important application domain for SSbD nanotechnology because reuse systems must combine high treatment efficiency with tight control of secondary emissions. In advanced wastewater polishing and potable reuse systems, NMs are most promising when integrated into existing multi-barrier treatment trains rather than used as freely dispersed particles. Their main advantages include improved selectivity toward trace contaminants, enhanced catalytic and photocatalytic reactions, better membrane permeability

and antifouling performance, and strengthened disinfection barrier [240, 252]. Accordingly, the future relevance of NMs in water reclamation depends not only on removal efficiency, but also on their ability to provide stable, regenerable, and monitorable performance under realistic lifecycle-oriented SSbD conditions. Supporting this perspective, the MACRAMÉ project investigates graphene oxide (GO) filters as a real-life industrial use case to improve filtration performance while minimizing environmental impacts across the product lifecycle [176]. Among carbon-based NMs, graphene-family materials and carbon nanotubes are among the most mature candidates for water reclamation. GO membranes provide tunable nanoscale transport channels for selective separation and high water permeance [253], while functionalized graphene systems have demonstrated selective remediation of organophosphorus contaminants [254]. Carbon nanotubes additionally support electrochemical oxidation and antifouling applications, particularly in conductive membranes and catalytic coatings [249]. Non-carbon NMs further expand this technological landscape through selective adsorption and rapid redox chemistry. Metal-organic frameworks (MOFs) have shown strong performance for PFAS monitoring and removal [250, 255], while nanoscale zero-valent iron (nZVI) demonstrates high reductive reactivity toward toxic metals such as Cr(VI) [256]. TiO_2-based photocatalytic systems also remain promising for oxidation and microbial control, although their efficiency depends strongly on water chemistry and operational conditions [249]. The principal application opportunities and associated SSbD constraints for major NM classes are summarized in Table 3.

Despite these advantages, the ecotoxicological horizon of nano-enabled water reclamation extends beyond treatment performance alone. Potential exposure routes include membrane wear, spent sorbents, sludge, concentrates, and reclaimed-water reuse environments. Studies have shown that graphene behavior in aquatic systems depends strongly on aggregation, transformation, and adsorption processes [251], while aging processes can significantly alter the reactivity and toxicity of nZVI systems [258]. Evidence across aquatic organisms further indicates bioaccumulation, behavioral impairment, developmental toxicity, and ecotoxicological effects associated with both carbon-based and non-carbon NMs [259–263]. These findings emphasize that nano-enabled water treatment systems must be evaluated not only at manufacture, but also under environmentally realistic aging and transformation conditions. The major ecotoxicological concerns and associated SSbD implications are summarized in Table 4.

From an SSbD perspective, future development should prioritize containment, stability, recoverability, and lifecycle monitoring over maximum intrinsic reactivity. These favors immobilized and regenerable systems such as composite membranes, structured MOF sorbents, and catalytic units integrated with downstream polishing technologies capable of retaining released particles and transformation products. OECD guidance and ISO/TS 19590:2024 further highlight the importance of nano-specific hazard testing and particle characterization for credible safety assessment [264–266]. Overall, the future of NMs in water reclamation lies not in broader nanoparticle deployment itself, but in the smarter integration of nano-enabled functions into treatment systems whose environmental performance and long-term safety can be verified across the full lifecycle.

5.1.4 Next-generation energy systems: SSbD in conversion and storage materials

Renewable energy technologies increasingly depend on engineered nanomaterials that enable high-efficiency energy conversion and storage [258]. Applying SSbD to such nanomaterials requires jointly reducing intrinsic hazards and improving life-cycle sustainability [269].

Table 3 Main nanomaterial classes, opportunities, and SSbD constraints in water reclamation

Nanomaterial class	Main opportunity in water reclamation	Representative advantage	Main SSbD constraint
Graphene oxide / reduced graphene oxide	High-permeance membrane polishing	Tunable nanochannels; very high permeance and strong rejection in composite membranes [253]	Long-term stability, fouling resistance, and release control
Carbon nanotubes	Conductive and electroactive membrane interfaces	Fast transport pathways and support for electrochemical oxidation/disinfection	Chronic ecotoxicity, bioaccumulation, and wear-particle containment
MOFs	Selective capture of PFAS and trace organics	Very high selectivity; potential to combine quantitation and removal [250]	Powder-to-device shaping, aqueous stability, and metal/linker release
nZVI	Rapid reductive polishing of toxic metals	Extremely fast removal kinetics for Cr(VI) and related contaminants [257]	Aging, passivation, and transformation-dependent toxicity
TiO_2-based composites	Photocatalytic oxidation and disinfection	Enhanced bacterial inactivation and catalytic polishing, especially in hybrid systems	Matrix sensitivity, ROS-related effects, and by-product control
Modified nanoclays	Low-cost adsorption support	Potentially scalable mineral-derived adsorbents	Surface modification may increase ecological hazard

