

Safe-and-Sustainable-by-Design Approach and Decision Support System for Advanced Materials

Susan Dekkers,* Veronique Adam, Veronica Di Battista, Andrea Haase, Julia Prinz, Gregor Nagel, Wouter Fransman, Michael Persson, Blanca Suarez-Merino, Wendel Wohlleben, Otmar Schmid, and Eugene Van Someren

To facilitate Safe-and-Sustainable-by-Design (SSbD), the HARMLESS project developed a practical SSbD approach and SSbD Decision Support System (DSS) for advanced materials. The HARMLESS SSbD approach and SSbD-DSS are in alignment with the EU-recommended SSbD framework and methods. The HARMLESS SSbD approach recommends New Approach Methodologies (NAMs) tailored to advanced materials and the innovation stage of the material under development. The approach follows a flexible stage-gate model with three innovation stages: 1) Ideation & Business Case Phase, 2) Lab Phase, and 3) Pilot Phase. The HARMLESS SSbD-DSS guides designers through a workflow starting with the Advanced Material Earliest Assessment (AMEA) tool. AMEA contains three questions enabling categorization and subsequently advice on design principles. A second tool, named Warning flags, Design Advice, Screening Priorities (WASP), consists of 12 questions to identify early warning flags and provide design and assessment advice. A third tool, named Alternative SSbD Design Inspector (ASDI), provides guidance on descriptors to measure in the Lab Phase for informed decision making on the most optimal SSbD version. By adapting the data and resource requirements to each innovation stage, the SSbD-DSS facilitates practical implementation of SSbD, supporting the user to find a transparent balance between safety, sustainability, and performance.

1. Introduction

The European Chemicals Strategy for Sustainability (CSS)^[1] is part of the EU's zero pollution ambition, one of the key commitments of the European Green Deal.^[2] The CSS aims to better protect citizens and the environment from harmful chemicals, boost innovation by promoting the use of safer and more sustainable chemicals and helps progressing the United Nation's Sustainability Development Goals (SDGs).^[3] The European Framework for Safe and Sustainable by Design (SSbD) of chemicals and materials as published by the Joint Research Centre (JRC) of the European Commission^[4] and its Methodological Guidance^[5] represent important steps toward the implementation of SSbD in product development. Yet, the European Framework published by JRC currently requires resources not compatible with the expected commercial value at early innovation stages and

S. Dekkers, W. Fransman, E. V. Someren
Risk Analysis for Prevention
Innovation & Development (RAPID)
TNO
Princetonlaan 6, Utrecht 3584 CB, The Netherlands
E-mail: susan.dekkers@tno.nl

V. Adam, B. Suarez-Merino
TEMAS Solutions GmBH
Lätteweg 5
Hausen 5212, Switzerland

V. D. Battista, W. Wohlleben
BASF SE
Carl-Bosch-Str. 38, 67056 Ludwigshafen, Germany
A. Haase, J. Prinz, G. Nagel
Department Chemicals and Product Safety
German Federal Institute for Risk Assessment (BfR)
Max-Dohrn-Str. 8-10, 10589 Berlin, Germany
M. Persson
Chalmers Industriteknik
Sven Hultins Plats 1
Gothenburg 41258, Sweden
O. Schmid
Institute of Lung Health and Immunity (LHI)
Ingolstaedter Landstrasse 1
Helmholtz Munich, 85764 Neuherberg, Germany

 The ORCID identification number(s) for the author(s) of this article can be found under <https://doi.org/10.1002/adsu.202500208>

© 2025 The Author(s). Advanced Sustainable Systems published by Wiley-VCH GmbH. This is an open access article under the terms of the [Creative Commons Attribution](#) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

DOI: 10.1002/adsu.202500208

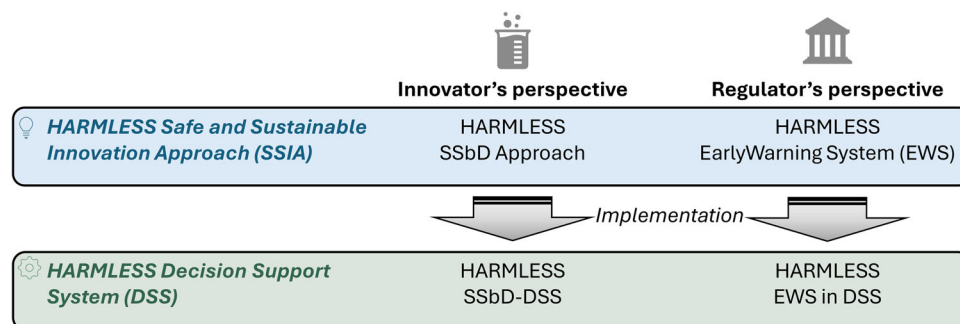


Figure 1. Overview of the HARMLESS Safe and Sustainable Innovation Approach (SSIA) and HARMLESS Decision Support System (DSS) for AdMa, aimed at supporting innovators to implement SSbD and regulators to improve their regulatory preparedness.

recommends methods that are not applicable to advanced materials (AdMa).

To address the need for simpler, less demanding approaches applicable to AdMa, the EU-funded HARMLESS project developed a practical Safe and Sustainable Innovation Approach (SSIA) for AdMa (Figure 1) to support innovators and regulators in the implementation of safe and sustainable innovation of AdMa. The OECD describes the SSIA as an approach to enhance the ability of all stakeholders to address the safety and sustainability assessment of innovations in a robust yet agile manner by combining (a) the SSbD concept for innovators and (b) the Regulatory Preparedness (RP) concept for regulators. Safe and sustainable by design (SSbD) is described by the OECD as an approach that focuses on providing a function (or service), while avoiding onerous environmental footprints and chemical properties that may be harmful to human health or the environment. Regulatory Preparedness, as described by the OECD, empowers regulators and policymakers to better anticipate and adapt governance to keep up with the pace of knowledge generation and innovations, including AdMa. Both SSbD and RP concepts are supported by a process to share and exchange knowledge, information, and views in a trusted environment. SSIA thus relies on dialogue between innovators and regulators.^[6] Within HARMLESS, the SSbD and RP concepts were made specifically and practically applicable to the development of AdMa resulting in the HARMLESS SSIA, consisting of the HARMLESS SSbD approach for innovators and the HARMLESS RP, known as the HARMLESS Early Warning System (EWS) for regulators. To facilitate practical implementation of the HARMLESS SSIA, both approaches are implemented in an online Decision Support System (DSS), resulting in (a) the HARMLESS SSbD-DSS (for innovators) and (b) the HARMLESS EWS in the DSS (for regulators). To foster the dialogue between innovators and regulators within a trusted environment, the questions within the HARMLESS SSbD-DSS and the HARMLESS EWS in the DSS are aligned ensuring that innovators and regulators think about the same crucial questions in the context of safety and sustainability.

This publication describes the HARMLESS SSbD approach and its implementation in the SSbD-DSS, while the HARMLESS EWS is described separately in Prinz et al.^[7]

Recent SSbD approaches for AdMa are inspiring but often remain conceptual.^[8–13] Some previous approaches have been implemented in practical tools or DSSs. Only a few of these approaches cover all SSbD dimensions, respect the specific require-

ments of AdMa and follow a tiered approach from qualitative to quantitative data.^[14,15] None of the previous approaches supports the user in a quantitative comparison of slightly different SSbD versions of the AdMa in a time and cost-efficient way using only a limited amount of questions, data, and resources.

This publication describes the HARMLESS SSbD approach and its implementation into the SSbD-DSS for the early innovation phases. The HARMLESS SSbD approach and SSbD-DSS are aligned with the European Framework for SSbD, complemented with a flexible stage-gate model and New Approach Methodologies (NAMs) tailored to AdMa. The HARMLESS SSbD approach and SSbD-DSS build on the frameworks, tools and methods developed within other initiatives, including NanoReg2,^[16] Gov4Nano,^[17] Early4AdMa,^[15] GRACIOUS,^[18] the Cefic Guidance^[13] and on the EU recommended SSbD Framework^[4] and Methodological Guidance as recently published by the JRC.^[5] Both the HARMLESS SSbD approach and the SSbD-DSS were developed and tested using several case study materials. The results of testing the SSbD-DSS with these case study materials are presented separately in Adam et al.^[19]

2. Overview of the HARMLESS SSbD Approach

The HARMLESS SSbD approach is tailored to AdMa that consist of particles or fibers or are expected to release particles or fibers within their life cycle, including but not limited to multi-component, metal- and carbon-based, and low and high-aspect-ratio nanomaterials. This is a very diverse class of emerging materials that present various specific properties which require specific considerations in the procedure used to assess their safety and sustainability. The HARMLESS SSbD approach is specifically designed to keep these specific properties in scope.

