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Developments in Delegations on the Safety of Manufactured Nanomaterials and Advanced Materials – Tour de Table

July 2022 – June 2023

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FOREWORD

The OECD Working Party on Manufactured Nanomaterials (WPMN) is a subsidiary body of the OECD Chemicals and Biotechnology Committee. This programme concentrates on human health and environmental safety implications of manufactured nanomaterials (limited mainly to the chemicals sector), and aims to ensure that the approach to hazard, exposure and risk assessment is of a high, science-based, and internationally harmonised standard. It promotes international co-operation on the human health and environmental safety of manufactured nanomaterials and involves the safety testing and risk assessment of manufactured nanomaterials.

This document compiles information provided by delegations on the 23rd WPMN meeting (June 2023). It aims to summarise relevant information on activities related to manufactured nanomaterials, as well as other activities on nanotechnologies at the international level.

This document is published under the responsibility of the Chemicals and Biotechnology Committee of the OECD.

Table of contents

1 National developments on human health and environmental safety on Nanomaterials/ Advanced Materials

1.1 Australia

Under the Australian Industrial Chemicals Introduction Scheme (AICIS), the introduction (import or manufacture) of a nanoscale chemical is categorised as an assessed introduction unless it meets the criteria for a commercial evaluation authorisation or for research and development. Further details are available at Categorisation of chemicals at the nanoscale.

Within the last 12 months, AICIS issued a certificate to authorise the manufacture of two physical forms of graphene (CAS number 1034343-98-0) in Australia. The certificate included a defined scope of assessment (DSA), which is a legal obligation for certificate holders, and it will be included in the inventory during listing of the chemical. A DSA typically describes introduction volume, uses and concentrations of the chemical in end use products. For chemicals at the nanoscale, the DSA also states particle size and size distribution, surface area, surface functionalisation, layer number, purity, etc. The terms added to certificates are expected to ensure safe introduction and use of only the specific nanomaterials assessed by AICIS, when there could be other nanomaterials with varying particle parameters and/or physicochemical properties identified by the same generic name or CAS number. If the circumstances of the introduction are not within the DSA, the introducer must categorise their introduction into the appropriate introduction category (that is Listed, Exempted, Reported or Assessed), or apply to vary the term of the certificate or the inventory listing. Details are available at Guide to categorising your chemical importation and manufacture.

1.2 Austria

The Austrian Nano Information Commission (NIK; chair: André Gazsó, Austrian Academy of Sciences) of the Austrian Federal Ministry of Social Affairs, Health, Care and Consumer Protection has entered its second function period (until 2024) and consists in the meantime of more than 30 members which represents an increase of roughly 25 percent. The members are coming from academia, regulatory authorities and non-governmental organisations. The NIK convenes two to three times a year having as main tasks i) to provide all members with information on the current research and developments in the field of nanotechnology safety, ii) to offer an opportunity to discuss and evaluate these findings and iii) to foster safety-relevant research concerning the use of nanomaterials in Austria. The NIK is concerned with the implementation of the Austrian Nano Action Plan and represents the diversity of opinions and the professionally sound state-of-knowledge of various scientific experts. The period under review included the 7th and 8th meeting of the NIK (11/14/2022 and 03/27/2023). The Nanoinformation Commission supports research on the safe and sustainable development and application of nanomaterials and

advanced materials. In this function the 8th NIK meeting was dedicated to present and discuss the results of ongoing research on nanocarriers. In this function Dr. Gazsó has been invited to the 6th meeting of the working party "Advanced Materials" of the German Federal Agencies in March. This working party is chaired by the German Federal Institute for Risk Assessment.

The long-term research project NanoTrust (lead: André Gazsó) at the Austrian Academy of Sciences, Institute of Technology Assessment, has been elongated in May 2021 for its sixth period until 2024 under the project name NanoTrust-Advanced. The transdisciplinary project – rather a governance process – has been established in 2007 and is funded by the Austrian Ministry of Climate Action, the Austrian Ministry of Health, and Austrian Workers compensation board. NanoTrust contributes to the Austrian Nano Governance system based on the Austrian Nanotechnology Action Plan since its installation in 2010 and is scientific advisor to the Austrian Nanosafety research programme "Nano EHS (NANO Environment Health and Safety)". The main task of the project is to continually survey, analyse and summarise the state of knowledge regarding potential health and environmental risks of nanotechnology. Dossiers (also in English language) on specific nano-related topics have been released: NanoTrust Dossiers (oeaw.ac.at)

Recent publications are available on "*Applications of Fluorescent quantum dots for medical and environmental science applications"*, NanoTrust-Dossier 59) and "*Marker materials and spectroscopic methods for sorting plastic waste*" (NanoTrust-Dossier No. 60) as well as "Nanomaterials in cosmetics - Regulation and safety assessment in the EU" (NanoTrust-Dossier No. 61). This publication series will be continued. The project NanoTrust-Advanced and all its activities are accessible through its new website (landing page): https://www.oeaw.ac.at/ita/nanotrust.

NanoTrust-Advanced joined the OECD-BNCT[1] working group on "Technology Assessment" in June 2022. The BNCT working group consists of experts from the European Parliament, France (CNRS), the US (NNI, NIH, GAO), the Netherlands (Rathenau Instituut), Portugal (IST), Japan (CSCD Osaka), Republic of Korea (STEPI), and Austria (Austrian Academy of Sciences). The working group focusses on the role of foresight technology assessment in innovation processes. A two-day workshop organised by the ITA-OeAW was held on 8th and 9th of June 2022 in Vienna.

The result of this workshop and the subsequent working group debates were recently published in an OECD policy paper under the title "Technology assessment for emerging technology: Meeting new demands for strategic intelligence" (POLICY PAPERS, April 2023, No. 146). The policy paper is available under the following address: https://www.oecd-ilibrary.org/docserver/e738fcdf-en.pdf?expires=1684848830&id=id&accname=guest&checksum=D13A0DB21C0C78E6E03AC49241E719F4. NanoTrust and the Austrian Nanogovernance System was presented as case study of national best practices regarding the deployment of technology assessment and foresight studies to appropriately manage uncertainties of emerging technologies.

The BNCT working party on TA has recently started a new biennial work programme which will also be supported by NanoTrust.

1.3 Belgium

The Royal Decree concerning the placing on the BE market of substances produced in nanoparticular state was published on 24th September 2014. This decree involves the registration of substances produced in nanoparticular state as well as mixtures that contain one or more of these substances.

The annual reports for years 2016 to 2021 are published and publicly available on our website. The 2022 report is in preparation.

[1] OECD Working Party on Biotechnology, Nanotechnology and Converging Technologies

In total, 2210 registrations were submitted by 210 registrants. These registrations involve about 213 different chemical substances (based on CAS-number). In total, nearly 90 000 tons of substances, produced in nanoparticular state, were introduced on the Belgian market, either by import or by production. The substances imported and/or produced in a quantity above 1 000 ton are carbon black, calcium carbonate, silicon dioxide; synthetic amorphous silicon dioxide (nano) and Pigment Blue 15. These numbers result only from the registrations submitted for nanomaterials and placed on the market as substances.

More information about the registry and access to the published reports can be found on the website www.nanoregistration.be.

1.4 Canada

Risk assessment decisions, including the type of: (a) nanomaterials assessed; (b) testing recommended; and (c) outcomes of the assessment.

The New Substances program is responsible for administering the New Substances Notification Regulations (Chemicals and Polymers) [NSNR(C&P)] of CEPA. These regulations ensure that no new substances (chemicals or polymers) are introduced into the Canadian marketplace before undergoing ecological and human health assessments, and that any appropriate or required control measures have been taken. In total, under the NSNR (C&P) Canada has assessed 16 nanomaterials and potential nanomaterials since WPMN22. In addition, three pre-notification consultations were completed. Pre-notification consultations provide clarity on regulatory requirements prior to submission of a new substance notification under the NSNR(C&P).

Titanium dioxide has been permitted for use as a food colour in Canada and other countries for many years. Food-grade TiO2 (also referred to as E-171), while not intentionally engineered as a nanomaterial, invariably contains a fraction of particles in the nanoscale. Recent analyses of food-grade TiO2 samples on the European market indicated that the portion of particles with a diameter < 100 nm may be as high as 33% on a mass basis and >70% on a particle number basis. In 2021, the European Food Safety Authority (EFSA) updated its food safety assessment of TiO2 as a food additive. While EFSA did not identify any immediate health concerns, due to uncertainties in the data it was concluded TiO2 could no longer be considered safe when used as a food additive. After reviewing EFSA's findings, on June 20, 2022, Health Canada published a State of the Science report and summary that considered the available scientific studies for TiO2 as a food additive in a variety of foods, including new scientific information available since the EFSA opinion. Although Health Canada's evaluation focused on food-grade TiO2, it was acknowledged that toxicity studies conducted with food-grade TiO2 simultaneously evaluate nanoparticles (TiO2-NPs) that may be present. Studies using engineered TiO2-NPs were also considered if they provided key support for conclusions reached by EFSA or other expert committees. Health Canada found no conclusive scientific evidence that food-grade titanium dioxide, used as a food additive, is a concern for human health.

Risk management of nanomaterials

Following two New Substance Notification risk assessments and the identification of potential risks to the environment and human health, two ministerial conditions were imposed concerning Carbopolycycle, acid-treated, oxidized and Carbopolycycle, acid-treated, oxidized, silver-doped. Ministerial conditions are control measures used to minimize risk to the environment or human health when a new substance is suspected to be, or capable of becoming, toxic under the Canadian Environmental Protection Act, 1999.

Updates, including proposals, or modifications to previous regulatory decisions.

