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SweNanoSafe

Swedish National Platform for Nanosafety

Safe and Sustainable by Design: a prerequisite for achieving a circular economy

A report from SweNanoSafe´s workshop

29th November, 2021

Foreword

Through a mandate from the Swedish Ministry of the Environment and the Swedish Chemicals Agency (KEMI), SweNanoSafe maintains a national platform for the safe handling of nanomaterials, to contribute to the achievement of the environmental quality goal of a non-toxic environment and protecting human health. The platform aims to disseminate knowledge and provide specific support to authorities on issues related to the safe handling and use of nanomaterials. SweNanoSafe brings together academia, authorities, industry and organisations for a joint dialogue on nanosafety. This also includes identifying needs for the safe handling of nanomaterials and contributing with proposals for solutions and concrete measures that meet the needs, as well as actively promoting improved nanosafety.

Since 2019, SweNanoSafe has been run at the Institute of Environmental Medicine, Karolinska Institutet (KI), by a Steering Board linked to an Operations Coordination Group, an Expert Panel, a Council of Government Agencies, a Research Network and an Education Network. SweNanoSafe organises workshops and meetings, collaboration nodes and communication via a website (www.swenanosafe.se).

The overarching Swedish goal of a non-toxic environment relates directly to the new Safe and Sustainable-by-Design (SSbD) concept, which is considered a prerequisite for achieving a circular economy. Therefore, SweNanoSafe organized a workshop on November 29th aimed at positioning Sweden and Swedish authorities in the ongoing development and implementation of SSbD.

The workshop attracted close to 90 participants. Here, an overview of the workshop contents and the key outcomes are summarised, including speakers' biographies and abstracts.

SweNanoSafe welcomes communication, comments and proposals regarding nanosafety, through swenanosafe@swenanosafe.se.

Penny Nymark, on behalf of SweNanoSafe

Stockholm, March 2022

SweNanoSafe

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Abbreviations

AdMa	Advanced Materials
AOP	Adverse Outcome Pathway
AI	Artificial Intelligence
CSS	EU Chemicals Strategy for Sustainability
BfR	German Federal Institute for Risk Assessment
EEA	European Environment Agency
FAIR	Findable, Accessible, Interoperable, Reusable
GD	Guidance Document
KEMI	Swedish Chemicals Agency (Kemikalieinspektionen)
KI	Karolinska Institutet
LCA	Life Cycle Analysis
MN	Manufactured Nanomaterial
NAM	New Approach Methodologies
NESSI	Novelty, Exposure, Severity, Scope, and Immediacy
NM	Nanomaterial
PARC	Partnership for the Assessment of Risk from Chemicals
QSAR	Quantitative Structure Activity Relationships
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RISE	Research Institutes of Sweden
RIVM	Dutch National Institute for Public Health and the Environment
SbD	Safe-by-Design
SG-SIA	Steering Group on the Safe(r) Innovation Approach
SG-AdMa	Steering Group on Advanced Materials
SIA	Safe(r) Innovation Approach
SSbD	Safe and Sustainable-by-Design
SVHC	Substances of Very High Concern
TG	Test Guidelines
WPMN	Working Party on Manufactured Nanomaterials
OECD	Organisation for Economic Cooperation and Development

Svensk sammanfattning

Safe by Design (SbD) är ett koncept som bygger på att beakta och minimera osäkerheter och risker för människors hälsa och miljön redan i ett tidigt skede av innovationsprocessen och igenom hela innovationens livscykel. Konceptet har tidigare använts t.ex. inom byggindustrin och senare vidareutvecklats inom forskningen kring nanosäkerhet. SbD riktar sig främst till industrin och ett fokusområde inom nanosäkerhet har varit att utvidga konceptet till att inkludera myndigheternas roll.

Detta arbete har lett till ett nytt tillvägagångssätt som kallas för Safe(r) Innovation Approach (SIA) och består av två komponenter (Soeteman-Hernandez et al. 2019). Dels 1) att industrin beaktar säkerhetsrisker med nanomaterial redan i ett tidigt skede av innovationsprocessen (dvs. SbD), och dels 2) att myndigheter är förberedda på utmaningarna som kommer med att bedöma risker med nanomaterial och nanoteknik (Regulatory Preparedness). Tillvägagångssättet inkluderar också aspekter av livscykelanalys och socioekonomisk analys, samt ett nytt koncept som omfattar så kallade tillförlitliga miljöer (Trusted Environments) som ska underlätta kommunikation och utbyte av information mellan innovatörer och myndigheter. Som SweNanoSafe tidigare rapporterat (SweNanoSafe 2019), så har det internationella organet för ekonomiskt samarbete och utveckling (OECD) publicerat en rapport som beskriver SIA och hur industrin och myndigheter kan samverka för att minska på osäkerheterna och riskerna kring nya nanomaterial och nanoteknik (OECD 2020).

Nästa steg i arbetet kring SbD och SIA är att inkludera hållbarhetsaspekter, alltså Safe and Sustainable by Design (SSbD) (Gottardo et al. 2021). SSbD är en förutsättning för en hållbar cirkulär ekonomi. Tillägget om hållbarhet syftar till att ta de globala hållbarhetsmålen (UN Sustainable Development Goals) i beaktande, samt att utvidga konceptet till att bli användbart för alltmer komplexa och avancerade material (AdMa). Målet är att etablera en systematisk och omfattande strategi som gör det möjligt att samtidigt beakta hållbarhets- och säkerhetsaspekter mycket tidigt i utvecklingen av nya material och produkter. Detta bygger grunden för återanvändning av säkra material och produkter i en cirkulär ekonomi.

För att SSbD ska lyckas och vara implementerbart i industriella och regulatoriska processes krävs accepterade och standardiserade testmetoder, samt harmoniserade data hanteringssystem. Flera pågående Europeiska projekt fokuserar på utveckling och implementering av SSbD inom utvecklingen av nanoteknologi, inklusive HARMLESS, SABYDOMA, SAbyNA, SbD4Nano, ASINA, DIAGONAL och SUNSHINE. Utveckling och implementering av SSbD är också en prioritet inom Europeiska kommissionens kemikaliestrategi (EC 2020a).

SweNanoSafe organiserade en workshop 29 november, 2021 för att samla aktörer inom nanosäkerhet och hållbarhet till en diskussion kring SSbD. Workshopen samlade 87 deltagare från myndigheter, akademi, industri och media (inklusive fyra svenska myndigheter, 20 andra svenska aktörer, samt deltagare från 21 andra europeiska och icke-europeiska länder). Aktörer från europeiska och tyska myndigheter framförde sina perspektiv på SSbD och deltagarna fick också höra mer ingående om konkreta lösningar som harmonisering av testmetoder för nano- och avancerade material, nya djurfria test metoder lämpliga för implementering i SSbD, samt modellering-/simuleringsmetoder och datahantering som har potential att underlättar och effektivera SSbD innan behovet av testning uppstår. Diskussionerna kretsade kring centrala koncept som tagits upp i presentationerna, bl.a. pålitliga miljöer (Trusted Environments) för utbyte av information mellan firmor och med regulatoriska instanser, nya concept för att identifiera högriskmaterial (Materials of Concern), strategier kring utveckling av tester, modellering/simulering och datahantering, det nya europeiska initiativet PARC (Partnership for the Assessment of Risk from Chemicals), användningen av data (FAIR-principer som syftar till att göra data sökbara, tillgängliga, kompatibla och återanvändbara) och artificiell intelligens (AI) inom SSbD, och slutligen behovet av fallstudier (case studies) kring implementing av SSbD i relevant miljöer.

Diskussionsämnena kunde översiktligt summeras med identifiering av 11 centrala framtidsaktiviteter som SweNanoSafe kommer att ägna sig åt att stöda och främja. Aktiviteterna ligger också i linje med fem forskningsbehov för att främja SSbD, som tidigare identifierats av Europeiska Miljöbyrån (EEA), nämligen behovet av i) [regulatoriska] kriterier och mål, ii) effektiva förebyggande metoder för toxikologiska och livscykelanalyser, iii) tillgänglig data, iv) standardisering [av testmetoder och verktyg], och en gynnsam miljö (van der Waals et al. 2019).