The HARMLESS SSbD approach is based on lifecycle thinking, it considers a flexible stage-gate model, and it has a modular structure for SSbD assessment (Figure 2). The HARMLESS SSbD approach aims to capture two distinguished scenarios: a) introducing a new product into the market or b) renewing an existing product. The approach adopts the Cooper stage-gate model^[20] and considers three innovation phases: 1) Ideation & Business Case phase, 2) Lab phase, and 3) Pilot phase, each of which ending with a decision on proceeding to the next stage (called the gate). SSbD is intended to be aligned with the “product development process”, i.e., the complete process of bringing a new product to the market, from idea generation to

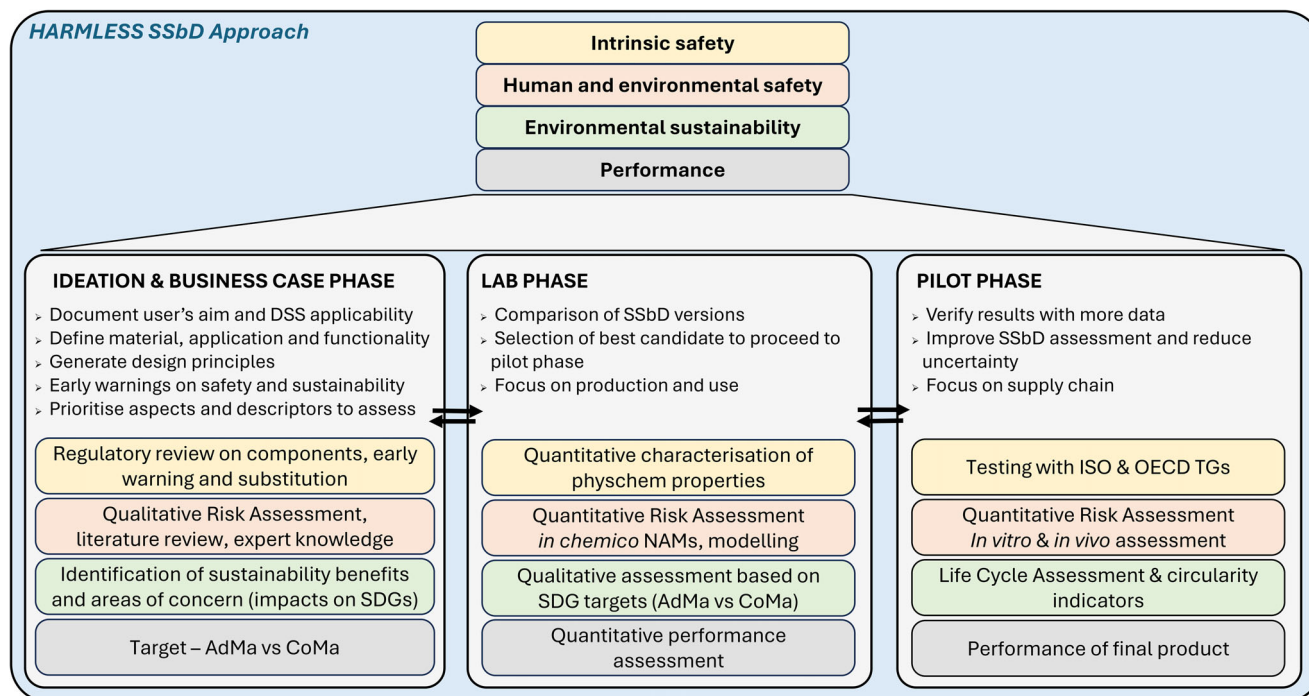


Figure 2. Overview of the HARMLESS SSbD approach. SDGs: Sustainable Development Goals, AdMa: Advanced Material, CoMa: Conventional Material, ISO: International Organization for Standardization, OECD: Organization for Economic Co-operation and Development.

market launch. Within the product development process, different companies apply different stage-gate models, but their general structure from early to late development stages is similar. The HARMLESS SSbD approach is flexible in the definition of its “innovation stages” to be adaptable to diverse product development processes happening in different companies and across sectors. Within each innovation stage of the product development, safety and sustainability aspects of the product are considered throughout its whole life cycle (Figure 2).

Four dimensions of SSbD are implemented (i.e., intrinsic safety, human and environmental safety, environmental sustainability, and performance), which can be (qualitatively and/or quantitatively) assessed in parallel. Intrinsic safety assessment is related to the characterization of intrinsic hazardous properties, i.e., potential regulatory hazard classification of chemical components and physicochemical characterization. Human and environmental safety are assessed using a risk-based approach, i.e., both, exposure, and hazard, are assessed in humans and environmental compartments with suitable NAMs, which are prioritized to make efficient use of resources. Environmental sustainability considers several aspects, including climate change, pollution, biodiversity, resource use, and circularity. Product performance is also a parameter to consider in the balancing of trade-offs at each stage gate and is therefore included in the HARMLESS SSbD approach. Data and resource availabilities along the product development process are considered for all SSbD aspects, moving from more cost-efficient qualitative NAMs employed during early phases to more expensive quantitative assessment methods in the later product development phases.

Figure 2 gives an overview of the HARMLESS SSbD approach, including the aim and recommended actions for the different di-

mensions for each of the innovation phases. At the Ideation and Business Case Phase, when the material, application, and functionality are defined, the main goal of the HARMLESS SSbD approach is to give early warnings on safety and sustainability and prioritize the aspects for further investigation in the following innovation stages. At Lab Phase, different SSbD versions (i.e. versions of the AdMa developed), reference material(s) (ReMa), and conventional material(s) (CoMa) are compared with the aim of selecting the best candidate to proceed to Pilot Phase. Production and use are the focus here, as they are the lifecycle stages best known by the material developer. At Pilot Phase, increased knowledge on the material and its production process strengthen the SSbD assessment. The whole supply chain can be considered in the assessment. The HARMLESS SSbD approach is implemented in the online SSbD-DSS that is freely available at: <https://diamonds.tno.nl/harmlesspublic>.

3. Overview of the Decision Support System

The SSbD-DSS is an online platform meant to support its users in making decisions during the design and re-design process of innovative products, such that they are safe and sustainable, and still performant. The SSbD-DSS is a practical implementation of the HARMLESS SSbD approach (as described above) in a system which recommends methods and tools tailored to the characteristics of the design process (e.g., the material or process type, product application, and stage of the innovation). To deal with the challenges dictated by data quality and data availability at each stage of the innovation process, the SSbD-DSS follows the same stage-gate model as the HARMLESS SSbD approach described above (Figure 2). At the early phase of the innovation process (i.e.,

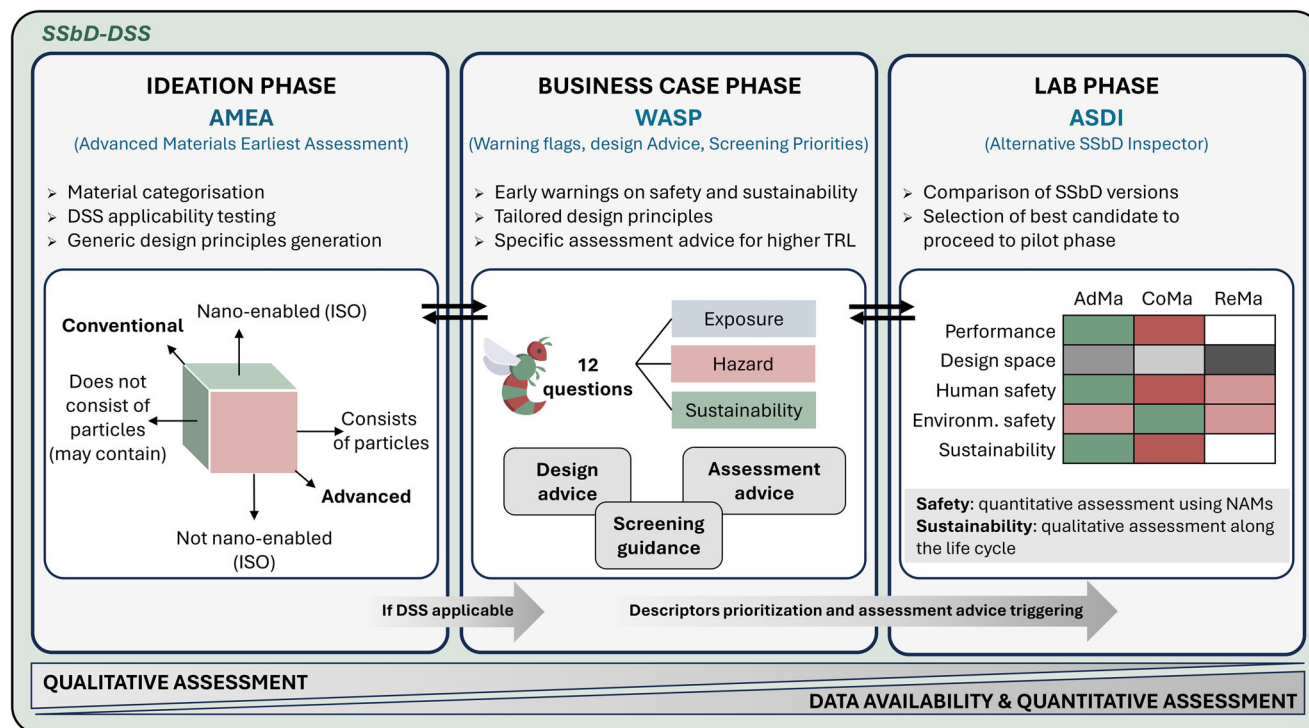


Figure 3. The workflow of the SSbD-DSS showing the SSbD-DSS components in the early innovation stages in relation to the data availability. AdMa: Advanced Material, CoMa: Conventional Material, ReMa: Reference Material. TRL: Technology Readiness Level. NAM: New Approach Methodology.

when no product prototype is available), only qualitative or semi-quantitative information can be acquired. Therefore, at this early phase only qualitative and semi-quantitative tools are proposed to drive the development of safe and sustainable products. Moving along the stage-gate model to higher TRLs, the quality and the quantity of data increases and a more quantitative evaluation of the safety and sustainability is possible; the SSbD-DSS adapts its recommendation to the user toward more data-driven methods and tools.