The significant new activity (SNAc) provisions of CEPA were applied to the substance lithium cobalt manganese nickel oxide (Chemical Abstracts Service [CAS] Registry Number: 182442-95-1) in 2009 pursuant to the Significant New Activity Notice No. 15274 and updated in 2012 pursuant to the Significant New Activity Notice No. 15274a. The SNAc provisions of CEPA were applied to address potential human health or environmental concerns and the uncertainty predicting environmental fate, hazard and exposure if the substance were to be used at the nanometer scale. In 2023, the substance was determined to meet the criteria for addition to the Domestic Substances List, the SNAc requirements were maintained, updated and added with the substance to the Domestic Substances List, pursuant to SNAc Order (2023-87-01-01). The technical requirements of the SNAc Order were updated to align with current best practices and updated OECD guidelines.

1.5 Germany

Federal Institute for Occupational Safety and Health (BAuA)

Based on a proposal by Germany, the European Commission included Multi-Walled Carbon Tubes MWCT (diameter ≥30 nm <3 µm; length ≥ 5 µm) into CLP regulation (EC No. 1272/2008) Annex VI as Carc. 1B (H35li) and STOT RE1.

BAuA (German Federal Institute for Occupational Safety and Health) together with BfR (German Federal Institute for Risk Assessment) has launched a Risk Management Option Analysis (RMOA) under REACH for the protection against critical fibre dust. As is known from the asbestos history, bio-persistent fibres of critical dimensions (WHO fibre criteria) can cause lung cancer upon inhalation. This risk is currently not sufficiently covered in European chemicals regulation. A public consultation on further risk information was successfully completed. The consultation results were evaluated and based on the results the different risk management options under REACH are discussed. A restriction of fibre material is preferred over authorisation as it is considered more efficient to regulate the placing on the market. The proposed assessment strategy for the “fibre pathogenicity paradigm” would be possible with a restriction.

1.6 Italy

The Italian Institute for Environmental Protection and Research (ISPRA), section of Hazardous Substances - DG-TEC, carried out an update of the ECHA guidelines for nanomaterials (Appendix R7- 1 for nanomaterials applicable to Chapter R7a) in relation to the following endpoints: water solubility, dissolution rate, dispersibility in the environmental matrices, mobility, log Kow coefficient, adsorption/desorption, toxicity in aquatic, terrestrial and sediment organisms, abiotic and biotic degradation/transformation, and bioaccumulation properties in aquatic and terrestrial organisms.

Moreover, in the context of the activities at the European Chemicals Agency (ECHA), DG-TEC contributes by participating in meetings and providing its expertise, particularly regarding the regulatory aspects of REACH/CLP Regulations and the assessment of emerging risks.

Among the other issues examined by the experts of ISPRA, a particular focus has been directed to the assessment of the hazards linked to nanoforms as well as the assessment of the harmonized classification of metals in nanoforms, such as silver, which was discussed during 2022 at two meetings of the Risk Assessment Committee (RAC).

The European Commission Directive 2019/1832/UE of 24 October 2019 amended the annexes I, II, and III of the Council Directive 89/656/EEC, introducing the use of personal protective equipment (PPE) to

protect workers in the activities in which nanomaterials exposure risk has been recognized. On December 20, 2021, the National Decree adopted the Directive 2019/1832/UE by updating the Annex VIII of the Legislative Decree no. 81/2008 that regulates occupational safety and health at national level. As a result, the employers should evaluate if their activities include the manufacturing/use of nanomaterials (as defined by EC Recommendation 2011/696/UE, recently updated by the EC Recommendation 2022/C 229/01) and provide PPE (such as face masks, gloves and/or suits) to the exposed workers who will be properly informed and trainee for the correct use and maintenance.

1.7 Japan

The Ministry of Economy, Trade and Industry (METI) first publicised information on safety test data and management methods of manufactured nanomaterials on its website in 2010 (only in Japanese). Such information was voluntarily provided and annually updated by the manufacturers. METI publicised the updated information in 2022.

1.8 Sweden

SweNanoSafe

The Swedish National Platform for Nanosafety (SweNanoSafe) is a forum for knowledge exchange on the safe handling and use of engineered nanomaterials. The platform was commissioned in 2016 by the Ministry of the Environment. Since 2019, the platform is hosted at the Institute of Environmental Medicine at Karolinska Institutet. However, the activities will end in 2023, while relevant parts will be transferred to the Swedish Chemicals Agency (KemI).

SweNanoSafe launched a national research network in 2018 and organized 5 annual workshops on different topics. In 2022, the annual workshop was held as an online event on the topic “Particle mixtures and advanced materials: from production and generation to environmental risk assessment” and about 40 participants mainly from academia, as well as industry, government, and research institutes. During 2022, the platform has also been extensively involved in supporting national government agencies in their work related to the safety of nanomaterials. In 2021, the platform established a council of national authorities, with members from seven national government agencies, and this group has met regularly to discuss relevant topics. Besides providing direct support to each agency in line with their specific needs, the platform organized a meeting in 2022 between the expert panel (researchers with expertise within complementary areas of nanosafety) and the council, in line with the overall objective of the platform namely to promote the bidirectional knowledge exchange between stakeholders.

In 2022, the platform also published three reports covering the content of two workshops and an overview of nanosafety in relation to the sustainable development goals, and these reports, which are available in English, can be downloaded from the webpage https://swenanosafe.ki.se/

The platform also publishes electronic newsletters which are widely distributed to stakeholders.

- SweNanoSafe Report 2022:01 “Safe-and-Sustainable-by-Design: a prerequisite for achieving a circular economy - a report from SweNanoSafe’s workshop”
- SweNanoSafe Report 2022:02 “Nanosafety, the Sustainable Development Goals and meeting EU policy ambitions”
- SweNanoSafe Report 2022:03 “Workshop report: Particle mixtures and advanced materials: from production and generation to environmental risk assessment”

SIO Grafen

SIO Grafen is a national strategic innovation program designed to support industrial graphene development in Sweden. SIO Grafen is supported by Sweden's innovation agency VINNOVA, the Swedish Energy Agency, and the Swedish Research Council FORMAS (Sweden's research council for sustainable development). The vision is that **Sweden is one of the leading countries in developing and using graphene and other 2D materials industrially.** SIO Grafen issues **open calls** for the funding of collaborative projects between companies and research partner**s**. SIO Grafen is a partnering project of the EU-funded Graphene Flagship (coordinated from Sweden).

1.9 Switzerland

The precautionary matrix for synthetic nanomaterials (PMX) has been partially revised as necessary and adapted to the state of knowledge.

- In terms of the exposure:
- The new reference values derived from toxicity studies for different nanomaterial categories and uptake pathways.
- The PMX user can select specific exposure scenarios based on matrixes (such as plastics, textiles). The room size and air exchange rate are now also queried, whereby also predefined scenarios can be chosen (such as household and workplace).
- Measured or modelled exposure values can be included in the precautionary matrix.
- The additional assessment parameter dustiness or a manually entered emission value can be used to estimate the exposure potential.
- In terms of evaluation:
- At certain parameter entries, the PMX user is asked for the related uncertainty in order to provide the final result with supplemented "uncertainty" information.

1.10 United States

Risk assessment decisions, including the type of: (a) nanomaterials assessed; (b) testing recommended; and (c) outcomes of the assessment.

The U.S. Environmental Protection Agency (EPA) completed review of four low volume exemptions (LVE) which included a graphene material, a titanium dioxide material, and two graphene oxide materials, one of which was a modification to an existing exemption. Two of the LVEs were denied, and two were granted under conditions that limited human and environmental exposures to prevent unreasonable risks.

Additionally, the EPA has under review 17 premanufacture notices, 16 of which are for multi-walled carbon nanotube chemical substances and one of which is for a graphene material. These 17 chemical substances are still being reviewed for potential risks to human health and the environment. One significant new use notice for a single-walled carbon nanotube was reviewed and completed. It was regulated with a consent order due to limited available data on nanomaterials. This consent order will limit uses and human and environmental exposures to prevent unreasonable risks.

Risk management approaches

Between June 2022 and June 2023, EPA received notification of 2 nanoscale substances based on metal oxides that met reporting criteria pursuant to its authority under the U.S. Toxic Substances Control Act

(TSCA) section 8(a), bringing the total number of notifications to 87. Reporting criteria exempted nanoscale chemical substances already reported as new chemicals under TSCA and those nanoscale chemical substances that did not have unique or novel properties. Most reporting has been for metals or metal oxides.

Since January 2005, EPA has received and reviewed more than 275 new chemical notices for nanoscale materials under TSCA including fullerenes and carbon nano-onions, quantum dots, semiconducting nanoparticles, and carbon nanotubes. EPA has issued consent orders and Significant New Use Rules (SNURs) regulating new chemical submissions of these nanoscale materials permitting manufacture under limited conditions. A manufacturer or processor wishing to engage in a designated significant new use identified in a SNUR must submit a Significant New Use Notice (SNUN) to EPA at least 90 days before engaging in the new use. A sanitized version (i.e., without confidential business information) of such a consent order is available. Because of confidential business information claims by submitters, EPA may not be allowed to reveal to the public the chemical substance as a nanoscale material in every new chemical SNUR it issues for nanoscale materials. EPA will continue to issue SNURs and consent orders for new chemical nanoscale materials in the coming year.

Because of limited data to assess nanomaterials, the consent orders and SNURS contain requirements to limit exposure to workers through the use of personal protective equipment, limit environmental exposure by not allowing releases to surface waters or direct releases to air, and limit the specific applications/uses to those described in the new chemical notification.

Updates, including proposals, or modifications to previous regulatory decisions.

The approaches used, given the level of available information, are consistent with previous regulatory decisions. EPA's assessments now assume that the environmental hazard of a nanomaterial is unknown unless acceptable hazard data is submitted with nanomaterial submission.

New regulatory challenge(s) with respect to any action for nanomaterials and or advanced materials

- Standards/methods for differentiating between different forms of the same chemical substance that is a nanomaterial.
- Standardized testing for the physical properties that could be used to characterize/identify nanomaterials.
- Differentiation between genuinely new nanoscale materials introduced in commerce and existing products which have been in commerce for decades or centuries.