11 framtidsaktiviteter för att främja implementering av SSbD, som SweNanoSafe kommer att stöda:

1. Behov av **drivande mandat** och en övergång från att arbeta i silos. Globala aktörer, t.ex. OECD är centrala i förändringen.
2. Behov av harmonisering av **definitioner/termer/begrepp**, inklusive övergripande för SSbD, men också för omfattningen av konceptet d.v.s. täckning av AdMa, nanomaterial, kemikalier, etc.
3. Utveckling av tydliga implementerbara **kriterier** för både säkerhet och hållbarhet för att göra SSbD handlingsbart genom reglerande medel
4. Utveckling av **poängsystem** som drivs av vetenskapliga rön, men även inkluderande samhälleliga perspektiv
5. Utveckling av harmoniserade och accepterade **testmetoder**, inklusive nya djurfria metoder (New Approach Methodologies), samt ett ökat förtroende för nya metoder
6. Implementering av FAIR-principer inom alla **data**genererande processer, inklusive vetenskapliga, industriella och regulatoriska, till stöd för maskindrivna tillvägagångssätt

(AI) för både säkerhets- och hållbarhetsbedömning (inklusive t.ex. toxicitetsprediction, livscykelbedömning och spårbarhet av material/kemikalier)

7. Behov av **fallstudier** (case studies) som visar praktisk implementering av SSbD
8. Behov av **investeringar** för att säkerställa ett effektivt och effektivt samarbete
9. Initiativ för implementering av tidiga varningssystem för att **undvika högrisk ämnen/material** som ger anledning till oro redan idag (Materials of Concern, som inte är att förväxla med REACH etablerade system för substances of very high concern). Tillvägagångssätt har föreslagits av många, bl.a. av de tyska federala myndigheterna i deras nya rapport (Schwirn et al. 2022)
10. Behov av att **överföra internationella aktiviteter** kring SSbD (OECD) för anpassning på europeisk och nationell nivå
11. Övergripande behov av **kulturell förändring**, d.v.s. att tänka utanför boxen (och bokstavligen kliva ur boxen) för att acceptera och effektivt implementera SSbD på bred nivå

Alla presentationer finns tillgängliga via SweNanoSafes YouTube-kanal.

Background and aim of the workshop

Safe and Sustainable-by-Design (SSbD) is based on the consideration and minimization of uncertainties and risks to human health and the environment from an early stage of the innovation process and throughout the lifecycle of the innovation product. The concept of SSbD stems from the development of Safe-by-Design (SbD) approaches within the nanosafety field, and is a component of the Safe(r) Innovation Approach (SIA) for more sustainable nanomaterials and nano-enabled products, which was recently described in detail by the Organization for Economic Cooperation and Development (OECD). In addition to SSbD, the SIA entails the idea of Regulatory Preparedness, which refers to public authorities being ready to face the inherent challenges of assessing the risks of nanomaterials and nanotechnology. The goal is to establish a systematic and comprehensive strategy that builds the basis for efficient development and reuse of safe materials and products in a circular economy. In parallel, there are ongoing efforts within the European Union member states to harmonize and implement SSbD on a comprehensive level[i], including for chemicals and Advanced Materials (AdMa), and from both a regulatory as well as an industrial/innovator perspective (EC 2020a).

In one of the recent SweNanoSafe reports (SweNanoSafe 2019), a set of proposals to overcome obstacles hindering efficient nanosafety were described, including a recommendation to "*establish a national strategy for nanotechnology whereby safety is integrated at an early stage of the innovation process*". Thus, a workshop was organized by SweNanoSafe with the aim to orient Swedish authorities in the ongoing development and implementation of the SSbD concept to face regulatory challenges related to nanomaterials and AdMa with the purpose of advancing circular economy.

The workshop was organized by Penny Nymark, Bengt Fadeel, Rune Karlsson (KI) and Gregory Moore (KEMI) from SweNanoSafe, and took place on Monday afternoon 29th November, 2021. It gathered 87 participants, including governmental, industrial, academic and media actors (e.g. four Swedish governmental authorities, 20 Swedish academic and industrial actors, as well as actors from 21 other European and non-European countries, and global international organisations).

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[i] The European Commission has adopted (14 October, 2020) the EU Chemicals Strategy for Sustainability. The Strategy is the first step towards a zero-pollution ambition for a toxic-free environment announced in the European Green Deal . The Strategy is envisaged to boost innovation for safe and sustainable chemicals and increase protection of human health and the environment against hazardous chemicals. This includes promoting safe and sustainable-by-design (SSbD) approach and taking into account the overall life cycle: production, use and end-of-life.

Overview and key outcomes

Safe and Sustainable-by-Design: An Introduction

The SSbD approach is an extension of the SbD concept which was first outlined within the field of nanosafety in the European project NANoREG (2013-2017) (Gottardo et al. 2017). The concept aims to support early-stage application of the precautionary principle by enabling consideration for health and environmental safety in parallel with functionality during the design of new materials and products. The concept is based on the so-called Cooper Stage-Gate model which is defined by a set of stages, during which development and assessment of the innovation happens, and gates at which go/no-go decisions are taken to move (or stop) an idea/innovation forward towards market launch (Cooper 2014). The model is in general recognised by industry, although it is applied to variable extent. Building further on NANoREG, the European project ProSafe called for a *Future proof approach* involving SbD enabled by harmonised methods, data and tools (ProSafe 2017). The call was coupled to the realisation that the developments within nanosafety were lagging behind those within nanomaterial and -technology innovation, and that the increasing complexity of nanomaterials requires efficient, adaptable test methods and strategies for assessing both fate and toxicity. This complexity is further enhanced today with the rise of increasingly AdMa often at the nanoscale, which however remain to be defined in harmonized manners (see the recently published joint perspective on risk governance of AdMa by the German Higher Federal Authorities (Schwirn et al. 2022)).

In the follow-up project, NanoReg2 (EU, 2015-2018), the SbD concept was coupled to the Regulatory Preparedness concept, establishing the first overview of the approach referred to as the SIA (Soeteman-Hernandez et al. 2019). The efforts led to recognition by the OECD who published the report "*Moving Towards a Safe(r) Innovation Approach (SIA) for More Sustainable Nanomaterials and Nano-enabled Products*" (OECD 2020). The SIA concept involves regulators through Regulatory Preparedness, which is characterised by improved understanding and anticipation by regulators in order to facilitate the development of safety regulation that can keep pace with newly generated knowledge and innovation of new nanomaterials and nano-enabled products (Soeteman-Hernandez et al. 2019). The challenge of Regulatory Preparedness, in the face of the increasing numbers of AdMa, was also described in further detail by the German Higher Federal Authorities, and includes the introduction of a new idea for mapping the regulatory readiness (Regulatory Readiness Level) of measurement, testing and risk assessment methods, tools and data, in order to facilitate policy advice and enable targeted funding for applied research (Schwirn et al. 2022). Recent efforts have in fact aimed at evaluation of New Approach Methodologies (NAM) for nanomaterials regarding their applicability to SbD and together with initiatives to make data Findable, Accessible, Interoperable, and Reusable (FAIR), such readiness concepts become relevant for continued development of these approaches (Jeliazkova et al. 2021; Nymark et al. 2020).

At around the same point in time (late 2019), SweNanoSafe has also in a commissioned report by the Swedish government identified the need for a national strategy in Sweden, in order to consider safety early on during the nanotechnology innovation process (SweNanoSafe 2019). Also, the EU Chemicals Strategy for Sustainability was published in 2020 and laid the basis for a strategy towards safe and sustainable chemicals (including nanomaterials) in line with the European Green Deal (EC 2020a, b). Moreover, a few months later the European Joint Research Centre initiated an effort to bring in the aspect of sustainability into the SbD concept, whereby materials should not only be safe, but also fit for a climate-neutral, circular, and resource efficient economy, while offering optimal properties and functionality through their life cycle, and stated; "*what is missing today is a holistic, systematic and comprehensive approach […] considering sustainability aspects hand in hand with safety considerations […] and the ability to reuse and recycle resources in a circular economy […]*" (Gottardo et al. 2021).

In the end of 2021, the OECD Working Party on Manufactured Nanomaterials (WPMN) established two new steering groups aimed at development and implementation of SSbD and beyond, the Steering Group on SIA (SG-SIA) and on AdMa (SG-AdMa), both including Swedish representatives from SweNanoSafe. A few years earlier, an informal working group led by the European Environment Agency (EEA) published a white paper identifying five research needs suggested as topics for the European innovation programmes, in order to accelerate the design, development, and adoption of safer materials, chemicals, products and services, including; i) [regulatory] criteria and targets, ii) efficient "preventative" toxicology and life cycle tools [i.e. predictive New Approach Methodologies], iii) accessible data [i.e. FAIR data], iv) standardisation [test methods and tools], and v) an enabling environment (van der Waals et al. 2019). One such initiative aimed at addressing these requirements is the upcoming Horizon Europe project Partnership for the Assessment of Risks from Chemicals (PARC).

The program of the workshop (Annex I) was designed to cover the aspects described above, and the presentations are summarised below together with short overviews of the key discussion points, conclusions and future perspectives, followed by speaker biographies. In addition, workshop participants are listed in Annex II, the original abstracts provided by the speakers ahead of the workshop are available in Annex III, and recordings of all presentations are available on the SweNanoSafe YouTube channel (and indicated by hyperlinks on each speakers name in the following).

