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Methods and tools for the safety assessment part of the European Commission's safe and sustainable by design framework when applied to advanced materials

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ABSTRACT

The Safe and Sustainable-by-Design (SSbD) framework by the EC-JRC (European Commission – Joint Research Centre) provides a structured approach to integrate safety and sustainability considerations from the earliest stages of chemical and material innovation. However, applying SSbD principles to advanced materials poses specific challenges due to their complex and diverse physicochemical properties. This work analyzes and maps hazard, exposure, fate and risk assessment methods and tools applicable to Steps 1, 2 and 3 of the EC-JRC SSbD framework, categorizing them across its three tiers to address different stages of product development. The analysis highlights the challenges of adapting conventional testing and modelling approaches to advanced materials, particularly for hazard assessment, and considers the relevance and limitations of tools originally developed for exposure and risk assessment of engineered nanomaterials when applied to broader advanced materials categories. An assessment of operational status, access conditions, and tool formats provides practical insights for researchers and industry stakeholders. The study identifies key methodological gaps and offers recommendations to improve and expand the current tool landscape. By providing a structured mapping of available resources and challenges, this work supports the effective implementation of SSbD principles, promoting the safe and sustainable development of advanced materials.

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1. Introduction

The Safe and Sustainable-by-Design (SSbD) framework by the EC-JRC (European Commission – Joint Research Centre) represents a pivotal shift in chemical and material innovation, emphasizing the integration of safety and sustainability considerations from the earliest design stages (Caldeira et al., 2022; Abbate et al., 2024). Its implementation supports the goals of the European Green Deal and the Chemicals Strategy for Sustainability (CSS), steering innovation towards minimizing adverse environmental and health impacts while maximizing sustainability throughout the lifecycle of chemicals and materials (Abbate et al. 2025). To effectively implement the EC-JRC SSbD framework, it is essential for industry to be equipped with detailed insights into the potential safety and sustainability concerns along the lifecycle of their products. This understanding is critical for enabling any necessary modifications that ensure that products' technological functionality remains in the economically viable range while achieving improved safety and sustainability as compared to their conventional counterparts. Importantly, the EC-JRC SSbD framework is not intended for regulatory compliance but rather to support research and innovation by guiding the development of safer and more sustainable chemicals and materials from the earliest stages of innovation.

A distinctive feature of the EC-JRC SSbD framework is its organization into a four-step assessment, with an optional fifth step. These steps include Hazard assessment (Step 1), Safety aspects in chemical/material production and processing (Step 2), Safety aspects in the final application (Step 3), and Environmental sustainability assessment (Step 4), with an additional optional Socio-economic assessment (Step 5) (Abbate et al., 2024). The framework applies an iterative approach composed of three main levels (tiers) of the SSbD assessment (Abbate et al., 2024), to address different stages of product development and to facilitate the iterative refinement of data and assessments, ensuring that decision-making remains robust and proportionate to the complexity and potential impact of the product under evaluation. Tier 1 supports early-stage development by relying on low-data approaches such as literature reviews, *in silico* tools, and qualitative screening to identify knowledge gaps and potential areas of concern (i.e. hot-spots). Tier 2 involves more refined methods and incorporates iterative assessments that evolve alongside the progressive availability of data. Tier 3 includes advanced, data-intensive assessments, conducted when sufficient data and resources are accessible. By providing this systematic and adaptable framework, stakeholders are better equipped to meet the dual objectives of safety and sustainability in the design of chemicals and materials while keeping competitive products on the market (European Commission, 2025).

Advanced materials (AdMa) encompass a vast and diverse array of substances engineered to exhibit novel or enhanced properties (Schwirn et al., 2023). Their unique properties play a crucial role in modern technological advancements but can also present challenges related to their safety and sustainability assessments due to a lack of adapted testing methods (Bhat et al., 2025). Therefore, existing and emerging methodologies and tools to be included within the EC-JRC SSbD framework must be evaluated to ensure they effectively assess these materials by considering their distinct physicochemical and hazard characteristics. Such activities complement the current work performed by the JRC on the EC SSbD Framework, which currently focuses on standard chemicals and lacks relevant tools for advanced materials.

Long before the formalization of SSbD and the advanced materials concept, researchers, in collaboration with industry and other key stakeholders such as regulatory agencies, developed numerous methods and tools to assess safety and sustainability (Sudheshwar et al., 2024). These efforts initially focused on chemicals, but in recent years, increasing efforts have been made toward engineered nanomaterials (ENMs) due to their unique properties with respect to the corresponding bulk materials but also their unknown risks (Pomar-Portillo et al., 2021). Engineered nanomaterials, defined as materials designed for specific purpose or function with at least one dimension between 1 nm and 100 nm (International Standards Organization, 2023), were easier to categorize compared to the broader concept of advanced materials. While expanding assessments to a wider range of advanced materials is valuable, their diversity presents challenges for developing universally applicable tools. As a result, many of the methodologies discussed in this paper were originally designed for engineered nanomaterials.

Existing literature has extensively reviewed various of these methodologies and tools, but their structured integration within the EC-JRC SSbD framework remains underdeveloped. For instance, Arvidsson et al. (2016) focused on screening risk assessment methods for nanomaterials, identifying and evaluating 20 different approaches, with an emphasis on simplicity and applicability for early-stage assessments. Hristozov et al. (2016) provided a critical review of frameworks and tools for the risk assessment of manufactured nanomaterials, highlighting the need for a transition towards more quantitative, high-tier models and the lack of an integrated data infrastructure. Nowack (2017) evaluated environmental exposure models for engineered nanomaterials, stressing the necessity of validated fate models for regulatory acceptance. Jantunen et al. (2018) compiled an inventory of publicly available tools for nanomaterial safety assessment, forming the NANoREG Toolbox to support regulatory and industrial needs. Isigonis et al. (2019) identified and analysed risk governance frameworks of nanomaterials, considering their capacity to communicate, evaluate and mitigate their risks.

Sørensen et al. (2019) and Franken et al. (2020) both explored the applicability of risk assessment models within the Stage-Gate innovation process, focusing on environmental and human health risks, respectively. Both studies highlighted the need for adaptive tools that balance simplicity for early-stage screening with increasing complexity for later, data-intensive assessments. Suhendra et al. (2020) reviewed environmental fate models predicting the distribution of nanomaterials in surface waters, categorizing them based on their ability to capture nano-specific behaviour. Shandilya et al. (2023) introduced the Transparency, Reliability, Accessibility, Applicability and Completeness (TRAAC) framework to quantify the readiness of different tools and methods towards their wider regulatory acceptance and downstream use by different stakeholders, while Hristozov et al. (2016) demonstrated for the first time that the TRAAC is applicable also to testing New Approach Methodologies (NAMs). Sarigiannis et al. (2023) introduced a toolbox of tools and methods for SSbD of chemicals (PARC Project, 2025). Finally, Sudheshwar et al. (2024) analysed past Safe-by-Design (SbD) approaches to inform SSbD implementation, advocating for lifecycle thinking and high-throughput screening models to enhance operationalization. Building upon this, Cassee et al. (2024) outlined a roadmap for SSbD implementation for advanced materials, providing the NanoSafety Cluster's (NSC) perspective on regulatory harmonization, data standardization, and the need for cross-sector collaboration. Collectively, these studies illustrate the evolution of methodologies for assessing the safety and sustainability of advanced materials. However, despite the availability of numerous tools and assessment approaches, to the authors' knowledge this paper presents the first integrated mapping of methods providing a clear and systematic integration of these tools within the structured steps of the EC-JRC SSbD framework and their categorisation along the three main levels (tiers). A comprehensive integration of this kind has so far been missing, limiting their practical implementation. In addition, many earlier reviews are now outdated, as new tools have been developed and existing ones have been updated or are not available anymore.

The work presented in this paper specifically focuses on the safety dimension (Steps 1, 2, and 3) of the EC-JRC SSbD framework. The primary focus is on identifying, categorizing, and evaluating tools applicable for advanced materials that align with SSbD principles, ensuring their applicability across the different tiers within these specific steps of the framework. By doing so, this work aims to bridge the gap between theoretical constructs of assessment frameworks and their practical implementation in real-world scenarios.

In addition, significant emphasis has been placed on evaluating the accessibility of tools by evaluating their operational status (i.e., available or unavailable), analysing access conditions (e.g., free, subscription-based, or restricted access), and classifying their formats, such as web-based tools, Excel files, or programming scripts. Furthermore, based on the compiled information and the authors' expertise, this paper identifies gaps in current methodologies and proposes areas for further development.

2. Understanding safety assessment tiers and identifying relevant methods and tools

The EC-JRC SSbD framework employs a robust, iterative, and tiered methodology that adapts to the progressive stage of the innovation phase. It is important to note, however, that the tiers are not fixed categories but rather stages along a spectrum reflecting increasing confidence in the assessment, depending on data availability and quality, methodological robustness, supporting evidence, time required and the expertise needed to collect the data and interpret the results.

In Step 1, which focuses on characterisation and identification of hazards to human health and the environment, the tiered approach reflects increasing confidence in hazard predictions (Abbate et al., 2024). This increase in certainty often goes hand in hand with the type of studies used—ranging from *in silico* methods to *in vitro* and *in vivo* tests—but such associations are indicative rather than normative. The placement of a method within a specific tier depends not only on its complexity or resource demand, but also on its maturity and reliability for the material under investigation. For conventional chemicals, validated *in silico* tools may support Tier 1-level, whereas for advanced materials, the same tools may require more inputs and higher expertise, and be better suited to higher-tier assessments.

In Steps 2 and 3, the EC-JRC SSbD framework focuses on exposure and risk assessments. For exposure assessment, adapted from Schlüter et al. (2022), Tier 1 serves as screening-level tools, while Tier 2 and Tier 3 involve progressively higher levels of complexity of exposure modelling and monitoring (Schlüter et al., 2022). However, the criteria for complexity—whether in terms of data requirements, scientific expertise, or other factors—and the boundary between Tier 2 and Tier 3 remain open to interpretation. The EC-JRC SSbD framework also outlines a tiered approach to exposure assessment, based on experimental needs, encompassing exposure control banding tools, modelling, monitoring, and validated monitoring (Abbate et al., 2024). However, it does not explicitly assign these methods to specific tiers. As with hazard assessment, the placement of a method within a given tier ultimately depends on the level of certainty it provides and the context in which it is applied, rather than on the method itself. In the case of risk assessment, the SSbD framework presents the tiered approach as a means to reflect the increasing certainty of the risk estimation, which builds upon both hazard characterisation and exposure assessment. While Tier 1 is often associated with qualitative or conservative screening-level evaluations, requiring minimal data and applying precautionary assumptions, Tier 2 tends to involve semi-quantitative approaches that integrate more specific input data and user expertise for a more refined modelling. Tier 3 typically includes quantitative risk assessments, based on detailed datasets and advanced methods, and is generally carried out by experienced professionals. Importantly, these tiers do not rigidly classify risk assessment methods but rather illustrate how the tiered structure enables a transition from precautionary screening approaches to more substantiated and quantitative evaluations along the innovation stage of the product.