1.11 European Union

In EU, nanomaterials are assessed alongside other chemicals. **Scientific committee on Consumer Safety** (SCCS) has in 2023 and at time of writing (June 2023) prepared preliminary opinion on Fullerenes, Hydroxylated Fullerenes and hydrated forms of Hydroxylated Fullerenes (nano) and finalized an opinion on Hydroxyapatite (nano). Details can be found on the committee's webpage. Since June 22, **Risk Assessment Committee** of the European Chemicals Agency finalized opinions on proposals for harmonized classifications for multiwall carbon nanotubes and nanosilver; details can be found here.

European Commission has in June 2022 published a revised Recommendation on the definition of nanomaterial (2022/C 229/01), replacing recommendation issued in 2011. The work is now ongoing in applying the recommendation by modification of definition in the legislation within different sectors (e.g. REACH). Joint Research Centre of the European Commission (JRC) released in 2023 the new Guidance

on the implementation of the Commission Recommendation 2022/C 229/01 on the definition of nanomaterial (print version: 10.2760/237496) supporting its implementation.

1.12 Malaysia

National Nanotechnology Policy and Strategy 2021-2030 (DSNN), launched on 15th November 2021 consists of four strategic thrusts which includes strengthening standards, safety, and regulation on nanotechnology. The Ministry of Science, Technology, and Innovation Malaysia, through the National Nanotechnology Centre (NNC), will oversee the planning and implementation of 32 initiatives under 15 strategies within this policy. The National Nano Product and Technology Roadmap 2021-2025 was launched on 13th April 2022 to support DSNN. The local nano ecosystem has been mapped towards these jumpstart sectors: Energy; Environment; Food and Agriculture; Medical and Well-being; Healthcare; and Electronics and Devices.

1.13 Business at OECD (BIAC)

The NIA (Nanotechnology Industries Association) takes part in the OECD SG of AdMa focusing on the identification of regulatory challenges regarding Advanced Materials and contributing feedback to current foresight warning tools and their implementation challenges. The NIA also takes part in the OECD SG SIA focusing on the identification of tools to help SIA implementation as well as the development of Trusted Environments.

2 Activities been initiated to implement the OECD Recommendation of the Council on the Safety Testing and Assessment of Manufactured Nanomaterials

2.1 Austria

Austria works on Guidance development regarding Environmental abiotic transformation of nanomaterials - a proposal for this project has been sent to WNT. The work is under the auspices of Austrian Federal Ministry of Climate Action, Environment, Energy, Mobility, Innovation and Technology (www.bmk.gv.at); the administrative lead will be made by Environment Agency Austria with the scientific input of the University of Vienna (Frank von der Kammer). The scientific work was co-funded by the EU Horizon 2020 Project Gov4Nano.

Since 2022 a follow-up project funded by the German Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection (BMUV) aims to develop a test guideline for the abiotic environmental transformation of nanomaterials. This project is coordinated by the Environment Agency Austria and the German Environmental Agency,

The Department of Environmental Geosciences of the University of Vienna (Frank von der Kammer) is working on the development of an OECD Test Guideline for the Solubility and Dissolution Rate of Nanomaterials under Environmental Conditions. This project combines the existing OECD project 3.10 (former US/DK) with a new project that develops a dynamic testing methodology. Funding is provided by the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety and Umweltbundesamt.

In parallel the Department of Environmental Geosciences of the University of Vienna (Frank von der Kammer) works on the development of a test guideline (TG) for the environmental transformation of nanomaterials and hetero agglomeration of nanomaterials. The work on the transformation of NM extends and complements the existing activities in developing a guidance document. These two topics are funded by the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety. Furthermore, the Department of Environmental Geosciences of the University of Vienna (Frank von der Kammer) supports the OECD activities in finalizing the guidance document on nanomaterial removal in wastewater treatment plants and the guidance document on sample preparation and dosimetry.

2.2 Canada

The Government of Canada published a nanomaterial regulatory risk assessment framework to inform the assessment of manufactured nanomaterials under the Canadian Environmental Protection Act, 1999 (CEPA). A 60-day comment period in June-July 2022 led to revisions and a comment table anticipated for publication in summer 2023. In addition, a new landing page providing information on the assessment and regulation of nanomaterials under CEPA has been published (Nanomaterials - Canada.ca).

2.3 Germany

Federal Institute for Occupational Safety and Health (BAuA)

BAuA coordinates the EU Horizon 2020 Project NanoHarmony "Towards harmonized test methods for nanomaterials". The project supports the development of OECD documents (TGs, GDs, technical recommendations and scoping reviews) towards 8 nano-specific endpoints. NanoHarmony held multiple webinars and three international virtual workshops together with NANOMET to facilitate the needed exchange. It furthermore aims at supporting the TG development process by developing a Process Mentor, training materials and a White Paper on TG development.

BAuA is leading a work package in the EU-project MACRAMÉ on Translation into Standards Policy-Information. Within MACRAMÉ we will continue the successful November workshops on TG development for nanomaterials held by NanoHarmony and NANOMET. The first virtual MACRAMÉ Workshop on Harmonisation & Standardisation will take place on 22.-23.11.2023 back-to-back with the first MACRAMÉ Risk Assessors Summit (27.-28.11.2023 in Berlin).

2.4 Italy

Activities related to the preparation of the new GD "Integrated in vitro approach for intestinal fate of orally ingested Nanomaterials" are ongoing. A meeting was held with the WNT expert group in November 2022. A specific task force for GD drafting is under definition at the Nanomaterials Working Group (NMWG) in the framework of the REACH Technical Coordination Committee. In this respect, in the context of the H2020 NanoHarmony EU project, the Inter Laboratory Comparison exercises are in progress for both the main endpoints addressed in the DG, i.e., the in vitro simulated digestion and the uptake/crossing of the digested samples through the advanced in vitro intestinal barrier model.

The Italian Institute of Health (ISS) actively participates in the ad hoc group for updating section 6.9 of the OECD Guidance on grouping of chemicals.

2.5 Japan

The Japanese Industrial Standards Committee (JISC), the national member body participating as a P-member in ISO/TC229 (Nanotechnologies), has nominated the Convenor and Secretary of TC229/JWG2 (Measurement and characterisation). In TC229/JWG2, JISC jointly (with ANSI, the American National Standards Institute) leads a project "Analysis of nano-objects using asymmetrical-flow and centrifugal field-flow fractionation" (IS 21362), and now this is under discussion. JISC leads "Positron annihilation lifetime measurement for nanopore evaluation in materials" (TS 23397), and now this is under discussion. In TC229/WG3 (Health, Safety and Environmental Aspects of Nanotechnologies), JISC leads "Characteristics of working suspensions of nano-objects for invitro assays to evaluate inherent nano-object toxicity" (IS 19337), and now this is under final ballot. JISC leads "Evaluation method for chronic inhalation

toxicity based on lung burden of nanomaterials" (PWI 7666), and now this is under discussion. In TC229/WG4 (Material specification), JISC leads "Silica nanomaterials -Specifications of characteristics and measurement methods for nanostructured porous silica samples with ordered nanopore array" (TS 22298), now this is under discussion. JISC leads "Nanocomposite materials for insulating - Specification of characteristics and measurement methods" (PWI 12948), now this is under discussion.

2.6 Korea

The Korea Research Institute of Standard and Science (KRISS) has participated in the development of OECD test guidelines.

- OECD test guideline development for particle size and size distribution of nanomaterials (TG110)

  KRISS has participated in round robin test (winter 2018 – Spring 2019) for determination of size and size distribution of fibres and particles using SEM, TEM, DLS and DMAS. The development of this test guideline was completed in June 22. (TG125)
- OECD test guideline development for determination of the (volume) specific surface area of manufactured nanomaterials

  KRISS has participated in round robin test using the BET technique. The development of this test guideline was completed in June 22. (TG124)
- OECD test guideline development for dustiness

  KRISS has participated in round robin test for determination of dustiness of non-high aspect ratio nanomaterial (non-HARN) and HARN using small rotating drum (SRD) and vortex shaker (VS).
- OECD test guideline development for surface analysis and, solubility and dissolution (OECD WNT project 1.5 and 1.6)

  KRISS is participated in round robin test for determination of solubility and dissolution using Scientific basis for testing solubility testing strategy(Sequential batch). And another round robin test for developing test guideline of surface analysis of nanomaterials using XPS and ToF-SIMS is participated.

2.7 Sweden

In general, official guidelines/methods on information requirements on ecotoxicity, toxicity and physical-chemical properties are based on approved OECD test guidelines which are continuously adopted by the EU.

2.8 Switzerland

WPMN/WNT Project 4.133: The Study Report on Applicability of the key event-based TG 442D for *in vitro* skin sensitisation testing of nano-materials has been adopted at the 35. WNT. This project has also been part of the EU Horizon2020 project Gov4Nano.

2.9 United Kingdom

NanoHarmony

The NanoHarmony (http://www.nanoharmony.eu) project (2020 – 2023) supports the development of a set of scientifically reliable test methods and good practice documents, based on the translation of existing scientific knowledge and data into a form that has regulatory relevance. NanoHarmony is focused on OECD TGs and GDs for eight nanomaterial test endpoints and will coordinate the collection and use of available data and information to support the finalisation of the TG/GDs. It is also developing a sustainable international network of experts, for data analysis and recommendations for test method maturation, plus future regulatory pathways and will also analyse processes in test method developments, to set up a framework structure for seamless and smooth cooperation between all stakeholders for timely developments of test methods ready for regulation. The UK is involved in the scientific co-ordination and has a role in all work packages. The UK is leading Task 1.2 (providing the scientific basis to support an approach for testing the bioaccumulation potential of NMs, including a potential tiered approach) and Task 1.4 (providing the scientific basis for a GD on the determination of concentrations of NMs in biological samples to support (eco)toxicity studies, and contributing to Task 1.3 (providing the scientific basis for a new TG on toxicokinetics of nanoparticles). In the past year significant progress has been made towards the production of the final project deliverables. Several joint NanoHarmony/OECD Expert Group workshops have been held, including one on the determination of concentrations of NPs in biological samples (Task 1.4) on 23 November 2022 and one on new toxicokinetic data and modelling to support TG development (Task 1.3) on 12 December 2022 with a further Task 1.3 joint meeting to be held on 23rd May 2023.