Summary of presentations

Safe(r) Innovation Approach - Towards an agile system to meet policy ambitions

Following a welcome note from SweNanoSafe presented by **Bengt Fadeel** and an introduction to the SSbD concept by **Penny Nymark** (in line with the above), invited speaker **Lya Soeteman-Hernandez** from the Dutch National Institute for Public Health and the Environment (RIVM) continued with a presentation of the SIA concept (**Figure 1**) and an emphasis on the challenges of *moving towards an agile system to meet policy ambitions*. Soeteman-Hernandez brought up the challenges of the many strategies and transitions currently in planning or already in play, such as the European Green Deal, the EU Chemicals Strategy for Sustainability, the EU Plastics Strategy, the Pharmaceutical Strategy for Europe, and many more. While these strategies vary in their goals and ambitions, a few aspects are common to all, including their overall urgency, the need for trustworthiness and preparedness/resilience, and their aim for inclusiveness, e.g. involvement of citizens/society. The challenges with an emerging technology such as nanotechnology include three main problems; i) the *pacing problem*, where the pace, scope and complexity of nanomaterials/nanotechnology causes challenges, ii) the *coordination problem*, where a lack of coordination in order to respond to innovations that do not clearly lie within regulators sectoral or geographical jurisdiction causes uncertainties, and iii) the *responsibility problem*, where a lack of clear responsibility areas causes struggle among regulators.

Soeteman-Hernandez argued that the SIA concept aligns the wide variety of strategies and work programs with policy goals, i.e. by enabling safe and sustainable innovations. SIA entails both the industry targeted SSbD approach and the proactive role of regulators, through the Regulatory Preparedness concept. The aim is that innovators would build *with* regulators and not *for* regulators in order to meet policy ambitions. Thus, to achieve this culture change a further concept is implemented with the two corner stones (SSbD and Regulatory Preparedness) of SIA, referred to as Trusted Environments, which should meet the aspects of trustworthiness, preparedness/resilience and inclusiveness. Trusted Environments are physical or virtual spaces where innovators and regulators can share and exchange knowledge, information and views on new technologies. In this context, Soeteman-Hernandez brings up examples of regulatory sandboxes where actors listen to stakeholders and citizens, build and develop solutions together, and communicate in a trustworthy way. These are all keys to meeting the common goals that bring together each of the current EU strategies in play.

Finally, Soeteman-Hernandez mentioned that these aims will be achievable only through working together to transform EU into a *powerhouse for innovation* to meet policy ambitions. She goes on to couple the role of SweNanoSafe to the success of this aim, i.e. to disseminate, communicate and initiate dialog between actors, and points in particular to two proposals in the SweNanoSafe report mentioned previously; Measures 11 and 12 stating that there is a need for increased resources for dialogue and cooperation between national (and international) parties within nanosafety, i.e. transfer of knowledge between academia and industry, as well as between academia and authorities, respectively (SweNanoSafe 2019).

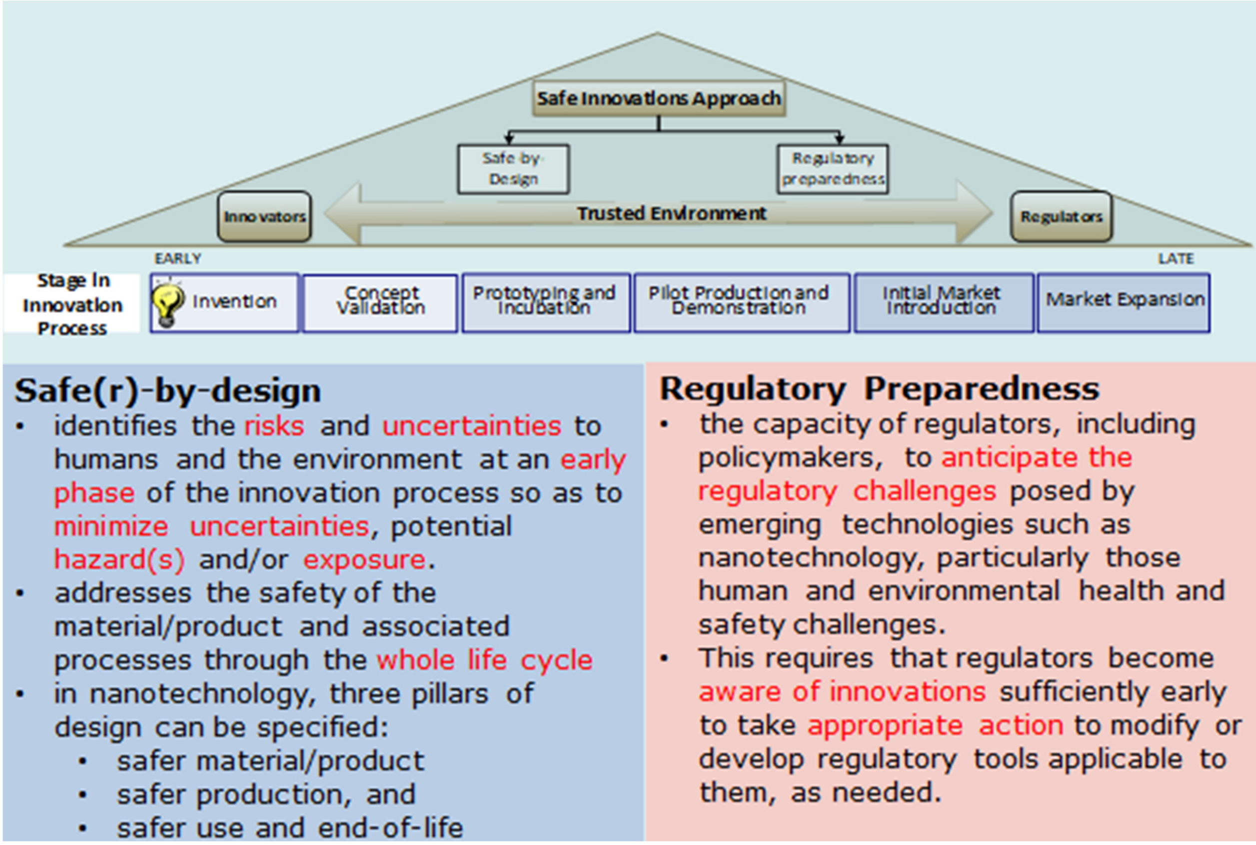

Figure 1. Overview of the Safe(r) Innovation Approach and its two corner stones, Safe-by-Design and Regulatory Preparedness. Figure modified from (Soeteman-Hernandez et al. 2019).

A regulatory perspective on Safe and Sustainable-by-Design (SSbD) approaches for advanced materials

Andrea Haase, from the German Federal Institute for Risk Assessment (BfR), covered a regulatory perspective on SSbD approaches for AdMa building on the recently published joint perspective on the matter from the German Higher Federal Authorities (Schwirn et al. 2022). Haase touched on the importance of AdMa for achieving several of the global sustainability goals, as well as the European Green Deal, while simultaneously posing a challenge in terms of ensuring inherent safety and sustainability of the materials themselves. The German Interagency Group have initiated the work by proposing a working definition for AdMa; "*AdMa are materials that are rationally structured and designed through the precise control of their composition and internal or external structure in order to fulfil new functional requirements*". In addition, the group provides examples of AdMa, including (nano-)carriers, multi-component (nano-)materials, advanced textiles and food contact materials, smart wearables and implants, and novel production processes (e.g. 3D printing).

Haase continued to provide an overview of the joint perspective on the challenges identified relating to AdMa and proposals for handling them. For example, a new concept is proposed, *Materials of Concern*, aimed at handling the wide variety of materials and identifying those that may raise concerns or pose challenges for safety or sustainability. The concept is inspired by the definition of hazardous chemical agents in Council Directive 98/24/EC (EC 1998), which covers beyond substances and mixtures also materials, articles and waste. The complete description and definition of the concept is available in the joint perspective report and an overview is provided in **Figure 2** (Schwirn et al. 2022). The concept is not to be confused with the REACH definition on substances of very high concern (SVHC), and should not be considered for inclusion in legislations, but rather as a support tool in daily risk assessment work.

Proposal for a definition of "Materials of Concern"

A "Material of Concern (MoC)" is

- (i) a material meeting the criteria for classification as a "hazardous substance" or "hazardous mixture" within the meaning of the criteria set out in Annex I to Regulation (EC) 1272/2008, or
- (ii) a material from which hazardous substances or mixtures according to (i) can arise or be released during its production or over its life cycle, or
- (iii) a material which does not meet the criteria (i) or (ii) but which, because of its morphological, physico-chemical, chemical, (eco)toxicological or release properties, could pose a risk to human or environment during its production or over its life cycle, or
- (iv) a material which could pose a concern regarding additional sustainability aspects

Figure 2. Overview of the proposed Materials of Concern concept. Figure reproduced with permission from (Schwirn et al. 2022).

Furthermore, Haase provided an overview of a newly proposed risk scoring system for emerging risks, the NESSI System which provides scores for a row of assessments relating to Novelty, Exposure, Severity, Scope, and Immediacy (see the original report for details (Schwirn et al. 2022)). The system was intentionally created as a generalised approach to risk scoring applicable for many different hazards and scenarios, not only AdMa. Thus, further development may be required. Another system proposed in the joint perspective regards the usefulness of measurements, testing and risk evaluation methods and tools, and is referred to as Regulatory Readiness Level, previously mentioned in the Introduction above. This approach is suggested in order to keep pace with innovation and matches the currently widely applied Technology Readiness Level used within industrial environments.

