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A suite of tools for safe-and-sustainable-by-design advanced materials from the EU projects DIAGONAL, HARMLESS and SUNSHINE

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Multi-component nanomaterials (MCNM) and High Aspect Ratio Nanomaterials (HARN) are advanced materials that present innovation potential but also challenge the innovation by Safe and Sustainable by Design (SSbD) principles. In 2021 to 2025, three EU-funded sister projects developed and implemented SSbD concepts in digital tools that are applicable to MCNM and HARNs despite their respective unique properties. The projects jointly established a tiered suite of tools that serves both industrial, SME (small and medium enterprise) and regulatory stakeholders. The tools for innovators are tiered by StageGate phases (projects SUNSHINE and HARMLESS) or organized in transversal topics (project DIAGONAL). Also the tools for regulatory preparedness comprise a range from simple to elaborate approaches. Key achievements include the alignment of tools for innovators and for regulators *via* a high overlap of the questions asked, and the systematic tiering of targeted input that is required. The suite of tools thus supports the OECD's Safe and Sustainable Innovation Approach (SSIA). With specific value to SME innovators, tools were developed that lower the previously perceived hurdles to implementation of SSbD concepts in product development. The suite of tools is demonstrated on three MCNM or HARN case studies provided by partners from industry and SMEs, specifically anti-stick coatings for baking trays ($SiC@TiO_2$), automotive catalysts (doped oxide perovskites) and flexible electronics (Ag nanowires). However, the cases also shed a light on remaining challenges in the SSbD concept that are not solved by tools alone, most notably the uncertainty of decision-support at early stages and the complexity of data gathering at later stages, which also implies a need of increasing data exchange among value chain actors while allowing actors to generate and protect intellectual property.

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Sustainability spotlight

To guide innovation in chemicals and materials towards sustainable development, innovators need to be supported in making the right decisions, *e.g.* by the concept of Safe-and-Sustainable-by-Design (SSbD). Especially advanced materials (AdMa) challenge the assessment first by their novelty, which implies a scarcity of data, and second by their "unique features", which imply uncertainty about the applicability of standardized tools. Lower-tier tools refer to sustainability design principles. Mid-tier tools make trade-offs between negative and positive contributions to different UN Sustainable Development Goals (SDG) transparent at the granularity of SDG targets. Some tools offer compatibility with the portfolio sustainability analysis that is already established in some industries. Only higher-tier assessments require comprehensive lifecycle sustainability assessments in several impact categories.

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1 Introduction

Advanced materials (AdMa) are described as being "rationally designed to have new or enhanced properties, and/or targeted or enhanced structural features with the objective to achieve specific or improved functional performance".[1] This description challenges the assessment of the safety and sustainability of these materials twice: first by their novelty, which implies a scarcity of data, and second by their unique features, which imply uncertainty about the applicability of standardized tools. Multi-component nanomaterials (MCNM) and High Aspect Ratio Nanomaterials (HARN) are examples of advanced materials that present both innovation potential and challenges in the assessment. MCNM can be described as nanocomposites formed by two or more functional components (*e.g.*, nanoparticles, nanocrystals, organic molecules, internal structures) conjugated by strong molecular bonds, or by a nanomaterial with a unique chemical composition, optionally modified by hard or soft coatings.[2–4] HARN are defined as nanoforms falling under ECHA's elongated shape category, with at least one dimension in the nanoscale (1–100 nm) and an aspect ratio greater than 3 : 1.[5,6] HARN can also be MCNM and include nanotubes and nanowires, with various shapes, such as helices, zigzags, and belts with diameter that varies with length.

Up to the end of 2020, projects on Safe by Design approaches had developed risk assessment tools and grouping strategies for nanomaterials such as fillers, pigments, and fibers.[7–16] Additional concerns for MCNM result *e.g.* from differing rates of degradation and toxicities of the components and their different interactions with biological and environmental systems. At the beginning of 2021, three "sister" projects started in parallel by NMBP-16-2020 funding, namely DIAGONAL, HARMLESS and SUNSHINE. Although the initial task from the funding agency was on SbD ("safe by design, from science to regulation: multi-component nanomaterials"), the scope was naturally enlarged to also assess sustainability in a SSbD approach (safe-and-sustainable by design) after the publication of the first version of the JRC SSbD framework around the midtime of the projects.[17] The assessment of sustainability is best performed by a comprehensive lifecycle sustainability assessment (LCSA),[18] which can consider several impact categories, including environmental, social and economic dimensions.[19] However, a full LCA requires high-quality data on various aspects of all lifecycle from raw materials and production to use and end of service life. Industry had at this time established tools for product portfolio sustainability analysis.[20] Many companies reported on corporate sustainability, and prioritized portfolio development accordingly.[21,22] But companies rarely performed an LCA of each individual product,[23] let alone for AdMa at early phases of research and development. Challenges that companies face when performing LCA include high demand in time and cost resources to gather the required data, hire consultants or purchase a software.[24,25] The LCA is also not seen as the best tool to use when reporting sustainability efforts, since results may be unfavorable to the business activities,[26] not peer reviewed[27] or deemed too complex to report and unsuited for the audience.[28,29] The field of alternatives assessment provides guidance for the typical trade-off between different dimensions of safety, sustainability, performance and cost.[30,31] However, for many AdMa the characterization factors that are needed to quantify the impact of each LCA indicator are missing and can be difficult to calculate from the models used for life cycle impact assessment, because models such as USEtox are mostly predictive for small organic molecules and simple inorganics and they are not applicable to nanomaterials without further adaptations.[32]

The scientific challenge for the three sister projects was thus to develop SSbD concepts and to implement them in digital tools that are applicable to MCNM and HARNs despite their unique properties – a key feature of advanced materials.[1,33] A specific challenge arises from the initial unknown extent of and rates by which variations of the environment modify the properties, since MCNM are prone to transformation. The pattern of release of different components may influence physiological responses, and may lead ultimately to mixture toxicity.[34] For HARN, the defining characteristic of fiber-like shape suggests the fiber paradigm as starting point for the hazard assessment,[35,36] but specific properties—incl. rigidity, biopersistence, reactivity, leaching impurities—and lifecycle considerations—incl. embodied energy, secondary fibril shapes and release from final products—were yet to be prioritized and integrated.[37–39]

Additionally to the scientific challenge, the stakeholder management represented a major challenge in the development of tools for SSbD-lead innovation: the need of the innovator, who seeks support in selecting one or the other innovation project for funding in a StageGate process,[40,41] is different from the need of the regulator, who seeks to prioritize AdMa classes for attention and potential adaptation of regulation for keeping pace with innovation (regulatory preparedness).[42,43] The combination of SSbD-lead innovation and regulatory preparedness has been touted as Safe Innovation Approach on OECD level.[44] But also within the regulatory community, horizon scanning for AdMa with low immediacy requires different tools than the prioritization amongst AdMa with higher immediacy. Within the innovator community, a small or medium enterprise (SME), who is knowledgeable about a certain technology and value chain, may need different support tools than a large industry who serves many different value chains and has in-house experts for several SSbD dimensions. Finally, it is obvious that early innovation phases (low technology readiness level, TRL) require different SSbD-support than ripe innovation phases (high TRL) for their respective next development stages.

In the present contribution we summarize the tools that the three sister projects generated to support SSbD approaches in the development of MCNM-enabled products with improved safety and sustainability profiles. We contextualize the tools according to their usefulness in different scenarios of SSbD, *i.e.* for use by innovators or by regulators, at early or ripe innovation stages. Guided by the call text and amended by the sustainability perspective, the projects strived to implement SSbD strategies in digital decision support systems (DSS), and demonstrated their uptake and utilization by SMEs and industry in a series of case studies. The case studies, of which three were selected for the present contribution, explored the effectiveness of the three separate DSS in scenarios of SSbD-lead innovation. At the same time, the case studies demonstrate the integration of specific characteristics of MCNM in an SSbD context.

Further achievements of the three sister projects to the scientific understanding of MCNM and HARN have been reported in detail elsewhere. These adaptation of guidelines for exposure and hazard assessment and categorization schemes to cluster MCNM in sector-specific approaches[45] have been instrumental for establishing the DSS.

2 Results: tiered suite of tools

The developed tools support the decision-making "gates" in the stepwise StageGate process (Fig. 1), where the "stages" represent a period of fixed duration, goals and budget, before the project is re-evaluated at the next gate. The StageGate process is used by industry to steer the company-internal competition of research projects for funding,[40,41] and serves as filter for ideas: The typical overall success rate of innovation ideas in chemical industry of 1% between Gate 2 (decision to elaborate a business case) and Gate 5 (decision to launch on market) is reflected by a probability of about 30% of passing the next gate (since $(30\%)^4 = 1\%$). Fig. 2 shows the alignment of the tiered suite of tools with the StageGate process; the tools are described in the subsequent sections.

2.1 SSbD for innovators: ideation and business case stages

At the end of the ideation and business case phase, the project plan must specify the design specifications, sustainability specifications, expected commercial value (based on the probability of technical success, probability of commercial success, projected earnings after launch, *etc*) and the budget required for the lab phase (Fig. 1). Gate 3 takes a stop/go decision based on the specifications and business case. The SSbD contribution of this specification has recently been termed "SSbD scoping" by the JRC guidance.[46] Considering the 99% probability that the AdMa targeted by the given innovation project will never be launched on the market, the tools supporting the ideation and business case phases (Fig. 2) are very lean and cost-efficient, requiring knowledge about the targeted product composition, the industry sector of use and the intended application.