This publication focusses on the first two phases of the innovation process (Ideation and Business Case Phase and Lab Phase), in which designers are guided through a workflow consisting of three online tools, i.e. the Advanced Material Earliest Assessment (AMEA) tool and the Warning flags, design Advice, Screening Priorities (WASP) tool at Ideation and Business Case Phase and the Alternative SSbD Design Inspector (ASDI) tool at Lab Phase (see Figure 3). The AMEA tool consists of only three questions (as further described below) and is used for early categorization and subsequent advice on design principles and applicability of the HARMLESS SSbD-DSS.^[21,22] If the SSbD-DSS is applicable, the designer is advised to apply the second tool, WASP.^[23] WASP is based on the AMEA advice and brings elements of several other existing tools together into a simplified approach to SSbD that requires relatively limited information compared to most existing tools. The WASP tool consists of 12 questions (as further elaborated below) meant to identify early warning flags on safety and sustainability and to provide detailed design and assessment advice. To support industrial innovators making an informed decision on the most optimal SSbD version in the Lab Phase, ASDI tool was developed, which explicitly asks for data

acquisition. Based on the early warning flags from WASP, ASDI provides guidance on which descriptors to measure (as further described below) and gives insight into the differences between the SSbD versions within the various dimensions (safety, sustainability, and performance). At the Pilot Phase, when more data is expected to be available, more complex methods and tools are suggested and made available in the SSbD-DSS. As Pilot Phase recommendations and methods are still under development at the time of writing this manuscript, this is out of scope of this publication.

4. SSbD-DSS Online Tools in the Ideation and Business Case Phase

The Ideation & Business Case Phase of an innovation process comprises several elements such as: defining the goal of the product development process (i.e., developing new product or modifying an existing product), brainstorming on new product ideas, identification of the potential applications (or market), and identification of the application field. In the Methodological Guidance of the JRC,^[5] the SSbD activities in this innovation phase are described in the Scoping analysis and Simplified SSbD assessment. At this stage of the innovation process, a safety and sustainability profile of the product is sketched out with the aim to anticipate and minimize its risks and potential negative impacts on human health and the environment before moving to later stages of product development. Ideally, at this stage various design principles can be identified at product or at process level to mitigate risks and impacts. An example of such a design principle is to reduce exposure to hazardous substances, e.g., to

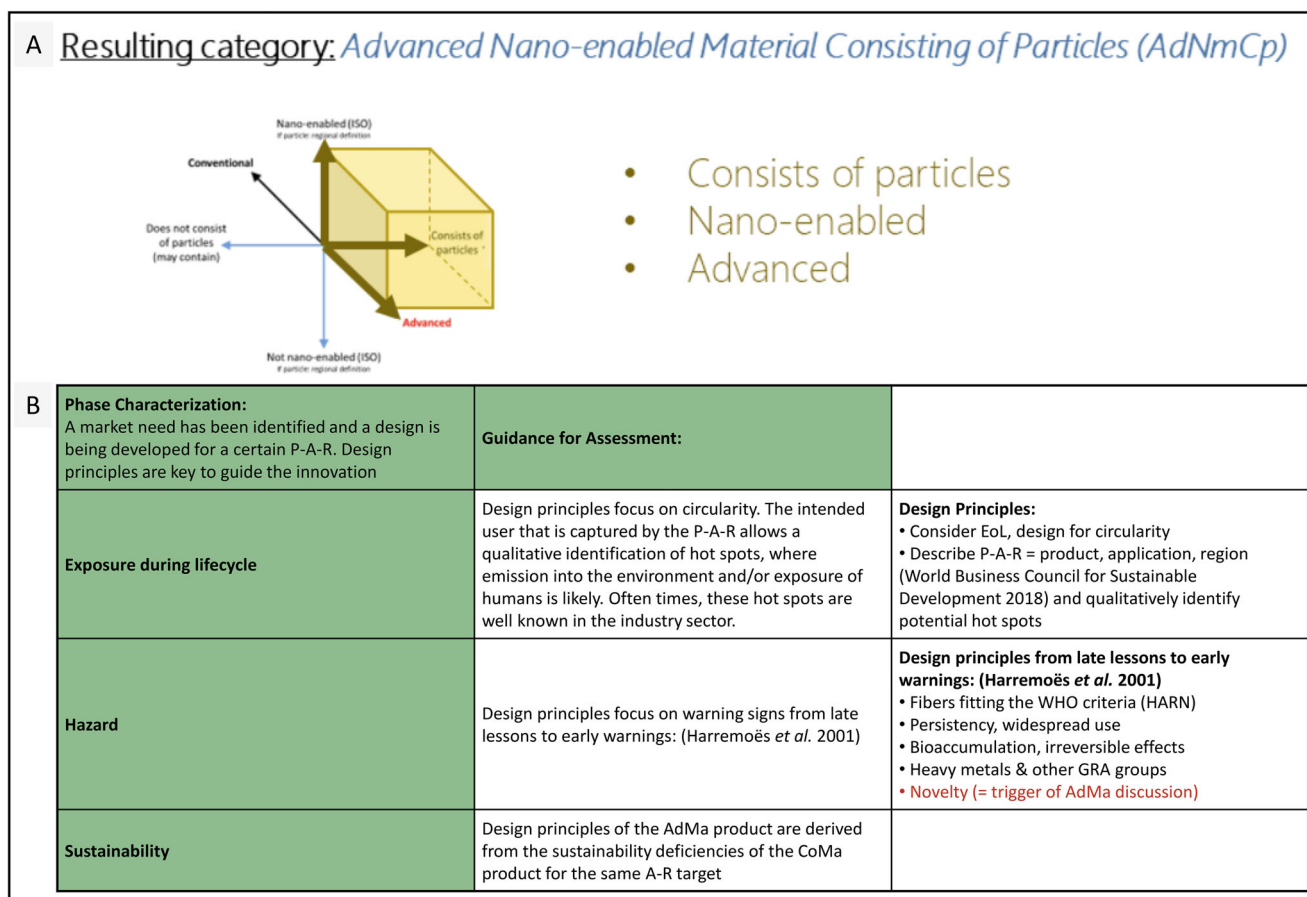


Figure 4. An example of the AMEA results in the SSbD-DSS. A) Categorization. B) Advice on design principles. WHO: World Health Organization, HARN: High Aspect Ratio Nanomaterial, GRA: General Risk Assessment, EoL: End-of-life, P-A-R: Product, Application, and Region (of intended use).

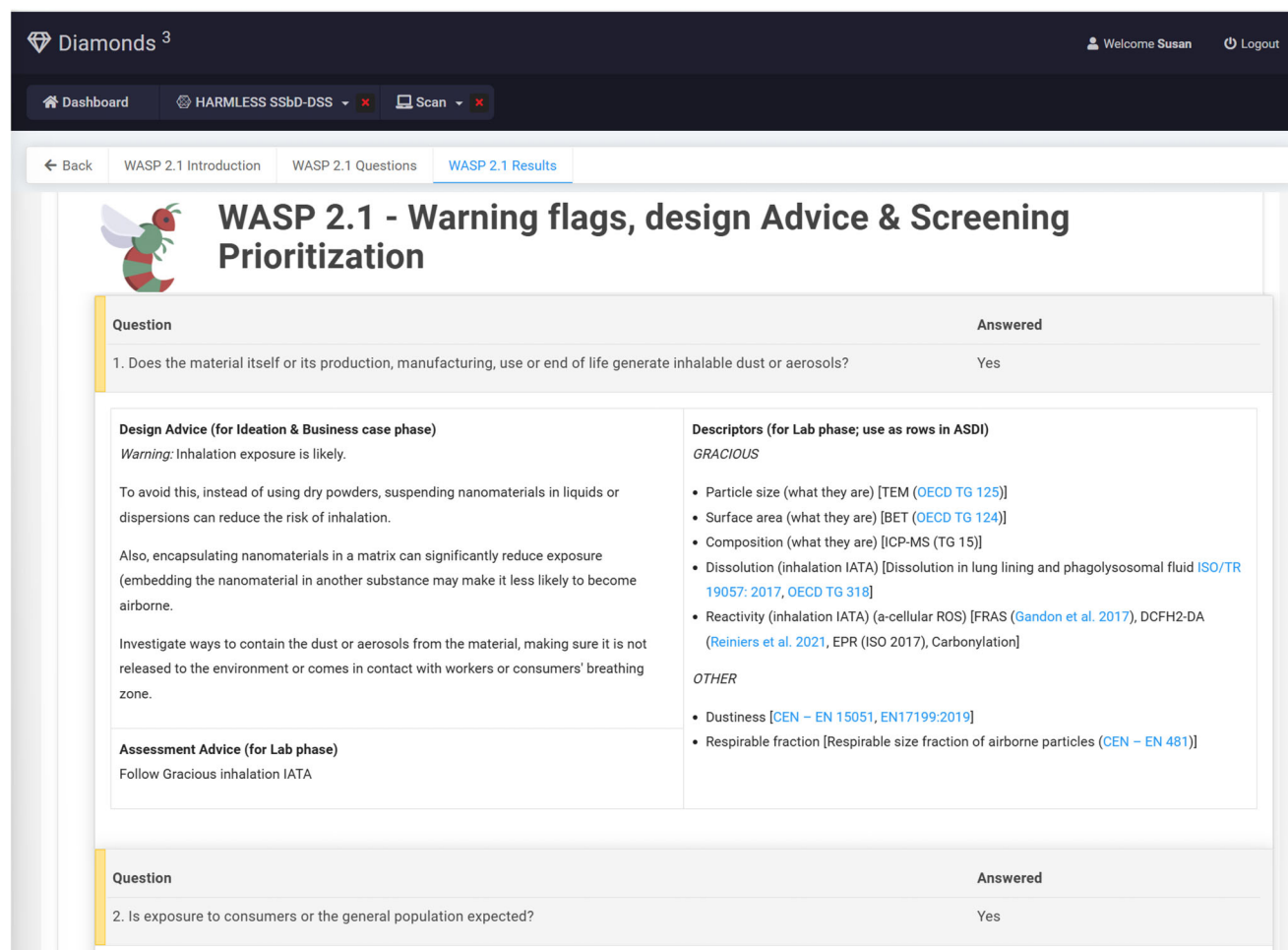
qualitatively identify potential hotspots for emission into the environment and/or exposure to humans based on the intended use and to try preventing or minimizing these hotspots. Another example of a design principle at this stage is to minimize the use of hazardous chemicals or materials, e.g. to substitute or minimize the use of materials which are known to have hazardous properties, such as fibers matching the World Health Organization (WHO) criteria or substances potentially causing irreversible adverse effects like Carcinogenic, Mutagenic or Reprotoxic (CMR) effects or very Persistent and very Bioaccumulative (vPvB) substances. Hence, different SSbD strategies for the production, manufacturing, use, and end-of-life phase of a product can be considered.