The concepts of Technology Readiness Level (TRL) and the Stage-Gate approach are well-established methodologies for managing the development and commercialization of technologies (Héder, 2017; Franken et al., 2020). TRLs provides a systematic framework for evaluating the maturity of a technology, progressing from TRL 1, where basic principles are observed, to TRL 9, where the technology is fully operational in a real-world environment (Olechowski et al., 2015). Complementing this, the Stage-Gate approach involves the innovation process divided into distinct stages, each concluding with a decision point (gate). At these gates, the project is evaluated against predefined criteria, and a decision is made to either proceed, pause, adjust, or terminate the product development process (Franken et al., 2020; Sørensen et al., 2019). The SSbD framework's tiered structure aligns with these concepts by evolving with the maturity of the innovation and the availability of data. Tier 1 methods, such as qualitative approaches (e.g. questionnaires) and *in silico* tools for hazard assessment, correspond to early TRLs and initial stages in the Stage-Gate process, where data is limited, and quick, cost-effective assessments are prioritized. As development advances, Tier 2 and Tier 3 methods, involving *more demanding resources*, align with higher TRLs and later stages in the Stage-Gate process, providing more comprehensive and detailed evaluations.

Fig. 1 adapts and builds upon the conceptual framework outlined by the JRC to illustrate the relationship between the SSbD framework's tiered methodology, Technology Readiness Levels (TRLs), and Steps 1–2-3. As shown in Fig. 1, the transition between Tiers is gradual, and overlaps often occur. For example, complex environmental exposure Tier 2 tools could be classified as simple Tier 3 tools and vice versa. It is important to note that certain tools can span multiple tiers, not only due to intermediate complexity among tiers, but also because their performance varies with the amount of available data. Such tools can adapt to different levels of complexity, providing outputs that range from qualitative to semi-quantitative to fully quantitative depending on the input data, further blurring the lines between tiers allocation of tools. This flexibility highlights the importance of understanding tool adaptability within the EC-JRC SSbD framework, ensuring appropriate application across varying stages of development.

In this paper, the identification and classification of tools and methods for advanced materials were guided by a pragmatic approach, leveraging the collective expertise of the authors and an extensive review of the available literature. Given the evolving nature of the EC-JRC SSbD framework and its application to advanced materials, this process focused on capturing tools that are currently relevant and applicable to the framework's tiered structure and stages of development. In addition to this expert-based evaluation, several existing reviews published between 2016 and 2024, which compiled tools, were also examined (Arvidsson et al., 2016; D. Hristozov, Gottardo, et al., 2016; Nowack, 2017; Sørensen et al., 2019; Franken et al., 2020; Suhendra et al., 2020;

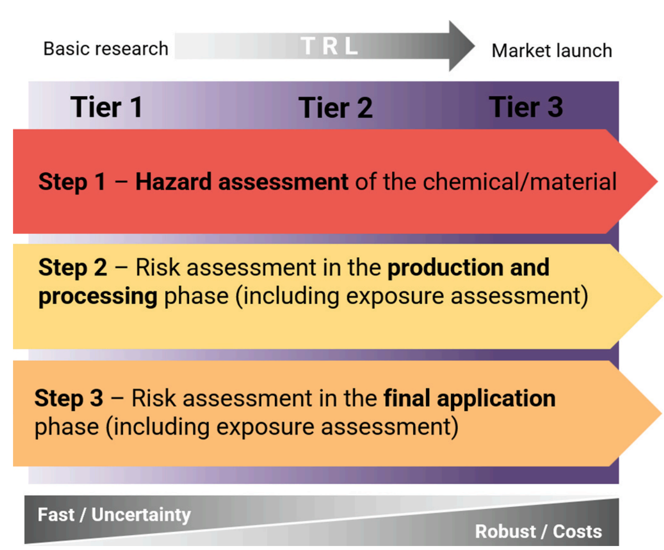

Fig. 1. Schematic representation of the relationship between the EC-JRC SSbD framework's tiered methodology in Steps 1–2-3, Technology Readiness Levels (TRLs), and risk assessment stages.

Shandilya et al., 2023; Sudheshwar et al., 2024). The tools identified through this literature review were then filtered, with exclusions made for those that were not specific to advanced materials, described only at a conceptual or methodological level without any accessible implementation (i.e. web-based platform, Excel file, or script), or that did not primarily focus on exposure, fate, and risk assessment. The authors, many of whom have long-standing experience in the field, provided critical insights into the evaluation of tools and methodologies. Their diverse backgrounds – spanning hazard assessment, exposure modelling/monitoring, risk assessment and management – aims to provide a comprehensive and balanced analysis.

3. Tools and methods for hazard assessment (step 1)

Step 1 of the EC-JRC SSbD framework focuses on identifying intrinsic hazards of chemicals and materials in pristine form. These properties provide the foundational data needed for hazard classification under the CLP Regulation (Regulation (EC) No 1272/2008), which includes three main hazard classes: human health, environmental, and physical hazards. While the CLP Regulation itself classifies hazards via specific hazard statements (H-phrases), the SSbD framework organizes hazard properties into three broad criteria groups (H1–H3) as a simplified means of guiding the assessment process.

Hazard assessment (Step 1) follows a tiered strategy that evolves from early data gathering and screening to more complex evaluations. This typically includes gathering existing data from literature and databases, applying *in silico* tools and qualitative assessments (commonly associated with Tier 1), followed by the use of simple *in vitro* assays and further computational methods (generally associated with Tier 2), and ultimately more complex *in vitro* systems and *in vivo* studies (commonly linked to Tier 3). In this section, tools and methods are classified by *in silico*, *in vitro* and *in vivo* for simplification.

The particular physicochemical properties that advanced materials possess constitute a challenge for their (eco)toxicological evaluation due to the ability of these materials to interfere with conventional toxicity assay systems, which is a critical point that can lead to results misinterpretation and data discrepancies. Several studies have emphasized the need to evaluate interferences between advanced materials and the assay during study design (Kroll et al., 2012; Andraos et al., 2020; El Yamani et al., 2024). Interference risk is often dose-dependent, with higher concentrations (e.g., those used in LD50 assays) more likely to induce artefacts than environmentally relevant levels (which present lower concentrations) (MacCormack et al., 2021). In addition, ensuring proper dispersion of the material is critical, for this reason standardized dispersion protocols are essential to ensure reproducibility and comparability in toxicological testing of advanced materials (Brunelli et al., 2024).

Certain assay endpoints are directly affected by the presence of advanced materials. They may interfere with fluorescence-based measurements due to light absorption or autofluorescence. Another challenge is that they may also agglomerate and sediment, leading to heterogeneous exposure and discrepancies between nominal and actual concentrations. These materials can also form heteroagglomerates with test organisms, altering bioavailability or causing mechanical effects such as immobilisation (e.g. in Daphnia), potentially leading to over- or underestimations of their toxicity. Moreover, advanced materials may undergo transformations or dissolution during testing, and insufficient or inconsistent physicochemical characterisation can compromise the reliability and comparability of results.

Importantly, the applicability of standard tests cannot be generalised across all types of advanced materials. Some methods may be suitable for certain materials but not for others, depending on their specific properties and behavior. For these reasons, several standard test guidelines may be inadequate for advanced materials, as they were developed for soluble chemicals and may not account for particle-specific effects. These limitations are summarised in Fig. 2. For developers, such constraints might have tangible consequences since compared with conventional chemicals, hazard assessment for advanced materials can be more resource-intensive, as additional controls, adapted protocols, and confirmatory tests are often required to account for interferences and ensure reliable results.

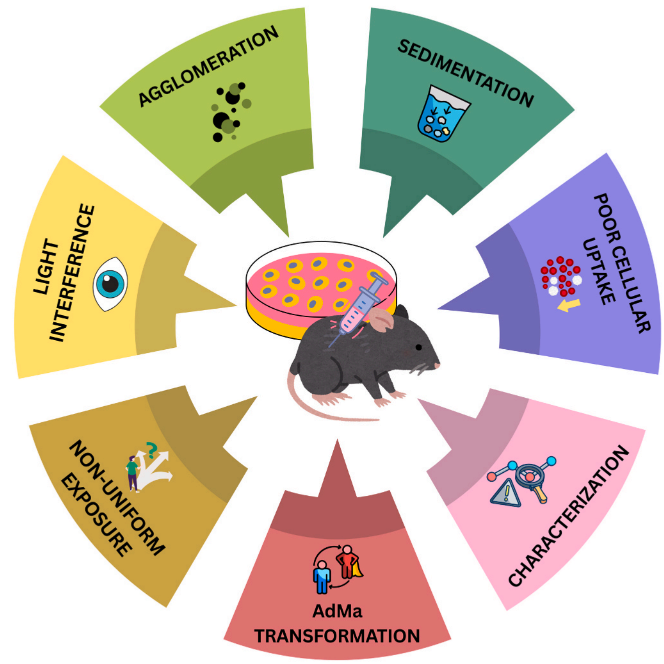

Fig. 2. Key experimental challenges in the hazard assessment of advanced materials.

To address these challenges, international bodies have worked to adapt test guidelines and protocols. The OECD Working Party on Manufactured Nanomaterials (WPMN) has led the development of guidance tailored to nanomaterials, including sample preparation, dispersion stability, and dosimetry (OECD, 2009a). The OECD's ongoing work under the Steering Group on Advanced Materials (SG AdMa) extends this effort to broader material classes (OECD, 2023a). Adaptations include dosing and metrics to account for different exposure routes (e.g. Guidance on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials) (OECD, 2012), dispersion protocols (OECD, 2020), genotoxicity through the publication of a guidance for *in vitro* micronucleus test (OECD, 2022), and fate of nanomaterials in soils through OECD TG No. 312 (OECD, 2004). Test methods are also being evaluated for their suitability based on the physico-chemical characteristics (e.g. hydrophobicity) and as well as the mode of action, which may be different to that of standard chemicals (Wareing et al., 2024). Besides the OECD, other international organisations such as the International Organisation for Standardisation (ISO) and its ISO Technical Committee ISO/TC 229 have been devoted since 2005 to the development of standards to account for terminology, characterisation and health and safety issues both to human and the environment with a focus on nanomaterials. The European Project Graphene Flagship has also dedicated intense resources to the development/adaptation of testing approaches for graphene and other 2D materials under Working Group 4 (Graphene Flagship WG4, 2025) and the Safegraph Project (Graphene Flagship — SafeGraph. (2025).).