The AMEA (Advanced Material Earliest Assessment) tool is implemented as online tool (https://diamonds.tno.nl/projects/amea) and is documented as scientific rationale.[45] Already before any synthesis, the intended use in specific categories and industry sectors guides the assessment to typical SSbD challenges, and categorisation of the targeted material by three questions helps to refine the assessment (Fig. 3). Materials identified as nano-enabled, as multi-component, as AdMa, as consisting of particles, fibers, platelets trigger each different and additive testing recommendations that should be budgeted for the SSbD work package in the project plan for the lab phase.[45]

The WASP (warning flags, design advice, screening priorities) tool is publicly available at https://diamonds.tno.nl/projects/wasp and described in a scientific publication.[47] It is based on the AMEA advice and brings together simplified elements of several other existing tools into a simplified approach to SSbD that requires relatively limited information compared to most existing tools to ensure its applicability in the early innovation phase. The WASP tool consists of 12 questions. Depending on the answers to these 12 questions, WASP identifies early warning flags that require additional attention. For each warning flag, the user is provided with more specific design advice to potentially alleviate the raised warning, as well as assessment advice for the next innovation stage to monitor and potentially revoke the potential issue, including detailed recommended descriptors to evaluate in the Lab Phase with the ASDI tool (Fig. 3, Section 2.2). The WASP tool (for innovators) was aligned for a high overlap and consistency with the $\mathrm{EWS}_{\mathrm{simple}}$ tool (for regulators, see below).

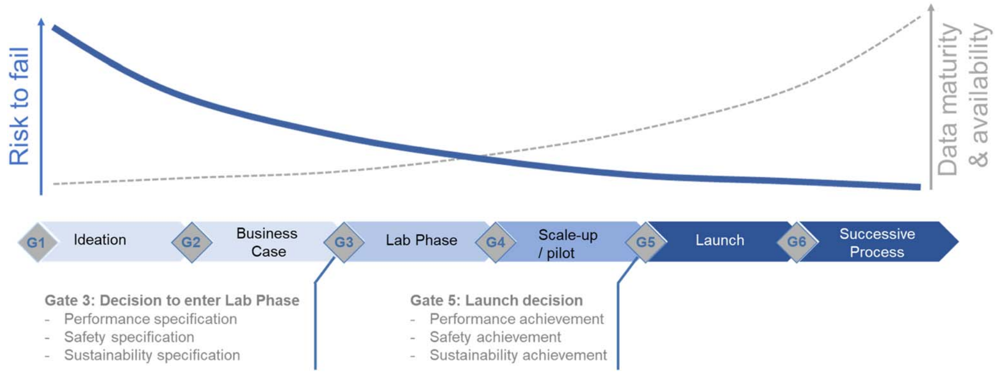
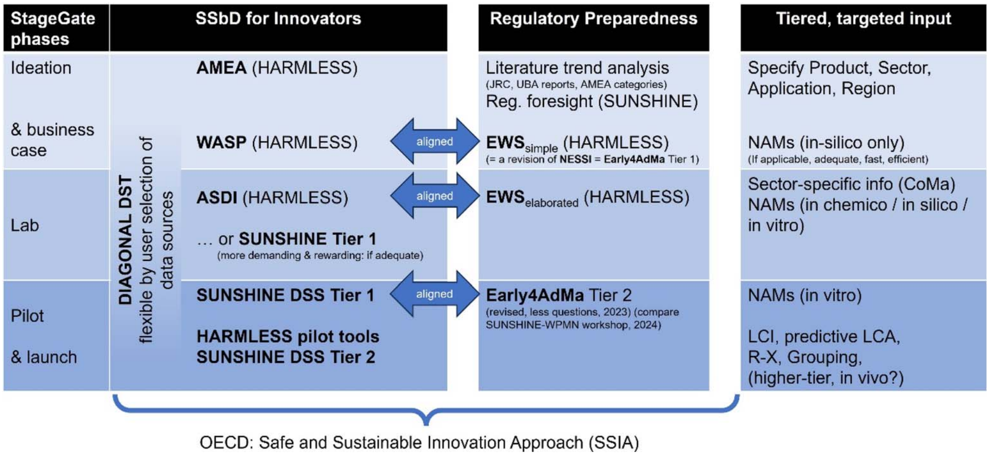


Fig. 1 Innovation in the StageGate process implemented for R&D project management: each gate represents a decision to stop the project, or to provide funding for the ensuing stage. Decision-support-systems support project managers in their preparation of the next gate decision with appropriate tools for each stage. For simplicity, Fig. 2 considers the stages "ideation" and "business case" jointly, helping project managers to prepare the specifications for Gate 3, that decides on budget for "lab" resources. If the project achieves its specified goals in lab phase, and if supported by the decision-support tools, Gate 4 approves "Pilot/Scale-up", and Gate 5 must be passed before "Launch" to the market. Again, Fig. 2 considers the stages "Pilot" and "Launch" jointly and assembles appropriate tools to guide the development and assessment.



StageGate phases	SSbD for Innovators	Regulatory Preparedness	Tiered, targeted input
Ideation	**AMEA** (HARMLESS)	Literature trend analysis (JRC, UBA reports, AMEA categories) Reg. foresight (SUNSHINE)	Specify Product, Sector, Application, Region
& business case	**WASP** (HARMLESS)	**EWS**$_{\text{simple}}$ (HARMLESS) (= a revision of **NESSI** = **Early4AdMa** Tier 1)	NAMs (in-silico only) (If applicable, adequate, fast, efficient)
Lab	**ASDI** (HARMLESS) … or **SUNSHINE Tier 1** (more demanding & rewarding: if adequate)	**EWS**$_{\text{elaborated}}$ (HARMLESS)	Sector-specific info (CoMa) NAMs (in chemico / in silico / in vitro)
Pilot & launch	**SUNSHINE DSS Tier 1** **HARMLESS pilot tools** **SUNSHINE DSS Tier 2**	**Early4AdMa** Tier 2 (revised, less questions, 2023) (compare SUNSHINE-WPMN workshop, 2024)	NAMs (in vitro) LCI, predictive LCA, R-X, Grouping, (higher-tier, in vivo?)

Fig. 2 Tiered suite of tools. SSbD tools for innovators are either tiered by StageGate phases (SUNSHINE and HARMLESS) or organized in transversal topics (DIAGONAL). Tools for regulatory preparedness are independent of industrial innovation stages but also comprise a range of simple and elaborate tools. As a result of the NMBP-16 projects, the tools for innovators and for regulators are now aligned for a high overlap of the questions asked and are aligned in the tiered and targeted input that is required. NAMs: new approach methodologies; CoMa: Conventional materials, LCI: life cycle inventory; LCA: life cycle assessment.

2.2 SSbD for innovators: laboratory stage

If the project is approved at Gate 3, several versions of the AdMa are iteratively synthesized, tested, and redesigned. We assume that an SSbD-compliant innovation project will plan budget for the work packages on synthesis, characterization, performance testing, and SSbD assessment. However, the overall probability of failure (Fig. 1) is still high, such that it is not economically sustainable to perform a "full SSbD" assessment, and instead it is wise to perform only "simplified SSbD" and "intermediate SSbD" assessments.[46] Tiering of tools for the lab phase also helps to curb the costs of the parallel assessments required for the comparison of different versions of the AdMa against each other and against the conventional material (CoMa) that serves the same purpose. Two tools were developed for the lab phase:

The ASDI (Alternative SSbD Design Inspector), is now publicly available at https://diamonds.tno.nl/projects/harmlesspublic and is described in a scientific publication.[47] ASDI helps industrial innovators to select the most optimal SSbD version of their material. Building on the default descriptors for assessing the warning flags identified with

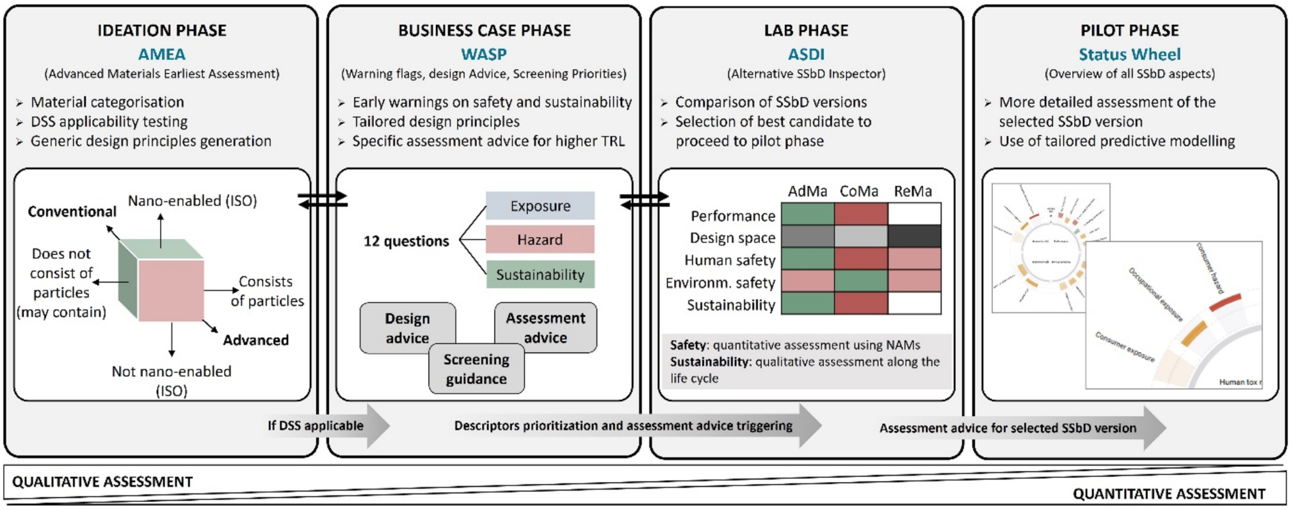


Fig. 3 HARMLESS DSS: the AMEA and WASP tools support the SSbD scoping in preparation of Gate 3 (see Fig. 1), for which they support the budgeting of SSbD work by assessment advice (based on IATAs) and (re)design advice that should be implemented in the lab phase. Both tools can be run as stand-alone tool, or embedded in the DSS. The targeted recommendations by WASP constitute an (initially empty) data matrix with specific descriptors and associated assays for the SSbD assessment. The industrial user has the freedom to delete from or add to the recommended assays, *e.g.* to add several descriptors of performance, or to delete descriptors that are not accessible locally. Once the data matrix is (partially) filled the ASDI tool supports the comparative assessment of different versions of the AdMa against each other and against the conventional and reference materials (CoMa and ReMa, respectively).