RiskGone

The H2020 project coordinated by NILU in Norway is continuing with Swansea University and the University of Birmingham as work package leads in human hazard assessment (Prof Shareen Doak) and ecotoxicity (Prof Iseult Lynch) respectively. The overarching goals of RiskGone are: 1) To establish a transparent, self-sustained and science-based Risk Governance Council composed of representatives (regulatory agencies, public bodies, industry, NGOs etc. 2) to contribute to the strengthening of safety governance of nanomaterials through the development of Risk Governance Cloud Platform which will facilitate the dynamic integration of scientific evidence as it evolves over time. 3) To provide state-of-the-art decision-making tools and support risk communication to relevant stakeholders. The UK partners in RiskGONE have been involved in both leading and contributing to several round-robin activities to harmonise human hazard testing approaches for nanomaterials. This has encompassed both cytotoxicity and genotoxicity testing methods that have existing OECD TGs and those under development. As a result of these round robins, the UK partners in RiskGONE are contributing to four Malta Initiative / OECD projects involved in the development of Test Guidelines or Guidance Documents for both human and ecological hazard assessment purposes. The round robin activities have now been completed and publications are currently being prepared, detailing the outcomes of the studies.

On the ecotoxicology side, the project has been refining the AOP related to reproductive failure in daphnia, including implementation of the dynamic energy budget (DEB) model. The molecular initiating event is particle accumulation in the gut microvilli which leads to reduced food consumption / energy intake, and oxidative stress, which then lead to a range of downstream effects including delayed growth, difficulties in shedding the carapace, in some cases induction of males, and culminating in reduced reproduction or failure to reproduce. The updated AOP-DEB model is currently being refined for publication (submission summer 2023).

The revised reproduction assay proposal which includes medium conditioning with Daphnia has been drafted and is ready for commenting prior to a potential submission as an SPSF in the next round. The

extended proposal also includes a suggestion for a multi-generational paired test (continuous exposure versus parent only exposure and recovery) that allows population-level effects to be explored as increased sensitivity of offspring has been observed in response to chronic exposure to NMs (10.3390/ijms22010015). Some interesting feedback has been received on presenting the proposal in conferences, including the potential to combine the chronic assay with acute tests on subsequent generations (see for example , which would reduce the testing burden, and this is being actively explored now. A set of updated data capture templates for the acute and chronic (reproduction) tests (OECD 202 and 211, respectively) that are being implemented into the Template Wizard (https://search.data.enanomapper.net/datatemplate/default/) of the NanoSafety Data Interface. A Nature Protocol paper describing the various templates (toxicity and ecotoxicity, as well as particle characterisation) is under revision currently.

In the final months of RiskGONE, we are contributing to the NanoHarmony round robins on OECD 201/202/203 (dispersion of NMs in fish food) to support ongoing activities in updating these TGs for nanomaterials.

TG305 Scoping Review

This project was presented at WPMN20 and was then added to the work programme and has been developed contingently with task 1.2 within NanoHarmony. Log Know may not be applicable to predicting the bioaccumulation potential of nanomaterials, since this relies on steady-state kinetics of soluble chemicals, rather than nanomaterials which exist as a suspension. The scoping review explores the development of a tiered approach to bioaccumulation assessment to ensure that only appropriate nanomaterials are tested in fish to minimize animal testing and to deliver cost savings to industry whilst maintaining a high level of environmental protection. An expert Steering Group was formed to input and provide strategic direction for the scoping document, and a workshop was held to review the scientific evidence linking lower and higher tier data. Based on findings, recommendations have been formulated for next steps in developing tools and guidance to support decision making around TG 305 for nanomaterials. A final version of the document is being drafted which we aim to send to the SGTA in due course and then shared with WPMN.

Project 4.095 Guidance Document on in Vitro Mammalian Genotoxicity for Nanomterials

This project was originally led by the JRC and they oversaw the first two phases of work. In April 2021, the UK and Germany took over leadership of the project to complete the final phase, which encompassed the development and writing of a preliminary guidance document (delivered by Swansea University, UK and Germany, BASF). The document was submitted for the first round of commenting to the WNT in November 2021. The comments received were addressed and a revised version of the preliminary guidance document was sent to the April 2022 WNT meeting for during which the document was approved. This preliminary guidance document was subsequently published in September 2022: "*Study Report and Preliminary Guidance on the Adaptation of the In Vitro micronucleus assay (OECD TG 487) for Testing of Manufactured Nanomaterials*" (Series on Testing and Assessment No. 359; ENV/CBC/MONO(2022)15).

2.10 United States

Regulation of new chemical substances that are nanomaterials with consent orders and SNURs.

2.11 Business at OECD (BIAC)

The NIA supports the implementation of Test Guidelines adapted to nanomaterials through its participation in two EU-funded initiatives devoted to such activities. These are Gov4Nano and NanoHarmony (both under the Malta Initiative). Under NanoHarmony, the NIA ensures that information is communicated to relevant stakeholders through the organisation of online and in-person events, where updates regarding several Guidelines adaptations are provided and discussed. The NIA also supports the dissemination of the relevant information by broadly advertising those events, as well as through member-only events. As part of NanoHarmony, the NIA is also working on the development of the NanoHarmony OECD Process Mentor, which will be an advice tool to help developers and users of TGs move smoothly through the TG development process.

In addition, the NIA actively participates and provides comments to Guidelines under development through its participation at the OECD SGTA group.

3 Developments related to good practice documents.

3.1 Australia

AICIS has updated its website with extra guidance on data requirements for introduction of chemicals at the nanoscale. The guidance is designed to help introducers and stakeholders to prepare and submit an online certificate application for chemicals at the nanoscale as a 'specified class of introduction'. It describes in detail how to identify the nanoscale chemical by each of their specified parameters where relevant. It also indicates which supporting evidence or testing results are required, either using available nanomaterial related OECD test guidelines and ISO standards or alternative detailed analyses and justification.

3.2 Austria

The permanent working group on Nanotechnology and Worker Safety, chaired by the Austian Workers' Compensation Board (AUVA), established in 2011 in co-operation with NanoTrust, has produced a revised edition of its guidelines on dealing with nanomaterials at the workplace (M310). The drafting of the new version took over half a year of intensive transdisciplinary teamwork with the participation of the NanoTrust project of ITA, experts from BOKU, ÖSBS and the Central Labor Inspectorate. The result is an extended guide to action (a so-called Merkblatt plus) for management personnel on the safe and responsible handling of nanomaterials. The guidance also includes a procedure for risk assessment of these materials. The official document has been published and can be found here: https://www.auva.at/cdscontent/?contentid=10007.756442&portal=auvaportal

The federal standardisation committee on "Nanotechnology" (ASI 052.73) continued observing and commenting the international standardisation activities (CEN/TC 352, ISO/TC 229) and convenes 4 times a year. The committee has been successful to integrate Austrian researchers as delegates in several working groups, such as on measurement and characterization, safe and sustainable by design, consumer and societal dimensions of nanotechnologies and HSE aspects of nanotechnologies. Since 2019 Austrian experts are active in 12 nanostandardisation projects. The Austrian standardisation committee is chaired by "NanoTrust-Advanced" (contact: André Gazsó). An extended overview over the activities has been presented on the 20th NanoNET-meeting on 22nd April 2022. A report and ITA-dossier on nanostandardisation is available on the NanoTrust-Advanced website (https://epub.oeaw.ac.at/ita/ita-dossiers/ita-dossier060.pdf).

3.3 Belgium

The FPS Economy, Service of Metrology – National Standards (SMD), is active as expert in ISO/TC229 – CEN/TC352 Nanotechnologies and ISO/TC201 Surface chemical analysis. SMD is involved in several WG

dedicated to the labelling of manufactured nano-objects and the determination of aggregation/agglomeration state of nano-objects.

SMD also participates to Versailles Project on Advanced Materials and Standards (VAMAS) pre-normalization studies:

- VAMAS/TWA2 Surface chemical analysis: round robin test for guidelines for shape and size analysis of nanoparticles by atomic force microscopy.
- VAMAS/TWA34 Nanoparticle Populations: Measurement of particle size, shape distribution and relative number concentration of titania and silica nanoparticles.