Haase finalised her talk with reference to a variety of initiatives in line with the joint German perspective, covering activities by the German Interagency Group on AdMa and in the EU project HARMLESS focused on comprehensive intelligent testing and SbD strategies for high aspect ratio and multi-component materials.

Short perspectives on the real-world situation and regulatory aspects of SSbD/SIA

The initial part of the workshop was followed by a second session with shorter perspectives on the practical aspects of real-world implementation of SSbD and SIA. **Ian Cotgreave** from the Research Institutes of Sweden (RISE) introduced the session composed of four talks focused on test methods, modelling and data.

Mar Gonzalez, from the OECD and Secretariat to the OECD WPMN, kicked off the session with an overview of OECD´s role to oversee and provide directions from the viewpoint of regulatory applicability of test methods for nanomaterials. The OECD is positioned beyond national and European level and connects countries, science and regulation. Focus lies on avoidance of duplication of test methods and resources, and to facilitate global trade. Check lists are applied to identify test methods with scientific and regulatory acceptance. Challenges have been faced regarding applicability of existing guidance developed for chemicals to nanomaterials, but the OECD has supported adaptation of a few to fit nanomaterials, and new test guidelines are in development for a variety of physico-chemical properties, as well as sample preparation and dosimetry (**Table 1**).

Table 1. OECD test guidelines (TG) and guidance documents (GD) applicable to, or in development to become applicable to, nanomaterials. (MN = Manufactured Nanomaterials)

	Test guideline
Physico-chemical properties	WNT 1.3 TG on Determination of the (Volume) Specific Surface Area of MNs (EU)
	WNT 1.4 TG on particle size and size distribution of MNs (Germany)
	WNT 1.5 GD on Determination of solubility and dissolution rate of NMs in water and relevant synthetic biological media (Denmark/Germany)
	WNT 1.6 GD on Identification and quantification of the surface chemistry and coatings on nano-and microscale materials (Denmark/Germany)
	WNT 1.8 TG on Determination of Surface Hydrophobicity of MNs (EU)
	WNT 1.9 TG on Determination of the Dustiness of MNs (Denmark/France)
	WNT 1.10 GD on the determination of concentrations of nanoparticles in biological samples for (eco)toxicity studies (UK)
Effects on biotic systems	WPMN Adaptation of OECD TGs 201, 202 and 203 for the determination of the ecotoxicity of MNs (France/Spain)
Environmental Fate and behaviour	WNT 3.10 TG on dissolution rate of NMs in aquatic environment (Germany)
	WNT 3.12 GD on assessing the apparent accumulation potential for NMs (Spain)
	WNT 3.16 GD Environmental abiotic transformation of NMs (Austria)
	WPMN Scoping review for a tiered approach for reliable bioaccumulation assessment of MNs in environmental organisms minimising use of higher tier vertebrate tests (UK)
Health effects	WNT 4.95 GD on the Adaptation of *In Vitro* Mammalian Cell Based Genotoxicity TGs for Testing of MNs (EU)
	WNT 4.133 Applicability of the key event based TG 442D for in vitro skin sensitisation testing of NMs (Switzerland)
	WNT 4.146 TG on toxicokinetics to accommodate testing of nano-particles (the Netherlands/ UK)
	WPMN Integrated *in vitro* Approach for Intestinal Fate or Orally Ingested NMs (Italy)
Other	TGs on sample preparation for NMs
	TGs on dosimetry of NMs

Gonzalez continued to touch on the challenge of harmonisation which takes time and requires major coordination efforts and pragmatic solutions. Finally, she covered the aspects of emerging issues with nanomaterials and beyond (e.g. AdMa) and the need for Regulatory Preparedness, which lies at the heart of the OECD initiatives (report on SIA and steering groups on SIA and AdMa) to bring SIA closer to practical implementation and to integrate the AdMa playing field closer to the work on chemicals.

Alexander Lyubartsev from Stockholm University continued the session with a short perspective on computational modelling of nanomaterials and AdMa. He provided examples of the usefulness of computational and predictive tools, including understanding of molecular/material mechanisms/interactions and prediction of functionality or toxicity based on screening for specific material properties (i.e. so called quantitative-structure activity relationships [QSARs]). Lyubartsev also touched on new approaches where material modelling meets systems biology, mentioning what is referred to as intelligent QSARs, which provide descriptors based on bio-nano interactions, link descriptors to Adverse Outcome Pathways (AOP), and are inherently "aware" of the molecular/biological mechanisms underlying the structure-activity relationship.

Roland Grafström, from KI and the small high-throughput screening company Misvik Biology, gave an overview of ongoing projects with an SSbD-focus and where high-throughput screening approaches are considered for advancing SSbD strategies, mentioning Gov4Nano, NanoSolveIT, SABYDOMA, HARMLESS, RISKHUNT3R, and PrecisionTox. Grafström referred to the importance of high-throughput tiered NAMs and how these do not stand alone but fit into the SSbD scenario where cost effective data-driven decisions need to be taken. The aim of the tiered high-throughput strategies is not to provide full conclusive assessment of risk, but to give a first overview and indication of the potential for hazard, which gradually increases along the SSbD approach towards a NAM-driven risk assessment available for regulatory reporting.

Penny Nymark concluded the session with a short overview of the current state of available data for SSbD. She touched on the importance of digitalised data to boost transformation towards a sustainable circular economy, whereby accurate information on availability, location, condition and safety of products and materials is needed in order to close the material loops. She continued with the importance of the recently established FAIR principles in order to fast track digitalisation. The FAIR principles provide guidance for making data Findable, Accessible, Interoperable and Reusable and were recently applied to data in the nanosafety field establishing the Nanosafety Data Interface. She also provided insight into a new FAIR implementation network, the AdvancedNanoIN, FAIR data-driven risk assessment along SSbD approaches, and the support FAIR data provides to Regulatory Preparedness.

Safe and Sustainable-by-Design – a prerequisite for achieving a circular economy

In a final part of the workshop, **Xenia Trier** from the EEA, concluded with a presentation focused on the alignment of SSbD with the EU Chemicals Strategy for Sustainability aiming for a toxic-free and circular future (EC 2020a). She brought up the overarching goal to avoid harm to the planet and people from the start instead of finding solutions later after problems have already arisen, and the need to control chemicals and exposure both within and beyond the EU to be successful. Trier provided examples of the complexity of circularity, including unforeseen reuse of materials and chemicals and the challenges it poses when surprising and innovative recycling leads to release and exposure to harmful substances (e.g. dioxins in toys produced from recycled plastics). Circularity relies on efficient material loops and documentation (i.e. digitalisation, see above regarding FAIR data). In addition, she brought up the urgent need for fast, cheap and reliable methods to comply with the requirements set by regulation and mentioned that *in vitro* testing and modelling is currently still too costly.

Trier continued with suggestions for moving towards future clean material cycles in SSbD by avoiding *Substances of Concern* (note that this is not the same as SVHC; **Figure 3**). It is foreseen that exposure to Substances of Concern increases as contaminated materials are recycled and climate change-related pollution increases. Thus, the risk for hazard should be reduced by avoiding the use of Substances of Concern. On the other hand, she mentions that if service is critical for health and the functioning of society, and cannot be provided without the use of Substances of Concern, i.e. if they are essential to society, then such substances may be permitted in cases of *Essential Use* (EC 2020a). The challenge is to meet sustainability goals without compromising safety, and criteria for minimum scores informed by protection goals of society need to be developed. Trier moves on to describe the requirements for enabling these goals, including enabling environments and tools to support assessments, including the use of existing data and knowledge. The final message includes the statement that SSbD is the key to unlock circular economy, whereby products need to be *Circular by design*, as described by the EEA (EEA 2017).