3.1. *In silico methods and tools for Step 1*

In an early stage of innovation, the available information on AdMa hazards is often highly limited. To fill this gap, external data sources become critical. These sources, in the form of databases, allow users to gather existing information to inform hazard assessments without the need for complex, resource-intensive testing. Multiple databases for chemicals exist such as the ECHA database, PubChem or CompTox Chemicals Dashboard. However, these databases do not capture the unique properties of some advanced materials. Specialized databases, although not so extensive, offer significant value for that purpose. A list of relevant databases for advanced materials is presented in Table 1. For instance, eNanoMapper is a dedicated repository that emerged from the eNanoMapper European Union (EU) project and has been further enriched through initiatives such as GRACIOUS, NanoReg2 and RiskGONE (Jeliazkova et al., 2015; Giusti et al., 2019; Stone et al., 2020). It compiles comprehensive data on nanomaterials, including physicochemical properties, ecotoxicological profiles, and exposure information. The project SUNSHINE developed an alternative database for advanced materials, which is specifically tailored for use with *in silico* modelling tools and decision support systems. This database is available as a stand-alone tool but is interoperable with other databases such as eNanoMapper and NanoPharos, facilitating cross-platform data exchange.

Similarly, the Nanomaterials Information and Knowledge Centre (NIKC) aggregates experimental data on material properties, toxicology, and environmental fate, supporting applications such as read-across and grouping strategies (Amos et al., 2021). Another noteworthy resource is the NanoCommons platform, which offers a harmonized infrastructure, integrating data from multiple nanosafety projects and providing interoperability for databases, models, and tools used in risk assessment and safe-by-design material development (Maier et al., 2023).

When direct data for a material are unavailable, *in silico* methods are used to generate predictions. Tools based on Quantitative Structure–Activity Relationships (QSARs) and Quantitative Structure–Property Relationships (QSPRs) are particularly relevant. These computational methods establish mathematical correlations between the molecular structure of a substance and its biological activity or physicochemical properties, respectively (Roy et al., 2015). While these models have been primarily developed and applied for conventional chemicals, progress has been made in adapting them to account for the specific behaviour of advanced materials (Moncho et al., 2024; Singh et al., 2024; Zhou et al., 2024). In particular, platforms such as NanoSolveIT, the Enalos Cloud platform and NanoInformaTIX provide access to predictive QSAR and QSPR models and curated datasets, primarily tailored to nanomaterials. These platforms are discussed in more detail in section 5. In parallel to such data-driven approaches, physics-based simulations provide complementary insights into material behaviour. Density Functional Theory (DFT) adds predictive power at the quantum level, allowing insights into electronic properties, surface reactivity, and thermodynamic stability, making it valuable for assessing multicomponent systems and complex advanced materials (Jones, 2015). Atomistic Molecular Simulations (AMS), including molecular dynamics (MD) and Monte Carlo (MC) methods, complement DFT by modelling the dynamics of molecular and material systems over time. Moreover, AMS extend the capability to study significantly larger and more complex systems — such as biological macromolecules, nanomaterials, and interfaces — that would be computationally prohibitive to address with DFT alone (Frenkel & Smit, 2023). While not QSARs or QSPRs themselves, such simulations can generate descriptors and mechanistic understanding that serve as valuable input for the development of predictive models.

The role of *in silico* tools in Tier 1 is further enhanced by their integration with comprehensive data repositories as the ones previously mentioned. These resources also allow for the application of read-across methodologies, where data from structurally or chemically similar substances can be extrapolated to untested materials, filling critical data gaps efficiently (Patlewicz et al., 2013; Soares et al., 2022).

Table 1
Overview of databases relevant to advance materials.

DATABASES	DESCRIPTION	LINK	REFERENCE
eNanoMapper	Public database hosting nanomaterials characterization data and biological and toxicological information	https://data.enanomapper.net/	(Jeliazkova et al., 2015)
NanoCommons	Harmonized infrastructure, integrating data from multiple nanosafety projects and providing interoperability for databases, models, and tools used in risk assessment and safe-by-design material development	https://www.nanocommons.eu/nanocommons-knowledge-base/	(Maier et al., 2023)
NanoPharos	Curated nanomaterial database supporting QSAR/QSPR modelling, grouping, read-across, and FAIR data integration within platforms like NanoCommons	https://db.nanopharos.eu/	(Papadiamantis et al., 2020)
NIKC	Aggregates experimental data on nanomaterial properties, toxicology, and environmental fate to support read-across, grouping, and risk assessment	https://nikc.egr.duke.edu/	(Amos et al., 2021)
Sunshine Database	For advanced materials and specifically tailored for use with *in silico* modelling tools and decision support systems. It is interoperable with other databases	https://www.sunshine.greendecision.eu/	(Livieri et al., 2025)

3.2. *In vitro* methods and tools for Step 1

This section describes relevant *in vitro* methodologies, including cellular and acellular methods, which enable the generation of material-specific data to support decision-making on human and environmental hazards by providing detailed mechanistic insights into toxicity. When aligned with guidelines and protocols from institutions like OECD and ISO, these methods ensure scientific robustness and regulatory compliance.

The applicability of testing guidelines to nanomaterials was already the focus of an OECD publication which includes an extensive review on the limitations of *in vitro* testing (OECD, 2009b). Further on, extensive work and resources have been devoted to identify *in vitro* relevant tests, and challenges that exist in their use, for assessing hazards of engineered nanomaterials and nano-enabled products in particular (Ruijter et al., 2023), or chemicals in general (Carramusa et al., 2024), but also for specific sectors (Usmani et al., 2024), or for specific biological endpoints (Snapkow et al., 2024; Gutleb et al., 2025). It is not the focus of this paper to present them in detail, rather, we aim to show here which key tests have shown applicability to advanced materials and what are the challenges, paying special attention to New Approach Methodologies (NAMs). According to ECHA, NAMs can be defined as any technology, methodology, approach, or combination that can provide information on chemical hazard and risk assessment avoiding the use of animals (ECHA, 2016), including *in silico, in chemico* and *in vitro* methods. In addition to supporting the 3R principles of replacing, reducing, and refining the use of animals in testing and research, the aim of NAMs is to improve the speed and reduce the associated costs of toxicological data generation for regulatory approval of advanced materials (Hristozov et al., 2016). However, while NAMs offer significant promise for accelerating hazard assessment and reducing animal testing, their regulatory acceptance remains limited. For many complex and chronic endpoints, Tier 3 *in vivo* studies are still considered the accepted standard, creating a substantial data and validation gap. Bridging this gap requires systematic efforts to validate NAMs, develop standardized protocols, and demonstrate their predictive reliability for advanced materials.

3.2.1. Human hazard assessment

In vitro cytotoxicity testing is central to hazard screening, and has been reviewed in the context of nanomaterials and nano-enabled products (Ruijter et al., 2023). However, there are inconsistencies in how reliable cytotoxicity testing is when considering *in vivo* effects, which may be dependent on the model used as well as the Mode of Action (MoA) that the material has induced (Ruijter et al., 2023). Given the complexity of advanced materials and the potential for complex mechanistic responses, the use of cytotoxicity tests should be targeted and with a clear purpose. Oxidative stress, a critical early marker of toxicity, can be predicted with measurements of reactive oxygen species (ROS) generation, which have recently been tested and optimized for use with nanomaterials and nano-enabled products, both for acellular (Boyles et al., 2022; Ruijter, Boyles, et al., 2024) and cellular (Ruijter, van der Zee, et al., 2024) ROS production, and compared to measurements of oxidative stress (Seleci et al., 2022). In all cases, however, there is a need to consider material complexity and having an approach that allows discernment of specific components driving toxicity that will be important for advanced materials. This has previously been done in the context of solubility and how to discern soluble and particle components in reactivity assessment (Peijnenburg et al., 2020), which is an approach that could be adapted for determining hazardous components of advanced materials. These methods help elucidate cellular damage mechanisms, providing a foundation for understanding downstream toxicological outcomes. For example, inflammatory and genotoxic responses are also commonly assessed via ELISA and DNA damage assays. These endpoints support mode-of-action analysis and are particularly relevant for nano-enabled materials (Rodríguez-Garraus et al., 2025). Further examples of assays frequently applied to nanomaterials include colorimetric and fluorometric cytotoxicity tests such as the Alamar Blue assay (Longhin et al., 2022), as well as label-free impedance-based measurements that allow real-time monitoring of cellular responses while avoiding potential interferences associated with dyes (Ostermann et al., 2020).

Genotoxicity and mutagenicity are generally assessed first through a battery of *in vitro* tests, which have been evaluated and adapted for nanomaterials, to ensure cellular uptake (Mu et al., 2012). The Bacterial Reverse Mutation Test (OECD TG 471, Ames) is not recommended for nanomaterials for this reason, since these are not able to cross the thick bacterial wall. On the same line, the OECD TG 478 *In vitro* Mammalian cell gene mutation test may only be used if cellular uptake has been demonstrated. Therefore, the OECD TG 487 *In vitro* Micronucleus Test (MNT) is considered the most suitable and adaptable for nanomaterials, especially when adapted with appropriate sample preparation and exposure protocols. It detects chromosomal damage in cultured mammalian cells and can account for genotoxic mechanisms relevant to advanced materials. Comprehensive overviews of the range of available assays and their applicability to nanomaterials are provided by Doak et al. (2023) and Bleeker et al. (2023), both of which highlight advances and ongoing challenges in ensuring reliability and regulatory relevance.