At this early innovation stage, no testing can be performed, so only qualitative or semi-quantitative assessments can be performed from information or data obtained from the literature or databases. The objective is to select two to six versions among the expected best-performing alternative products and/or strategies (which could include existing ones) for more precise comparison at the next innovation stage. To identify relevant design principles and select the most promising alternative products and/or strategies, the designer is first asked to answer the following three questions of the online AMEA tool:^[21,22]

- 1) Does the material consist of particles and/or contains particles or not at all?
- 2) Is the nanomaterial nano-enabled and/or a nanomaterial in regulatory terms, or none thereof?
- 3) Is the manufacturing process or the material itself considered as “advanced”?

Each of the questions has an explanation to help the user to correctly answer this question. Based on the answers (yes/no/unknown) to these questions, the product will be categorized into one of the AMEA categories (see **Figure 4**). Based on this category, AMEA provides advice on design principles^[24,25] for each of the innovation stages and on the applicability of the SSbD-DSS.

Although the SSbD-DSS is specifically tailored to AdMa that consist of particles or fibers or are expected to release particles or fibers within their life cycle, it is also applicable to non-advanced materials that consist of particles or fibers or are expected to release particles or fibers within their life cycle. As some of the tools and methods for safety assessment in the SSbD-DSS are tailored to the behavior and toxicity of particles and fibers, the SSbD-DSS is not applicable to materials that do not contain or potentially release any particles or fibers throughout their life cycle.



WASP 2.1 - Warning flags, design Advice & Screening Prioritization

Question	Answered
1. Does the material itself or its production, manufacturing, use or end of life generate inhalable dust or aerosols?	Yes

Design Advice (for Ideation & Business case phase)

Warning: Inhalation exposure is likely.

To avoid this, instead of using dry powders, suspending nanomaterials in liquids or dispersions can reduce the risk of inhalation.

Also, encapsulating nanomaterials in a matrix can significantly reduce exposure (embedding the nanomaterial in another substance may make it less likely to become airborne).

Investigate ways to contain the dust or aerosols from the material, making sure it is not released to the environment or comes in contact with workers or consumers' breathing zone.

Assessment Advice (for Lab phase)

Follow Gracious inhalation IATA

Descriptors (for Lab phase; use as rows in ASDI)

GRACIOUS

- Particle size (what they are) [TEM ([OECD TG 125](#))]
- Surface area (what they are) [BET ([OECD TG 124](#))]
- Composition (what they are) [ICP-MS (TG 15)]
- Dissolution (inhalation IATA) [Dissolution in lung lining and phagolysosomal fluid [ISO/TR 19057: 2017, OECD TG 318](#)]
- Reactivity (inhalation IATA) (a-cellular ROS) [FRAS ([Gandon et al. 2017](#)), DCFH2-DA ([Reiniers et al. 2021](#), EPR (ISO 2017), Carbonylation)]

OTHER

- Dustiness [[CEN – EN 15051, EN17199:2019](#)]
- Respirable fraction [Respirable size fraction of airborne particles ([CEN – EN 481](#))]

Question	Answered
2. Is exposure to consumers or the general population expected?	Yes

Figure 5. An example of the WASP results on the first question in the SSbD-DSS including warning flags and design advice for the Ideation & Business Case Phase and assessment advice and suggested descriptors for the Lab Phase. Where possible, the SSbD-DSS provides regulatory-approved test guidelines for each of the recommended descriptors to facilitate reproducibility and regulatory relevance of acquired data.

If, according to the outcome of the AMEA tool, the SSbD-DSS is applicable, the SSbD-DSS recommends the designer to continue with the online WASP tool and answer its 12 questions. For development of the safety part of the WASP tool, the AMEA advice,^[21] GRACIOUS Integrated Approaches to Testing and Assessment (IATAs),^[26–31] LICARA nanoSCAN,^[32,33] Stoffenmanager Nano,^[34] Nano Exposure Quantifier (NEQ),^[35–37] and the Swiss Precautionary Matrix^[38] were used together with the expertise of different stakeholders in the HARMLESS consortium to create a simplified questionnaire requiring relatively limited information to be answered so as to ensure its applicability in this early innovation phase.

Most of the questions on safety can be answered with yes or no, where yes generally triggers a warning flag indicated by a yellow color in the result page (see **Figure 5**). To build the sustainability part of WASP, SDGs and associated targets, developed by the United Nations^[3] were selected based on their relevance to the HARMLESS scope, i.e., environmental sustainability of AdMa. When performing environmental sustainability assessment in the early innovation stages, it is usual to consider fewer impact categories or make assumptions in the data used (e.g.,

the use of proxy data), using more limited (generic) data sources, and lower quality data.^[5] Therefore, the selected SDGs targets do not include all indicators of the environmental sustainability assessment as described in the EC JRC SSbD Framework and the Product Environmental Footprint (PEF) method.^[4] Instead the SDG targets that were considered most relevant for AdMa and for which some information was expected to be available at the early innovation stage were selected. The selected SDG targets include aspects within each of the four groups described in the EC JRC SSbD framework: toxicity, climate change, pollution, and resources.^[4] At later innovation stages, when more knowledge and data is available, all PEF indicators may be considered when performing a full LCA. The sustainability question offers three answer options (no impact, positive impact, or negative impact) for each selected SDG target, where a negative impact triggers a warning flag indicated by a yellow color in the results page. Depending on the answers to the 12 questions, WASP will identify early warning flags that require additional attention. For each warning flag the user will be 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

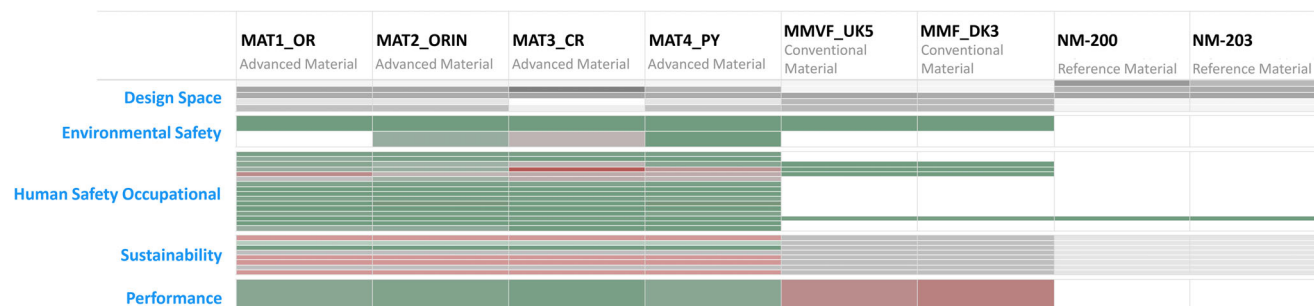


Figure 6. An example of the ASDI results for four SSbD AdMa as compared to two CoMa and two ReMa as columns and diverse descriptors (rows) categorized in the five dimensions (groups of rows with blue label). In this example, several rows show very similar values for the four AdMas, but clearly the third column (MAT3_CR) stands out as an AdMa with less favorable values for some descriptors (some cells have more red colors compared to other AdMa) without remarkable improvements (no cells visible with more green colors compared to other AdMa) (screenshot from the SSbD-DSS).

potentially revoke the potential issue, including detailed recommended descriptors to evaluate in the Lab Phase with the ASDI tool (Tables 1 and 2 and Figure 5).

Most of the descriptors in Table 1 are based on the GRA-CIOUS IATAs, complemented with some additional descriptors from existing exposure and risk assessment tools. Where possible, the SSbD-DSS provides regulatory-approved test guidelines for each of the recommended descriptors to facilitate reproducibility and regulatory relevance of acquired data. For descriptors for which no regulatory approved test guideline, such as an OECD Test Guideline is available, the SSbD-DSS provides references to peer-reviewed publications. The importance of the compatibility of test methods with regulatory frameworks has previously been emphasized and evaluated for several NAMs for (advanced) nanomaterials.^[39,40]

5. SSbD-DSS Tools in the Lab Phase

The Lab Phase represents the stage of the innovation process where the product is being produced as a prototype. The goal is to select the SSbD version with the best compromise between safety, sustainability, and performance that will proceed toward the Pilot Phase. At this stage, product performance can be improved by tailoring the properties of the product with the highest impact on its function, while maintaining a sufficiently high safety and sustainability profile. Despite the lower budget and data availability compared to the Pilot Phase, quantitative or semi-quantitative data can now be obtained, which allows for more accurate safety and sustainability assessments compared to the Ideation & Business Case Phase. Here, the user can already perform experiments to quantitatively assess various aspects related to the safety and performance of the various SSbD versions of the material. The comparison of different SSbD versions requires sensitivity in the tools used for the assessment as often a small design variation induces a significant change in the performance.