3.4 Canada

Listing of internally funded projects undertaken by Environment and Climate Change Canada on engineered nanomaterial (ENM) including environmental toxicity testing and fate studies.

a) Hazard characterization following characterization of nanomaterials and exposure to mixtures:

- Information on research or strategies on life cycle aspects of nanomaterials, as well as positive and negative impacts on environment and health of nano-enabled applications.
- Development of a read across framework for the toxicity of silver nanoparticles in aquatic organisms. Special attention on the influence of size, surface coatings and geometry (sphere, cube and prism) towards toxicity in aquatic invertebrates was given. We recently added the influence of mixtures (nAg, nCeO and nZnO) and nAg-carbon nanotube composites
- Recent publications:
  - Auclair J., Turcotte, P., Gagnon, C., Peyrot C., Wilkinson KJ, Gagné F. 2023. Form dependent toxicity of silver nanomaterials in rainbow trout gills. Nanomaterials, Submitted.
  - Auclair J, Turcotte P, Gagnon C, Peyrot C, Wilkinson KJ and F., Gagné 2023. Investigation on the Toxicity of Nanoparticle Mixture in Rainbow Trout Juveniles. Nanomaterials 13, 311.
  - Auclair J, Peyrot C, Wilkinson KJ and F., Gagné 2022. The Influence of Silver Nanoparticle Form on the Toxicity in Freshwater Mussels. J Appl. Sci. 12, 1429.
  - Auclair J and F., Gagné 2022. Shape-Dependent Toxicity of Silver Nanoparticles on Freshwater Cnidarians. Nanomaterials 12, 3107.
  - Gagné F. 2022. Isolation and Quantification of Polystyrene Nanoplastics in Tissues by Low Pressure Size Exclusion Chromatography. J Xenobiot. 12, 109-121.

b) Inflammation as a mechanism of action

- The National Research Council's Nanotechnology Research Centre has on-going projects investigating the allergic inflammation potential for a variety of nanomaterials. These studies aim to understand the molecular mechanisms of inflammation, and how exposure to a variety of materials modulates these mechanisms.

c) Identification and quantification of nanomaterials in the environment

- In addition, the Nanotechnology Research Centre is also investigating the development of new sensing technologies capable of sensing water and air quality in remote, low-resource environments. Finally, we also have some developing technologies that may be investigated for measurement of nano- and micro-plastics in the environmental. Overall, we carry out lower-technology readiness levels (TRL) of work (1-4) to create new knowledge in these areas.

d) Characterization and fate of nano-CuO in surface water:

- Nano-CuO in surface river water tended to remain in suspension/solution with more than half as dissolved transformed products. The river water matrix (natural organic rich) tends to degrade nano-CuO faster than pure Milli-Q water. To fully understand the environmental impacts of natural organic matter on nano-CuO transformation, these particles must be further characterized to properly identify the state of the nanoparticles. A physical particle size separation using a field flow fractionation system (AF4) is developed in parallel with the ICP-MS single particle mode detection technique for more specific analyses of particulate and colloidal metallic forms.

e) Development of single particle TOF-ICP-MS (time of flight inductively coupled mass spectrometry) and single particle ICP-MS in order to distinguish natural and anthropogenic nanoparticles in water, soils, air, food and biota:

- Detection and characterization of nanoparticles in the different matrices
- Discrimination of natural and anthropogenic nanoparticles using composition and ISO TC229 tope ratios
- Quantification of anthropogenic nanoparticles in the various matrices (water, soil, air, food and biota)
- Recent bibliography:
  - Amiri, N., Hadioui, M., Chalifoux, A., Wilkinson, K.J. 2022. Characterizing silver nanoparticles in beverages and following their release from silver-containing food containers using sector field single particle inductively coupled plasma mass spectrometry (SP-ICP-MS). Measurement: Food, 8: 100061.
  - Chalifoux, A., Hadioui, M., Amiri, N. Wilkinson, K.J. 2023. Analysis of silver nanoparticles in ground beef by single particle inductively coupled plasma mass spectrometry (SP-ICP-MS). Submitted.

f) Research on the fate and bioavailability of nanomaterials in the terrestrial environment

- Evaluation of the fate, bioaccumulation, and toxicity of CeO_2 nanomaterials to soil services (invertebrate reproduction, and soil nutrient cycling via microbial processes). Comparison of the toxicity of CeO_2 to soluble Ce (as $Ce(NO_3)_3$) showed less for the nanomaterial and non-Signiant effects over time.
- Publications:
  - Samarajeewa, A., Velicogna, J., Schwertfeger, D., Meier, M., Subasinghe, R., Princz, J., Scroggins, R., Beaudette, L. 2023. Cerium oxide nanoparticles (nCeO2) exert minimal adverse effects on microbial communities in soils with and without biosolids amendment. *Environmental Science and Pollution Research* https://doi.org/10.1007/s11356-023-27313-6.
- Fate, bioavailability (metal solubility), bioaccumulation and toxicity of CuO nanomaterials of varying particle size (10 and 25-55 nm) and coatings (uncoated and coated: PVP, stearic acid, and mineral oil) in soil. Coating of CuO nanomaterials did not impact dissolution and available Cu^{2+} released over time (i.e., 56 days), as evidenced by the comparable toxicity across the uncoated and coated CuO nanomaterials. However, particle size matters in that increased amounts of Cu from the 10 nm CuO nanomaterials were significantly bioaccumulated within earthworm tissue (BSAF > 1.5); bioaccumulation was non-significant (BSAF < 1.0) for 25-55 nm, regardless of presence or absence of coating. Similar results were observed for soil microbial processes in that there was no difference in effects between the uncoated and coated 25-55 nm nanomaterials; experiments with 10 nm nanomaterials are on-going.
- The influence of soil type (i.e., varying pH, organic matter content, etc. across different field-collected natural soils) on the solubility and dispersivity of CuO nanomaterials (10 and 25-55 nm, uncoated and coated (PVP and stearic acid)) is also being investigated. The goal will be the

derivation of an empirical model that may be useful as an initial screening tool to identify soil environments that present the greatest ecotoxicological risk from CuO nanomaterial exposure, in addition to provision of read-across data to inform on the relative dissolution / dispersivity behaviour of differentially sized and coated CuO nanomaterials. Research includes adaptation and validation of nanoparticulate extraction method across different soil types, chemical screening across amended soil types, followed by model derivation and validation using screening-based phyto- and microbial-based toxicity assays.

Development of New Approach Methodologies for Human Health Hazard Identification

Research projects are underway in the Environmental Health Sciences and Research Bureau (EHSRB), Health Canada on engineered nanomaterial (ENM) toxicity testing for health and safety aspect of various nanoforms of chemicals in the Domestic Substances List (Canada) prioritized by the New Substances Assessment and Control Bureau (NSACB). These projects (Investigators: Dr. Prem Kumarathasan, Dr. Azam Tayabali) are funded by CMP (Chemical Management Plan) and Collaborative Research Agreement (CRA)-NSACB-EHSRB. These research projects are relevant to IATA (4- as identified in OECD-WPMN template) due the integrated nature of toxicity testing and are amenable to the development and consideration related to multicomponent/complex advanced materials (5- as identified in OECD-WPMN template). Information generated from these studies include determination of relative *in vitro* potencies of these nanoforms in multiple cell types, underlying potential toxicity pathways, identification of physico-chemical determinants of toxicity, and toxicity testing in Zebrafish embryo model as an alternative strategy to animal testing for these nanoforms of various chemicals. These projects are conducted in collaboration with National Research Council of Canada and academic partners, and the work is on-going.

In vitro toxicity testing of nanoforms of various chemicals

In this work, pristine, surface-modified, different structure/shaped nanoparticles (NPs) of different chemicals are being tested for in vitro cytotoxicity in multiple cell types. These NPs include nano TiO2, nano SiO2, nano ZnO, nano CeO2 and nano CuO. High-throughput high content proteomic analysis based on mass spectrometry and affinity-based methods are explored to assess nanoform specific protein-level changes to understand toxicity mechanisms. In vitro cell culture exposure experiments are being carried out using multiple cell lines (human lung epithelial cells-A549; mouse monocyte/macrophage cells-J774; human neuroblast cell-SH-SY5Y cells) and Integrated toxicity testing approach is applied for multiple cytotoxicity endpoints analysis, secreted and cellular protein changes, followed by testing for mechanistic pathways underlying toxicity and identification of physicochemical determinants of toxicity. This work will generate in-depth mechanistic information relevant to KEs in adverse outcome pathway (AOP) model refinement. (please see bibliography relevant to this project below)

- Note: All NM exposure experiments adhered the proper toxicity testing protocols, namely avoidance of experimental artifacts in assays due to presence of NMs and inclusion of positive and negative controls, etc.
- Recent bibliography:

Scientific journal publications:

- Kumarathasan P, Nazemof N, Breznan D, Blais E, Aoki H, Gomes J, Vincent R, Phanse S, Babu M. In vitro toxicity screening of amorphous silica nanoparticles using mitochondrial fraction exposure followed by MS-based proteomic analysis. Analyst. 2022 Aug 8;147(16):3692-3708.

Presentations at Scientific meetings:

- N. Nazemof, D. Breznan, E. Blais, Y. Dirieh, A. Tayabali, Linda Johnston, J. Gomes and P.Kumarathasan. Exposure to TiO2 Nanoforms and Cellular Effects.Women in STEM Symposium 2022. February 10-11.
- N. Nazemof, N. Assudani, D. Breznan, Y. Dirieh, E. Blais, L. Johnston, A. Tayabali, J. Gomes, P. Kumarathasan. *In vitro* toxicity screening of metal oxide nanoparticles. Health Canada Science Forum 2022. February 14-18.
- Nazila Nazemof, Erica Blais, Yasmine Dirieh, Hiroyuki Aoki, Sadhna Phanse, Dalibor Breznan, Azam Tayabali, James Gomes, Mohan Babu and Prem Kumarathasan. Cytotoxicity and protein changes in A549 cells exposed to amorphous silica nanoforms. 13th Annual Canadian National Proteomics Network Symposium. 2022 May 1-18. Montreal, QC, Canada.
- Nazila Nazemof, Dalibor Breznan, Erica Blais, Yasmine Dirieh, Azam Tayabali, James Gomes and Prem Kumarathasan. In vitro toxicity of amorphous silica nanoforms in multiple cell lines. American Chemical Society Fall Meeting. 2022 August 21-25, Chicago, IL, USA. (Hybrid meeting- presented virtually)
- Nazila Nazemof, Erica Blais, Yasmine Dirieh, Hiroyuki Aoki, Sadhna Phanse, Dalibor Breznan, Azam Tayabali, James Gomes, Mohan Babu and Prem Kumarathasan. Cellular effects including protein expression changes after exposure to amorphous silica nanoforms. The Society of Toxicology Canada Annual Symposium. 2022 30 Nov-02 Dec. Ottawa, Canada.