WASP (Fig. 3), data for the various SSbD versions, the CoMa and relevant reference material(s) (ReMa) should be gathered for each relevant descriptor. These data, gathered from scientific publications and existing databases or generated using the recommended test methods, need to be entered into the ASDI data matrix, which is flexible and adaptable by the user. Based on the data matrix ASDI provides a heatmap supporting the user to find a transparent balance between safety, sustainability and performance (Fig. 3). Each line of the heatmap, represents one descriptor, with a color scale calibrated to its chemically or biologically relevant range (as introduced for similarity assessments in nanoform grouping).[22,23] Different color shades between the different SSbD versions indicate that there is room for optimization of this specific descriptor, whereas similar color shades indicate that other dimensions can be optimized without trade-offs in this specific descriptor. The type of data requirements for to the ASDI tool (for innovators) was aligned for consistency with the $\mathrm{EWS_{elaborate}}$ tool (for regulators, see below).

SUNSHINE Tier 1 (Fig. 4) involves a questionnaire for pre-evaluation of safety, sustainability and functionality which can be applied to qualitatively assesses and compare possible SSbD design alternatives.[48] Tier 1 questionnaire is structured into four distinct sections, the first section provides an overview of the adopted SSbD approach. The second section contains general questions on the material under assessment, while the third section gathers more comprehensive information about the target MCNM/product. Finally, the fourth section comprises detailed questions aligned with the five lifecycle stages: (1) Raw materials and resources required to produce the material/product, (2) Manufacturing process of the MCNM, (3) Production process of the product incorporating the MCNM, (4) Utilization of the product, and (5) End-of-life management. For each of the five lifecycle stages, the questions to be addressed are divided by aspects such as safety, functionality, economic, environmental and social sustainability. The questions can be answered yes, no, I don't know and not applicable. The answers to these questions help to identify hotspots of safety and/or sustainability concerns as well as uncertainties already in the very early stages of innovation and they generate a score based on which different SSbD alternatives can be compared to select best options. The SUNSHNE Tier 1 tool (for innovators) was aligned for consistency with the Early4AdMa Tier 2 (for regulators).[49] One concern in applying Tier 1 was the time needed to collect information to reply with sufficient certainty to all of its 155 questions. This is surely an issue if there is the need to compare a relatively high number (>10) of possible SSbD alternatives, which is a typical scenario for large industries, but our experience with SMEs showed that they usually need to compare small number of alternatives (*e.g.*, 2–3) for which they already have detailed information, *i.e.* they motivate innovation by sustainability, but start applying the formal SSbD process at later gates than industry. So, the experience of the SMEs involved in SUNSHINE was that Tier 1 was relatively easy for them to apply and the time it took them was acceptable. In contrast, the feedback we received from large industry is that they need a much simpler approach for fast screening of larger number of alternatives as early as gate 3 (Fig. 1), similar to the

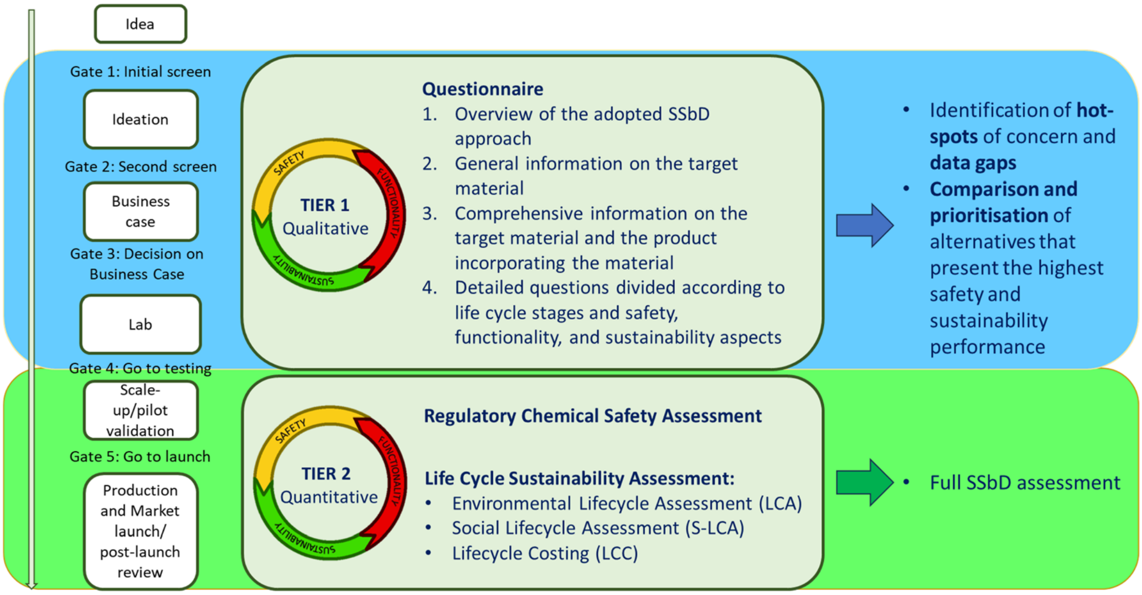


Fig. 4 SSbD tiered assessment proposed in the SUNSHINE project plotted against the Stage-Gate innovation process of industry. Tier 1 can be applied before the strategic decision 'go to testing' at Gate 4 (see Fig. 1), while Tier 2 covers the product/process scale-up, and pilot validation stages before launching the product on the market and can be applied also in the post-launch review. Tier 1 is qualitative and includes a questionnaire, which helps to identify 'hotspots of concern' along the lifecycle and the supply chain of innovative products and to compare SSbD design alternatives. Tier 1 may be applied as early as in the ideation and business case stages, particularly in data-rich cases and when major investment decisions are at stake, whereas in other cases the lab phase may be more appropriate. Tier 2 is quantitative and includes the established environmental and social LCA as well as LCC methodologies to provide a full SSbD assessment.

HARMLESS WASP before making a decision to kill or proceed with an innovation project. This is why in the SUNRISE project we are also developing such a fast screening approach, which will be labeled Tier 1a.

Depending on the SSbD scenario, the assignment of the tiered suite of tools to specific StageGate phases is only indicative: *e.g.* a more incremental innovation project may postpone recommended tests in ASDI from lab phase to pilot phase, or may find the SUNSHINE Tier 1 tool more appropriate for the pilot phase. On the contrary, an innovator in a sensitive application with direct business to consumers may prefer to add higher-tier screenings to the ASDI heatmaps. The suite of tools is open to such adaptations.

At the end of the lab phase, the tested design space is assessed for the best balance of all SSbD dimensions, patents are filed, and the best AdMa version is re-assessed against the specifications that were set as targets at Gate 3, and against the market standard, which may also have changed over the years of the lab phase. By involving units beyond research and toxicology, such as production, marketing, regulatory, raw materials sourcing, the project team determines if the business case is still viable, if regulations are likely to be passed, if the sustainability segmentation is favorable, if there is sufficient market pull by future customers, and then pitches to management at Gate 4.[50,51]

2.3 SSbD for innovators: pilot stage

If selected for funding in Gate 4, the pilot stage focuses on one or few versions of the AdMa, fine-tunes the AdMa in a narrower design space, with a focus on scale-up and system integration, *e.g.* by generating demonstrators of a final product in-house or, if patents have been filed and NDAs negotiated, in cooperation with selected customers. The value chain and future production processes and locations are starting to be developed, such that a lifecycle inventory can be drafted. One tool was developed for this phase.

SUNSHINE Tier 2 is an online tool available at sunshine.greendecision.eu which integrates results related to the five steps of JRC's SSbD framework into normalized scores used for prioritization of alternatives. The tool applies MCDA methods to normalize and aggregate results from the Hazard Assessment (Step 1), the application of the REACH Chemical Safety Assessment (CSA) (Step 2 and Step 3) and the established Life Cycle Sustainability Assessment (LCSA) methodologies, including environmental lifecycle assessment (LCA) (Step 4), Social LCA and lifecycle costing (LCC) (Step 5). When conducting an LCA, Social LCA or LCC, all life cycle stages of the product being studied are mapped, including raw materials acquisition, manufacturing as well as use and end-of-life, from cradle to grave. LCA is performed based on the ISO 14040 standard.[52] Social LCA follows the "guidelines for social life cycle assessment of products" released by UNEP in 2009 using data from the social hotspots database (SHDB). Finally, LCC involves assessment of all costs associated with the life cycle of the product that are directly covered by any one or more of the actors in the product supply chain (*e.g.*, manufacturer, supplier, user or consumer, or EoL actor) with complementary inclusion of externalities. The LCC is supported by Techno-Economic Assessment (TEA) to estimate the economic performance of the SSbD alternatives and evaluate their economic feasibility. This includes estimating: (1) fixed and total capital investment considering the total purchase equipment costs, and (2) product manufacturing costs (*e.g.* raw materials, labour, utilities, fixed capital-related costs). In our experience in SUNSHINE the above approaches require significant expertise in EHS and sustainability assessment, which is typically not present in SMEs, which also do not have the time and resources to acquire and apply such expertise even in the late stages of the product development when more information/data are available. Therefore, the support of consultants in applying these methods is of paramount importance and therefore consultants should be considered important stakeholders in the SSbD assessment and decision-making process.

The HARMLESS DSS offers several individual tools for the pilot phase at the Diamonds platform **https://diamonds.tno.nl/projects/harmlesspublic**.[47] To complement the LCA approaches by risk assessment approaches, the HARMLESS SSbD approach (Adam *et al.*, to be published) provides a rationale and a selection of standardized *in vitro* NAMs, higher-tier *in vitro* NAMs, and ecotoxicity tests, including a three-tier point-of-entry bioaccumulation strategy.[45] The assessment in five sustainability categories is directly compatible with the portfolio sustainability analysis that is already established in industry.[50,53,54]

Depending on the SSbD scenario,[55] "intermediate SSbD" or "full SSbD" may be required,[46] and can be implemented by the above tools. At the end of the pilot phase, the resulting technology incl. the final product is re-assessed, patents on material and production processes are filed, and the business case is updated. If the sustainability segmentation and all economic signals are favorable, the project team pitches to management at Gate 5. If approved, the market launch is prepared by generating high-tier toxicological data by OECD TGs under GLP for the REACH and applicable sector-specific registration, and by installing production facilities. Even then, the innovation may still fail technically (and never be launched) or by lack of market adoption.