Several existing tools used in the early innovation stages, such as LICARA nanoSCAN and Stoffenmanager Nano are useful for early SSbD assessment, but not sensitive enough to compare the safety and sustainability profile of various SSbD versions of a new material or product. The differences between the SSbD versions are too small to arrive at a different safety or sustainability assessment outcome with these more coarse-grained existing tools. Therefore, the ASDI tool aims to provide quantitative insight into

the differences between the SSbD versions within the safety and performance dimensions and semi-quantitative insight within the sustainability dimension. Based on these differences innovators can make an informed decision on the most optimal SSbD version with respect to the various safety and sustainability aspects.

The goal of ASDI is to obtain a visual overview of the various safety, sustainability, and performance descriptors to allow the selection of the best SSbD version to continue further with in the Pilot Phase. Within ASDI the SSbD-DSS helps the user to create a matrix with the different descriptors on the rows and the different materials on the columns (see Figure 6). The columns contain the various SSbD versions of the AdMa and their current CoMa and the ReMa for comparison. The rows contain descriptors categorized into the design space (indicating the differences between the various SSbD versions), performance, human safety, environmental safety, and sustainability. The design space and performance descriptors are case-specific and should be entered by the designer, while default human safety, environmental safety, and sustainability descriptors recommended by the SSbD-DSS are already included in the ASDI tool.

The online ASDI tool builds on the outcomes of the WASP tool of the SSbD-DSS which provides a set of early warning flags and relevant default descriptors to assess these warning flags. For each of the descriptors, data for the various SSbD versions, the CoMa and ReMa should be gathered from scientific publications and existing databases (e.g. eNanomapper) or generated using the recommended test method indicated by the assessment advice from the SSbD-DSS. Table 3 gives an overview of the recommended test methods for the safety descriptors. The recommended sustainability descriptors can be found in the last column of Table 2. For the sustainability descriptors no test methods are recommended. Instead, a semi-quantitative assessment of the AdMa or a semi-quantitative comparison of the AdMa with the CoMa is recommended (see Supporting Information). The data on the various descriptors need to be entered into a SSbD-DSS-provided data matrix, which is flexible and adaptable by the user. Users can delete descriptors for which they cannot gather data (e.g., because no contract research organization (CRO) is available) and they can also add additional descriptors. These descriptors may emerge from knowledge on the toxicological mechanism of action (ideally an AOP-based key initiating event) of the specific materials to be assessed, or from practical considerations

Table 1. All 12 WASP questions on safety and subsequent design advice, assessment advice and descriptors triggered for the SSbD assessment in the next innovation phase (Lab Phase).

Question	Design advice	Assessment advice	Descriptors triggered
1	Does the material itself or its production, manufacturing, use or end of life generate inhalable dust or aerosols?	If yes, inhalation exposure is likely. To avoid this, use liquids or dispersions. Also encapsulating the material into a matrix can significantly reduce exposure. Investigate ways to contain the dust or aerosols from the material, making sure it is not released to the environment or does not come in contact with workers or consumers' breathing zone.	GRACIOUS inhalation IATA - Particle size - Surface area - Composition - Dissolution - Reactivity OTHER (exposure): - Dustiness - Respirable fraction
2	Is exposure to consumers or the general population expected?	If yes, look into ways to prevent exposure, i.e., encapsulation, granulation. For agricultural products, ensure biodegradability of plant protection products.	For each form of exposure: GRACIOUS IATAs: - Particle size - Surface area - Composition - Dissolution - Reactivity OTHER (exposure): - Dustiness - Respirable fraction - Expected amount (or %) of material to which the consumers could be exposed.
3	Is occupational exposure via inhalation expected?	If yes, look into ways to prevent exposure i.e., closed automated systems (SBD4Nano Risk Management Measures e-cards). Look into ways to generate less dust during handling i.e., less mechanical stress. Regarding the agricultural sector, consider the use of spray drift reduction (TOPPS project).	For each stage: - Dustiness - Respirable fraction - Type of release - Composition of released material - Mass percentage of release
4	Is there more than one form of expected human exposure (i.e., different chemical composition and/or particle size)?	If yes, look into ways to prevent exposure, i.e., encapsulation, granulation.	For each form of exposure: GRACIOUS IATAs: - Particle size - Surface area - Composition - Dissolution - Reactivity OTHER (exposure): - Dustiness - Respirable fraction

(Continued)

Table 1. (Continued)

Question	Design advice	Assessment advice	Descriptors triggered
5	Is wide-dispersive use foreseen, based on the sector, product, and final application in which the material is intended to be used?	Since wide disperse use increases the potential ways and amount of human and environmental exposures, consider a more elaborated assessment of the potential health and environmental risks using the appropriate GRACIOUS IATA (Tier 2 or 3 NAMs) for inhalation; ^[26,27] oral; ^[29] dermal; ^[38] genotoxicity; ^[30] or aquatic systems. ^[31] Since a high tonnage level increases the potential of human and environmental exposure, consider a more elaborated assessment (if > 100 tons/year or large-scale production is expected) Since environmental exposure is expected, assess environmental risks using the GRACIOUS aquatic systems IATAs ^[31]	Consider adding additional descriptors such as in vitro toxicity testing or higher-tiered NAMs of the GRACIOUS IATAs: - Genotoxicity - Inflammation - In vitro reactivity - Cytotoxicity - Membrane integrity - Etc. GRACIOUS aquatic system IATA: - Dissolution relevant media - Dispersion stability - Chemical transformation If available: - Toxicity to algae, daphnia, fish cell lines, GRACIOUS aquatic systems IATA: - Dissolution - Dispersion stability - Chemical transformation Dissolution (in relevant media).
6	Could you enter the tonnage assumed to calculate the Expected Commercial Value (ECV)? If you don't know, is large-scale production of your material expected?		
7	Is there exposure for any environmental compartment expected?	If yes, look into ways to reduce the environmental release.	
8a	Is the material expected to be persistent?	If yes, make it less persistent (e.g., weaken physical binding and chemical bonding).	
8b	If answer to 8a is yes: Is the material foreseen to contain or consist of fibers with a critical morphology (rigid, persistent, aspect ratio >3), especially fibers with a length >5 µm and diameter <3 µm?	If yes, make it less persistent, shorter, or more flexible.	GRACIOUS HARN IATA - Fiber length and diameter - Dissolution (in relevant media)
9	Is the material expected to show high/enhanced reactivity?	If yes, try to reduce the reactivity, e.g., by coating the material.	Reactivity assessed with in silico NAM (e.g., electronegativity) or in chemico NAM (e.g., acellular ROS). In vitro (e.g., cellular carbonylation) if available.
10	Is your material multicomponent?	If yes, transformation issues likely. Ensure that the transformed materials do not contain harmful (e.g., registered, classified) components.	- Dissolution of transformed materials - Reactivity of the transformed material
11	Is the material and/or its chemical components expected to be hazardous for the human health or environment? (if no information, specify chemical components and use SIS to check for human and environmental hazard band and/or classification).	If yes, substitute or reduce the quantity of components with hazard band E and D.	- Quantity (w/w%) of hazardous components in the material or of the hazardous material in the final application.
12	Will your novel material or product impact any of the selected SDG targets?	The design advice depends on the SDG target.	See Table 2.

Table 2. SDG targets selected for the WASP question on sustainability with a short explanation and the descriptors triggered for the SSbD assessment in the next innovation phase (Lab Phase).

SDG target	Explanation	Descriptors triggered
12a	SDG 3 (Good Health & Well-being) Target 3.9: Substantially reduce the number of deaths and illnesses from hazardous chemicals and air, water, and soil pollution and contamination	<i>All lifecycle stages:</i> Potential for pollution (content and released amount)
12b	SDG 6 (Clean water and sanitation) Target 6.3: Improve water quality by reducing pollution, eliminating dumping, and minimizing release of hazardous chemicals and materials, halving the proportion of untreated wastewater, and substantially increasing recycling and safe reuse globally	<i>All lifecycle stages</i> Proportion of safely treated wastewater Proportion of toxic waste Direct or indirect releases of hazardous chemicals or materials to surface or groundwater
12c	SDG 6 (Clean water and sanitation) Target 6.4: Substantially increase water-use efficiency across all sectors and ensure sustainable withdrawals and supply of freshwater to address water scarcity and substantially reduce the number of people suffering from water scarcity	<i>Production and manufacturing:</i> Proportion of discharged water <i>Use:</i> Water requirement for use <i>End of life:</i> Water requirement for waste treatment <i>Production and manufacturing:</i> Proportion of renewable energy used in the process <i>Use:</i> Capacity to use renewable energy for power (if applicable)
12d	SDG 7 (Affordable and clean energy) Target 7.2: Increase substantially the share of renewable energy in the global energy mix	<i>Production and manufacturing:</i> Energy intensity, in terms of primary energy used per item produced, as expected at pilot scale <i>Use:</i> Energy efficiency during use
12e	SDG 7 (Affordable and clean energy) Target 7.3: Double the global rate of improvement in energy efficiency	<i>All lifecycle stages:</i> CO ₂ emissions (for production and manufacturing: as expected at pilot scale)
12f	SDG 9 (Industry, innovation, and infrastructure) Target 9.4: Upgrade infrastructure and retrofit industries to make them sustainable, with increased resource-use efficiency and greater adoption of clean and environmentally sound technologies and industrial processes, with all countries taking action in accordance with their respective capabilities	