Beyond simple 2D *in vitro* models more complex 3D co-culture models exist for most organs such as Air-Liquid Interface (ALI) models for various regions of the lung (García-Salvador et al., 2021), which have recently been further advanced, with attempts to standardize their use for nanomaterial testing to improve physiological relevance (Elje et al., 2024), reconstructed human epidermal (RhE) models for the skin (McLean, Marshall, et al., 2024), gastrointestinal tricultures for the gut (Guo et al., 2019; Cao et al., 2021), hepatic spheroids for the liver (Li et al., 2020; Hurrell et al., 2020), etc. These more advanced *in vitro* models offer more representative animal-free alternatives to simple 2D *in vitro* models and due to their higher complexity, would generally align with Tier 3 of the EC-JRC SSbD framework. However, their regulatory applicability remains limited, with the exception being the RhE models of the dermal barrier (TG 431 and 439) and the human cornea-like epithelium models of the eye (TG 492). Additional endpoints such as sensitization, carcinogenicity, mutagenicity, genotoxicity, and endocrine disruption can be assessed via non-animal NAMs and OECD approved *in vitro* methods, providing key information on the MoAs of material being studied. Emerging *in vitro* methods are extending to chronic endpoints to assess persistent exposure providing nuanced information regarding delayed toxicological responses.

In general, the OECD approved methods are not specific to advanced materials, therefore it is important to consider their specific issues when applying these methods. McLean et al. (2024b) assessed the suitability of RhE models for SbD decision making and highlighted the importance of not diverging from the OECD guidance on exposure concentration when using these models for nanomaterials as this can significantly affect the classification of the material. Additional considerations for advanced materials include selecting an appropriate dispersion protocol particles and ensuring the dose applied to the testing system is delivered to the cells (Ruijter et al., 2023).

3.2.2. Environmental hazard assessment

3.2.2.1. Freshwater. Assessing the toxicity of advanced materials to freshwater organisms critically relies on *in vitro* assays. Rapid screening tools like Microtox (ISO 11348–3), which are typically applied as lower-tier approaches, provide sensitive indicators of acute toxicity across various water chemistry conditions. Acute toxicity on photosynthetic microorganisms is assessed using Microalgae Growth Inhibition Tests (OECD TG 201). To avoid fluorescence interference with advanced materials, alternative endpoints such as direct cell counts or chlorophyll extraction are recommended (Hund-Rinke et al., 2022).

Emerging approaches for environmental hazard assessment extend the utility of cell-based methods, such as the Fish Cell Line Test (OECD TG 249), which uses gill-derived cells from rainbow trout (*Oncorhynchus mykiss*) to simulate long-term exposures for up to 28 days. Although not yet validated for regulatory purposes, these assays represent an innovative, animal-free alternative to traditional whole-organism tests, aligning with the goals of the SSbD framework by reducing reliance on *in vivo* testing while maintaining predictive accuracy. Limitations to using this test are aligned with those previously reported in the human hazard section under *in vitro* cultures.

3.2.2.2. Seawater. Hazard assessments in seawater often adapt methods used in freshwater systems to the unique conditions of marine environments. For instance, the Microtox assay (ISO 11348–3) is effective in both saline and freshwater conditions, and the microalgae growth inhibition test (ISO 10253) is analogous to OECD TG 201 for freshwater. The Fish Cell Line Assay (OECD TG 249), used with gill-derived cells, remains applicable across aquatic systems, with modifications to account for marine-specific parameters. Furthermore, exclusive to marine environments, mussel-derived cell assays provide detailed insights into sub-lethal effects (Katsumiti et al., 2015, 2017, 2021). Mussel cells are particularly sensitive to contaminants, making them invaluable tools for understanding material behaviour in marine ecosystems (Katsumiti et al., 2019).

3.2.2.3. Soil. In the context of soil hazard assessment, the use of *in vitro* methods is less established. *In vitro* assays using earthworm coelomocytes are applied primarily in ecotoxicology to evaluate the cellular and subcellular effects of pollutants, including metals, pesticides, nanomaterials, and microplastics. These assays serve as an ethical, cost-effective alternative to whole-organism testing, allowing screening of environmental contaminants for immunotoxicity, genotoxicity, oxidative stress, and cytotoxicity. Unlike aquatic and human health assessments, soil evaluations still rely heavily on *in vivo* tests with full organisms like earthworms, enchytraeids, and collembolans. Therefore, those methods have been classified within Tier 3.

3.3. In vivo methods and tools for Step 1

In vivo experimental methods provide detailed insights into long-term and systemic effects, addressing complex endpoints which may require whole-organism data and even, in some instances, can be addressed by a battery of NAMs (Gomes et al., 2021). Currently, even if efforts are put forwards to developed NAMs to reproduce Adverse Outcome Pathways (AOPs), most regulatory endpoints to evaluate acute and chronic toxicity, reproductive and developmental hazards, and cumulative environmental impacts are based on *in vivo* approaches (Scott-Fordsmand et al., 2017; Scott-Fordsmand & Amorim, 2023). This section outlines key *in vivo* approaches for human and environmental hazard assessments available for advanced materials, aligned with internationally recognized guidelines and regulatory frameworks.

3.3.1. Human hazard assessment

Tier 3 recommends regulatory accepted methods, most of which are related to *in vivo* experimentation. In Europe, advanced materials, as chemicals, follow the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation (European Commission, 2006). REACH is tonnage driven and therefore registrants need to provide varying amounts of information (including human safety) depending on the annual tonnage being produced, which range from 1 to over 1000 tonnes/year, as indicated by REACH Annexes VII-X. Amendments were introduced in 2020 specifically addressed to nanomaterials, recognizing the need to adapt test guidelines, justify cellular uptake in certain assays, and emphasize the inhalation route as a key exposure pathway (European Commission, 2018).

For low-tonnage bands, endpoints such as skin/eye irritation, sensitisation and acute toxicity are required. Skin/eye irritation is generally performed *in vitro* (OECD TG 439, OECD TG 437, OECD TG 438, OECD TG 491), and tests have been shown to be applicable to advanced materials (Carlin et al., 2023). In contrast, *in vivo* alternatives like the Local Lymph Node Assay (OECD TG 429) or Acute Eye Irritation/Corrosion Test (OECD TG 405) are limited in their applicability to advanced materials due to issues of tissue permeability and appearance of mechanical effects rather than chemical toxicological ones. Skin sensitisation, required even at low tonnage, is preferentially addressed *in vitro* and can be performed through a series of NAMs which represent the full skin sensitisation AOP (OECD, 2021). Efforts on the adaptations of the different Key Events (KE) have been carried out in various EU projects (Gov4Nano Project, 2022; Lin et al., 2024), and the applicability of OECD TG 442D to different types of nanomaterials was reported in the update of this guideline (OECD, 2023c). However other KE of this approach may not be suitable for nanomaterials (Wareing et al., 2024). *In vivo* Genotoxicity Tests (OECD TGs 474, 475, and 488) may need to be used in case of inconclusive *in vitro* results, but should only be considered at high tonnage levels, or where confirmatory data on genotoxic effects following realistic exposure is required.

For acute and chronic toxicity, inhalation is deemed the most relevant exposure route. OECD TG 412 and TG 413 (28-day and 90-day inhalation studies) have been adapted for nanomaterials with guidance on aerosol generation, characterisation, and lung burden assessment. By contrast, the Acute Dermal Toxicity Test (OECD TG 402), developed for soluble chemicals, presents limitations for nanomaterials due to particle agglomeration and non-uniform exposure due to sedimentation or uneven skin contact. Proper dispersion and relevant dose metrics are critical and the European Chemicals Agency (ECHA) advises against dermal testing unless significant exposure or skin penetration is a key route of concern.

Toxicokinetics describes the absorption, distribution, metabolism, and excretion (ADME) of toxic substances, helping to understand their behaviour and potential health effects. In the particular case of advanced materials, the OECD has already published a document to assist in the design of *in vivo* biokinetic studies for nanomaterials (OECD, 2016). Adaptations were proposed to account for factors like agglomeration, dissolution, and interaction with biological components. However, key challenges persist, including detection in biological matrices (e.g. for carbon-based materials like graphene) and the selection of appropriate dose metrics reflective of realistic exposure.

Reproductive and developmental toxicity is a major area of focus, assessed through studies such as the Reproduction/Developmental Toxicity Screening Test (OECD TG 421) (OECD, 2015) and the Extended One-Generation Reproductive Toxicity Study (OECD TG 443) (OECD, 2025). However, both guidelines generally rely on oral administration, which may lead to false negative results if the nanomaterials are not absorbed through the intestinal track. Furthermore, both guidelines do not provide detailed characterisation of the test material in the dosing vehicle or biological matrix, such as agglomeration, dissolution, or surface transformations. Finally, they do not require direct measurement of internal dose (e.g., amount of nanomaterial in tissues), making it impossible to assess dose–response and interpret negative findings. Hence, to evaluate these endpoints it is important to first identify the route of exposure and perform a biokinetic study (as indicated in the above paragraph) (Hund-Rinke et al., 2016).

3.3.2. Environmental hazard assessment

3.3.2.1. Freshwater. In freshwater systems, *in vivo* experiments focus on the reproductive and developmental impacts of advanced materials on aquatic organisms. The *Daphnia Magna* Immobilization Test (OECD TG 202) is a standard acute assay but may yield artefactual results when advanced materials aggregate on the organisms' appendages, physically impairing movement. Therefore, it is essential to distinguish between physical and chemical modes of action (Baun et al., 2008). The fish Embryo Acute Toxicity Test (OECD TG 236) is a key tool for assessing developmental toxicity. These assays are indispensable for understanding disruptions along the aquatic food web, providing early warnings of ecosystem-level risks. Yet, besides the limitations previously mentioned for other guidelines, in this case the chorion (protective membrane) of fish embryos can act as a barrier, limiting the uptake of certain advanced materials and potentially leading to underestimated toxicity. Dechorionation (removal of the chorion) may enhance exposure but introduces variability and additional embryo stress (OECD, 2024).

Chronic toxicity studies, such as the Daphnia Reproduction Test (OECD TG 211) provide a sensitive indicator of long-term ecological health. The Fish Early-Life Stage Toxicity Test (OECD TG 210) evaluates both lethal and sub-lethal impacts on embryonic and larval stages, addressing critical periods of aquatic life. The OECD Test Guideline 203 outlines a method to assess the acute toxicity of chemicals to fish. In this test, fish are exposed to different concentrations of a substance for up to 96 h, and mortality is recorded at specified intervals with the objective to determine the LC50.

Beyond standard ecotoxicological tests, Species Sensitivity Distributions (SSDs) offer a broader perspective on the environmental hazards of advanced materials. SSD is a statistical approach used to model the variability in species sensitivity to a particular chemical or stressor (Garner et al., 2015). This method allows for a more comprehensive risk assessment by accounting for interspecies differences and improving the predictability of ecological impacts (Gottschalk & Nowack, 2013; Semenzin et al., 2015). While SSDs are widely used in freshwater ecotoxicology, they are also applicable to other environmental compartments such as oceans and soils.