2.4 From SSbD to safe and sustainable innovation approach (SSIA) through regulatory preparedness

Regulatory trends are a routine criterion in StageGate with sustainability segmentation processes.[50,53,54] Obtaining the right information in a timely manner can accelerate the agendas of innovators and manufacturers. There are however challenges for regulators in accessing all relevant data sources to search for early indications of upcoming trends in innovation and research which need to be checked for compliance with existing or proposed regulation.

The Safe and Sustainable Innovation Approach (SSIA) aims at reducing the time gap between the emergence of technological innovations and the development of suitable risk assessment tools and frameworks. SSIA combines SSbD with regulatory preparedness. The Regulatory Preparedness (RP) concept aims to improve the anticipation of regulators in order to facilitate the development of adaptable (safety and sustainability) regulation that can keep up with the pace of knowledge generation and innovation of innovative materials such as nanomaterials, nano-enabled products, and advanced materials. Both SSbD and RP concepts are supported by a process to share and exchange knowledge, information and views in a Trusted Environment. Dialogue between innovators and regulators is a vital component of SSIA.[56]

During the course of the projects, the "Early4AdMa" framework (Early Awareness and Action System for Advanced Materials), developed at OECD level for regulatory preparedness for AdMa, was revised, and specifically the data-demanding tier 2 was slightly simplified from over 150 questions to 65.[49,57] Workshops that were jointly organized by the OECD and HARMLESS,[58] and by OECD and SUSNHINE, respectively, had indicated the need of improvement by simplification. And yet, a gap in the toolset was perceived between the very qualitative Early4AdMa_tier_1 and the very data-demanding Early4AdMa_tier-2, and two tools were developed:

SUNSHINE regulatory foresight is a tool which can inform regulators in a timely manner of early warning of developments of new and emerging materials, The Foresight Framework comprises of two stages. The first is the use of text mining using the Tools for Innovation Monitoring (TIM) software developed by JRC,[59] on the SCOPUS and other databases.[60] This provides a selection of the most likely upcoming and emerging advanced materials, which is refined. In the second stage, this selection is reduced to a priority list by a process of discussion and evaluation by a team of selected experts who include regulators and industry, but also experts from outside material science such as social scientists and environmentalists. In order to maintain confidentiality, the work of this stage is performed within a Trusted Environment, which comprises the expert group of invited evaluators, and is not open to other stakeholders. The emerging AdMa are then shared with experts in the OECD Advanced Materials Steering Group for a Tier 2 Early4AdMa analysis.

The HARMLESS Early Warning System (EWS) was designed as an easy and practically applicable tool for screening a variety of materials in a reasonable amount of time in order to support regulatory preparedness. The HARMLESS EWS is organized in two tiers, each underpinned by a specific methodology and facilitated by a dedicated online tool. The initial Tier 0 categorizes the materials using AMEA. Tier 1 firstly screens materials by asking 15 easy questions that do not require detailed expert knowledge. Thus, it is ideal for data-poor materials at early innovation stages. The questions cover issues related to human and environmental exposure and hazard, sustainability and applicability of existing regulations and are aligned with the WASP tool fostering stakeholder dialogue in a trusted environment. In a more elaborated version of the EWS, experimental assessment based on new approach methodologies (NAMs) is suggested, which is largely aligned with ASDI (described above). As outcome, the user is provided with (1) material-related concerns, (2) prioritization of advanced materials and (3) recommendations for (regulatory) follow-up actions. Importantly, the tool could be easily integrated into the existing OECD Early Awareness and Action System for Advanced Materials (Early4AdMa).[49]

2.5 Tiered tools, tiered & targeted requirements of input data

The tiered suite of tools is positioned for different stakeholder requirements—be it innovators, regulators, or others—also by the tiered & targeted requirements of data to run the tools (Fig. 2).

Specifically, the tools for innovators at early innovation stages (AMEA, WASP) and the tools for regulatory preparedness ($\text{EWS}_{\text{simple}}$ and SUNSHINE foresight) require no numerical data, but generic description of the targeted product, application and material category. If *in silico* NAMs are applicable and efficient, they can support initial assumption *via* structural similarity. The listed tools require the use to reflect on the positive and negative impact on Sustainable Development Goals (SDG targets). The sustainability segmentation in industrial practice differentiates between global regions. Some EU drafts of regulation such as the ESPR refer to the SSbD framework, such that SSbD may change its character from voluntary to mandatory for certain classes of chemicals and materials. Hence the region of applicability of the present suite of tools is the EU, although especially the tools for early innovation stages are not specific to EU regulations. The tools match the requirements of the "SSbD scoping" by the JRC guidance.[46]

The tools for intermediate technological readiness (ASDI and SUNSHINE Tier 1 for innovators, $\text{EWS}_{\text{elaborated}}$ for regulators) require semi-quantitative data, which is typically acquired by *in chemico* NAMs, *in silico* NAMs or *in vitro* NAMs. Such data is comparative and increases its predictivity by including reference materials in the data matrix. Additionally, sector-specific information on the system integration allows a comparative assessment of the impact on prioritized SDG targets compared to the CoMa. Importantly, the tools allow for limited availability of data and assess uncertainties (SUNSHINE Tier 1), and allow the user to modify the data matrix, where also the results from additional transversal tools (DIAGONAL, see below) can be integrated in the ASDI heatmaps. The tools can thus be adapted to match the requirements of the "simplified SSbD" or "intermediate SSbD" by the JRC guidance,[46] as appropriate for the specific innovation scenario.

Finally, for the higher technological readiness at pilot stage semi-quantitative and quantitative data is generated by *in vitro* NAMs, possibly also by *in vivo* assessment if synergistic with REACH registration requirements. The data generated for SSbD purposes can possibly support read-across. LCA tools are enabled by value chain cooperation and upscaling of the production processes. The tools can thus implement the "full SSbD",[46] if required.

The strong tiering of the data requirements and methodology in the SUNSHINE DSS and HARMLESS DSS is key to retain the incentives of implementing SSbD practices widely. But in some scenarios, the initial SSbD scoping may prioritize specific aspects, which are then assessed from early to mid to high technological readiness in the DIAGONAL transversal approach.

2.6 DIAGONAL transversal approach: set of predictive tools and decision support tool (DST)

DIAGONAL has developed a comprehensive suite of instruments, all of them being centrally available *via* the DIAGONAL-specific App in the Enalos Cloud Platform (**https://enaloscloud.novamechanics.com/diagonal.html**), following the FAIR data principles. This dedicated instance provides tools for risk assessment, risk management, and SSbD methodologies. Moreover, it includes services designed for the collection and curation of experimental data (Electronic Laboratory Notebooks System) and a dynamic repository for nanomaterial-related data (DIAGONAL DB). In total, nine different instruments are available, with the DIAGONAL nano-awareness survey as a broader initiative targeting a wide range of SMEs and operating at a more generic level than the HARMLESS and SUNSHINE pre-screening tools for the ideation and business case phases. By identifying whether SMEs engage with nanomaterials – intentionally or incidentally – this survey raises awareness of the SSbD principles among those who are not yet involved.

In terms of regulatory readiness, two of the DIAGONAL instruments (Nanotube Construct, NanoBioAccumulate) have been evaluated using the TRAAC framework,[61] which provides a comprehensive multi-criteria methodology to ensure that these solutions meet both regulatory requirements and stakeholder expectations. Further details on the DIAGONAL instruments with specific predictive functionalities are presented in the following subsections. In this context, the DIAGONAL Decision Support Tool (DST), shown in Fig. 5, plays a central role by enabling the identification of SSbD strategies. With regard to SMEs as potential users of the DST, expert interviews revealed that a simple, efficient and user-friendly tool with step-by-step guidance and clear regulatory relevance is essential. Other needs include pre-checks for compliance, integration with existing databases, TRL-based assessments, and benchmarking against industry standards, while ensuring data transparency and quality.

2.6.1 DIAGONAL DST and other predictive tools

2.6.1.1 DIAGONAL DST (decision support tool). The DIAGONAL DST is a stepwise approach adapted on the basis of the SSbD framework (*c.f.* Fig. 5). Being publicly available in the Enalos Diagonal Cloud platform (**https://enaloscloud.novamechanics.com/diagonal/dst/**), this approach tries to assess and provide suitable strategies to follow in order to improve the safety and sustainability of either of the material and the process for MCNM and HARNs production. The resulting score system evaluates individually each one of the four steps covered by the tool: (1) hazard of the material, (2) production and processing, (3) final application phase and (4) environmental sustainability. The resulting evaluation for each step is a score from 1 to 5, with 1 being the rating for a safe step and 5 the most hazardous grading. To estimate the scores for the hazard and the process steps, control banding tools also developed within the DIAGONAL project are used. In the case of the evaluation of the final application, a model has been adapted to predict the fate of the MCNM and HARNs based on the SimpleBox4Nano model, which is specific for nanomaterials. Finally, the environmental stage assessment allows to compare an LCA from a nanomaterial with the results of the redesigned materials implemented