3.5 Germany

Federal Institute for Risk Assessment (BfR)

NanoHarmony has continued a series of interactive webinars covering the path of an OECD test guideline through the initiation, development, and final application phases to understand the challenges and barriers that need to be addressed at each stage.

The last workshop in this series, organised by the EU projects NanoHarmony and NANOMET, took place on November 29. – 30. 2022, and covered the topic "Development of Test Guidelines for Nanomaterials" (https://nanoharmony.eu/2022/12/01/nanomet-nanoharmony-hold-online-workshop-on-test-guideline-development-for-nanomaterials/).

Federal Institute for Occupational Safety and Health (BAuA)

BAuA continued the work in the project for the development of an OECD Guidance on Release Test for Manufactured Nanomaterials. The project will be presented at 23rd WPMN. All partners (BAuA, UBA, BfR (Germany), NRCWE (Denmark), LEITAT (Spain) and ECHA) met in spring 2023 for a two-days online working meeting in which the content of the guidance was further developed. The guidance is planned to contain an overview of standardised and not yet standardised release tests as well as a decision framework on the choice of suitable release test methods and a link to possible applications of gained release test data for regulatory assessments. These sections of the guidance will be further developed within the upcoming months and the first draft of the guidance is planned to be ready in autumn 2023.

3.6 Italy

Some scientific papers have been published by Italian research group:

- Towards the Standardization of Intestinal In Vitro Advanced Barrier Model for Nanoparticles Uptake and Crossing: The SiO2 Case Study. Vincentini O, Prota V, Cecchetti S, Bertuccini L, Tinari A, Iosi F, De Angelis I. Cells (2022),11(21):3357. doi: 10.3390/cells11213357.
- A follow-up study on workers involved in the graphene production process after the introduction of exposure mitigation measures: evaluation of genotoxic and oxidative effects. Cavallo D, Ursini CL, Fresegna AM, Ciervo A, Boccuni F, Ferrante R, Tombolini F, Maiello R, Chiarella P, Buresti G, Del Frate V, Poli D, Andreoli R, Di Cristo L, Sabella S, Iavicoli S. Nanotoxicology (2022) 16(6-8):776-790. doi: 10.1080/17435390.2022.2149359.
- ASINA Project: Towards a Methodological Data-Driven Sustainable and Safe-by-Design Approach for the Development of Nanomaterials. Furxhi I., Perucca M., Blosi M., Lopez de Ipiña J., Oliveira J., Murphy F. and Costa AL. Front. Bioeng. Biotechnol. (2022), Sec. Nanobiotechnology, Vol 9. https://doi.org/10.3389/fbioe.2021.805096

3.7 Japan

The National Institute of Advanced Industrial Science and Technology (AIST) and the University of Fukui are currently conducting a five-year project "Cellulose Nanofiber (CNF) Related Technology Development to Contribute to a Carbon Cycle Society/ Development of CNF use technology/ Development of Hazard Assessment Methods and Safety Assessment for Various Product Applications" (JFY 2020-2024), commissioned by the New Energy and Industrial Technology Development Organization (NEDO), and led by METI. The research subjects of this project include development and evaluation of inhalation toxicity using in vitro cell-based assay, evaluation of possibility of mesothelioma induction, ecotoxicity assessment, and emission/exposure assessments. Based on the obtained results and literature review, a safety assessment document (written in Japanese) was published in December 2022 to support voluntary safety assessment in CNF-related companies.

The Ministry of Health, Labour and Welfare (MHLW) has promoted research on the human health aspect of several nanomaterials since 2003 through the Health and Labour Sciences Research Grants. In JFY 2023, no survey and four research projects, including a basic research on development of methods for evaluating hazard and adverse effect of nanomaterials on human health, are progressing.

From JFY 2011 the Ministry of the Environment (MOE) has been focusing their efforts on environmental risk of manufactured nanomaterials via understanding of their environmental fate and ecotoxicity. In JFY 2022-23 MOE continues collecting and reviewing existing literature on ecotoxicity of manufactured nanomaterials including TiO2, silver and CNTs to summarize their harmful effects to aquatic organisms.

3.8 Korea

The nano safety metrology center of Ministry of Science and ICT has published 5 standards and is developing 5 additional new items in ISO/TC 229 Nanotechnologies.

- ISO/TS 20787:2017 - Aquatic toxicity assessment of manufactured nanomaterials in saltwater lakes using Artemiasp. Nauplii
- ISO/TR 19733:2019 - Matrix of properties and measurement techniques for graphene and related 2D materials
- ISO 20814:2019 - Testing the photocatalytic activity of nanoparticles for NADH oxidation
- ISO/TS 22082:2020 - Assessment of nanomaterial toxicity using dechorionated zebrafish embryo
- ISO/TR 22455:2021 - High throughput screening method for nanoparticles toxicity using 3D cells
- ISO/AWI 4962 - *in vitro* acute nanoparticle phototoxicity assay (WG3)

- ISO/PWI 4961 - Determination of size and size distribution of nano-objects in liquid using aerosolization differential electrical mobility analysing system (JWG2)
- ISO/PWI 23653 - Experimental Considerations when Evaluating Nanoparticle Performance of Cellular Uptake (WG5)
- ISO/PWI - Toxicity assessment of manufactured nanomaterials in soils using plant Arabidopsis thaliana (WG3)
- ISO/PWI - Toxicity assessment of nanomaterials using intratracheal instillation (WG3)

3.9 The Netherlands

Together with European experts, RIVM has published an overview of the information requirements across different EU regulatory areas where nanomaterials receive specific attention. For each information requirement, a group of 22 experts identified **potential needs for further action to accommodate guidance and test guidelines to nanomaterials** with a focus on OECD. Apart from specific needs for action on specific information requirements, three overarching issues were identified: 1) resolve issues around nanomaterial dispersion stability and dosing in toxicity testing, in particular for human health endpoints, 2) further develop tests or guidance on degradation and transformation of organic nanomaterials or nanomaterials with organic components, and 3) further develop tests and guidance to measure (a)cellular reactivity of nanomaterials. Efforts towards addressing these issues and needs identified will result in better fit-for-purpose test methods for (EU) regulatory compliance. Moreover, it secures validity of hazard and risk assessments of nanomaterials. The results of the study accentuate the need for a structural process of identification of information needs and knowledge generation, preferably as part of risk governance and closely connected to technological innovation policy.

De European projects NANOMET and NanoHarmony jointly published a report in which they provide an **overview on progress in the development of OECD Test Guidelines and Guidance Documents for nanomaterials**. The report provides an overview of OECD TGs and GDs that have been published already and progress for those that are still on-going in the Test Guideline Programme. In a final section the report provides an overview of method developments in research projects that may be expected to be brought forward to OECD in the near future. By focussing on content descriptions of the different projects, the report provides a useful addition to the more timeline-focussed descriptions in the yearly update of the OECD Work plan for the Test Guidelines Programme. The NANOMET/NanoHarmony report is intended to be a living document that will be updated regularly.

The European project NanoHarmony will finish in September 2023 and is currently working towards the **NanoHarmony legacy**. This legacy comprises several items. As contribution to the Malta Initiative NanoHarmony will provide the **scientific background for a range of different OECD documents** on different nanomaterials related topics, including surface chemistry, solubility and dissolution rate in water and biological media, dustiness, quantification of nanomaterials in biological samples, toxicokinetics, intestinal fate, bioaccumulation and ecotoxicology. Furthermore, it will provide **support for developers of OECD Test Guidelines** with an online process mentor and training materials, and exploring continuation of the yearly NanoHarmony workshops (e.g. in other EU projects) to facilitate exchange among experts involved in Test Guideline development. Last but not least NanoHarmony will provide a **White Paper** with recommendations to (further) optimise the Test Guideline development process, and to ensure a continuous effort in keeping test guidelines up-to-date with advances in material innovations, test method/technology developments, and new regulations and policy strategies. A first draft of the White Paper has been presented in a NanoHarmony Policy Meeting in Brussels on 23th May 2023. together with the Position Paper of the Malta Initiative that advocates a European Test Methods Strategy that ensures continuous financial support for the systematic (further) development of OECD Test Guidelines.

Together with UK, the Netherlands leads the development of the **OECD TG on toxicokinetics** (TGP Project 4.146). to accommodate testing of nanoparticles. Activities from the European project NanoHarmony will be considered in the TG development. A workshop was organised in December 2022 that provided on overview of the status of the toxicokinetic studies performed or underway in view of the development of the TG. These studies address gaps in the existing information needed to develop minimum requirements with respect to in vivo toxicokinetic studies of nanoparticles. Around July/August a Deliverable report will become available on results from the NanoHarmony project to facilitate a smooth transfer of these results into the OECD process.