3.3.2.2. Seawater. Seawater *in vivo* assessments encompass both acute and chronic responses of marine organisms. The ISO/TS 20787:2017 method using *Artemia nauplii* provides a standardized short-term assay (24–48 h) for consistent nanomaterial testing in artificial seawater and is applicable to a wide range of nanomaterials. Mussels, widely regarded as bioindicators due to their sessile nature and continuous exposure to surrounding waters, play a pivotal role in chronic toxicity studies, emphasizing the sensitivity of marine organisms to long-term exposure. These assays focus on sub-lethal endpoints, such as impaired growth, reproduction, metabolic alterations, and oxidative stress, to assess the cumulative effects of pollutants, including nanomaterials and microplastics. Molecular and biochemical biomarkers, such as enzyme activity and DNA damage, are integrated to unravel the mechanisms of toxicity. Similar to freshwater testing, efforts to characterize the materials in ecotoxicological media are of critical importance to enable a standardized ecological hazard assessment (Brunelli et al., 2024).

3.3.2.3. Soil. Soil ecosystems are assessed through methods that evaluate both acute and reproductive effects on terrestrial organisms. The Earthworm Acute Toxicity Test (OECD TG 207) evaluates short-term lethality in *Eisenia fetida* or *Eisenia andrei* after 14-day exposure (with LC50 as the main outcome). For long-term effects, the Earthworm Reproduction Test (OECD TG 222) assesses survival, growth, and reproduction (i.e. number of offspring) over 56 days. The test provides data on the sub-lethal effects of substances, helping to assess the potential risk of chemicals to soil-dwelling organisms. The Collembolan Reproduction Test (OECD TG 232) extends assessment to springtails, providing sensitive measures of survival, growth and reproduction under chemical stress. These tests provide sensitive endpoints for both water-soluble and insoluble substances, supporting a comprehensive evaluation of soil health over four to eight weeks. Depending on the usage and classification of the material the test used may differ.

4. Tools and methods in the chemical/material production and processing (step 2) and final application phase (step 3)

The hazard component of the safety assessment is covered by Step 1 in the SSbD framework, while the overall safety aspects arising from

Table 2
Step 2 and 3 tools accessibility indicating the readiness, cost, platform, last update and link. Colour codes have been established for each parameter ranging from green, yellow and red to indicate more to less optimum accessibility, respectively.

TOOL	READINESS	COST	PLATFORM	LAST UPDATE	LINK
AdMaCat	Not yet available	-	-	Jul-24	-
ANSES CB	Unavailable	-	-	Jan-2013	-
CB Nanotool 2.0	Available	Free	Excel file	2021	https://controlbanding.llnl.gov/
ConsExpo Nano	Available	Free	Web-based	Aug-24	https://www.consexponano.nl/
Diagonal DST	Available	Free	Web-based	Oct-24	https://enaloscloud.novamechanics.com/diagonal.html
Early4AdMa	Available	Free	Excel file	2023	https://www.oecd.org/chemicalsafety/
Engineered NP Airborne exposure tool	Available	Free	Web-based	May-2018	https://pages.nist.gov/CONTAM-apps/webapps/NanoParticleTool/index.htm
GUIDEnano Tool	Available	Free	Web-based	Apr-17	https://tool.guidenano.eu/
HARMLESS DSS	Available	Free	Web-based	Mar-25	https://diamonds.tno.nl/projects/harmlesspublic
Hot Spot Scan	Available	Free	Web-based	2022	https://diamonds.tno.nl/projects/hotspotscan
LICARA nanoSCAN	Available	Free	Web-based	2025	https://acc-diamonds.tno.nl/licara/scan
MendNano	Unavailable	-	-	2018	
Nano Exposure Quantifier	Available	Free	Web-based	2022	https://diamonds.tno.nl/neq/scan/103
NanoFASE	Available	Free	Script	Jan-25	https://github.com/NERC-CEH/nanofase
NanoFATE	Available	Free	Script	May-20	https://github.com/klaris-ak/ChemFate
NanoSafer CB	Available	Free	Web-based	May-19	http://www.nanosafer.org/
Precautionary Matrix	Available	Free	Web-based	Mar-25	https://www.bag.admin.ch/en/precautionary-matrix-for-synthetic-nanomaterials
SAbyNA	Not yet available	-	-	May-24	-
SB4N	Available	Free	Excel file / Script	Apr-24	https://www.rivm.nl/en/soil-and-water/simplebox4nano
Stoffenmanager nano	Available	Free	Web-based	Jan-11	https://nano.stoffenmanager.com/default.aspx
SUN DSS	Available	Free	Web-based	Jul-22	https://sunds.gd/sections
SUNSHINE DSS	Available	Free	Web-based	Feb-25	https://www.sunshine.greendecision.eu/

exposure of the advanced materials are covered in Steps 2 and 3 (Abbate et al., 2024). In these steps the primary goal is to identify and mitigate "release hotspots"—critical operations or scenarios along the life cycle of a chemical or advanced material where exposure potential is notably high, requiring focused assessment and targeted intervention (González-Gálvez et al., 2017). Exposure assessments can be *in silico* or involve *in site* workplace monitoring. Although workplace monitoring is not covered within the scope of this paper, it remains an essential method supported by established tiered approaches and regulatory guidance (McLean, Hanlon, et al., 2024) and is also of critical importance for SSbD assessments (Leso et al., 2025).

The tiered approach employed for Steps 2 and 3 follows the same logic as for Step 1 and is based on data availability and quality, methodological complexity, required time, and the level of expertise. This classification can still be somewhat subjective, as no strict boundary exists between one tier and the next. Nevertheless, organizing methods according to increasing technical sophistication and detail helps users systematically select tools that align with their available data, expertise, and the particular stage in the innovation process.

Table 2 presents a compilation of tools, each of which is described and classified by Tier in the following subsections. While accessibility is detailed in section 5, it is also included in the table to enhance readability.

4.1. Tier 1 methods and tools for Step 2 and 3

Within the SSbD framework, control banding (CB) models are intended to be used in Tier 1 (European Commission - JRC, et al., 2022). Control banding tools are simplified models that combine hazard labelling (e.g., GHS classification) with exposure factors (e.g. dustiness, quantity, and handling frequency) into "bands". These hazard–exposure bands are then merged to determine an overall risk band, which guides the selection of protective measures (Brouwer, 2012; Riediker et al., 2012). Because hazard and exposure data are often incomplete in the early stages, control banding tools apply the precautionary principle, emphasizing preventive action despite scientific uncertainty and mitigating potential risks without conclusive evidence. By recommending the highest feasible level of protection (e.g., local exhaust ventilation or enclosure), this principle helps prevent harm while more data are gathered to refine risk evaluations. As a result, control banding tools enable prompt and informed risk-management decisions even when comprehensive information is unavailable (Dunn et al., 2018).

NanoSafer CB stands out as a tool designed to assess the risk level and recommend exposure control measures for nanomaterials and nanoparticle-forming processes. By combining data from technical and safety sheets with workplace-specific conditions, it evaluates risks using hazard endpoints and read-across techniques, offering practical control band recommendations in occupational assessments. Another relevant tool is **Stoffenmanager Nano**, which adapts the widely used Stoffenmanager platform to address nano-specific properties like particle size, shape, and surface reactivity. With a focus on inhalation exposure, it allows users to input workplace-specific data to generate exposure scenarios and recommend safety measures such as engineering controls and personal protective equipment. Its user-friendly interface and focus on occupational health align it closely with regulatory requirements, making it particularly effective for industries employing nanomaterials.

The **CB Nanotool 2.0** also provides a systematic framework for managing nanomaterial risks in occupational settings. It combines hazard and exposure banding, offering recommendations such as engineering controls and personal protective equipment. Unique to this tool is its use of both deterministic and Monte Carlo models: the former provides fixed outcomes based on known inputs, while the latter simulates variability to account for uncertainty, enabling a deeper understanding of risk under complex scenarios. The **AdMaCat tool** serves as a control-banding tool aimed at early-stage safety and sustainability assessments. While not yet released, AdMaCat uses a qualitative, color-coded framework to highlight potential risks and guide researchers in identifying areas requiring redesign (Rubalcaba Medina et al., 2024). Similarly, **Early4AdMa** supports early decision-making for advanced materials. Unlike other tools focused solely on occupational settings or hazard banding, it uses structured criteria to assess both safety and broader sustainability aspects, including regulatory relevance and innovation context (Oomen et al., 2022; OECD, 2023b). Finally, the **ANSES Control Banding Tool**, developed by the French Agency for Food, Environmental and Occupational Health & Safety, was designed to manage risks associated with nanomaterials in occupational settings.

The **HARMLESS Decision Support System (SSbD-DSS)** complements these tools by integrating multiple modules that assess hazard, exposure, and Safe-by-Design strategies for complex nanomaterials. The **AMEA (Advanced Material Earliest Assessment)** module provides early design-stage guidance, the **WASP (Warning flags, Advice & Screening Priorities)** module identifies risk hotspots and suggests risk-mitigation measures, and the **ASDI (Alternative Safe-by-Design Design Inspector)** module evaluates safer material design options. On top of that, the HARMLESS SSbD-DSS, as a separate module, provides guidance across all innovation stages, directing users toward the most appropriate modules based on their specific needs. Due to its modular structure, it can be classified within multiple tiers. AMEA and WASP are designed to fit in ideation and business case stages (Tier 1), while ASDI is more suitable for the lab phase (Tier 2).

In addition to the control banding tools, there is a suite of existing semi-quantitative screening, ranking and prioritisation tools that use methodologies from decision science (e.g., weight of evidence) such as multi-criteria decision analysis (MCDA) for assessing health and environmental hazards, exposure or risks. These tools are particularly useful in SSbD context as they enable comparison of materials or exposure/use scenarios directly. Hristozov et al. (2014a; 2014b; 2016) proposed three of the first MCDA-based tools, which enable human hazard screening of nanomaterials as well as prioritisation of occupational exposure scenarios and risks.. Similarly, Tervonen et al. (Tervonen et al., 2009) developed a semi-quantitative tool for health and environmental risk classification of nanomaterials based on the 'Stochastic multicriteria acceptability analysis (SMAA-TRI) method'. This tool also assesses uncertainty and its results are easy to interpret.