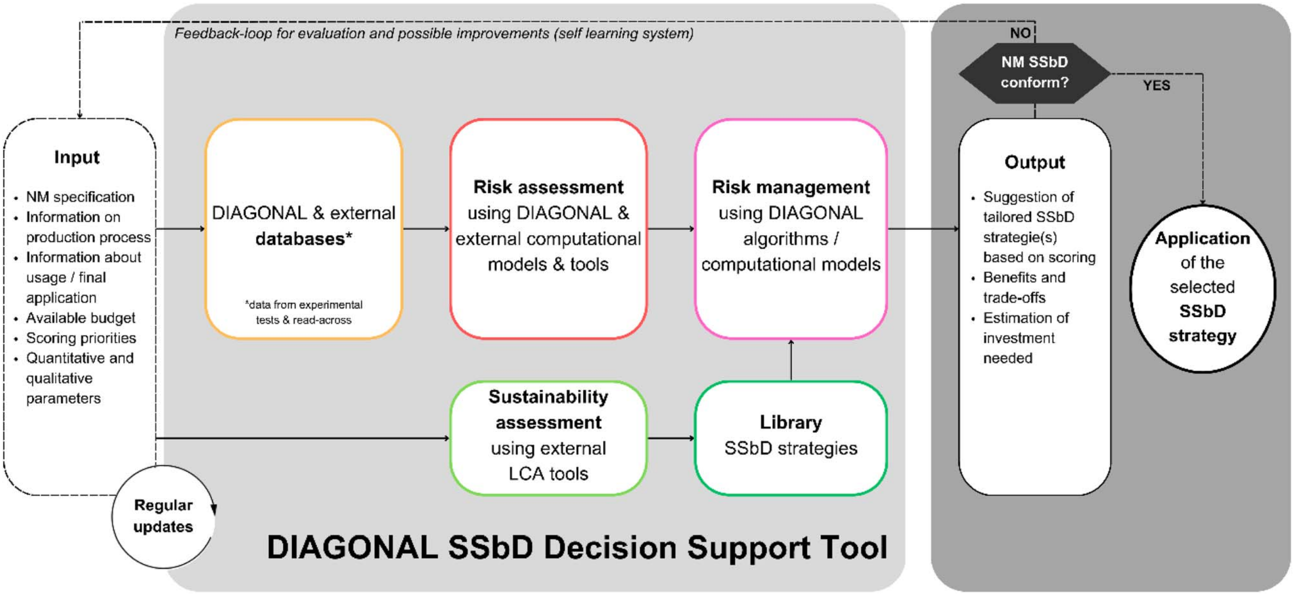


Fig. 5 Graphical representation of the DIAGONAL Decision Support Tool (DST), outlining the iterative process for identifying safer and more sustainable nanomaterials. It includes the key steps of sustainability assessment, risk assessment, and risk management, alongside integrated databases and SSbD strategy libraries. Necessary inputs and resulting outputs are also depicted, guiding users in selecting appropriate strategies based on assessment results.

within DIAGONAL. Once the four steps are evaluated, a list of strategies aiming to improve the material production are proposed. These strategies are grouped in three different sets: safe by material design, safe by process and sustainability. Along with this list of strategies, a final score of each step is also provided. Consequently, users can select the best options to be applied for the material improvement.

2.6.1.2 NanoBioAccumulate tool. The NanoBioAccumulate Tool is publicly available in the Enalos DIAGONAL Cloud Platform (**https://www.enaloscloud.novamechanics.com/diagonal/pbpk/**), and was described recently.[62] Designed with the aim to support the implementation of SSbD strategies considering environmental risk assessments of nanomaterials, it is a user-friendly tool accessible to researchers and stakeholders. The NanoBioAccumulate tool is able to model the uptake and bioaccumulation of nanomaterials in invertebrate organisms from soils and aquatic environments including two models: the simple One-Compartment model (organisms are considered as single compartments) and the One-Compartment with Stored Fraction model (for NMs accumulated in the organism). Through experimental data provided by the users, kinetic rate constants and other parameters are estimated. Moreover, this tool is able to simulate NM accumulation in different organisms based on available data.

2.6.1.3 Nanotube Construct tool. The Nanotube construction tool is publicly available in the Enalos DIAGONAL Cloud Platform (**https://enaloscloud.novamechanics.com/diagonal/nanotube/**). Its development and functionality were recently described[63] and promoted *via* a EU Observatory on Nanomaterials (EUON) “nanopinion”.[64] This tool allows the digital construction of energy-minimised nanotubes composed of single-layer materials, including both carbon-based and non-carbon materials. Thus, Nanotube Construct tool provides great support to researchers and users, allowing them to calculate relevant atomic descriptors to understand the properties of these materials.

2.6.1.4 Nano Graphene Impact tool. The NanoGraphene Impact tool is publicly available in the Enalos DIAGONAL Cloud Platform (**https://enaloscloud.novamechanics.com/diagonal/grapheneimpact/**) and a scientific publicationrelated with its development was recently published.[65] This tool operates by analysing user-provided data and enables the evaluation of the comparative toxicity level of Graphene NanoFlakes on human cells by predicting the biological interaction of these nanomaterials with proteins and membranes through pre-trained machine learning random forest regression models. The tool classifies the toxicity levels (low, medium, high, or very high) providing an associated impact score, and a categorised impact level, which support researchers in the identification of the relative toxicological impact of the Graphene Nanoflakes under study.

2.6.1.5 Risk Management tool. The Risk Management tool is a robust model that aids regulatory bodies, industries, and stakeholders in selecting the most appropriate risk mitigation strategies to configure safe working environments, being publicly available on the Enalos DIAGONAL Cloud Platform (**https://www.enaloscloud.novamechanics.com/diagonal/dss/**). This is a control banding tool that addresses exposure risks at various stages of the life cycle of HARNs and MCNMs, ensuring compliance with safety regulations in working environments through uploading as inputs different data regarding workspace and tasks conditions, as well as material specifications and detailed characteristics. The Risk Management tool enhances stakeholders' ability to manage risks effectively, supporting safer product development and manufacturing processes.

2.6.1.6 Zeta predict tool. Zeta-predict toolbox is publicly available in the Enalos DIAGONAL Cloud Platform (**https://www.enaloscloud.novamechanics.com/diagonal/zpredict/**). This tool constitutes a method to calculate the zeta potential based on electron microscopy images of colloidal dispersions made by liquid cell or cryogenic electron microscopy, the DLVO theory and atomistic force-fields. Moreover, particle radius and the interparticle distance can also be calculated. Users insert as inputs different parameters of nanoparticles and solvent, and the surface electric potential and the surface charge density are calculated and provided as output.

3 Discussion: case studies

3.1 Case study on SiC@TiO$_2$ anti-stick coatings (SUNSHINE)

The company Laurentia Technologies specializes in the development, production, and marketing of microencapsulated active ingredients and functional coatings based on nanomaterials. The company has introduced a MCNM coating made of silica carbide and titanium dioxide (SiC@TiO$_2$), which offers non-stick properties for applications such as bread baking trays. This innovative material serves as an alternative to perfluoroalkyl and polyfluoroalkyl substances (PFAS)-based non-stick coatings, like Teflon (polytetrafluoroethylene or PTFE). Polytetrafluoroethylene (PTFE), is extensively utilized across various industries due to its chemical, thermal, and electrical stability, as well as its low friction properties.[66] Teflon is employed as a coating material in non-stick cookware to prevent food from adhering during cooking. However, at typical cooking temperatures, PTFE-coated surfaces release chemicals and gases that range from mildly to severely toxic. Furthermore, the synthesis of PTFE involves the use of PFOA (perfluorooctanoic acid), a well-known environmental pollutant, and there are reports of PFOA being detected in the gas phase emitted from cooking utensils under normal cooking conditions.[66] Since the exposure to elevated levels of certain PFAS cause adverse health effects, including diminished antibody responses to vaccines, elevated cholesterol levels and reduced birth weight in infants,[67] there is a concerted effort within industries to identify safer and more sustainable alternatives to these type of materials. Eliminating the use of toxic and carcinogenic substances such as PFAS represents a significant advancement towards safer products. For this reason Laurentia realized a Sol–Gel-Derived Silicon-Containing Hybrids modified with SiC@TiO$_2$, which enhance anti-sticking properties when used as coatings on baking trays.[48] The incorporation of SiC within the core of the TiO$_2$ enhances its mechanical and thermal properties, durability, and anti-sticking capabilities.[48] The MCNM comprises two material components: a 60 nm SiC@TiO_2 and a 500 nm SiC@TiO_2. As previously mentioned, Tier 1 and Tier 2 depicted in Fig. 4, have been applied to this case study and are described in the following chapters.

The application of SUNSHINE Tier 1, identified higher safety and sustainability performance of the MCNM product from Laurentia compared to the conventional benchmark (Teflon) across various aspects and life cycle stages.[48] The data indicates that the MCNM-enabled coating is characterized by higher percentages of positive contribution to safety and sustainability aspects than Teflon in four out of five evaluated life cycle stages and considering the overall percentage of positive contributions. The EoL stage is the sole phase where the MCNM shows fewer positive contributions compared to the benchmark. Furthermore, the MCNM-enabled coating excels in all evaluated aspects except functionality, where it matches the benchmark. These findings highlight that the innovative coating is not only competitive with Teflon but also offers enhanced safety and sustainability, without compromising functionality.

The application of Steps 1, 2, and 3 of the EC-JRC Framework to the Laurentia case study did not identify any significant hazard properties or risks for the analyzed exposure pathways (*i.e.* inhalation occupational pathway and ingestion of the innovative material used for the coating). However, uncertainty remains a highly relevant factor, primarily due to partial available information on intrinsic properties of the MCNM (Step 1) and the unassessed exposure scenarios resulting from insufficient data (*i.e.* occupational exposure during the applications of the MCNM on baking trays).

For the application of Steps 4 and 5 of the EC-JRC Framework, a Life Cycle Sustainability Assessment (LCSA) was conducted, including LCA, LCC, and S-LCA. The LCA results showed that the MCNM-coated baking tray has lower environmental impacts than the Teflon-coated tray. This is mainly due to the quantity of steel used, which contributes significantly to the environmental impact, whereas the coating weight has a minor impact. For the Teflon-coated tray, the environmental impact is even higher due to its disposal every year. The economic assessment (LCC) revealed that the Laurentia scenario outperforms the benchmark in terms of economic impacts, which have been evaluated across three different contexts: European, Chinese, and USA benchmarks. The highest costs are attributed to the steel used for the production of the baking tray. The downstream phase contributes most to the total cost for both the Laurentia and benchmark scenarios. Finally, the S-LCA results showed that the upstream phase contributes most to social impacts. Improving supplier selection and transparency could enhance social sustainability for Laurentia's products. The application of the approach *via* the e-infrastructure significantly facilitated the development of the case study product. The e-infrastructure provides graphical results obtained for each tier (left side of Fig. 3), as well as general and conclusive results, as shown on the right side of Fig. 3, where it can be observed that all the assessed aspects fall into the higher performance classes (*i.e.* "High" and "Very High"). Additionally, it allows for the easy and quick identification of potential safety and sustainability issues. This brought the identification of SSbD strategies, thereby enabling more informed and efficient decision-making processes. For example, the Tier 1 application identified a potential hotspot related to the end-of-life phase of the innovative antistick coating when compared to the benchmark. The adopted strategy was to investigate this potential hotspot during the Tier 2 application, which revealed that the environmental impacts of the innovative material were lower than those of the benchmark at the end-of-life stage (Fig. 6).