Table 4 Ecotoxicological horizons relevant to nano-enabled water reclamation

Ecotoxicological horizon	Relevance to reclamation	Illustrative evidence	SSbD implication
Aging and transformation	Released nanoforms may differ from pristine materials used in treatment units	GO transformation and nZVI aging alter reactivity and toxicity [258, 267]	Test aged and transformed forms, not only fresh materials
Primary producers	Algae and microbes may be exposed in receiving waters or reuse systems	MOF toxicity in *Chlamydomonas reinhardtii* [268]	Include primary-producer assays in screening
Aquatic invertebrates	Early food-web receptors of reclaimed-water residuals	Swimming impairment and stress in *Daphnia* exposed to CNMs [269]	Assess chronic and behavioral endpoints
Fish and higher trophic levels	Relevant for reuse-linked surface-water exposure and trophic transfer	CNT/nanofiber ecotoxicity trends in fish [270]	Extend safety assessment beyond standard acute tests
Material modification effects	Surface engineering may create new hazards	Modified nanoclays more toxic than natural nanoclays [271]	Treat functionalization as a new hazard-design step
Measurement uncertainty	Nano-release may be underestimated without validated analytics	Sample preparation strongly affects spICP-MS analysis [272]	Integrate validated particle monitoring into process verification

In solid-state batteries, nanostructured electrolytes and cathodes are being developed to deliver high performance while reducing reliance on scarce and toxic metals such as cobalt [270]. In green hydrogen production, intensive efforts are underway to replace costly, potentially hazardous PGM nanocatalysts with earth-abundant systems, including nickel–iron-based electrocatalysts [262]. The SSbD approach promotes a shift toward earth-abundant, low-toxicity catalyst systems, such as nickel–iron-based materials, so that the core building blocks of energy conversion are intrinsically safe [268]. To tackle energy-intensive synthesis and unproven recyclability in many next-generation nanostructures, the SSbD concept focuses on concrete design rules rather than generic circularity claims [271]. In perovskite solar cells, introducing selectively removable transport and contact layers can enable targeted recovery and recycling of toxic or scarce metals at end-of-life [273]. When such structural innovations are coupled with comprehensive LCA, functional performance can be maintained without sacrificing process-level sustainability [274].

5.2 Current knowledge gaps and methodological deficits

5.2.1 Current limitations of SSbD implementation

Although the conceptual alignment between SSbD and ESG frameworks is well recognized, a significant practical gap remains in corporate implementation [221]. Within the broad spectrum of ESG criteria, the management of chemical hazards and NM safety represents only a limited component [272]. At present, global corporate sustainability agendas and investor-driven priorities are predominantly focused on carbon emission reductions, Net-Zero targets, and climate change mitigation. Because carbon metrics are standardized, quantifiable, and highly visible, industries tend to allocate resources toward decarbonization initiatives [257]. In contrast, chemical safety assessments are inherently material-specific, complex to measure, and often embedded within lower-tier indicators of the environmental pillar [275]. Consequently, senior management frequently perceives the extensive research and innovation required for SSbD integration as a regulatory obligation rather than a strategic driver of ESG value creation [217]. This structural imbalance poses a major barrier to the proactive and widespread adoption of SSbD methodologies in industrial practice [1].

These limitations highlight a fundamental need for approaches that can provide mechanistic, scalable, and data-rich insights into nanomaterial safety. In this context, emerging omics-based and AI-assisted methodologies offer a promising pathway to overcome current bottlenecks and enable more predictive and design-oriented SSbD implementation.

Beyond organizational and policy-related challenges, several scientific and technical barriers continue to limit the widespread implementation of SSbD. Nanomaterial heterogeneity, including variations in size, morphology, surface chemistry, and impurity profiles, can result in substantial batch-to-batch variability, making reproducible safety assessment and quality control difficult. Furthermore, predicting long-term environmental and human health effects remains challenging because chronic exposure data and validated predictive models are still limited. Additional obstacles include incomplete and non-standardized datasets, limited interoperability across databases, and the lack of harmonized testing and reporting protocols, and divergence between the data needed for assessment in early innovation stages versus the availability of data in late innovation stages, which restrict the broader application of computational models and read-across approaches [276]. From an industrial perspective, translating laboratory-scale SSbD strategies into large-scale manufacturing while maintaining reproducibility, functionality, and cost-effectiveness remains a significant challenge. Addressing these scientific, technical, and regulatory barriers will be essential for the routine implementation of SSbD across research, industry, and regulatory practice.