The Netherlands is involved in **CEN/TC 352/WG 3 "Health, safety and environmental aspects"** in developing two new standards:

- prCEN/TS, PWI 00352047, Safe-by-Design concept dedicated for nanoscale materials (MNM) and products containing nanomaterials
- prCEN/TS, PWI 00352040, Nanotechnologies – Quick start guide for deploying a relevant nano health and safety risk management)

Furthermore, The Netherlands chairs **CEN/TC137/WG3 on "Particulate Matter"** (Convenor: Wouter Fransman, TNO, The Netherlands; Secretary: Caroline van Hoek, NEN, The Netherlands). This WG currently has the following Work Items developed under Mandate NOAA in the workplace:

- WI 137085: Workplace exposure – Sampling of nano-objects and their agglomerates and aggregates in the workplace for electron microscopy (CEN/TS)
- WI 137086: Workplace exposure – Counting rules for the characterization of airborne nano-objects and their agglomerates and aggregates for scanning electron microscopy (SEM) and transmission electron microscopy (TEM) (CEN/TS)
- WI 137087: Workplace exposure – Direct-reading low-cost particulate matter sensors for measuring airborne NOAA – Guidelines for application (CEN/TS)
- WI 137089: prEN 15051-2 rev Workplace exposure – Measurement of the dustiness of bulk materials – Part 2: Rotating drum method
- WI 137090: prEN 15051-1 rev Workplace exposure – Measurement of the dustiness of bulk materials - Part 1: Requirements and choice of test methods
- WI 137091: prEN 15051-3 rev Workplace exposure – Measurement of the dustiness of bulk materials – Part 3: Continuous drop method
- Revision EN 481 Workplace exposure – Size fraction definitions for measurement of airborne particles. This standard is under revision together with ISO 7708.
- Amendment EN 17199-5:2019 Workplace exposure – Measurement of dustiness of bulk materials that contain or release respirable NOAA or other respirable particles – Part 5: Vortex shaker method

3.10 Sweden

Two Swedish scientists participate as delegates in the OECD WPMN steering groups for Safe and Sustainable Innovation Approach (SG-SSIA) and Advanced Materials (SG-AdMa), respectively. The work has involved contributions to working descriptions on each of these subjects. In addition, Swedish scientists contributed with comments on a number of international reports and surveys, including from ECHA and the European Union Observatory for Nanomaterials (EUON), the European Joint Research Centre (JRC), and OECD. Documents included the description of the Framework for Safe and Sustainable by Design (JRC), "*Chemical Accidents Involving Nanomaterials: Potential Risks and Review of Prevention, Preparedness and Response Measures*" (OECD), Working descriptions for Sustainability and Safe and

Sustainable by Design, and for Advanced Materials (OECD WPMN), ”*Revision and updating of the OECD Guidance on sample preparation and dosimetry*” (OECD), "*Test Guidelines addressing physical-chemical properties of nanomaterials*" (OECD), ”*Guidance on consumer exposure models/tools for manufactured nanomaterials and advanced materials*” (OECD), and ”*Dustiness and nanomaterials*” (OECD).

3.11 United Kindom

HSE Science and Research Centre have led on the revision of ISO/TS 12901:2012 (Nanotechnologies — Occupational risk management applied to engineered nanomaterials Part 1: Principles and approaches) under ISO TC 229. ISO/TS 12901-1 is and will continue to be complementary to ISO/TR 12885:2018 (Nanotechnologies — Health and safety practices in occupational settings). The revision has been finalised. There was a consultation on the revised ISO/CD TS 12901-1 document, which was closed in April 2023. Following the consultation, the submitted comments were discussed in May and changes will be implemented soon. This revised document should be soon published by ISO.

Graphene Standardization

Graphene Standardization work. NPL (UK) leading and contributing to the development of ISO documents for the characterisation of graphene and graphene platelets. There are standardisation activities on graphene under ISO TC 229, focussed on characterisation. The National Physics Laboratory in the UK is leading some of the work and is having a major input.

NanoCommons

The NanoCommons H2020 research infrastructure project started in 2018 and is coordinated by the University of Birmingham (Prof Iseult Lynch). It is working on a range of initiatives to promote good laboratory practice in nanosafety evaluation, focusing on the developing best practice in data and knowledge management.

The NanoCommons project ended in June 2022, but work has been ongoing to wrap up a number of publications including on the KnowledgeBase, the contribution of FAIR nanosafety data and nanoinformatics to the UN Sustainable Development Goals (submitted to RSC Sustainability) and the developed KNIME workflows for the various nanoinformatics tools, including the nanoinformatics Risk Assessment tool, the NanoXtract tool and the Safe by Design tools. The NanoCommons User Guidance handbook has been transformed to a community resource that continues to be developed and extended with contributions on all aspects of nanosafety data management and FAIR resources and nanoinformatics approaches and resources.

Experimental verification and refinement of an atomistic in silico model for prediction of the protein corona acquired by NMs was undertaken, using a set of allergenic proteins binding to silica NMs (10.1016/j.nantod.2022.101561) and the model was made available with full training materials as a batch processing command line and user-friendly graphical interface.

All NanoCommons services and corresponding training materials are found at: (i) Knowledge Base, (ii) User Guidance Handbook, which includes tools/services and training materials. Knowledge exchange and content update of each of these resources are conducted by follow-up projects, such as NanoSolveIT and WorldFAIR.

3.12 United States

Development of graphene nomenclature by the Graphene Council.

In 2022, NIOSH published a Technical Report: Occupational Exposure Sampling for Engineered Nanomaterials (https://www.cdc.gov/niosh/docs/2022-153/default.html) providing guidance for workplace sampling for three engineered nanomaterials: carbon nanotubes and nanofibers, silver, and titanium dioxide, each of which have an elemental mass-based NIOSH Recommended Exposure Limit (REL). In addition, NIOSH developed a practical approach to exposure sampling for other engineered nanomaterials that do not have exposure limits.

3.13 European union

In March 2023, the Commission adopted a relevant Recommendation which provides guidance for researchers and innovators, pinpoints good practices and addresses R&I activities in relation to standardisation (**Recommendation on a Code of practice on Standardisation**).

The JRC has developed an online **course on Nanomaterials in EU Legislation** available at https://academy.europa.eu/search/index.php?search=nanomaterial. Course details: In this course, you will learn how European Union legislation addresses nanomaterials. You will learn what a nanomaterial is from a scientific point of view and what makes it special in a legal context. You will understand the European Commission overarching regulatory definition of nanomaterial and how the challenges to implement it can be met. You will gain insights into the basis for EU legislation in general, the processes for developing it, different types of EU legislative acts and understand why there are differences.

Notable progress in OECD: The 35th meeting of the OECD WNT agreed **a new TG on the Determination of the Hydrophobicity Index of Nanomaterials through an** Affinity **Measurement**. While the Secretariat is progressing with the further steps of adoption by CBC and publication, JRC is working on the publication of the Report of the related interlaboratory study, planned for early summer 2023.

European Union Observatory for Nanomaterials (EUON) has published several reports in 2022:

- Study on (bio)degradation, persistence and safe by design of nanomaterials
- Assessment of the potential impact of graphene, graphene oxide and other 2D materials on health, and the environment
- Study of the EU market for nanomaterials, including substances, uses, volumes and key operators

DG Environment of the European Commission has published Issue 27 of its Future Brief series: **Nanoplastics: state of knowledge and environmental and human health impacts**. The full report, together with further rmaterial (video, infographics) can be find here.

JRC Scientific Publications 2022 and 2023, relevant for the WPMN:

- Lucian Farcal, Amalia Munoz, Juan Riego Sintes, Hubert Rauscher, Kirsten Rasmussen. Advanced materials foresight: Research and innovation indicators related to advanced and smart nanomaterials. Accepted for publication in F1000Research. Article number 127810;. https://f1000research.com/articles/11-1532/v1 . 2022
- Eric A.J. Bleeker, Elmer Swart, Hedwig Braakhuis, María Luisa Fernández-Cruz, Ilse Gosens, Frank Herzberg, Keld Alstrup Jensen, Frank von der Kammer, Jolinde A.B. Kettelarij, Jose María Navas, Kirsten Rasmussen, Kathrin Schwirn, Maaike Visser. *Towards Harmonisation of Testing of Nanomaterials for EU Regulatory Requirements on Chemical Safety.* Regulatory Toxicology and Pharmacology, Vol.139, March 2023, 105360. https://doi.org/10.1016/j.yrtph.2023.105360. 2023
- Hubert Rauscher, Andrej Kobe, Vikram Kestens, Kirsten Rasmussen. *Is it a nanomaterial in the EU? Three essential elements to work it out.* Nano Today 49 (2023) 101780. https://doi.org/10.1016/j.nantod.2023.101780. 2023