3.2 Case study on AgNWs (DIAGONAL)

3.2.1 General overview. The Danish Technological Institute (DTI) is a self-owned and non-profit research and development organization. As part of their focus on advanced materials, processes, and technologies for the production of lightweight, flexible, and embedded electronics, DTI has developed silver nanowires (AgNW) to be used in conductive tracks for printed electronics. The synthesis of AgNW-based results in pastes, which through purification and ink formulation can be tailored for printing on various substrates. The applications include smart wearables, touch-responsive films and "invisible" sensors on *e.g.* clear plastic or glass.

The physico–chemical characteristics of AgNWs, namely morphology and redox reactivity, has raised safety concerns, since these materials may exhibit fiber-like toxicity. Indeed, the internalized AgNWs showed diverse adverse effects in several cell lines, including lysosomes and mitochondrial damage or toxicity and pro-inflammatory effects in a length-dependent way in murine macrophages.[68,69] Moreover, exposure-related health risks were also described by i*n vivo* tests, since pulmonary toxicity produced by short and long AgNWs was reported,[70] as well as their potential ecotoxicity due to its ability to adversely affect the reproductive output of *D. magna*.[71]

3.2.2 AgNWs data gathering in DIAGONAL. AgNWs developed by DTI were used in DIAGONAL to obtain experimental data to feed the DST with information regarding these particular nanomaterials. In addition, different strategies to improve their safety and the sustainability of the production process were defined and developed to test their effectiveness, being those that proved to be successful included as output in the DST.

Several physicochemical properties of an original batch of AgNWs and printing ink containing these NPs were analysed through different methodologies. By the same token, the potential toxicity of these materials was evaluated applying different realistic and advanced *in vitro* models that mimic human exposure. DTI AgNWs consist in a heterogeneous population of NMs with dimensions of 80–200 nm width and 8–30 μm length and some safety issues associated to their interaction with the immune cells were observed in terms of cytotoxicity and inflammatory response. Regarding the sustainability of the process, a full LCA, LCC and −LCA was developed using primary data from DTI. From the environmental perspective, the main drivers for sustainability were the use of silver for the production of $AgNO_3$ followed by the energy consumption. The use of acetone has a medium impact, but it can be recycled, lowering

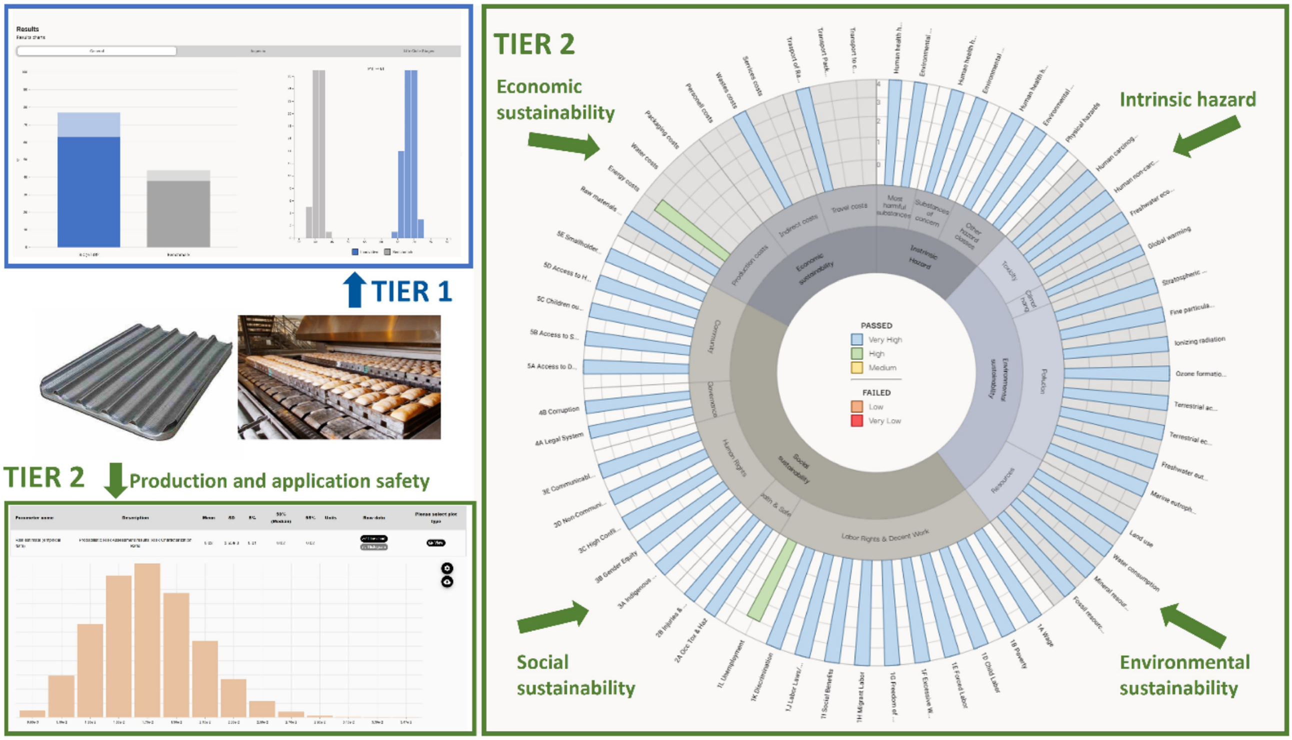


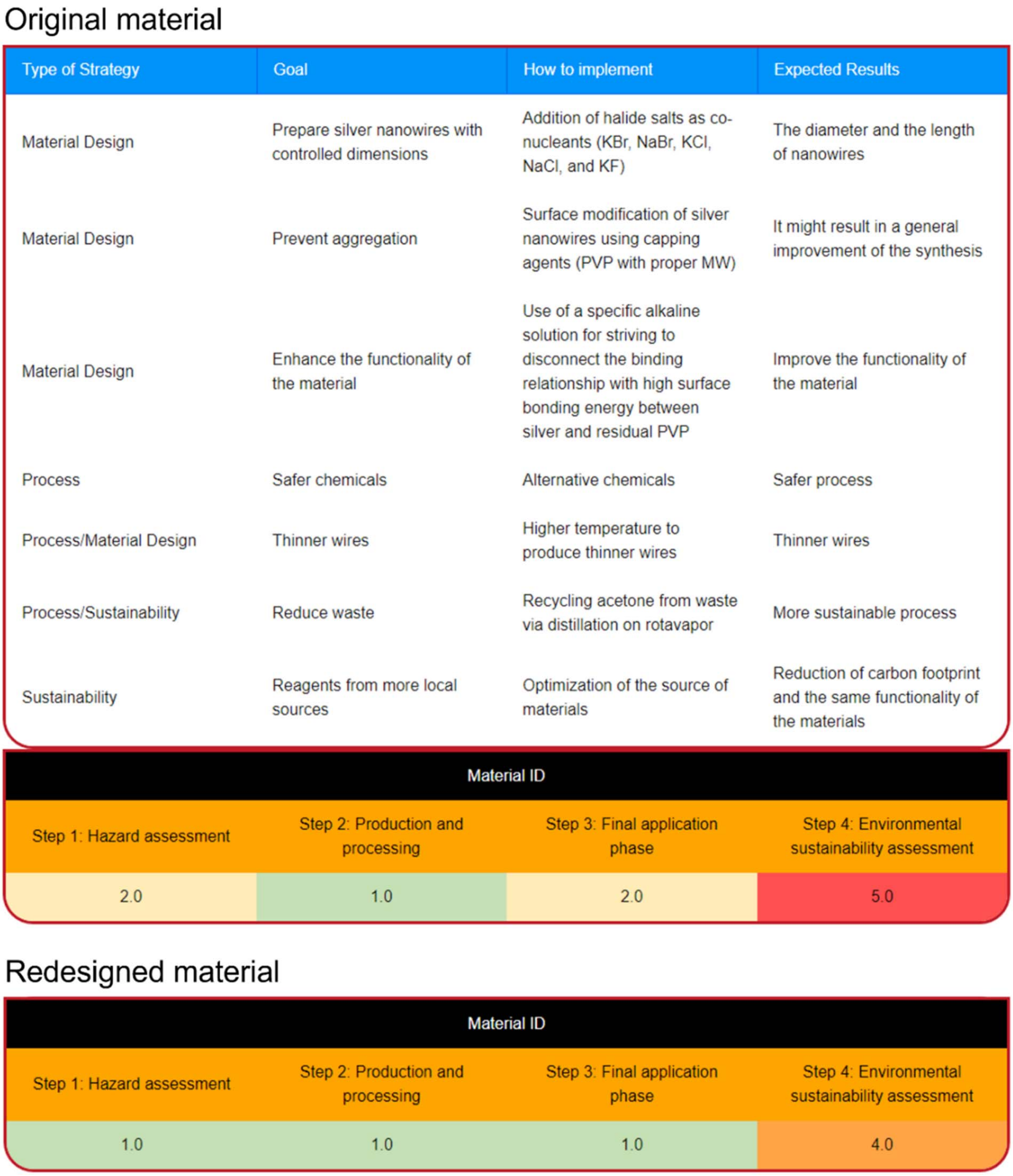
Fig. 6 Case study on anti-stick coatings for baking trays using SiC@TiO$_2$ instead of PFAS-based non-stick coatings, and compared to Teflon. Tier 1 of the SUNSHINE e-infrastructure shows percentage of positive contributions for the SiC@TiO$_2$ anti-stick coating in dark blue and the Teflon in dark grey along with the related uncertainty, and the probability that the first is better or equal to the second, identifying potential hotspots regarding safety, sustainability and functionality aspects. Tier 2 delves deeper into these hotspots, assessing the aspects considered across the five steps outlined by the JRC. The results are presented through a scoring system, which highlights the improvement of the SiC@TiO$_2$ anti-stick coating compared to the Teflon for each assessed criterion.

significantly the environmental impact linked to its use. From the socioeconomic aspects, the equipment and labour dominate the impacts, which can be modulated at higher TRLs.