5.2.2 Toward proteomics-integrated and AI-assisted mechanistic toxicology for SSbD

The limitations discussed in Sect. 5.2.1 highlight the need for more predictive and mechanistically grounded approaches for chemical safety assessment within SSbD. While toxicotranscriptomics has become an important tool in mechanistic nanotoxicology, transcriptomic data alone cannot fully capture cellular signaling, adaptation, or post-translational regulation, since mRNA abundance does not always reflect protein function [277]. Consequently, future SSbD-oriented toxicology will likely move toward integrated toxicoproteomics approaches capable of directly measuring intracellular stress signaling and early key events at single-cell resolution. Technologies such as mass cytometry already enable simultaneous quantification of multiple protein and signaling markers in heterogeneous cell populations [278], while recent studies demonstrate that proteomic and single-cell analyses can resolve nanomaterial-specific cellular responses and oxidative stress pathways relevant to hazard assessment [279–281]. These approaches may strengthen AOP development and improve mechanistic confidence in nanosafety assessment.

At the same time, artificial intelligence (AI) and LLM-based systems are emerging as important tools for automating mechanistic knowledge extraction from the rapidly expanding nanotoxicology literature. Recent pipelines have already demonstrated the ability to extract material descriptors, assay conditions, and toxicity outcomes from published studies. Future developments may extend this capability toward structured extraction of material–omics relationships linking nanomaterial properties, exposure conditions, and molecular pathway responses. Such approaches could support semi-automated AOP curation, mechanistic read-across, dynamic evidence updating, and knowledge graph construction, thereby transforming dispersed toxicological evidence into actionable SSbD design knowledge.

5.3 Concluding remark

SSbD represents a fundamental shift from reactive risk assessment toward proactive, mechanism-informed material design in nanotechnology. This review highlights how integrating scientific advances, policy frameworks, and industrial practices enables the early identification and mitigation of potential risks while maintaining functionality and performance. The convergence of mechanistic understanding, lifecycle thinking, and data-driven approaches provides a strong foundation for more predictive and reliable safety assessment.

Despite significant progress, key challenges remain, including the need for standardized methodologies, improved data integration, and stronger alignment between regulatory expectations and industrial implementation. Addressing these gaps will be essential to ensure the scalability and practical adoption of SSbD across sectors.

Overall, SSbD has the potential to become a central paradigm for responsible innovation, supporting the development of safer, more sustainable nanotechnologies while enhancing public trust and regulatory confidence in emerging materials.

Abbreviations

AOP	Adverse outcome pathway
AI	Artificial intelligence
ANSI	American national standards institute
ASINA	Anticipatory and sustainable innovation approach
ASTM	American society for testing and materials
CLP	Classification, labelling and packaging
CSS	Chemicals strategy for sustainability
DOE	Department of energy
EC	European commission
ECHA	European chemicals agency
ENM	Engineered nanomaterial
EPA	Environmental protection agency
ESG	Environmental, social, and governance
EU	European union
FDA	Food and drug administration
ISO	International organization for standardization
KDF	Key decision factor
KPI	Key performance indicator
LCA	Life cycle assessment
LLM	Large language model
ML	Machine learning
MoA	Mechanism of action
MOF	Metal–organic framework
NAM	New approach methodology
NIST	National institute of standards and technology
NMs	Nanomaterials
NSF	National science foundation
OECD	Organisation for economic co-operation and development
PCF	Physical-chemical feature
PFAS	Per- and polyfluoroalkyl substances
PGM	Platinum group metal
QD	Quantum dot
QLED	Quantum dot light emitting diode
R&D	Research and development
REACH	Registration, evaluation, authorisation and restriction of chemicals
RoHS	Restriction of hazardous substances
S-LCA	Social life cycle assessment
SEM	Scanning electron microscopy
SHAP	SHapley additive exPlanations
SSbD	Safe and sustainable by design
TEM	Transmission electron microscopy
TGx	Toxicogenomics
UNEP	United nations environment programme
US	United states
USDA	United states department of agriculture

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Data availability
No new datasets were generated or analyzed during the current study. All relevant information was obtained from previously published sources, which are appropriately cited in the manuscript.

Declarations

Competing interests
The authors declare that they have no competing interests.

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