The "Tool for ENM-Application Pair Risk Ranking (TEARR)" (Grieger et al., 2015), Screening Tree Tool (Askham, 2011; Askham et al., 2012, 2013), NRST (Nanomaterial Risk Screening Tool) (Beaudrie et al., 2015) and NanoRiskCat (Hansen et al., 2011, 2014) are screening tools that combine hazard and exposure information with nanomaterial physicochemical properties for ranking nanomaterials in terms of health risk. The Nano Guidance for Risk Informed Deployment (NanoGRID) framework was developed by the U.S. Army Engineer Research & Development Center (ERDC) (Collier et al., 2015) as a risk-screening tool for nanomaterials. NanoGRID applies a tiered approach to risk (pre-) assessment, which allows identifying when a new material requires additional risk testing or when it can be addressed within traditional regulatory and safety frameworks. It is a semi-quantitative tool, easy to use but does not offer uncertainty analysis.

4.2. Tier 2 methods and tools for Step 2 and 3

After the simplified approach of Tier 1, Tier 2 builds on moderate data availability to provide more detailed assessments. Compared to control-banding techniques, these tools offer greater resolution in estimating exposure pathways and evaluating operational conditions, improving the precision of risk characterization without the full complexity and extensive data demands of Tier 3.

In this publication, for Tier 2 and 3, tools are categorized as either (i) exposure and fate-oriented or (ii) risk-oriented due to the fundamental differences in their objectives, methodologies, and applications within the SSbD framework. Exposure and fate-oriented tools primarily focus on estimating the potential contact between an advanced material and a biological or environmental compartment. In contrast, risk-oriented tools integrate exposure data with hazard characterization to evaluate the likelihood and severity of adverse effects.

While exposure-oriented tools provide critical input data, risk-oriented tools offer a more comprehensive assessment by integrating hazard information. However, while risk-oriented tools provide a broader assessment, in cases where practitioners require only exposure estimates, dedicated exposure and fate-oriented tools often offer greater accuracy. Risk tools, in contrast, may yield overly generalized results when hazard data is incomplete or unavailable, making exposure and fate tools more fit-for-purpose in such scenarios. This distinction ensures that tools are applied appropriately within the SSbD framework, allowing for more reliable and targeted assessments based on the specific data needs and objectives of the evaluation.

4.2.1. *Exposure and fate-oriented*

NanoFATE predicts time-dependent accumulation of metallic nanomaterials in air, water, and soils. In addition, NanoFATE's structure allows for regional specificity by incorporating local hydrometeorological data and environmental characteristics, making it adaptable to different regions and scenarios (Garner et al., 2017). NanoFATE is integrated into the larger ChemFate framework, which includes models for non-ionizable organic chemicals (organoFate), ionizable organic chemicals (ionOFate), and metal ions (metalFate) (Tao & Keller, 2020). The full ChemFate framework with the four submodels are available from GitHub for free download. **MendNano** was designed to estimate potential environmental exposure levels of nanomaterials and to enable rapid analysis of "what if" scenarios via a web-browser interface.

The **Hot Spot Scan** offers a qualitative screening approach to identify environmental and occupational exposure hotspots throughout a product's life cycle. It is particularly useful in early development stages, where it supports risk prioritization and guides further assessment efforts. To address workplace exposure, the **Nano Exposure Quantifier (NEQ)** is a mechanistic model developed to estimate airborne exposure to engineered nanomaterials in occupational settings. The model can operate with varying levels of input data, offering flexibility for different assessment contexts (Vermoolen et al., 2025). Focusing on consumer exposure, **ConsExpo nano** is an extension of the ConsExpo model specifically developed to estimate exposure of substances released as an aerosol during the use of spray products. The model combines predictions of aerosol concentration in indoor air with estimation of the deposition and clearance of inhaled nanomaterial in the alveolar region of the respiratory tract (Delmaar & Meesters, 2020). Finally, the **Engineered Nanoparticle Occupational Exposure Tool (E-Nano OET)** was developed to estimate consumer exposure to airborne engineered nanoparticles in indoor environments. It includes two components: a simplified online tool for single-size particle estimates and a more advanced size-resolved model that accounts for nanoparticle-specific processes such as coagulation. Together, these models help assess how nanomaterials released from consumer products may impact indoor air quality and occupant exposure (Dols et al., 2018).

A relevant methodology in this context is **Probabilistic Material Flow Analysis (PMFA)**, which quantifies material flows and stocks while incorporating uncertainty and variability (Gottschalk, Scholz, et al., 2010). PMFA tracks the movement of advanced materials across the different stages of the life cycle, identifying potential environmental releases at each stage and providing insights into long-term exposure patterns and environmental hotspots. Additionally, it can determine the forms in which materials are released, contributing to further fate assessments (Adam et al., 2018). Although data-intensive, PMFA remains valuable even with limited datasets, making it particularly relevant at the interface between Tier 2 and Tier 3 assessments. In Tier 2, it provides preliminary estimates of material flows and potential accumulation areas, while in Tier 3, its detailed modelling capabilities enable more refined exposure and fate assessments (Nowack, 2017).

Within this tier, **QSAR (Quantitative Structure-Activity Relationship)** and **QSPR (Quantitative Structure-Property Relationship)**, which were previously discussed in Step 1 for hazard assessment, also offer valuable tools for predicting the environmental fate and behaviour of advanced materials. QSAR models primarily focus on predicting biological activity and interactions, such as bioavailability and potential toxic effects, based on molecular and physicochemical descriptors. In contrast, QSPR models are used to estimate physicochemical properties that influence environmental fate, including Z-potential, solubility, partition coefficients, and degradation rates. Recent advances have enabled QSPR models to predict the dissolution of metal-based nanomaterials in different water chemistries (Zhou et al., 2024), while QSAR approaches help assess their biological uptake and toxicity potential (Kar & Leszczynski, 2021). These models are inherently more complex than QSARs for general chemicals, which are typically considered Tier 1 tools (PARC Project, 2025).

4.2.2. *Risk-oriented*

The **Precautionary Matrix for Synthetic Nanomaterials** evaluates the need for nano-specific safety measures across a material's lifecycle, from production to disposal. The Precautionary Matrix is designed to be user-friendly and is particularly effective in highlighting gaps in knowledge and uncertainties. It supports a structured and iterative evaluation process, allowing for initial rapid assessments (Tier 2) followed by more detailed investigations (Tier 3) as necessary (Höck et al., 2023). Similarly, the **LICARA nanoSCAN** covers all life-cycle stages (i.e., production, manufacturing, use, and end-of-life) but adds economic viability and social benefits of using nanomaterials compared to conventional alternatives, to guide early-stage decisions, making it especially useful for SMEs. Additionally, the tool helps ensure that the nanomaterials comply with relevant regulations and guidelines (Van Harmelen et al., 2016).

4.3. *Tier 3 methods and tools for Step 2 and 3*

Tier 3 marks the most comprehensive stage, where fully quantitative models and detailed datasets are employed to capture complex exposure scenarios and life-cycle interactions. Tools at this level typically require significant expertise and robust input data, but they provide the most accurate and nuanced risk evaluations. This tier is especially critical for high-risk applications or cases where refined predictions are essential for regulatory compliance or final decision-making.

4.3.1. *Exposure and fate-oriented*

NanoFASE is a spatiotemporal environmental fate and exposure model specifically developed for engineered nanomaterials. It predicts their concentrations with kilometre-scale spatial resolution and daily-scale temporal resolution across environmental compartments such as soil, surface water, and sediments. By integrating key transformation processes—including aggregation, dissolution, sedimentation, and chemical transformation—NanoFASE identifies potential hotspots where nanomaterials may accumulate, posing risks to ecosystems and human health.

SimpleBox4Nano (SB4N) is an environmental exposure model specifically adapted from the original SimpleBox model to assess the fate and transport of nanomaterials in various environmental compartments. It accounts for their unique particle behaviour such as the tendency for aggregation, transformation, and surface chemistry, predicting their distribution in air, water, soil, and sediments. SB4N supports sustainable nanotechnology development by enhancing the understanding of how different properties of nanomaterials affect their distribution and transformation in the environment.

Another relevant approach is the combination of **PMFA with fate models** to enhance the assessment of advanced materials. PMFA provides essential data on material flows, tracking their distribution across environmental compartments and identifying potential exposure hotspots (Gottschalk, Sonderer, et al., 2010; Adam et al., 2018; Hong et al., 2022). This information serves as a crucial input for fate models, which further refine predictions on degradation, transformation, and persistence such as SimpleBox4Nano or watershed model, e.g. WASP (Suhendra et al., 2025). Combining PMFA with fate models provides a holistic view of material flows from production through environmental dispersion to biological interactions, offering a complete lifecycle perspective.

4.3.2. Risk oriented

Tier 3 risk assessment involves a high level of complexity and requires extensive data, including comprehensive information on all aspects such as detailed toxicological and environmental fate data. The advantages of Tier 3 results include offering the highest precision in risk assessments, supporting detailed scenario analysis and life cycle assessments. However, this tier requires significant data collection efforts and resources, as well as higher computational complexity and expertise for interpretation. With comprehensive data, the tools can significantly enhance predictive accuracy, allowing for precise modelling of advanced material behaviour in various contexts. It supports robust scenario analysis, providing a more comprehensive risk profile and enabling the development of specific, actionable risk management strategies based on precise risk predictions. Additionally, thorough documentation supporting regulatory submissions demonstrates compliance with safety and environmental regulations, ensuring that stakeholders can make informed decisions regarding the safe and sustainable use of nanomaterials. While this paper focuses on Steps 1–2–3 of the SSbD framework, tools that also support other steps such as environmental sustainability or socio-economic assessment, are mentioned where relevant, to reflect their broader applicability and added value for integrated assessments.

SUN DSS integrates occupational, consumer, and environmental risk assessments, including a Life Cycle Assessment (LCA) module that tracks material and energy flows from production to disposal. It also supports socio-economic evaluations, scenario modelling for risk management strategies, and multi-criteria decision analysis (MCDA) to compare safety and sustainability options (Subramanian et al., 2016; Widler et al., 2016; Pizzol et al., 2019). The **BIORIMA DSS**, built within the SUN DSS, extends these assessments to nanobiomaterials and nano-enabled biomedical products, evaluating risks for patients, healthcare workers, and the environment. The **SUNSHINE** e-infrastructure builds on the SUN DSS, enhancing exposure models, expanding the nanomaterial database, and improving user functionalities to support more detailed scenario modelling/predictive and SSbD decision support capabilities. The SUNSHINE e-infrastructure provides a virtual platform for collaboration and controlled exchange of information between actors along the supply chain (using blockchain technology) as well as an Open & FAIR database, access to more than 50 modelling tools for (advanced) nanomaterials and a SSbD decision support module aligned to the 5 steps of the EC-JRC SSbD framework (Livieri et al., 2025). The ongoing **SUNRISE** project continues to advance the SSbD module of SUNSHINE e-infrastructure by developing an Integrated Impact Assessment Approach (IIAA) of advanced methodologies for health, environmental, social and economic assessment for each of the three tiers addressed in this manuscript.