(Continued)

Table 2. (Continued)

SDG target	Explanation	Descriptors triggered
12g	SDG 11 (Sustainable cities and communities) Target 11.6: Reduce the adverse per capita environmental impact of cities, including by paying special attention to air quality and municipal other waste management	<i>All lifecycle stages:</i> Emission of fine particulate matter (for production and manufacturing: as expected at pilot scale)
12h	SDG 12 (Sustainable consumption and production) Target 12.2: Achieve the sustainable management and efficient use of natural resources	<i>Production and manufacturing:</i> Proportion of critical raw materials Proportion of non-renewable, non-reusable, and non-recyclable material Secondary (recycled) materials <i>Use:</i> Product lifetime <i>End of life:</i> Ability for reuse, for recycling
12i	SDG 12 (Sustainable consumption and production) Target 12.4: Achieve the environmental sound management of chemicals and all wastes throughout their life cycle, in accordance with agreed international frameworks, and significantly reduce their release to air, water, and soil in order to minimize their adverse impacts on human health and the environment	<i>Production and manufacturing, as expected at pilot scale:</i> Proportion of hazardous waste Proportion of safely treated hazardous waste Reuse of water, reagents, and solvents <i>Use:</i> Proportion of hazardous waste Release of chemicals and waste <i>End of life:</i> Release of chemicals
12j	SDG 12 (Sustainable consumption and production) Target 12.5: Substantially reduce waste generation through prevention, reduction, recycling, and reuse	<i>Production, manufacturing, and use:</i> Amount of waste generated <i>End of life:</i> Ability to be reused, recycled
12k	SDG 13 (Climate action) Target 13.2: Integrate climate change measures into national policies, strategies, and planning	<i>All lifecycle stages:</i> Emissions of greenhouse gases (for production and manufacturing: as expected at pilot scale)
12l	SDG 14 (Life below water) Target 14.1: Prevent and significantly reduce marine pollution of all kinds, in particular from land-based activities, including marine debris and nutrient pollution	<i>All lifecycle stages:</i> Release of plastic debris, nutrients, and other hazardous substances
12m	SDG 14 (Life below water) Target 14.3: Minimize and address the impacts of ocean acidification, including through enhanced scientific cooperation at all levels	<i>All lifecycle stages:</i> Difference of pH between released water and receiving environment

Table 3. Recommended test methods for recommended safety descriptors.

Descriptors triggered	Recommended method
Particle size	TEM (OECD TG 125) ^[41]
Surface area	BET (OECD TG 124) ^[42]
Composition	ICP-MS
Dissolution	ISO/TR 19057:2017; ^[43] OECD TG 318 ^[44]
Reactivity (a-cellular)	FRAS; ^[45] DCFH2-DA; ^[46] ESR (ISO/TS18827:2017) ^[47]
Dustiness	CEN – EN 15051; ^[48] CEN- EN17199:2019 ^[49]
Respirable fraction	Respirable size fraction of airborne particles (CEN – EN 481) ^[50]
Dispersion stability	OECD TG 318 ^[44]
Genotoxicity	Chromosomal damage (OECD TG 473, ^[51] OECD TG 487), ^[52] Gene mutation (OECD TG 476, ^[53] OECD TG 490) ^[54]
Inflammation	Inflammasome activation, measuring cytokine production
Reactivity (in vitro)	Cellular protein carbonylation
Cytotoxicity	Cell viability: MTS, LDH, Alamar Blue, Neutral Red
Membrane integrity	Membrane integrity
Toxicity in algae	OECD TG 201 ^[55]
Toxicity in Daphnia	OECD TG 202; ^[56] OECD TG 211 ^[57]
Toxicity in fish cell lines	OECD TG 249 ^[58]
Reactivity (in silico)	Predictive models e.g., based on electronegativity

like the existence of a large body of data on the CoMa and/or ReMa. As the data generation in this innovation stage still needs to be relatively easy, quick, and resource lean, no cellular (in vitro) assays are recommended as default descriptors in this innovation phase. However, if in vitro data is available, the user can add this as one of the descriptors to the data matrix.

Based on the data entered into the data matrix and the chemically and/or biologically relevant range of each descriptor, the SSbD-DSS provides a “heatmap” of the various SSbD aspects to help innovators making an informed decision on the SSbD version to be continued in the Pilot Phase (see Figure 6). To understand the importance of each measured value, it is imperative to understand the chemical or biological range in which this measurement is relevant. Whereas a technological range expresses the technical boundaries of measurement values of a descriptor, the chemical or biological range is a narrower range expressing the chemically or biologically meaningful range of values, for example from values of negative controls to values of positive controls. The coloring within the heat map indicates how preferable a material is with respect to the specific descriptor (green coloring is preferable, grey coloring is neutral, and red is less preferable). If the user adds new descriptors into ASDI, they can define the corresponding color coding associated with the biological range with some guidance provided in the online tool. For default biological descriptors, the biologically relevant range of each property was determined based on existing data from ReMa. For sustainability descriptors, a semi-quantitative assessment of the expected impact of the AdMa itself or of the AdMa compared to the CoMa is recommended (see [Supporting Information](#)).

The selection of the SSbD version to proceed toward Pilot Phase is not always straightforward, as some SSbD versions may

have a positive impact on one SSbD aspect, while having a negative impact on another SSbD aspect. Although the SSbD-DSS provides an overview of both positively and negatively impacted SSbD aspects for the product in scope, it intentionally does not provide one aggregated SSbD score. Trade-offs between dimensions are inevitable and yet there is no generally applicable consensus on how to weigh the various SSbD aspects against each other or on which absolute cut-off values should be applied for most of the criteria used for the assessment. Therefore, the decision on how to balance the trade-offs between the various SSbD aspects is not provided by the SSbD-DSS but is left to the designer. This enables the transparency in decision-making and leaves the designer enough freedom to further consider the design goal, the available budget for SSbD assessment and the priorities and policies of the company developing the product.

6. Discussion and Conclusion

The HARMLESS SSbD approach and SSbD-DSS were developed together with industrial partners, which resulted in an approach that is in alignment with the current practice of the innovation process within companies, increasing the applicability of the SSbD-DSS for industrial developers.

The SSbD-DSS is developed in a modular fashion which allows new individual tools to be added and become part of the integrated SSbD-DSS. Similarly, the AMEA and WASP tools that are currently integrated in the SSbD-DSS, can also be utilized as standalone tools independent of the SSbD-DSS. Next to AMEA, WASP, and ASDI which are part of the recommended workflow for the early innovation stages within the SSbD-DSS (as described in this document), the SSbD-DSS also offers several optional additional tools. Examples of such additional tools are the LICARA nanoSCAN^[32] for risk-benefit analysis, Substance Information System (SIS)^[59] for compound-related hazard and exposure information, HotSpot Scan^[60] for finding release factors, NEQ^[37] for tiered occupational exposure assessment, ECEL^[35] for risk management measures and several models to predict in vivo toxicity.

The online AMEA and WASP tools are aimed to be used by innovators or product designers. Since product designers will generally have no in-depth knowledge on safety and sustainability assessment the questions were selected and formulated in such a way that they could be answered with no expertise on safety and sustainability assessment. Feedback from beta-testers revealed that although the questions in the AMEA and WASP tools are generally accompanied by a clear explanation and are easy to answer for consultants, some questions may require consultation with experts on the various SSbD domains within a company. For each WASP question a comment box is available which allows the user to track the rationale in giving answers and/or changing the answers, should additional knowledge or a different perspective on a particular issue appear. Comparing to other methods applicable in the early innovation stages, such as LICARA nanoSCAN,^[32] the SUNSHINE Tier 1 self-assessment questionnaire,^[14] or the Early4AdMa Tier 1 assessment,^[15] the authors consider the expertise needed to answer the questions of the AMEA and WASP tools is either similar or less.

For the online ASDI tool the user requires more SSbD expertise, as some data interpretation of experimental data on

performance testing and several descriptors related to safety may be required to retrieve the input values for the ASDI data matrix from scientific publications, existing databases, or experimental test reports. Also, balancing the various SSbD aspects in a transparent way, may require some SSbD expertise and the ability to bring together experts from multiple domains to come to a collaborative decision. As the SSbD-DSS provides no aggregated SSbD score, comparing the various SSbD versions requires some knowledge about the various SSbD aspects. LICARA nanoSCAN,^[32] the SUNSHINE Tier 1 self-assessment questionnaire,^[14] the Early4AdMa Tier 1 assessment,^[15] and the European Framework for SSbD^[4] all aggregate the outcome of the SSbD assessment into aggregated scores per dimension or even one overall SSbD score. This makes it easier to compare different materials with respect to their safety and sustainability performance but also less transparent. Moreover, it also prevents the designer to assign more weight to aspects that are important to the company.

One of the often-mentioned challenges in applying the European Framework for SSbD of chemicals and materials^[4] is that it requires a lot of data and resources already in the early innovation stages. In the Methodological Guidance of the JRC,^[5] this is addressed by the introduction of the Scoping analysis and Simplified SSbD assessment. However, many of the recommended methods in this Methodological Guidance are not applicable to AdMa. With these challenges in mind, the HARMLESS SSbD approach and its implementation in the online SSbD-DSS were developed with the aim to provide innovators of AdMa a practical way to implement SSbD in the early innovation stages. The online AMEA and WASP tools can be used in the Scoping analysis and Simplified SSbD assessment. They address the need for a screening method applicable in the very early innovation stage using a relatively limited amount of information to identify relevant safety and sustainability aspects or warning flags to further assess in the later innovation stages. The online ASDI tool can be used in the Simplified and Intermediate SSbD assessment to quantitatively compare various SSbD versions of the material in the Lab Phase with respect to descriptors related to the identified warning flags. By using a heat map with a continuous color coding scale instead of semi-quantitative categories such as risk bands, also more subtle differences between the various SSbD versions can be distinguished. For the default descriptors within ASDI the SSbD-DSS recommends the use of NAMs that are applicable to AdMa.