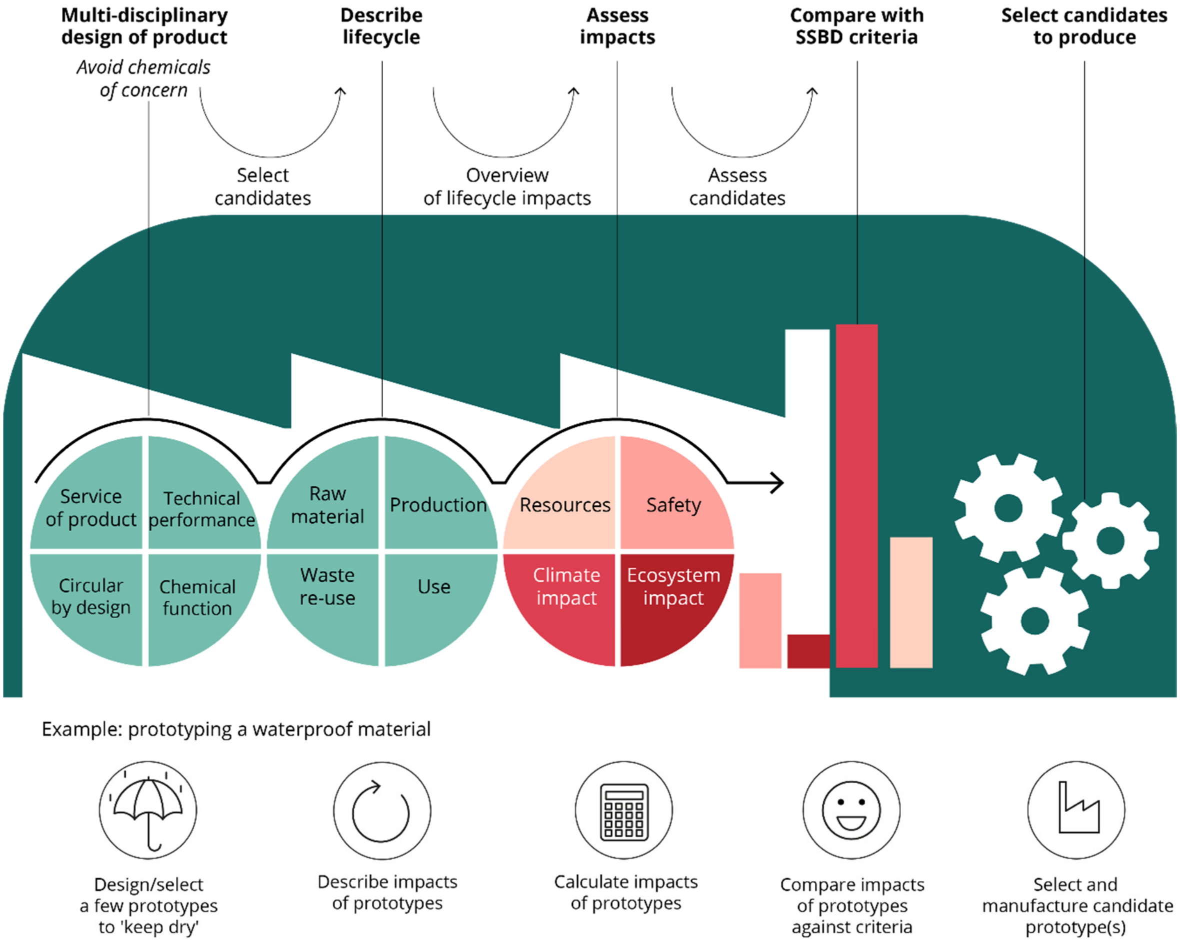

Figure 3. Overview of SSbD where *Substances of Concern* are avoided in order to maintain clean material cycles. Figure from (EEA 2021).

Key discussion points

The initial presentations by Lya Soeteman-Hernandez (RIVM) and Andrea Haase (BfR) were followed by a Q & A session where questions regarding the SIA concept and the regulatory perspectives on SSbD were brought up. In particular, discussion was spurred around the concepts of ***regulatory sandboxes*** and Trusted Environments coupled to SIA. Details regarding how confidentiality is preserved were raised and listed among other things legal confidentiality and agreements, different types of sandboxes where the most common types consist of one regulator and one company. An example from the tire industry was brought up, where companies have come together to share information on a common concern regarding health and the environmental impact of tires. The industry has established a global voluntary initiative, the Tire Industry Project, focused on sustainability issues, including safety aspects, of tires. The initiative aims to share resources on safety and sustainability but maintain confidentiality agreements regarding functionality innovation and design.

Furthermore, the concept of ***Materials of Concern*** was raised to discussion and whether it could fit into current EU legislation. Andrea Haase pointed out that it is not currently targeted for implementation into legislation but enables development of specific criteria for identifying Materials of Concern and provides a pragmatic approach towards substitution. The aim is to develop it in line with sound scientific evidence. She also pointed out that the Materials of Concern concept should not be confused with the well-established and legislation implemented SVHC. It is not currently clear how useful the Materials of Concern concept will be, however BfR and the other German Federal Authorities invite others to join the effort!

The concept of ***SbD Space*** was further brought up for discussion. The concept is currently developed within the EU project HARMLESS and aims at identifying the space that spans the flexibility and the possibilities available to modify the system/innovation safely. Currently the concept is mainly focused on reducing hazard and exposure (within the realm of the HARMLESS project), however it paves the way for inclusion of business and economic aspects.

The second part of the workshop consisting of four talks focused on real-world application of SSbD, including Mar Gonzalez (OECD), Alexander Lyubartsev (SU), Roland Grafström (KI) and Penny Nymark (KI and SweNanoSafe), was followed by a second Q & A session where questions regarding ***testing, modelling and data*** were brought up. Discussion spurred around the need for quicker approaches focused on data, including read across. A need for case studies for demonstration was brought up, as well as a need for moving beyond the current practice of property-by-property based read across, where one parameter of a nanomaterial is correlated with one toxic endpoint. There is a need for combinations of diverse data describing characteristics, including both physicochemical and biological data. In addition, there is a need for reference databases, which to some extent can be provided from chemical data, but also recently started EU projects such as HARMLESS where ~100 million data points will be generated covering aspects of physicochemical, exposure, and hazard characteristics of AdMa. Currently the claims for similarity are not robust enough for regulatory use and thus, there is an urgent need for available (FAIR) data and model development. In addition, needs beyond making data FAIR, hence reusable, include extensive data curation efforts and ensuring that data is trustworthy (i.e. high quality).

Another aspect brough up during the second session of the workshop was the previously mentioned large European initiative, ***PARC***, which may advance the implementation of SSbD on a broad level and beyond nanosafety. The project involves almost all European member states, has a budget of over 400 M Euro, and spans 7 years with the kick-off scheduled for March 2022. **Adriënne Sips** from RIVM, co-lead of the task driving SSbD within the project, provided the workshop participants with a brief overview of the aim of PARC and in particular the aspect of *SSbD beyond nano* (note the hyperlink to the recording on the SweNanoSafe YouTube channel). She emphasised the close connection to policy within the project. PARC includes on the one hand robust scientific development tasks focused on implementation into regulatory frameworks, but the urgent need for the outputs of the project to fit societal needs is also reflected in the structure of PARC through alignment with e.g. the EU Chemicals Strategy for Sustainability and other strategies and policy ambition goals. SSbD is included in the project as a task under the work package of "New concepts and tools", focusing on identifying criteria, methods and tools for SSbD in order to make it acceptable within regulatory application. SSbD has been more extensively explored within the nanosafety community than within the chemical field. Overall, Sips points out that we need to take time to level with each other both regarding SSbD and other new concepts such as FAIR data (which has its own work package in PARC) etc. There is still a need to learn from each other, both between the fields of nano- and chemical safety, but also between the fields of safety and sustainability assessment.

The third and final part of the workshop, covering the presentation by Xenia Trier (EEA) was followed by a final discussion focused on the overall goal of enabling circularity through the SSbD concept. The discussion initiated with a spotlight on the need for tools for ***life cycle analysis (LCA)*** of nanomaterials. LCA tools have been included in the current version of the SIA toolbox, however further developments are needed to assess the applicability of chemical-specific LCA tools to nanomaterials. There is an urgent need to implement these tools in practice. Further discussion revolved around a question regarding the role of ***data mining and artificial intelligence (AI)*** in these contexts and the fact that such approaches are currently most applicable within the area of hazard, where better structure and methods exists as compared to exposure (including on OECD level). Approaches mainly aim to identify which families of chemicals are not hazardous. However, when it comes to exposure data it is more difficult and there is a lack of data regarding which chemicals were used at what concentration and for what purpose. It is very costly to fill the gaps of knowledge and more information on what types of uses and transformations take place at different stages of the life cycle is needed. Within the EU project PARC there are ambitions to look closer at filling the exposure gap. However, overall data in the pre-market phase is still a large challenge. Examples of AI and text mining were also brought up in the context of the EUToxRisk project, which has used such approaches to identify chemicals that have never been classified as toxic in any test systems (Hartung 2019).

Finally, ***case studies*** as a means of "learning by doing" were also brought up during this part of the discussion and a few case studies performed in the Netherlands were mentioned, including one regarding antifouling of ships. However, it was also brought up that case studies are complex and often highly diverse and difficult to compare. Overall, a basic principle worth considering for SSbD was mentioned: "*if you use less materials, you create less problems*". The statement is aligned with KEMI´s recent remark that "*the right chemicals are more important than more chemicals*". It is also strongly linked to the main conclusion in the recent study on the planetary boundaries and that we are operating outside the safe space of the boundaries (Persson et al. 2022). The study suggests that the planet cannot handle more toxic chemicals and that we have reached a tipping point. Overall, the challenges regarding how to handle the overwhelming information flow both for development of SSbD strategies and for implementation of the concept, as well as a need for clear regulation was emphasized, were identified as highly important in order to be successful.