The **GUIDEnano Tool** is a decision-support system for safe and sustainable nanomaterial production, manufacturing, use, and disposal. It integrates risk assessment, risk management strategies, and LCA to support manufacturers, regulators, and researchers. The tool operates with varying data availability, supporting Tier 2 assessments for preliminary risk insights and Tier 3 evaluations for higher-tier regulatory assessments. By combining qualitative and quantitative inputs, GUIDEnano enables scenario modelling to identify exposure hotspots and estimate risks across different compartments through a flexible platform for informed decision-making. **The DIAGONAL Decision Support Tool (DST)** helps regulators, industries, and stakeholders select optimal strategies to minimize risk and control exposure throughout the life cycle of multi-component nanomaterials (MCNMs) and high aspect ratio nanomaterials (HARNs). Following the four-step SSbD approach—hazard assessment, production and processing, final application, and environmental sustainability—it provides structured risk evaluations. The tool is accessible via the ENALOS cloud platform, promoting safer innovation and regulatory compliance in nanomaterial management. In a complementary effort, Wohlleben et al. (2025) presented a suite of SSbD tools developed within the DIAGONAL, HARMLESS, and SUNSHINE projects, designed to support the safety assessment and sustainable innovation of multi-component and high-aspect-ratio nanomaterials. The **SAbyNA Guidance Platform** is a tool developed to support the safe and sustainable development of nanomaterials and nano-enabled products. It integrates risk assessment tools covering hazard, exposure, functionality, sustainability and cost across all the lifecycle, helping industry stakeholders implement SSbD strategies early in development. The platform consolidates databases, testing methods, and risk assessment tools into an interactive and user-friendly system that simplifies complex information for industrial applications, particularly in paints and 3D printing sectors. It includes "Usability Cards" summarizing key SSbD resources, a screening module for initial risk assessment, and advanced tools for detailed exposure and hazard analysis (Cazzagon et al., 2025). Although currently unavailable, efforts are underway to merge SAbyNA with SbD4Nano, creating a more comprehensive platform for SSbD implementation in nanomaterial innovation.

A relevant approach in Tier 3 risk assessment is **probabilistic environmental risk assessment (pERA)**, which enhances risk characterization by integrating probabilistic exposure and hazard modelling (Gottschalk et al., 2013). pERA predicts environmental concentrations (PECs) of different advanced material forms using material flow models. For hazard assessment, probabilistic species sensitivity distributions (PSSDs) estimate predicted-no-effect concentrations (PNECs), allowing for a more refined risk evaluation. Risk is then quantified through the risk characterization ratio (RCR), which compares PECs to PNECs, providing a probabilistic measure of potential harm. The use of Monte Carlo simulations further improves assessment reliability by incorporating variability and uncertainty. By considering the transformations and different forms of engineered nanomaterials throughout their life cycle, pERA offers a more comprehensive and realistic risk assessment than traditional deterministic methods, making it a valuable tool for SSbD strategies (Wigger et al., 2020).

5. Tools usability and accessibility for the EC-JRC SSbD framework

This section provides an overview of relevant methods and tools that can be used to operationalize Steps 1, 2, and 3 of the SSbD framework. Fig. 3 illustrates the distribution of methodologies and tools categorized by their respective SSbD step and tier. Tools and methods are color-coded based on their focus, distinguishing between computational approaches, toxicological assessments (human, freshwater, seawater, and soil), and exposure and fate or risk-oriented frameworks. The visualization highlights how tools are allocated within the tiered approach of the SSbD framework, showing their applicability in different stages of material safety and sustainability assessment. While the assignment of methods and tools to tiers can be more complex in practice, as discussed in previous sections, Fig. 3 adopts a simplified representation for hazard methodologies, categorizing them broadly as *in silico* (Tier 1), *in vitro* (Tier 2), and *in vivo* (Tier 3) approaches to aid clarity and usability. The hazard-related methods shown (i.e. Step 1) are not exhaustive but reflect those commonly applied to advanced materials.

By structuring the tools by tiers, as well as by hazard, exposure and fate- or risk-oriented objectives, potential users can more easily identify and select solutions that fit their specific stage of development and data availability. Overall, the aim is to facilitate informed tool selection, streamline assessment workflows, and support the effective implementation of SSbD principles in real-world product and process design.

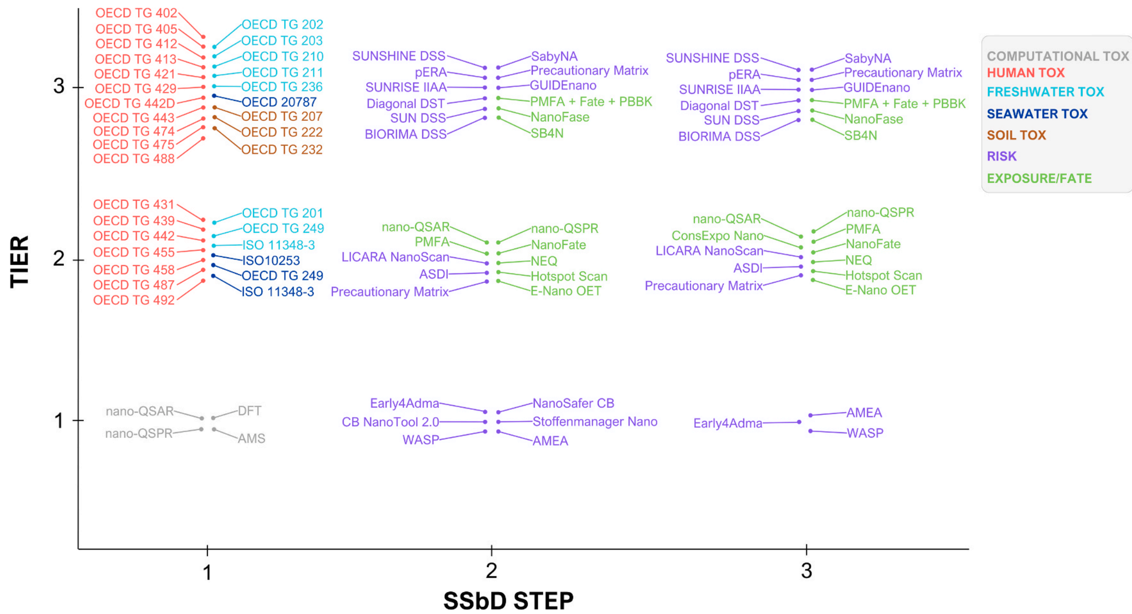

Fig. 3. Mapping of methodologies and tools across SSbD steps and tiers.

Over the years, numerous models and tools have been developed to support the risk, exposure, and hazard assessment of advanced materials. While the tools discussed in this paper are comprehensive, others are highly specialized, focusing on specific applications such as consumer spray products (Delmaar & Meesters, 2020), particular material categories like carbon nanotubes and metal oxides (Papadiamantis et al., 2020; Varsou et al., 2019), key physicochemical properties such as zeta potential and colloidal stability (Varsou et al., 2020a; Papadiamantis et al., 2021; Badetti et al., 2021), or exposure effects on specific organisms (Karatzas et al., 2020). Additionally, some of them were developed long ago and are no longer widely recognized or maintained, making them difficult to locate.

Model repositories play a crucial role in consolidating these resources, ensuring that researchers, regulators, and industry professionals have access to relevant tools for informed decision-making. A list of relevant tool repositories for advanced materials is presented in Table 3. The **Enalos Cloud Platform** is an online, freely available cheminformatics and nanoinformatics cloud platform that hosts a broad range of predictive models provided as web services (Varsou et al., 2020b). It offers a user-friendly environment specifically designed for non-informatics experts, providing access to state-of-the-art modelling tools for hazard prediction, exposure and risk assessment, reducing the barriers to entry for complex scientific calculations. Through the Enalos Cloud Platform, any model can be made available under the technology of Software as a Service (SaaS), allowing for greater accessibility and ease of use.

Similarly, the **NanoInformaTIX platform** provides a web-based Sustainable Nanoinformatics Framework (SNF) platform for risk management of engineered nanomaterials. By incorporating big data analytics, machine learning, and computational modelling, it contributes to advance nanomaterial research. It offers a broad range of models, including material property prediction, environmental fate modelling, and exposure assessment, making it a multi-disciplinary repository for nanomaterial safety and design. A key feature of NanoinformaTIX is its ability to link experimental data with theoretical models, fostering a collaborative ecosystem where researchers can refine and share insights (CORDIS, 2023). This integration allows for safer and more sustainable advanced materials development, supporting regulatory alignment and informed decision-making (Amorim et al., 2023).

NanoSolveIT is another advanced platform designed to provide integrated solutions for nanoinformatics-based risk assessment. Implemented through a decision support system available as both standalone open software and via a cloud platform, NanoSolveIT integrates validated databases, *in silico* models, web services, and software applications dedicated to nanomaterials. This framework leverages extensive experimental and computational characterizations, including biological

Table 3
Overview of tool repositories relevant to advance materials.

TOOLS REPOSITORIES	DESCRIPTION	LINK	REFERENCE
Enalos Cloud Platform	Web-based nanoinformatics and cheminformatics platform offering user-friendly access to predictive models and tools for hazard, exposure, and risk assessment.	https://www.enaloscloud.novamechanics.com/index.html.	(Varsou et al., 2020b)
NanoInformaTIX platform	Sustainable nanoinformatics framework combining big data analytics, machine learning, and computational modelling to advance safe and sustainable nanomaterial design.	https://nanoinformatix-platform.greendecision.eu/index	(CORDIS, 2023)
NanoSolveIT	Integrated decision support system combining databases, *in silico* models, and software tools to support nanomaterial safety and Safe-by-Design approaches	https://nanosolveit.eu/resources/tools-services/	(Afantitis et al., 2020)
DIAMONDS platform	Generic data management and integration system combining tools, algorithms, and workflows for risk governance, including environmental and human health assessments.	https://diamonds.tno.nl/	(Stierum et al., 2019)

and environmental transformations, toxicological, ecotoxicological, and exposure studies, to advance nanomaterial research and support safe-by-design approaches (Afantitis et al., 2020).