Although the AMEA, WASP, and ASDI tools are intended for voluntary use by companies for product development, the advice for improved safety can also facilitate regulatory preparedness for AdMa entering the market. Therefore, the three questions in the AMEA tool and the 12 questions developed in the WASP tool are also used in Tier 0 and Tier 1 of the HARMLESS EWS for regulators.^[7] Furthermore, the ASDI descriptors recommended based on the answers to the WASP questions are also aligned with Tier 1 of the HARMLESS EWS. The HARMLESS EWS contains several additional questions related to regulatory aspects with the aim to provide prioritization of materials, identify critical issues timely, and suggest regulatory actions instead of design advice. The alignment of the AMEA, WASP, and ASDI tools with the HARMLESS EWS was established to foster stakeholder dia-

logue by ensuring that innovators and regulators think about the same crucial questions in the context of safety and sustainability.

Further perspectives of the HARMLESS SSbD approach and SSbD-DSS include their further development for the Pilot Phase and expanding or adapting the applicability domain to other types of AdMa. Although the Pilot Phase of the SSbD-DSS is still under development, it already contains several more detailed assessment tools, including in vivo hazard prediction methods based on physicochemical and in vitro data. As one of the important human health and environmental risks of AdMa, is their potential to release particles or fibers which may have an enhanced reactivity and ability to interact with biological systems due to their relatively small size and large surface area, the applicability domain of the HARMLESS SSbD approach and SSbD-DSS is limited to materials that consist of particles or fibers or are expected to release particles or fibers within their life cycle. Consequently, some of the tools and methods for safety assessment in the SSbD-DSS are tailored to particle and fiber behavior and toxicity, e.g., to assesses their surface-specific reactivity, or their ability to release toxic ions under biologically relevant conditions. To expand or adapt the applicability domain, the structure and tiered logic of the HARMLESS SSbD approach and SSbD-DSS do not need to be changed, but specific tools and methods would need to be adapted. If, for example the SSbD-DSS would be adapted for the innovation of Advanced Plastics, the GRACIOUS IATA should be replaced by a recent IATA developed for the hazard assessment of microplastics,^[61] and the recommendation to assess dustiness should be replaced by a recommendation to assess lifecycle release testing.^[62] Much of the rest of the SSbD-DSS may remain similar. The current online SSbD-DSS, including the AMEA, WASP, and ASDI tools (available at: <https://diamonds.tno.nl/projects/harmlesspublic>), already facilitates the practical implementation of SSbD in the early innovation stages and supports innovators to find a transparent balance between safety, sustainability, and performance of their material under development.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

The research for this work has received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 953183.

Conflict of Interest

Veronica De Battista and Wendel Wohleben are employed at BASF a company that produces advanced materials in scope of the assessment.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords

advanced materials, decision support system, safe-and-sustainable-by-design

Received: February 22, 2025

Revised: July 21, 2025

Published online:

- [1] European Commission, *Chem. Strategy Sustain.* **2020**, 53, 25.
- [2] European Commission, *The European Green Deal, Brussels* **2019**, <https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52019DC0640>.
- [3] P. P. Walsh, A. Banerjee, E. Murphy, *Partnerships and the Sustainable Development Goals*, Springer, Cham **2022**.
- [4] C. Caldeira, R. Farcas, I. Garmendia Aguirre, L. Mancini, D. Tosches, A. Amelio, K. Rasmussen, H. Rauscher, J. Riego Sintes, S. Sala, *Safe and Sustainable by Design Chemicals and Materials - Framework for the Definition of Criteria and Evaluation Procedure for Chemicals and Materials*, Publications Office of the European Union, Luxembourg **2022**.
- [5] E. Abbate, I. Garmendia Aguirre, G. Bracalente, L. Mancini, D. Tosches, K. Rasmussen, J. M. Bennett, H. Rauscher, S. Sala, *Safe and Sustainable by Design Chemicals and Materials – Methodological Guidance*, Publications Office Of The European Union, Luxembourg **2024**.
- [6] OECD, Safe(r) and Sustainable Innovation Approach (SSIA): Nano-Enabled and other Emerging Materials, <https://www.oecd.org/en/topics/sub-issues/nanomaterials-and-advanced-materials/safe-and-sustainable-innovation-approach-ssia-nano-enabled-and-other-emerging-materials.html> (accessed: January 2025).
- [7] J. Prinz, G. Nagel, S. Dekkers, E. P. van Someren, V. Adam, V. D. Battista, B. Suarez-Merino, W. Wohlleben, M. Persson, A. Baun, O. Schmid, A. Haase, *Adv. Sustain. Syst.* **2025**, 2500217.
- [8] A. Kennedy, J. Brame, T. Rycroft, M. Wood, V. Zemba, C. Weiss, M. Hull, C. Hill, C. Geraci, I. Linkov, *Risk Anal.* **2019**, 39, 1783.
- [9] E. Valsami-Jones, F. R. Cassee, A. Falk, *Nano Today* **2022**, 42, 101364.
- [10] A. Kostapanou, K.-R. Chatzipanagiotou, S. Damilos, F. Petrakli, E. P. Koumoulos, *Sustainability* **2024**, 16, 10439.
- [11] A. Sudheshwar, C. Apel, K. Kümmerer, Z. Wang, L. G. Soeteman-Hernández, E. Valsami-Jones, C. Som, B. Nowack, *Environ. Int.* **2024**, 183, 108305.
- [12] I. Furxhi, A. Costa, S. Vázquez-Campos, C. Fito-López, D. Hristozov, J. A. Tamayo Ramos, S. Resch, M. Cioffi, S. Friedrichs, C. Rocca, E. Valsami-Jones, I. Lynch, S. J. Araceli, L. Farcas, *RSC Sustain.* **2023**, 1, 234.
- [13] CEFIC (European Chemical Industry Council), Safe and Sustainable-By-Design: A Guidance to Unleash the Transformative Power of Innovation, www.cefic.org (accessed: January 2025).
- [14] L. Pizzol, A. Livieri, B. Salieri, L. Farcas, L. G. Soeteman-Hernández, H. Rauscher, A. Zabeo, M. Blosi, A. L. Costa, W. Peijnenburg, S. Stoycheva, N. Hunt, M. J. López-Tendero, C. Salgado, J. J. Reinoso, J. F. Fernández, D. Hristozov, *Clean. Environ. Syst.* **2023**, 10, 100132.
- [15] OECD, *Early Awareness and Action System for Advanced Materials (Early4AdMa): Pre-Regulatory and Anticipatory Risk Governance Tool to Advanced Materials*, OECD SerieOECD Publishing, Paris **2023**, p. 100132.
- [16] L. G. Soeteman-Hernandez, M. D. Apostolova, C. Bekker, S. Dekkers, R. C. Grafström, M. Groenewold, Y. Handzhiyski, P. Herbeck-Engel, K. Hoehener, V. Karagkiozaki, S. Kelly, A. Kraegeloh, S. Logothetidis, C. Micheletti, P. Nymark, A. Oomen, T. Oosterwijk, I. Rodríguez-Llopis, S. Sabella, A. Sanchez Jiménez, A. J. A. M. Sips, B. Suarez- Merino, I. Tavernaro, J. van Engelen, S. W. P. Wijnhoven, C. W. Noorlander, *Mater. Today Commun.* **2019**, 20, 100548.
- [17] P. Nymark, M. Bakker, S. Dekkers, R. Franken, W. Fransman, A. García-Bilbao, D. Greco, M. Gulumian, N. Hadrup, S. Halappanavar, V. Hongisto, K. S. Hougaard, K. A. Jensen, P. Kohonen, A. J. Koivisto, M. Dal Maso, T. Oosterwijk, M. Poikkimäki, I. Rodríguez-Llopis, R. Stierum, J. B. Sørli, R. Grafström, *Small* **2020**, 16, 1904749.
- [18] V. Stone, S. Gottardo, E. A. J. Bleeker, H. Braakhuis, S. Dekkers, T. Fernandes, A. Haase, N. Hunt, D. Hristozov, P. Jantunen, N. Jeliaskova, H. Johnston, L. Lamon, F. Murphy, K. Rasmussen, H. Rauscher, A. S. Jiménez, C. Svendsen, D. Spurgeon, S. Vázquez-Campos, W. Wohlleben, A. G. Oomen, *Nano Today* **2020**, 35, 100941.
- [19] V. Adam, V. Di Battista, F. Testard, M. Persson, D. Persson, D. Gargouri, A. Filoramo, R. Grafström, P. Kohonen, V. Honisto, M. Conolly, J. M. Navas, L. M. Skjolding, A. Gajewicz-Skretna, P. Danielsen, U. Vogel, K. A. Jensen, E. van Someren, S. Dekkers, O. Schmid, W. Wohlleben, B. S. Merino, Decision Support System for Safe-and-Sustainable-by-Design Advanced Materials Case study demonstration accepted for publication in Advanced Sustainable Systems **2025**.
- [20] R. G. Cooper, *Res. Technol. Manag.* **2014**, 57, 20.
- [21] W. Wohlleben, M. Persson, B. Suarez-Merino, A. Baun, V. Di Battista, S. Dekkers, E. P. van Someren, D. Broßell, B. Stahlmecke, M. Wiemann, O. Schmid, A. Haase, *Environ. Sci. Nano* **2024**, 11, 2948.
- [22] TNO Innovation for Life, AMEA, <https://diamonds.tno.nl/projects/amea> (accessed: October 2024).
- [23] WASP Online Tool, WASP, <https://diamonds.tno.nl/projects/wasp> (accessed: December 2024).
- [24] P. Harremoës, D. Gee, M. MacGarvin, A. Stirling, J. Keys, B. Wynne, S. Guedes Vaz, Late lessons from early warnings: the precautionary principle 1896-2000. Environmentatl issue report No 22. European Environmental Agency, Copenhagen **2013**.
- [25] W. B. C. S. Development, P. S. Assessments, (PSA) v2.0. A framework developed by leading chemical companies for all sectors, WBCSD, Geneva, **2023**.
- [26] H. M. Braakhuis, F. Murphy, L. Ma-Hock, S. Dekkers, J. Keller, A. G. Oomen, V. Stone, *Appl. Vit. Toxicol.* **2012**, 7, 112.
- [27] F. Murphy, N. R. Jacobsen, E. Di Ianni, H. Johnston, H. Braakhuis, W. Peijnenburg, A. Oomen, T. Fernandes, V. Stone, *Part. Fibre Toxicol.* **2022**, 19, 1.
- [28] L. Di Cristo, G. Janer, S. Dekkers, M. Boyles, A. Giusti, J. G. Keller, W. Wohlleben, H. Braakhuis, L. Ma-Hock, A. G. Oomen, A. Haase, V. Stone, F. Murphy, H. J. Johnston, S. Sabella, *Nanotoxicology* **2022**, 16, 310.
- [29] L. Di Cristo, A. G. Oomen, S. Dekkers, C. Moore, W. Rocchia, F. Murphy, H. J. Johnston, G. Janer, A. Haase, V. Stone, S. Sabella, *Nano-materials* **2021**, 11, 2623.
- [30] R. Verdon, V. Stone, F. Murphy, E. Christopher, H. Johnston, S. Doak, U. Vogel, A. Haase, A. Kermanizadeh, *Part. Fibre Toxicol.* **2022**, 19, 32.
- [31] R. K. Cross, D. Spurgeon, C. Svendsen, E. Lahive, S. Little, F. von der Kammer, F. Loosli, M. Matzke, T. F. Fernandes, V. Stone, W. J. G. M. Peijnenburg, E. A. J. Bleeker, *Nano Today* **2024**, 54, 102065.
- [32] T. van Harmelen, E. K. Zondervan-van den Beuken, D. H. Brouwer, E. Kuijpers, W. Fransman, H. B. Buist, T. N. Ligthart, I. Hincapié, R. Hischer, I. Linkov, B. Nowack, J. Studer, L. Hilty, C. Som, *Environ. Int.* **2016**, 91, 150.
- [33] LICARANanoScan Online Tool, <https://diamonds.tno.nl/projects/licara> (accessed: October 2024).
- [34] B. Van Duuren-Stuurman, S. R. Vink, K. J. M. Verbist, H. G. Heussen, D. H. Brouwer, D. E. Kroese, M. F. van Niftrik, E. Tielemans, W. Fransman, *Ann. Occup. Hyg.* **2012**, 56, 525.
- [35] B. Jeddi, H. Goede, R. Franken, E. V. Someren, N. Shandilya, R. Vermoolen, J. Steck, S. Artous, J. S. Hermosilla, W. Fransman, *Ann. Work Expo. Heal.* **2024**, 69, 310.