Conclusions and future perspectives

A few central conclusions arose from the presentations and discussions, which were summarised by **Gregory Moore** from KEMI. Overall, it was agreed that a holistic approach is needed where the aim of the SSbD concept is to decrease both the chemical footprint (safety) and the ecological footprint (sustainability) of human activity and innovation. The importance of aligning and integrating safety, functionality and circularity in innovation is central. This aim is clearly met by the SIA concept incorporating not only SSbD, but also Regulatory Preparedness and Trusted Environments to achieve industrial relevance, regulatory effectiveness and societal trust (and awareness). It is clear that *the window of opportunity is now* with the rise of policy ambition goals towards safety and sustainability, evidenced by a number of EU and OECD driven strategies, including in particular the EU Chemical Strategy for Sustainability, the EU Green Deal, the OECD report on the SIA concept and many more.

These conclusions align with the five research needs identified by the EEA; the needs for i) criteria, ii) efficient tools, iii) data, iv) standardisation and v) enabling environments as mentioned in the Introduction (van der Waals et al. 2019). Overall, eleven key future activities for the success of SSbD were identified as listed below. SweNanoSafe will aim to continue to support these activities.

1. The need for **drivers, mandates**, and a move away from working in silos. Global players such as the OECD are central to the change.
2. The need for high level harmonisation of **definitions/terms/concepts**, including overall for

SSbD, but also for the scope of the concept i.e. coverage of AdMa, nanomaterials, chemicals, etc.

3. Development of clear implementable **criteria** for both safety and sustainability in order to make SSbD actionable through regulatory means
4. Development of **scoring approaches** driven by scientific evidence, but also including societal considerations
5. Development of harmonised and accepted **test methods**, including considerations of New Approach Methodologies and overcoming the issues of trust in new methods
6. Implementation of FAIR principles throughout all **data** generating processes, including scientific, industrial and regulatory, in support of machine-driven approaches (AI) for both safety and sustainability assessment (including e.g. toxicity prediction, life cycle assessment and traceability of materials/chemicals)
7. The need for **case studies** demonstrating practical implementation of SSbD
8. The need for **investment** to assure effective and efficient cooperation
9. Efforts to implement early warning systems in order to **avoid substances/materials of concern** already today (not to be confused with the REACH Substances of Very High Concern compliance). Approaches have been suggested by many, including the Materials of Concern concept proposed by the German Federal Authorities in their report (Schwirn et al. 2022)
10. The need for **translating** international activities on SSbD (OECD) to fit European and national level implementation
11. The overall need for **cultural change**, i.e. thinking (and literally stepping) out of the box in order to accept and effectively implement high level SSbD

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Hyperlinks provided in the text:

"the right chemicals are more important than more chemicals"
https://www.altinget.se/miljo/artikel/kemikalieinspektionen-ratt-kemikalier-ar-viktigare-an-fler-kemikalier
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Essential Uses
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EU Chemicals Strategy for Sustainability
https://ec.europa.eu/environment/strategy/chemicals-strategy_en
Workshop - European Commission (SSbD)
https://ec.europa.eu/environment/events/safe-and-sustainable-design-criteria-chemicals-materials-and-products-first-stakeholders_en
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https://www.wbcsd.org/Sector-Projects/Tire-Industry-Project

ANNEXES

Annex I - Program

13.00 Welcome (**Bengt Fadeel, SweNanoSafe/KI**)

13.05 Introduction (**Penny Nymark, SweNanoSafe/KI**)

13.20 Safe Innovation Approach: Towards an agile system to meet policy ambitions (**Lya Hernandez-Soeteman, RIVM**)

13.45 A regulatory perspective on Safe and Sustainable-by-Design (SSbD) approaches for advanced materials (**Andrea Haase, BfR**)

14.10 Q&A

14.30 *Break*

14.35 Short perspectives on the real-world situation and regulatory aspects of SSbD/SIA **(Ian Cotgreave, RISE, session moderator)**

Testing and standardized methods for SSbD of nanomaterials (**Mar Gonzalez, OECD**) 20 min

Modelling of nano- and advanced materials in research (**Alexander Lyubartsev, SU**) 10 min

Ongoing European SSbD projects – towards high-throughput testing (**Roland Grafström, KI**) 10 min

Digitalized and reusable data for SSbD of nano- and advanced materials (**Penny Nymark, KI**) 10 min

Q&A 30 min

15.55 *Break*

16.00 SSbD as a prerequisite for achieving circular economy (**Xenia Trier, EEA**)

16.25 Discussion

17.00 Final remarks/Future perspectives (**Gregory Moore, KEMI**)

17.15 End

All presentations are publicly available on the SweNanoSafe YouTube channel.

Annex II – List of participants

Name	Profession	Organization
Veronique Adam	Consultant in sustainability / Researcher	TEMAS Solutions
Aileen Bahl	PhD student	German Federal Institute for Risk Assessment
Chiara Battistelli	Researcher	Istituto Superiore Sanità
Nathan Bossa	Researcher	LEITAT Technological Center
Cecilia Bossa	Researcher	Istituto Superiore di Sanità
Hedwig Braakhuis	Toxicologist	Dutch National Institute for Public Health and the Environment (RIVM)
Gustaf Bäck	Administrative officer	Arbetsmiljöverket
Ulrika Carlander	PhD student	Karolinska Institutet (KI)
Simon Clavaguera	Project manager	French Alternative Energies and Atomic Energy Commission (CEA)
Ian Cotgreave	Senior Researcher	Research Institutes of Sweden (RISE)
Pernille Høgh Danielsen	Postdoc	The National Research Centre for the Working Environment
Isabella De Angelis	Researcher	Istituto Superiore di Sanità
Jana Drbohlavova	Policy officer, researcher, chemists	European Commission, DG RTD
Naouale El Yamani	Senior scientist	Norwegian institute for Air Research
Barbro Eriksson	Consultant	Origo Group
Carl-Henrik Eriksson	Chemist	The Swedish Chemicals Agency
Sara Espinoza	Scientist	DECHEMA e.V.
Bengt Fadeel	Professor	KI/SweNanoSafe
Lucian Farcal	Project Officer	EC - Joint Research Centre
Natalia Fernández Bertólez	Researcher	University of A Coruña
Sabine Frey	Scientific Officer	Federal Office of Public Health
Masashi GAMO	Researcher	National Institute of Advanced Industrial Science and Technology (AIST)
Fredrika Gilljam Norberg	Intern	Naturvårdsverket
Mar Gonzalez	Global relations officer	Organization for Economic Cooperation and Development (OECD)
Roland Grafström	Professor	KI
Khara Grieger	Assistant professor	North Carolina State University
Andrea Haase	Head of department	German Federal Institute for Risk Assessment
Lya Hernandez	Senior Scientific Advisor	RIVM
Ellen Ingre-Khans	Investigator	Kemikalieinspektionen (KEMI)/Swedish Chemicals Agency
Wigren Jane	Chemist	SundaHus i Linköping AB
Selvaraju Kanagarajan	Researcher	Swedish University of Agricultural Sciences

Rune Karlsson	Coordinator	KI/SweNanoSafe
Helen Karlsson	Environmental Chemist, Professor	Linköping University
Andrej Kobe	Policy Officer	European Commission DG Environment
Judy Fabienne Kool	Master Student	KI
Harald Krug	Nanotoxicologist	NanoCASE GmbH; Emeritus University of Berne, Switzerland
Blanca Laffon	Professor	University of A Coruña
Guilherme Lenz e Silva	Professor	University of São Paulo
Evelina Lindmark	Study Director	RISE
Chrysovalanto Louka	Postdoc	Swiss Federal Laboratories for Materials Science and Technology (EMPA)
Alexander Lyubartsev	Professor	Stockholm University/SweNanoSafe
Klara Midander	Assistant professor	KI/SweNanoSafe
Mirella Miettinen	Senior Researcher	University of Eastern Finland (UEF) Law School
Linda Molander	Environmental health analyst	Public Health Agency of Sweden
Andrea Montano Montes	PhD Student	KI
Gregory Moore	Investigator	KEMI/Swedish Chemicals Agency
Shanda Moorghen	Journalist	Chemical Watch
Katja Nau	Biologist	Karlsruhe Institute of Technology (KIT)
Trond Nordtug	Researcher	SINTEF Ocean
Jessica Norrgran Engdahl	Environmental chemist	Swedish Chemicals Agency
Penny Nymark	Assistant professor	KI/SweNanoSafe
Michael Persson	Senior Material Advisor	Chalmers Industriteknik
Francis Peters	Consultant	Business and Industry Advisory Committee to the OECD (BIAC) / World Business Council for Sustainable Development (WBCSD)
Alexander Pogany	Policy Expert	Federal Ministry for Climate Action, Environment, Energy, Mobility, Innovation and Technology (BMK)
Ievgen Pylypchuk	Researcher	Stockholm University
Efstathios Reppas Chrysovitsinos	Researcher	Independent Researcher
Juan Riego Sintes	Scientific Officer - Team Leader	European Commission - JRC
Sarah Robinson	Regulatory Scientist	Department of Health at Northern Territory Government
Isabel Rodríguez Llopis	Researcher	Fundación GAIKER
Elise Rundén-Pran	Senior scientist toxicology	NILU - Norwegian institute for air research, Health Effects Laboratory
Abdelaziz Saafane	PhD student	Armand-Frappier Santé Biotechnologie Research Centre
Beatrice Salieri	Sustainability Consultant	TEMAS Solutions