The **DIAMONDS platform** is a generic data management and integration platform for the life sciences. It brings together data, knowledge, and algorithms, encompassing clinical studies, omics data, and personalized health information. By integrating diverse tools and algorithms, such as statistical tools, text mining methods, and network visualization, DIAMONDS facilitates the systematic collection, organization, and analysis of information (Stierum et al., 2019). This integration supports informed decision-making in various domains, including risk governance of advanced materials, by providing structured workflows and multi-criteria assessments that consider environmental and human health risks.

These platforms illustrate the growing role of model repositories in facilitating accessible, data-driven decision-making for advanced materials. As these repositories evolve, they will continue to enhance risk prediction capabilities and contribute to the SSbD approach by integrating advanced modelling methodologies into advanced materials assessment frameworks.

Despite the advancements in model repositories and the increasing accessibility of computational tools, challenges remain in their practical implementation, particularly for *in silico* hazard assessment. While approaches such as QSARs and QSPRs are relatively well-established and standardized for conventional chemicals, their applicability to advanced materials remains a challenge. The intrinsic complexity of these materials, influenced by factors such as shape, size, crystallographic structure, or surface chemistry, complicates model development and reduces predictive reliability. As a result, existing tools may not always align with Tier 1 assessments, as is typically the case for conventional chemicals. To address these limitations, further research is needed to develop tailored computational approaches capable of capturing the unique properties and behaviour of advanced materials (Sarigiannis et al., 2023).

These challenges in adapting *in silico* tools for hazard assessment underscore broader concerns about the availability and applicability of tools across the SSbD framework. In this context, evaluating the accessibility of tools for exposure and risk assessment is equally important. Table 2 presents the accessibility status of tools used for Step 2 and Step 3 assessments within the SSbD framework. Step 1 tools are not included in Table 2, as most hazard assessment methods described in this paper are experimental (i.e. *in vitro* or *in vivo*), and therefore not subject to the same accessibility constraints as computational tools. For the *in silico* methods described for hazard, such as QSARs or QSPRs, only general methodological aspects are discussed in previous sections, rather than specific tools whose accessibility could be evaluated.

As shown in Table 2, four out of the 22 tools considered (18 %) are currently unavailable. ANSES CB and MendNano, both developed years ago, are no longer operational, while AdMaCat and SAbyNA are more recent initiatives still under development. Among the available tools, all are free of charge, as they were developed within publicly funded projects. The platform classification highlights that most tools are web-based (green), which is considered the most user-friendly and accessible format. Excel-based tools (yellow) are somewhat less optimal due to potential compatibility issues, reliance on macros, and limited visualization capabilities. However, the ability to run the tool fully locally eliminates any issues that companies may have with data confidentiality. Script-based tools (red) require higher technical expertise, making them less accessible for non-expert users. Nevertheless, they offer transparency and customization, in contrast to web-based tools, which may act as "black boxes" when their algorithms are not properly reported. The last update of each tool is another critical factor, given the rapid advancements in materials science. Regular maintenance ensures the relevance and reliability of assessments. Tools updated between 2025 and 2023 are classified as highly optimal (green), those updated between 2022 and 2020 as moderately optimal (yellow), and tools with updates older than 2020 as non-optimal (red). The lack of recent updates in some tools raises concerns regarding their applicability to the latest advancements in advanced materials. To enhance accessibility, links to each available tool have been included in the table, allowing practitioners and researchers to quickly verify availability, functionality, and recent updates.

These findings highlight key challenges in ensuring that assessment tools remain functional, user-friendly, and adaptable to the evolving landscape of advanced materials. While the prevalence of freely available web-based tools is beneficial, the discontinuation of several tools and the lack of recent updates for others present significant barriers to their long-term usability in SSbD implementation. Sustained efforts are needed to maintain and expand these resources, ensuring they remain aligned with emerging materials and regulatory requirements.

6. Current challenges and future directions

One of the key challenges in implementing SSbD for advanced materials is the broad and evolving nature of the term itself. What is considered "advanced" today may become standard in the near future as technology progresses. Moreover, the wide range of materials classified as advanced introduces complexities that may require specialized risk considerations and adaptable methodologies, similar to what was developed for engineered nanomaterials, which still represent a significant portion of advanced materials. In any case, creating models that apply universally to all advanced materials is challenging due to the vast differences in properties, behaviour, and applications across the spectrum.

Significant research efforts have been dedicated to assessing the risks of nanomaterials, leading to the development of specific tools and methods tailored to their unique characteristics. The focus on advanced materials is relatively recent, which explains why most existing tools still concentrate on nanomaterials. Updating existing tools or evaluating their applicability to other types of advanced materials beyond engineered nanomaterials is essential to maintaining the relevance of safety and sustainability assessments. However, many of these tools were developed within specific nanosafety projects, most of which have already ended, limiting the capacity for further modifications or expansions.

New efforts should be focused on expanding the applicability of existing tools to a broader range of advanced materials while ensuring their scientific robustness and regulatory relevance. The likelihood that a given tool can be applied depends strongly on how nano-specific it is. For materials close to the nanoscale, many existing approaches may still be relevant, whereas for microscale or larger materials the applicability becomes much more limited. However, this cannot be generalized, as applicability is highly case dependent, not only on the advanced material under consideration but also on the flexibility of the specific tool. This requires refining current methodologies to better capture the diverse properties and behaviours of advanced materials, as well as developing flexible frameworks that allow for continuous updates as new materials emerge. Encouraging cross-disciplinary collaboration and maintaining long-term support for tool development will be key to adapting SSbD approaches to the evolving landscape of material innovation.

Another critical aspect is the accessibility and usability of tools, as many existing methodologies require advanced technical expertise, limiting their adoption among non-specialist users. The development of more user-friendly platforms and standardized workflows, together with efforts to map how existing tools could be combined into practical sequences, would greatly enhance the implementation of SSbD assessments and help reveal both their value in real applications and the gaps that remain to be addressed. Additionally, integration with emerging digital technologies, such as machine learning and artificial intelligence, could improve predictive capabilities, enabling faster and more accurate assessments of material safety and sustainability. Finally, establishing a more interconnected ecosystem of SSbD tools, databases, and frameworks will enhance the overall efficiency and impact of risk assessments, supporting the transition toward safer and more sustainable material development.

According to information available to the authors on the ongoing revision of the SSbD framework, the safety assessment is likely to no longer be structured as "Steps 1, 2, and 3." Instead, the revised version proposes organizing the same elements of safety assessment (i.e. hazard, exposure, fate and risk) without using stepwise terminology (Garmendia et al., 2025). This adjustment affects mainly the framing rather than the substance of the assessment, since the underlying requirements remain unchanged. Our analysis therefore remains consistent with the revised framework, although it is presented here according to the stepwise structure of the published version that is available at the time of writing. Future work should ensure continuity by bridging between the earlier and revised structures to support alignment across projects and stakeholders.

7. Conclusions

The SSbD framework represents a critical shift in chemical and material innovation, aiming to integrate safety and sustainability considerations from the earliest design stages. While substantial progress has been made in developing methodologies and tools for hazard, exposure, and risk assessments, their alignment with the SSbD framework, particularly for advanced materials, remains an ongoing challenge.

This paper highlights the most relevant tools and methodologies currently available for Steps 1, 2, and 3 of the SSbD framework, evaluating their usability, accessibility, and limitations. The analysis reveals that while hazard assessment methods applied to advanced materials originate primarily from models developed for conventional chemicals; in contrast, exposure, fate, and risk assessment tools have largely focused on engineered nanomaterials. Consequently, as the concept of advanced materials continues to evolve, it is crucial to determine whether these tools require adaptation or if new methodologies must be developed to ensure comprehensive assessments.

In this context, key challenges include the broad diversity of advanced materials, the complexity of their transformation processes, and the need for specialized risk assessment approaches. Additionally, many of the tools reviewed in this work were developed within now concluded nanosafety projects, limiting their capacity for further updates and expansions (with a small fraction of tools no longer available and others still under development). Ensuring the continued relevance of these tools will require sustained research efforts, the integration of new scientific insights, and ongoing regulatory engagement.

Despite these challenges, the findings of this review emphasize the significant progress made in risk and sustainability assessment tools. The development of web-based, freely available platforms has improved accessibility, and recent efforts have sought to expand the scope of methodologies to include broader material categories. For future efforts, three priorities appear particularly critical: the establishment of clear maintenance and sustainability plans to prevent tools from becoming outdated; the extension and validation of instruments to cover the full range of advanced materials beyond nanomaterials; and the creation of more user-friendly interfaces and integrated platforms to bridge the gap between industry needs and advanced tool capabilities.

By addressing these challenges and opportunities, the SSbD framework can become a key driver of innovation, ensuring that new materials are designed with both safety and sustainability at their core. Continued investment in methodological development, regulatory harmonization, and stakeholder engagement will be essential to fully operationalizing SSbD principles in the rapidly evolving landscape of advanced materials.

CRediT authorship contribution statement

Vicenç Pomar-Portillo: Writing – review & editing, Writing – original draft. **Blanca Suarez-Merino:** Writing – review & editing, Writing – original draft, Conceptualization. **Santiago Aparicio:** Writing – review & editing, Conceptualization. **Elena Badetti:** Writing – review & editing, Conceptualization. **Mathew Boyles:** Writing – review & editing, Conceptualization. **Andrea Brunelli:** Writing – review & editing, Conceptualization. **Carlos Fito-López:** Writing – review & editing, Conceptualization. **Irantzu Garmendia-Aguirre:** Writing – review & editing, Conceptualization. **Elisa Giubilato:** Writing – review & editing, Conceptualization. **Alberto Katsumiti:** Writing – review & editing, Conceptualization. **Erik Laurini:** Writing – review & editing, Conceptualization. **Morgan Lofty:** Writing – review & editing, Conceptualization. **Domenico Marson:** Writing – review & editing, Conceptualization. **Lisa Pizzol:** Writing – review & editing, Conceptualization. **Isabel Rodríguez-Llopis:** Writing – review & editing, Conceptualization. **Carlos Rumbo:** Writing – review & editing, Conceptualization. **Janeck J. Scott-Fordsmand:** Writing – review & editing, Conceptualization. **Vicki Stone:** Writing – review & editing, Conceptualization. **Sara Trabucco:** Writing – review & editing, Conceptualization. **Danail Hristozov:** Writing – review & editing, Conceptualization. **Bernd Nowack:** Writing – review & editing, Conceptualization.

Declaration of competing interest

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

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Data availability

No data was used for the research described in the article.

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