- [36] R. Vermoolen, R. Franken, T. Krone, N. Shandilya, H. Goede, H. Ben Jeddi, E. Kuijpers, C. Ge, W. Fransman, *Ann. Work Expo. Heal.* **2025**, 69, 323.
- [37] NEQ Online Tool, <https://diamonds.tno.nl/projects/neq> (accessed: February 2025).
- [38] J. Höck, R. Behra, L. Bergamin, M. Bourqui-Pittet, C. Bosshard, T. Epprecht, V. Furrer, M. Gautschi, H. Hofmann, K. Höhener, K. Hungerbühler, K. Knauer, C. Kropf, H. Krug, L. Limbach, P. Gehr, B. Nowack, M. Riediker, K. Schirmer, K. Schmid, C. Som, W. Stark, B. Suarez Merino, F. S. Ul, Guidelines on the Precautionary Matrix for Synthetic Nanomaterials, Version 4.0, 2023, Version 4.0, Federal Office of Public Health (FOPH), Bern **2023**.
- [39] D. Hristozov, E. Badetti, P. Bigini, A. Brunelli, S. Dekkers, L. Diomedea, S. H. Doak, W. Fransman, A. Gajewicz-Skretina, E. Giubilato, L. Gómez-Cuadrado, R. Grafström, A. C. Gutleb, S. Halappanavar, R. Hischier, N. Hunt, A. Katsumiti, A. Kermanizadeh, A. Marcomini, E. Moschini, A. Oomen, L. Pizzol, C. Rumbo, O. Schmid, N. Shandilya, V. Stone, S. Stoycheva, T. Stoeger, B. S. Merino, L. Tran, et al., *NanoImpact* **2024**, 35, 100523.
- [40] S. M. Usmani, S. Bremer-Hoffmann, K. Cheyns, F. Cubadda, V. I. Dumit, S. E. Escher, V. Fessard, A. C. Gutleb, T. Léger, Y.-C. Liu, J. Mast, E. McVey, B. Mertens, D. Montalvo, A. G. Oomen, V. Ritz, T. Serchi, H. Sieg, K. Siewert, D. Stanco, E. Verleysen, O. Vincentini, C. W. S. Yeo, D. Yu, M. van der Zande, A. Haase, *EFSA Support. Publ.* **2024**, 21, 8826E.
- [41] OECD, *Test No. 125: Nanomaterial Particle Size and Size Distribution of Nanomaterials*, OECD GuideOECD Publishing, Paris **2023**.
- [42] OECD, *Test No. 124: Determination of the Volume Specific Surface Area of Manufactured Nanomaterials*, OECD GuideOECD Publishing, Paris **2022**.
- [43] ISO, ISO/TR 19057:2017 Nanotechnologies – Use and Application of Acellular In Vitro Tests and Methodologies to Assess Nanomaterial Biodurability, ISO in Geneva **2017**.
- [44] OECD, *Test No. 318: Dispersion Stability of Nanomaterials in Simulated Environmental Media*, OECD GuideOECD Publishing, Paris **2017**.
- [45] A. Gandon, K. Werle, N. Neubauer, W. Wohlleben, *J. Phys. Conf. Ser.* **2017**, 838, 012033.
- [46] M. J. Reiniers, R. F. van Golen, S. Bonnet, M. Broekgaarden, T. M. van Gulik, M. R. Egmond, M. Heger, *Anal. Chem.* **2017**, 89, 3853.
- [47] ISO, ISO/TS 18827:2017 Nanotechnologies – Electron Spin Resonance (ESR) as a Method for Measuring Reactive Oxygen Species (ROS) Generated by Metal Oxide Nanomaterials <https://www.iso.org/standard/63502.html> (accessed: October 2024).
- [48] CEN, CEN-EN 15051: 2013. and Part 3: Continuous drop method, <https://www.nen.nl/en/nen-en-15051-1-2013-en-190281> (accessed: October 2024).
- [49] CEN, <https://www.nen.nl/en/nen-en-17199-1-2019-en-257512> (accessed: October 2024).
- [50] CEN, <https://www.nen.nl/en/nen-en-481-1994-en-10534> (accessed: October 2024).
- [51] OECD, *Test No. 473: In Vitro Mammalian Chromosomal Aberration Test*, OECD GuideOECD Publishing, Paris **2014**.
- [52] OECD, *Test No. 487: In Vitro Mammalian Cell Micronucleus Test*, OECD GuideOECD Publishing, Paris **2023**.
- [53] OECD, *Test No. 476: In Vitro Mammalian Cell Gene Mutation Tests using the Hprt and xprt genes*, OECD GuideOECD Publishing, Paris **2016**.
- [54] OECD, *Test No. 490: In Vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene*, OECD GuideOECD Publishing, Paris **2016**.
- [55] OECD, *Test No. 201: Freshwater Alga and Cyanobacteria, Growth Inhibition Test*, OECD GuideOECD Publishing, Paris **2011**.
- [56] OECD, *Test No. 202: Daphnia sp. Acute Immobilisation Test*, OECD GuideOECD Publishing, Paris **2004**.
- [57] OECD, *Test No. 211: Daphnia Magna Reproduction Test*, OECD GuideOECD Publishing, Paris **2012**.
- [58] OECD, *Test No. 249: Fish Cell Line Acute Toxicity – The RTgill-W1 Cell Line Assay*, OECD GuideOECD Publishing, Paris **2021**.
- [59] Substances Information System Online Tool, <https://diamonds.tno.nl/projects/sis> (accessed: September 2024).
- [60] HotSpot Scan Online Tool, <https://diamonds.tno.nl/projects/hotspotscan> (accessed: October 2024).
- [61] A. Vogel, J. Tentschert, R. Pieters, F. Bennet, H. Dirven, A. van den Berg, E. Lenssen, M. Rietdijk, D. Broßell, A. Haase, *Part. Fibre Toxicol.* **2024**, 21, 48.
- [62] W. Wohlleben, N. Bossa, D. M. Mitrano, K. Scott, *NanoImpact* **2024**, 34, 100510.