All the data obtained were used to feed the DST with information regarding the toxicology of AgNWs associated to their specific physico–chemical properties and the sustainability of the specific process used in their production.

For the development of the strategies to be included as output in the DST, the physicochemical and toxicological data, together with their formulations, were studied in detail to design new and safer nanomaterials from early stages without affecting functionality. The production and processing of the NMs was also studied to evaluate the occupational safety and the sustainability. Different strategies were proposed based on the toxicity and sustainability results, the occupational exposure and the scientific studies found in the literature. Once a set of strategies were compiled, meetings were held with DTI with the aim to evaluate the feasibility of their implementation in the demonstrator's facilities. For this specific case study, the strategies selected are shown in Fig. 7. The toxicity of AgNWs is diameter-dependent, being significantly decreased by reducing this parameter.[72] In terms of Safe by Material Design, the application of this strategy did not meet expectations, since similarly to the original materials some toxicity concerns arose regarding the immune cells. On the other hand, the Safe by Process design/material design/sustainability strategies yielded satisfactory results, as increasing the production temperature led to thinner wires and, as mentioned above, improving thus their performance, which impacted also in the sustainability of the redesigned product. Recycling systems for the acetone solvent were included, improving the environmental performance, and the sources to obtain the raw materials were reconsidered, achieving social benefits. The overall reduction of the environmental footprint thanks to the redesign strategies applied was of 33%, achieving also socioeconomic benefits.

3.2.3 Application of the DST in the case study. In a first stage, at safety level, control banding tool is used to estimate the hazard of the material by selecting the option from the list that fits best for the material regarding some physicochemical properties as well as choosing the H-phrases that may apply. With this information, it was identified that the original material was reasonably safe, but this low hazard was reduced in the case of the redesigned material. Regarding the process, another control banding tool is used to evaluate its safety. In this case, information about the working environment, the task performed and the material is required to select the most accurate option for the AgNWs. In addition, the occupational concentrations of the material in the working environment should be provided either using a file including on-site measurements or using specific occupational *in silico* models to estimate the



Original material

Type of Strategy	Goal	How to implement	Expected Results
Material Design	Prepare silver nanowires with controlled dimensions	Addition of halide salts as co-nucleants (KBr, NaBr, KCl, NaCl, and KF)	The diameter and the length of nanowires
Material Design	Prevent aggregation	Surface modification of silver nanowires using capping agents (PVP with proper MW)	It might result in a general improvement of the synthesis
Material Design	Enhance the functionality of the material	Use of a specific alkaline solution for striving to disconnect the binding relationship with high surface bonding energy between silver and residual PVP	Improve the functionality of the material
Process	Safer chemicals	Alternative chemicals	Safer process
Process/Material Design	Thinner wires	Higher temperature to produce thinner wires	Thinner wires
Process/Sustainability	Reduce waste	Recycling acetone from waste via distillation on rotavapor	More sustainable process
Sustainability	Reagents from more local sources	Optimization of the source of materials	Reduction of carbon footprint and the same functionality of the materials

Material ID

Step 1: Hazard assessment	Step 2: Production and processing	Step 3: Final application phase	Step 4: Environmental sustainability assessment
2.0	1.0	2.0	5.0

Redesigned material

Material ID

Step 1: Hazard assessment	Step 2: Production and processing	Step 3: Final application phase	Step 4: Environmental sustainability assessment
1.0	1.0	1.0	4.0

Fig. 7 Comparison of the four steps scores computed by the DST for the original (top) and the redesigned AgNWs after applying the selected strategies (bottom). A value of 1 represents the best score while 5 represents the worst result, as also indicated by the color scale behind (from green (best score) to red (worst score)). Along with the rates for the original material, the list of the proposed strategies is shown indicating information about type, goal, implementation and expectations after their application.

average concentrations. In this case, on site measurements data were used, obtaining the process carried out for the development of the material the best score. The final application step aims to evaluate the fate of the material in the environment. A fate model was developed within the Project to calculate the predicted environmental concentrations (PECs) and compare them with the baseline hazard level of the material (Step 1), which shows that the environmental hazard of the original material was low, obtaining a score of 2 which was improved for the redesigned material.

Finally, the environmental sustainability step was ideated to support the progressive optimizations of the baseline material based on quantitative measurements of the redesigned processes. Two cases will be considered: if the material to be evaluated has been already included in the DIAGONAL's database, the outcome will be a comparison between this input and the baseline (from DIAGONAL's experience). In this case, the user will include the results of each indicator from a full LCA to obtain a comparison between it and a previous (DIAGONAL's) scenario. The score is obtained based on the improvement of each indicator (following the Environmental Footprinct Method). If the material is not included in the database, then a real or estimated percentual improvement of the environmental indicators is needed to obtain the environmental score. In the next step, different strategies to improve the sustainability of the material are provided. This approach allows to adjust the level of information from the user to the outcome of the tool. In Fig. 7, the environmental score is 5 as the baseline material performs worse than the redesigned (optimized material).

3.3 Case study on automotive catalysts by oxide perovskites (HARMLESS)

To initiate the SSbD scoping, the AMEA tool categorized the oxide–perovskites: they consist of particles that are not nanomaterials according to the EU recommendation for their definition, but they are nano-enabled by ISO definition and "advanced", *i.e.* they are specified to achieve a superior functionality, are not on the market since more than a decade nor available from more than 10 suppliers in similar quality in ton scale.[45] Also the CoMa of an automotive catalyst was categorized as a nano-enabled material consisting of particles.

At ideation and business case, the user (BASF company) answered WASP for the targeted design space of oxide–perovskite containing Ni, Co, La and either Pd or Pt dopants. The case is described in detail by Adam *et al.*[73] In short, seven flags were raised with respect to exposure, hazard and sustainability, redesign advice was given, as well as assessment advice with specific descriptors to characterize at Lab Phase. Based on a search in the TNO Substance Information System (SIS) and ECHA database, Co, Ni and their oxides were identified as classified and hazardous for human health and the environment. The user replied to WASP that occupational exposure may occur, but due to encapsulated use, neither consumer nor environmental exposure are expected. The tonnage assumed in the business case of more than 1000 tonnes triggered the WASP recommendation to perform a more elaborate hazard assessment, including *in vitro* or higher tier NAMs. The sustainability assessment was prioritized on the trade-off between Goal 12.2 (due to the presence of critical raw materials) and 11.6 (due to the benefit of cleaner air by use of an exhaust catalyst).

Gate 3 was approved, and the lab phase was started with synthesis of six different oxide–perovskite versions with varying content of Ni, Co and dopants, as motivated by the design space described in academic reports (TRL 3).[74,75] The flags from WASP automatically preconfigured a data matrix in ASDI that the user had to fill with data measured by *in chemico* and *in vitro* NAMs and with comparative sustainability descriptors. The user was prompted for a reference material with higher-tier data (selecting $ZnNiFe_4O_8$ and $NiFe_2O_4$)[76] and for a CoMa in the same application (selecting CeO_2_Pd). The user decided to select two descriptors of performance. The NAMs were derived by WASP/ASDI from the inhalation IATA[77] *i.e.*, particle size, surface area, composition, dissolution and reactivity, as well as dustiness and respirable fraction. Due to the luxury of public funding, also genotoxicity, cytotoxicity, aquatic dissolution & aquatic dispersion stability, transformation and toxicity to algae, daphnia and fish cell lines were determined during lab phase. Numerical descriptors of sustainability (triggered by SDG 12.2) included the proportion of critical raw materials, of non-renewable, non-reusable and non-recyclable materials, of secondary (recycled) materials, product lifetime, and ability for reuse and recycling. The measured dustiness index triggered a re-design recommendation of handling only suspensions. This was rejected by the synthetic labs, since calcination was a necessary step to convert intermediates to the oxide product. Instead, risk was managed by containment (in accord with routine lab hygiene for Ni compounds).

ASDI enables the reader to compare all materials *via* the colors attributed to each value. This color coding is described in detail in the original publication.[47] Briefly, biological ranges were defined for each descriptor, and green and red colors attributed to the limits of those ranges, considering green as "safest" or "preferable" and red as "most problematic". Sustainability descriptors were assessed on a 5-point scale, consistent with industrial practice.[50] The differences in hazard-related descriptors leveled out to some extent after transformation, but LaCoNi_Pd was still less reactive than the other oxide–perovskites after transformation.[78] In ecotoxicity results, several descriptors reflected increasing toxicity with increasing Nickel content. Concerning performance, LaCoNi_Pd was nearly 2-fold better than the CoMa. LaCoNi_Pd surpassed all other oxide–perovskites in catalyst turnover activity, where it is 7-fold higher, but remained below the performance of the CoMa. Three-way catalysts have the main function of removing pollutants such as CO, NO_x and hydrocarbons from the car exhaust, ultimately providing cleaner air.[79,80] In this perspective, the lack of primary performance as catalytic converter cannot be compensated by the above-benchmark performance in oxygen storage capacity, which is only a secondary requirement. In full industrial settings, even more descriptors of performance would need to be considered, and the ASDI flexibly allows users to add lines for such purposes.

As described in detail by Adam *et al.*,[73] there is no trade-off between the sustainability and performance dimension in this case, and LaCoNi_Pd constitutes the best alternative in the predefined design space. But the systematic trends in the safety dimension are small in comparison to the decisive differences in the performance and sustainability dimensions: After synthesis and testing, it was found that the perovskites did not achieve the targeted improvement on SDG 11.6. All in all, the oxide–perovskite R&D project is likely to be stopped after Lab Phase and will not proceed further to Pilot Phase (Fig. 8).