Araceli Sanchez Jimenez	Health & Safety Consultant	INSST - Instituto Nacional de Seguridad y Salud en el Trabajo
Javier Sanfelix	Policy Officer	European Commission
Kathrin Schwirn	Scientific staff member	German Environment Agency (UBA)
Lars Sickert	Analyst	Tetra Pak
Adrienne Sips	Research coordinator nanomaterials & advanced materials	RIVM
Christoph Steinbach	Chemist	DECHEMA e.V.
Anna-Karin Sternbeck	Researcher	RISE
Tobias Storsjö	Assistant Researcher	Gothenburg University
Leigh Stringer	Editor	Chemical Watch
Emma Strömberg	Expert polymeric materials	IVL Swedish Environmental Research Institute
Blanca Suarez	Director of Regulatory Affairs	Nanotechnology Industries Association
Koto Sugiura	Consultant	JFE Techno Research Corporation
Junia Teixeira	Engineer	Centro de Desenvolvimento e Tecnologia Nuclear
Xenia Trier	Project manager on Chemicals	European Environment Agency (EEA)
Audrun Utskarpen	Senior environmental adviser	Ecolabelling Norway
Vanessa Valdiglesias	Researcher	University of A Coruña (Spain)
Eva Valsami-Jones	Professor	University of Birmingham
Gunther Van Kerckhove	HS lead manager	OCSiAl Europe Sarl
Rakesh Vazirani	Engineer	TUV Rheinland
Socorro Vázquez-Campos	R&D Area Manager	LEITAT Technological Center
Chiara Venturini	Director General	Nanotechnology Industries Association (NIA)
Peter Wick	Head of Research Laboratory for Particles-Biology Interactions	EMPA

Annex III - Speaker biographies and abstracts

Lya Soeteman-Hernandez - Senior Scientific Advisor, Dutch National Institute for Public Health and the Environment, RIVM, The Netherlands. Dr. Soeteman-Hernandez is a senior risk assessor, toxicologist and scientific advisor with vast experience in the development of system approaches and translating them into operational tools. She is one of the main developers of the Safe Innovation Approach which contains the concept of Regulatory Preparedness, Safe-by-Design and Trusted Environment. These concepts originate from the awareness that new technologies like nanotechnology have uncovered the limits of present regulatory systems and demand more agile governance systems. Dr. Soeteman-Hernandez is co-chair and Leading Expert at the OECD Working Party on Manufactured Nanomaterials Safe Innovation Approach Steering Group, where she assesses how the international community apply innovative ideas/approaches in the context of regulatory frameworks. Here, we gather experiences and insights on which factors and actions are pivotal in international regulatory frameworks to move away from the traditional checklist mentality and towards pro-active, co-creative and inclusive approaches to improve nano risk governance.

Safe Innovation Approach: Towards an agile system to meet policy ambitions

Lya Hernandez-Soeteman, Dutch National Institute for Public Health and the Environment

The Safe Innovation Approach (SIA) is a framework outlining the necessary elements needed to cover safety aspects of nanomaterials and nano-enabled products. SIA consists of the combination of the Safe-by-Design (SbD) and regulatory preparedness (RP) concepts; as both industry/innovators and regulators need to be proactive and vigilant. Recent policy ambitions such as the Green Deal and the Chemical Strategy for Sustainability demand the integration of sustainability aspects to SIA towards a Safe-and-Sustainable Innovation Approach. SbD recommends industry to integrate safety considerations as early as possible in the innovation and product development process. Sustainable-by-Design is in a more explorative phase, where a first description of the concept can be found in the Horizon Europe research programme: "Sustainable-by-Design concept takes a systems approach by integrating safety, circularity and functionality of advanced materials, products and processes throughout their lifecycle. This concept can be defined as a pre-market approach that focuses on providing a function (or service), while avoiding properties that may be harmful to human health or the environment. from a lifecycle perspective." [First EC working description, p.111]. Regulatory preparedness aims to improve anticipation of regulators in order that they can facilitate the development of regulation supportive to the pace of knowledge generation and innovation of nanomaterials and nano-enabled products. The progress of bringing these concepts to practical applicability will be discussed along with their relevance in supporting policy ambitions.

Andrea Haase studied biochemistry at the University of Tübingen, obtained a PhD from the University of Heidelberg, finished a postgraduate toxicology study at the University of Leipzig and completed her habilitation in toxicology at the Freie Universität Berlin. Since 2008 she is working at the German Federal Institute for Risk Assessment (BfR) in Berlin, where she is heading the unit "Fibre- and Nanotoxicology". The unit is in charge of health risk assessments for (nano-) particles and fibres in consumer products, which also includes assessments of fibres and substances in nanoform within the overarching European chemicals legislation, REACH. The unit is also actively engaged in several large research projects (e.g. GRACIOUS, NanoInformaTIX, Gov4Nano, nanoCommons, InnoMatLife, HARMLESS) addressing the safety of nano- and other innovative materials. Current research focuses on the establishment of nanomaterial grouping approaches and the development of data-driven methods, considering nano-specific modes of action as assessed e.g. by Omics methods.

A regulatory perspective on Safe and Sustainable-by-Design (SSbD) approaches for advanced materials

Andrea Haase, Department Chemical and Product Safety, German Federal Institute for Risk Assessment (BfR)

Advanced materials (AdMat) are in the focus of current research and innovation with anticipated benefits for the economy, the society and the environment. They may provide solutions for several of the biggest global challenges such as renewable energy, e-mobility, digitalisation or healthcare. This, however, requires safe and sustainable solutions. AdMat pose several challenges from a regulatory perspective. The first challenge is the lack of a common understanding what AdMat actually are. The second challenge is that AdMat comprise a large variety of different materials and material types. Moreover, constantly new AdMat and variants thereof are developed, demanding for new data-driven approaches for hazard and safety assessment. Certainly, one can build on experiences, methods and knowledge developed in the last decades on nanomaterials. Nevertheless, for several AdMat appropriate test and assessment strategies still need to be developed. Therefore, research plays an important role to clarify and substantiate the scientific basis. Moreover, only collaborations of experts from industry, academia and regulatory agencies allow for developing Safe and Sustainable-by-Design approaches. Safety and sustainability aspects have to be considered as early as possible during the innovation process.

This talk will provide an overview on the current state of the art and the challenges with respect to AdMat from a regulatory perspective. It will also highlight research needs and provide some insights into current research activities, mainly from the projects InnoMat.Life and HARMLESS.

Mar Gonzalez - Administrator, Environment Directorate, Organisation for Economic Cooperation and Development. Mar Gonzalez joined the Organisation for Economic Co-operation and Development (OECD) in 2004 to work at the Environment, Health and Safety Division. Over the years, she has had a number of responsibilities addressing the safety/ risk assessment and international harmonisation in the regulation of chemicals and products of modern biotechnology. Since she joined OECD, she has been involved in various technical programmes covering biosafety, the safety of novel foods and feeds, chemical accidents prevention, preparedness and response, nanomaterials and test guidelines. From 2010 to 2018, she became responsible for the outreach work on chemicals, as well as reviewing the legal frameworks of non-OECD countries seeking a partnership at OECD. In joining the OECD, Mar had the opportunity to be involved in the establishment of the Working Party on Manufactured Nanomaterials in 2006. Since then, Mar has been working on the implementation of its programme of work, which includes the development of tools for assessing the hazards of nanomaterials, and more recently looking at the next generation of materials to ensure their safety. Mar has a BA in Physical Anthropology, a Master degree in Biotechnology and Ethics from the University of Sheffield, UK and a Diploma on Biosafety.

Alexander Lyubartsev - Professor, Stockholm University, Sweden. Graduated (1985) and PhD (1988) from St. Petersburg State University, Russia. Researcher at Stockholm University since 1993, Associate prof. since 2001, Full Professor since 2007. Research focused on development of novel computer modelling and simulation approaches with applications in biomolecular, material science and safety assessment of nanomaterials. Over 180 publications and involved in several EU-funded projects focused on nanosafety, e.g. EU H2020 SmartNanoTox. Member of the SweNanoSafe Expert Panel.

Modelling of nano- and advanced materials in research

Alexander Lyubartsev, Stockholm University

With the fast development of computer technologies, computer modelling and simulations have emerged as a new way of acquiring the scientific knowledge. Nowadays modelling has matured to be able to predict properties of not yet synthesized molecular compounds or materials, and it is widely used not only in the fundamental research, but also in many applied research areas such as materials and drug design. This presentation briefly overviews possibilities of modern computer modelling in design of nano- and advanced materials, to optimize their functional properties, and to ensure that new materials are safe for the human health and environment.