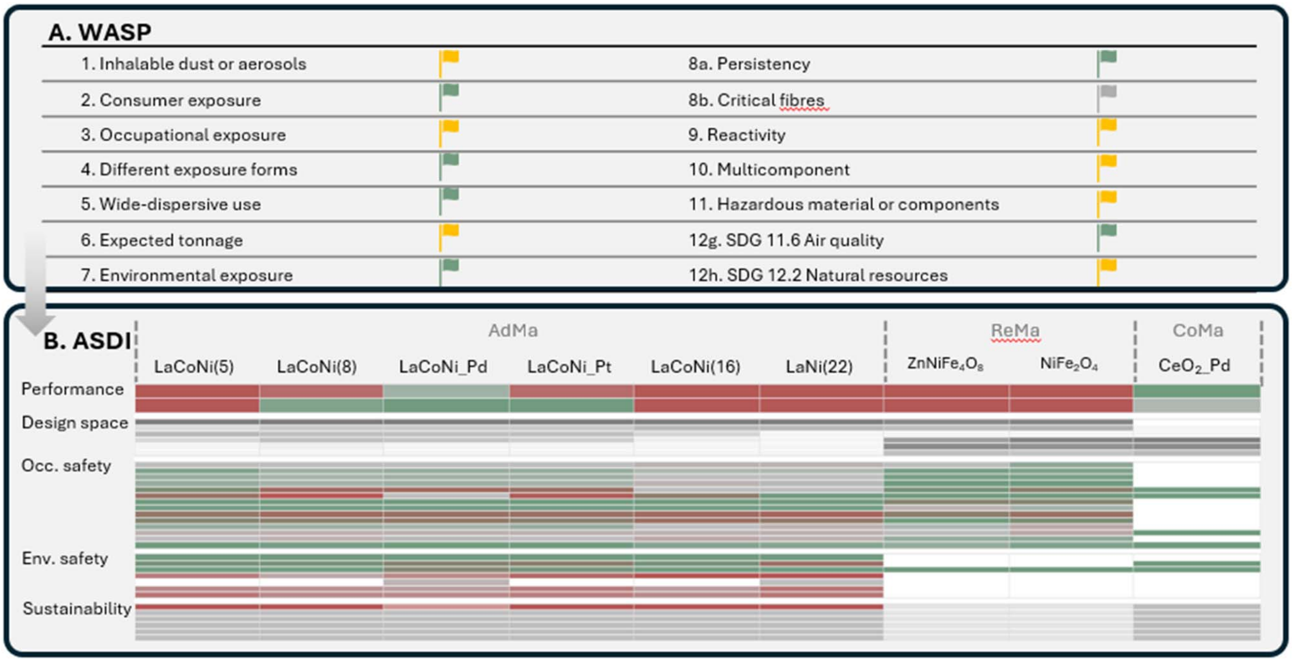


Fig. 8 Case study on automotive catalysts using perovskites instead of the CoMa of Pd on CeO$_2$, and compared to two reference materials (Ni-containing Spinels) that were previously characterized with higher-tier *in vivo* data (HARMLESS project). The WASP tool raises flags and identifies trade-offs between sustainable development goals. The recommendations by the lower stage WASP tool to assess specific endpoints and descriptors (not shown here) generate a data matrix in the ASDI tool, where each line represents one descriptor that is normalized to the biologically relevant range. There is no trade-off between the sustainability and performance dimension in this case, and the systematic trends in the safety dimension are small in comparison to the decisive differences in the other dimensions.[73]

4 Conclusions

The suite of complementary decision support systems (DSS, Fig. 2) that was delivered by DIAGONAL, SUNSHINE and HARMLESS established a common framework of aspects and indicators for safety, as well as an initial attempt at sustainability assessments. The results clarified terminology[4] and produced joint test cases (quantum dots, described elsewhere),[81] serving as a prerequisite for comparable and harmonized SSbD assessments. The suite of tools provides both SMEs and large industries with a shared foundation for the operationalization of the SSbD approach,[82] and the ASDI tool is also compatible with industrial practice of assessing safety and sustainability during R&D.[53,54,83] These indicators and aspects are not limited to the material categories of MCNM and HARN, but the tools recommended here for data gathering, *e.g.* grouping, environmental stability, transformation, are specific to MCNM and HARN. The suite of DSS facilitates the identification of available methods and tools applicable to different levels of assessment, based on the maturity of the alternatives being evaluated, the availability of data at various stages of the development process, and the available financial resources.

SSbD demands a systems approach that not only focuses on knowledge, data and tools but also on the development of processes and the organizational infrastructure to bring all the stakeholders together in a co-creation process. This includes not only innovators, but also regulators and policymakers who interact with the innovators in a trusted environment. Within the OECD Working Party on Manufactured Nanomaterials (WPMN) SSIA Steering Group, a system approach is taken by combining SSbD with Regulatory Preparedness in such a trusted environment.[56] The suite of tools supports the OECD's SSIA by a high level of alignment between tools for use by innovators and tools for use by regulators (Fig. 2). The SSIA was adopted by both SUNSHINE and HARMLESS, and SUNSHINE even incorporated it in its SSIA e-infrastructure.

SSbD implementation is supported by the present suite of DSS by offering tools with a very low hurdle to implementation of SSbD scoping and simplified SSbD, also for SME. Expert interviews by DIAGONAL highlighted that many SMEs struggle with the complexity of tools, limited access to data, and lack of data sharing across the value chain, making SSbD adoption a challenge. Without regulatory mandates or business-driven incentives ("SSbD pull"), adoption will remain low. Both SME and large industry (and academic innovators) face the same challenge that the SSbD design and SSbD qualitative assessment at very early innovation stages will not be done by sustainability professionals, but by chemists and engineers. A DSS can support efficient & harmonized screening without consultation and data gathering from too many other units of the company. For intermediate or full SSbD, the present suite of DSS offers useful tools, but challenges persist in the costs of performing the full SSbD assessment, including data generation, for both industry and SME. The complexity of data gathering is especially high for SMEs, because they need several external partners for this purpose, potentially supported by consultants. This challenge cannot be solved by DSS tools.

5 Outlook

During the development (Section 2) and demonstration (Section 3) of the current suite of tools, several open issues were identified. Towards the end of the NMBP-16 projects, the JRC guidance acknowledged the need for scoping, tiering and prioritization of hot spots.[46] The integration of safety and sustainability into the different stages of the innovation process (Fig. 1) is crucial for the operationalization of SSbD. However, it is not clear if only the R&D stage (potentially represented by TRL), or also other aspects such as the innovation context (SME or industry), the SSbD pull in the targeted sector of use, and more, determine the mapping of stages to SSbD tiers and DSS tools.[55] Guidance on how to apply the tools or toolboxes in each tier to address specific assessment and decision-making scenarios by different stakeholders is required. This includes several aspects to consider in future projects:

- Cost of performing SSbD screenings: costs influence the industrial investment decision to fund a project, or not. All present case studies are not representative of implementation in SME or industry, because the SSbD work in the present projects was subsidized by the EU.
- The increasing need for companies to demonstrate safety and sustainability compliance with various regulations, such as eco-design directives, corporate sustainability reporting directive (CSRD), REACH *etc.* will further strengthen the relevance of applying holistic approaches such as SSbD, enabled by the use of the decision-support described in this publication.
- Sector-specific implementations: many of the “flags” that are raised for different MCNMs by the tools for the Ideation and Business Case phases are the same flags for a specific sector of use, *i.e.* the discriminative value of these flags is limited. There is potential to increase the efficiency of assessment by generating sector-specific tools or guidance, in analogy to sector-specific ECHA use maps, sector-specific regulation, and upcoming sector-specific delegated acts to implement the eco-design for sustainable products regulation (ESPR).
- How to deal with trade-offs is an important question for the successful implementation of SSbD. In the current SSbD approaches, this question is covered only superficially or not at all. The hierarchical approach recommended in the JRC framework helps to avoid trade-offs on specific safety aspects due to pre-defined cut-off criteria. The Cefic approach includes a guidance on trade-offs but without providing specifics. It is quite clear, though, that SSbD decision making is not a technocratic task and therefore should consider not only technical criteria and indicators but also the trade-offs as defined by the involved actors. These trade-offs should be transparently considered in the future SSbD assessment and decision support tools (*e.g.*, by weights, cut-offs *etc.*).
- The influence of SSbD thinking on the innovation process is highest at early R&D stages, but the application of lower-tier assessments in the early stages presents challenges due to the purely qualitative assessment. Should it result in a summarizing SSbD assessment of AdMa compared to the CoMa? This requires integrating safety and sustainability aspects, along with the potential inclusion of weights, trade-offs, or even cut-off criteria. Or instead, should the considerable uncertainty in lower-tier assessment only raise flags for refinement? Many flags imply higher costs by higher-tier tools, and thus make the passing of the next gate less likely, but leave the freedom (and risk) of entrepreneurial decisions to the innovator.
- To reduce the uncertainty, the innovator could involve more value chain actors upstream and downstream, and could involve other stakeholders such as regulators. This approach may help in “open innovation” testbeds, with unknown implications on decision-making: Who takes responsibility? How to retain speed? Who pays all actors and stakeholders, and what is the reward? but most importantly, the open approach contradicts the globally accepted business model that requires each actor in the value chain to generate and file IP, in order to claim its share of the value. Communication during the lab phase is common only in static, long-term commitments such as joint development agreements (JDA) that in themselves take long to negotiate in anticipation of each partner's value creation.

More inter-stakeholder dialogue, change in the mindset and SSbD pull by downstream actors, and incentives to industry are needed to implement SSbD as common practice, starting from early project stages that facilitate the design and development of innovative products *via* decision support systems.

Conflicts of interest

WW is employee of a company developing and marketing advanced materials. VA, CD, LP, DH, AZ, SP are employees of consultancies offering SSbD services. The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

This study was carried out using publicly available case studies with data reported in previous publications of the safety screenings and sustainability screenings, as cited in the main text and here.[84–87] The digital tools are publicly available at **https://www.enaloscloud.novamechanics.com/diagonal/**, **https://diamonds.tno.nl/projects/harmlesspublic**, **https://www.sunshine.greendecision.eu/sign-in?origin=/sunshine**.

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