Roland Grafström - Medical Science degree, 1980. Full professor at Karolinska Institutet, 2000. CV lists ~150+ peer-review publications and international prizes in environmental medicine, toxicology, alternative methods research and risk assessment. Experience with human cell models-driven toxicity analyses, omics-based biomarker discovery, methods development, standardization, marketing and IPR. Knowledge in advanced materials, safety research and regulation from coordination of Safety-by-Design/nanotechnology for a professors/senior scientists-group and 400+ persons at Technical Research Centre of Finland. Involved in EU projects PATROLS, Gov4Nano (NMBP-13), NanoSolveIT (NMBP-14), SABYDOMA (NMBP-15), HARMLESS (NMBP16), RiskHunt3R (SC1-BHC-11-2020) and PrecisionTox (SC1-BHC-11-2020), and several H2020/ FP projects since 1993. Advisor for Misvik Biology Oy, Finland and BioTeSys GmbH, Germany.

Ongoing European SSbD projects – towards high-throughput testing

Roland Grafström, Karolinska Institutet

Complex behaviour and potential for mixture toxicology requires the adoption of Safety-by-Design (SbD) to the manufacturing of many nanomaterials and multi-constituent, advanced materials, several of which are characterized by high aspect ratio shapes and abundant heavy metal contents. Rapid, cost-effective and reliable product evaluation assessments are key to enable their application under a circular sustainable economy concept. Considering these aspects, high-throughput screening (HTS) safety testing technologies and data-driven assessments are central to recently initiated EU projects SAfety BY Design of nanOMAterials (SABYDOMA) and Advanced High Aspect Ratio and Multicomponent materials: towards comprehensive intelLigent tEsting and Safe by design Strategies (HARMLESS). These projects emphasize the principles of lower toxicity while preserving functionality, addressing thereby the issues of bioactivity versus adversity and prediction versus protection. To be discussed, these SbD projects are aimed to generating tools, guidance and decision support to ensuring that next generation materials are sustainably safe.

Penny Nymark is an Assistant Professor at the Institute of Environmental Medicine, Karolinska Institutet, Sweden. She serves at the Swedish National Platform for Nanosafety (SweNanoSafe) and as Swedish representative in the OECD Working Party for Manufactured Nanomaterials Safe Innovation Approach Steering Group. Her research (~50 peer-reviewed publications) and involvement in multiple EU-funded projects over the past 15 years (incl. past projects eNanoMapper, NanoReg2, caLIBRAte, PATROLS, and the ongoing Gov4Nano, HARMLESS, and PARC) has focused on mechanisms of particle-induced toxicity and development of animal-free, data-driven New Approach Methodologies, Adverse Outcome Pathways and Findable, Accessible, Interoperable, Reusable (FAIR) data for safety assessment of nano- and advanced materials, including implementation in Safe-by-Design approaches. She serves on the Editorial Board and as Collection Advisor for the next-generation open access journals Frontiers in Toxicology and F1000 Research.

Digitalized and reusable data for Safe and Sustainable Design of nano- and advanced materials

Penny Nymark, Karolinska Institutet

Data reuse is central in the assessment of health and environmental risks of nano- and advanced materials. The effective management and reuse of data from both standardized testing methods and new animal-free, high-throughput methods, accelerates and improves risk assessment of nanomaterials. The newly proposed FAIR principles provide guidance for making data Findable, Accessible, Interoperable, and overall Reusable. Over the past decade, several European projects have focused on developing and implementing solutions to make nanosafety data FAIR and the Nanosafety Data Interface, as well as a FAIR Implementation Network for nanosafety data (AdvancedNanoIN) were recently established. FAIR nanosafety data effectively contributes to digitalization and sustainable industrial processes through enabling efficient information exchange. Overall, this talk will illustrate a much-needed path towards concrete and practical FAIR data-driven safety decisions in support of safe and sustainable design of nano- and advanced material-enabled technology.

Reference: Jeliazkova, N. et al. Towards FAIR nanosafety data. Nat. Nanotechnol. 16, 644–654 (2021). doi:10.1038/s41565-021-00911-6

Gregory Moore - Toxicologist and senior scientific officer in Regulatory matters in the unit of EU-coordination at the Swedish Chemical Agency (KEMI; 2013 to date). Worked with nanomaterials (NM) for around 10 years starting at the Danish Environmental Protection Agency (Miljøstyrelsen, MST) with the "Better Control of Nano Materials" project (2012 - 2013). EU Member State representative in the EU Commission's CARACAL Subgroup on Nanomaterials (CASG Nano; 2012 - 2017), REACH Committee and ECHA's NanoMaterial Working Group (NMWG; 2013 - 2017) and Expert Group (NMEG; 2017 to date). Serve(-d) as a member of the Swedish national platform for nanosafety (SweNanoSafe) expert panel (2014 - 2019) and steering group (2019 to date). Head of delegation at the OECD Working Party on Manufactured Nanomaterials (WPMN) and member of the Nordic Working Group for Chemicals, Environment, and Health (NKE) subgroup for NM and the Safe-by-Design Policy International NEtwork (SPINE).

Future perspectives

Gregory Moore, Swedish Chemicals Agency

The Swedish Chemicals Agency (KEMI), as detailed in its response and comments to a public consultation in June 2021, strongly supports the European Commission´s aim to implement Safe and Sustainable-by-Design (SSbD) as presented in their first workshop (March 2021) organised by the Directorate-General for Environment and Directorate-General for Research and Innovation. In brief, the SSbD initiative encompasses: "*The European Green Deal which defines a clear vision and objectives to put European economy and society on a sustainable pathway, in particular to move towards climate neutrality, a circular economy and a zero pollution/toxic-free ambition. Key for this societal transformation will be the transition to a safe and sustainable by design approach, so that chemicals, materials and products are designed, produced and used in a way which does not harm people and the environment.*", and; "*The Circular Economy Action Plan which provides an agenda for achieving a cleaner and more competitive Europe, where safe and sustainable products are the norm, improving their durability, reusability, upgradability and reparability, and addressing the presence of hazardous chemicals. The EU Chemicals Strategy for Sustainability (CSS) aims to catalyse the shift towards chemicals, materials and products that are inherently safe and sustainable, from production to end of life, and announces that the EU Commission will develop criteria on Safe and Sustainable-by-Design by 2022.*"

Xenia Trier has since 1998 worked in compliance, enforcement and research institutions with chemical analyses and advice to national and EU institutions on pollutants such as food contact materials. Since joining the European Environment Agency in 2016, she works with risk governance of chemicals (EEA 2018, EEA SOER2020), supporting EU policy processes, particularly the EU chemicals Strategy for Sustainability (CSS) and leading the country EIONET network 'Ad hoc expert group on chemicals'. Topics include Safe and Sustainable-by-Design (SSbD), Essential Uses, early warning systems, chemicals in the circular economy, managing classes of chemicals, PFAS (EEA 2019), environmental and biomonitoring, indicators, and data management (IPCHEM).

Bengt Fadeel - Professor of Medical Inflammation Research and Head of the Unit of Molecular Toxicology, Institute of Environmental Medicine (IMM), Karolinska Institutet. Dr. Fadeel is the chair of the expert panel of the national platform for nanosafety (SweNanoSafe) (since 2016) and a member of the steering group of the platform. SweNanoSafe is commissioned by the Swedish Ministry of the Environment and hosted at IMM. Dr. Fadeel is a Fellow of the US Academy of Toxicological Sciences (ATS) (since 2012, re-certified in 2018). He has been actively involved in several EU-funded nanosafety consortia in FP7 and H2020 and he is a current member of the EU-funded Graphene Flagship (2013-2023) as well as the national MISTRA Environmental Nanosafety consortium. He has published 270 papers and his current H-index is 67 (Web of Science) or 81 (Google Scholar).

Ian Cotgreave - Senior Researcher, Research Institutes of Sweden (RISE), Sweden. Ian is a former professor of toxicology from the Karolinska Institute (still affiliated) and has held posts as head of molecular toxicology at AstraZeneca safety assessment for 10 years, where he was involved in progressing novel drug candidates over all stages of development, and senior research scientist and strategist at Swetox, the Swedish academic center for chemical and pharmaceutical safety. Ian is currently senior scientist and business developer at the newly formed department of Chemical and Pharmaceutical Safety within the Division of Biosciences and Materials at the Research Institutes of Sweden (RISE: www.ri.se), where he leads efforts to develop an internal platform which can serve, together with other national hubs, Swedish business needs in the future. Ian has worked for many years academically, industrially and from a regulatory perspective on the development of mechanism-based safety assessment, in particular the development of new safety assessment methods, where Ian has partaken international research programs such as SEURAT-1 EuToxRisk and currently RISKHUNT3R. Ian is currently a member of EURL ECVAMs science advisory Committee (ESAC) and is author of over 150 articles in the field of toxicology.