- Kirsten Rasmussen, Reinhilde Schoonjans, Paula Jantunen and Hubert Rauscher. *European Union Legislation addressing environment, health and safety aspects of nanomaterials* in 'Environmental Nanopollutants: Sources, Occurrence, Analysis and Fate'' edited by Joanna Szpunar, Javier Jiménez-Lamana. Royal Society. 978-1-83916-658-7. 2022.
- Falk A., Pogany A., Aungkavattana P., Bañares M.A., Beitollahi A., Bim V., Briffa S., Bochon A., Cassee F., Doridot F., Exner T., Farias P.M.A., Favre G., Franzese G., Friedrichs S., Hristozov D., Hunt N., Indaraprasirt R., Karim M.E., Khandelwal N., Malsch I., Marcoulaki E., Marjovi A., Rasmussen K., Rocca C., Singh P.P., Thongkam W., Tsuruoka S., Wilkins T.A., 2022, "*INISS-Nano: revised concept and action plan (International Network Initiative on Safe and Sustainable Nanotechnologies)*"; DOI: 10.5281/zenodo.6818049.
- Harald R. Tschiche, Frank S. Bierkandt, Otto Creutzenberg, Valerie Fessard, Roland Franz, Ralf Greiner, Karl-Heinz Haas, Andrea Haase, Andrea Hartwig, Bernhard Hesse, Kerstin Hund-Rinke, Pauline Iden, Katrin Löschner, Diana Mutz, Anastasia Rakow, Kirsten Rasmussen, Hubert Rauscher, Hannes Richter, Janosch Schoon, Otmar Schmid, Claudia Som, Lena M. Spindler, Carmen Gruber-Traub, Günter E. M.Tovar, Paul Westerhoff, Wendel Wohlleben, Andreas Luch and Peter Laux. *Analytical and toxicological aspects of nanomaterials in different product groups: Challenges and opportunities*. NANOIMPACT (2022), https://doi.org/10.1016/j.impact.2022.100416
- Dora Mehn, Agnieszka Mech, Kirsten Rasmussen, Hubert Rauscher and Douglas Gilliland. "Regulatory and technical challenges in the size characterization of nanoparticulate systems" in *Particle Separation Techniques*, edited by Catia Contado. Publisher: Elsevier ISBN: 978-0-323-85486-3. 2022.
- Fiona Murphy, Helinor Johnston, Susan Dekkers, Eric Bleeker, Agnes Oomen, Teresa F. Fernandes, Kirsten Rasmussen, Anna Paula Jantunen, Hubert Rauscher, Neil Hunt, Danail Hristozov, Wendel Wohlleben, and Vicki Stone. *A Template for Hypothesis Generation to Facilitate Grouping and Read-Across of Nanomaterials and Support Risk Decision-Making*. ALTEX - Alternatives to animal experimentation, June 2022. doi: 10.14573/altex.2203241
- Harald Bresch, Vasile-Dan Hodoroaba, Alexandra Schmidt, Kirsten Rasmussen and Hubert Rauscher. *Counting small particles in electron microscopy images – proposal for rules and their application in practice.* Nanomaterials, 2022, 12(13), 2238; https://doi.org/10.3390/nano12132238.
- Harald R. Tschiche, Frank S. Bierkandt, Otto Creutzenberg, Valerie Fessard, Roland Franz, Bernd Giese, Ralf Greiner, Karl-Heinz Haas, Andrea Haase, Andrea Hartwig, Bernhard Hesse, Kerstin Hund-Rinke, Pauline Iden, Katrin Löschner, Diana Mutz, Anastasia Rakow, Kirsten Rasmussen, Hubert Rauscher, Hannes Richter, Janosch Schoon, Otmar Schmid, Claudia Som, Günter E. M.Tovar, Paul Westerhoff, Wendel Wohlleben, Andreas Luch and Peter Laux. *Environmental considerations and current status of grouping and regulation of engineered nanomaterials.* Environmental Nanotechnology, Monitoring & Management, Volume 18, December 2022, 100707. https://doi.org/10.1016/j.enmm.2022.100707
- Agnieszka Mech, Stefania Gottardo, Valeria Amenta, Alessia Amodio, Susanne Belz, Søren Bøwadt, Jana Drbohlavova, Lucian Farcal, Paula Jantunen, Aleksandra Małyska, Kirsten Rasmussen, Juan Riego Sintes and Hubert Rauscher. *Safe-and-Sustainable-by-Design: the Case of Smart Nanomaterials. An outlook based on a European Workshop.* Regulatory Toxicology and Pharmacology. Volume 128, February 2022, 105093. https://doi.org/10.1016/j.yrtph.2021.105093
- Frédéric Loosli, Kirsten Rasmussen, Hubert Rauscher, Richard K Cross, Marianne Matzke, Claus Svendsen, David Spurgeon, Nathan Bossa, Willie Peijnenburg, Josje Arts, Per Axel Clausen, Wendel Wohlleben, Emmanuel Ruggiero and Frank von der Kammer. *Refinement of the selection of Physicochemical Properties for Grouping and Read-Across of Nanoforms*. NanoImpact 25, 100375, https://doi.org/10.1016/j.impact.2021.100375 .

- Ghanem, Vasile-Dan Hodoroaba , Agnieszka Mech, StefanWeigel, Wendel Wohlleben, Hubert Rauscher.
- *NanoDefiner Framework and e-Tool Revisited According to the European Commission's Nanomaterial Definition 2022/C 229/01*. Nanomaterials 13 (2023) 990; https://doi.org/10.3390/nano13060990
- Reinhilde Schoonjans, Jacqueline Castenmiller, Qasim Chaudhry, Francesco Cubadda, Takis Daskaleros, Roland Franz, David Gott, Jan Mast, Alicja Mortensen, Agnes G. Oomen, Hubert Rauscher, Stefan Weigel, Maria Chiara Astuto, Irene Cattaneo, Eric Barthelemy, Ana Rincon, José Tarazona. *Regulatory Safety Assessment of Nanoparticles for the Food Chain in Europe*. Trends in Food Science and Technology 134 (2023) 98-111. https://doi.org/10.1016/j.tifs.2023.01.017

3.14 Malaysia

Department of Standards Malaysia (DSM) continues to participate in ISO/TC 229 Nanotechnology standardization meetings. Malaysia co-leads a project, with Colombia, in the revision of ISO/TS 12901-2:2014 Occupational Risk Management Applied to Engineered Nanomaterials – Part 2: Use of the Control Banding Approach. This revision will suggest references to two recently published OECD documents – Evaluation of Tools and Models for Assessing Occupational and Consumer Exposure to Manufactured Nanomaterials: Part 1 Compilation of tools/models and analysis for further evaluation (No. 346); and Part II Performance testing results of tools/models for occupational exposure (No. 347).

DSM has submitted a New Work Item Proposal titled 'Radiotelemetry-SpectralEchocardiography Based Real-time Surveillance Protocol for In Vivo Toxicity Detection and Monitoring of Engineered Nanomaterials' for consideration by ISO/TC 229 experts. This proposal was previously registered as a Preliminary Work Item (PWI 4963) under Project Group No. 35 (PG35).

The ISO/TS 13830:2013 'Nanotechnologies – Guidance on labelling for consumer products containing manufactured nano-objects' (last reviewed and confirmed in 2020) has been adopted as a local standard in year 2018. NNC will propose adoption of the ISO/TR 13329 'Nanomaterials -- Preparation of safety data sheets (SDS)' once its revision has been confirmed.

3.15 Business at OECD (BIAC)

For example: standards, technical guidance, technical reports, and notable articles in the popular and technical literature.

The **NIA** follows standardisation activities through ISO/TC 229 Nanotechnologies and CEN/TC 352 Nanotechnologies. Relevant updates from those activities are communicated to NIA members at relevant events organised by the NIA. As part of NanoHarmony, the NIA will be contributing to the development of best practice guidelines for developers of future Test Guidelines (NanoHarmony OECD Process Mentor).

Through newly funded Horizon Europe initiatives such as the iCare project, the NIA will promote the development of a Standard Operating Procedure (SOP) inventory focusing on neurotoxicity and alternatives, supporting the development and regulatory update of NAMs. The Horizon Europe project nanoPASS will also be looking at possible future adaptations to existing TGs or new TGs, including introducing new assays for 2 AOPs (reduced lung function - AOP302; cardiovascular disease - AOP237).

3.16 UNITAR

UNITAR collaborated with the Adolphe Merkle Institute of the University of Fribourg to develop an academic paper on “the need for awareness and action in managing nanowaste”, published in Nature Nanotechnology in March 2023. The full article is freely available online: https://rdcu.be/c6PcI.

Waste containing nanomaterials — or nanowaste — is an emerging safety concern worldwide, requiring environmentally sound management and regulation that still need to be established. Researchers at the University of Fribourg point out the gaps and provide first solutions for guidance. The research paper was also a direct contribution to discussions under the Basel Convention, as well as being of relevance to the Strategic Approach to International Chemicals Management.

4 Information related to Integrated Approaches to Testing and Assessment (IATA) for NM/ AdMa

4.1 Germany

Federal Institute for Risk Assessment (BfR)

The BfR is involved in the following developments related to IATA:

The EFSA funded project NAMS4NANO, which started in April 2023, aims to develop NAMs and establish integrated approaches to testing and assessment (IATA) to cover nano-specific considerations. These IATAs will also be applied in five risk assessment case studies that cover different applications within EFSA's responsibility (e.g. nutrients, food and feed additives, food contact materials, and pesticides).

4.2 Belgium

The FPS Economy, Service of Metrology – National Standards (SMD), has a laboratory dedicated to nanometrology. SMD is active on the development and validation of instruments for the metrological characterization of nanomaterials. The nanometrology laboratory is accredited ISO17025 for the calibration of the diameter and size distribution of spherical nanoparticles and Step-Height standards using Atomic Force Microscopy.

SMD is developing a platform to characterize the size and concentration of nanoparticles dispersed in liquid and complex media (gel, cream,…). This characterization platform is composed of a Field Flow Fractionation-based separation technique, alongside light scattering and scanning probe microscopy-based measurement techniques.

In parallel, SMD participates in projects of the Research Programmes from the European Association of National Metrology Institutes (EURAMET):

- POLight (2021-2024): Pushing boundaries of nano-dimensional metrology by light. The goal of SMD in this project is to evaluate the uncertainties related to size distribution measurement of nanoparticles using FFF-MALS-DLS to improve the comparability with other (novel) optical methods.
- PlasticTrace (2022-2025): Metrological traceability of measurement data from nano to small-microplastics for a greener environment and food safety. SMD will contribute to the preparation and characterisation of nanoplastic samples using Atomic Force Microscopy and Field Flow Fractionation – Multi-Angle Light Scattering techniques.

- MetrINo - Metrology for innovative nanotherapeutics (will start in 2023): MetrINo responds to the immediate metrological needs expressed by industry, regulatory agencies and policymakers to develop, and validate traceable analysis methods and reference materials for the assessment of the critical quality attributes of nanotherapeutics. The project focuses on clinical formulations, including synthetic lipid-based and metal oxide nanoparticles used for localised cancer treatment, gene therapy, vaccines (COVID-19) or as contrast agents. Candidate reference materials will be developed and used for measurement control. MetrINo will develop and validate traceable methods to measure nanoparticle physical properties, biotransformation in biological media, and methods for their identification and quantification in cells and tissues.

4.3 Italy

As a follow-up to the H2020 EU project GRACIOUS, the Italian Institute of Technology was involved in the following publications:

- Integrated approaches to testing and assessment for grouping nanomaterials following dermal exposure. Di Cristo L, Janer G, Dekkers S, Boyles M, Giusti A, Keller JG, Wohlleben W, Braakhuis H, Ma-Hock L, Oomen AG, Haase A, Stone V, Murphy F, Johnston HJ, Sabella S. Nanotoxicology (2022), 16(3):310-332. doi: 10.1080/17435390.2022.2085207.
- Grouping of orally ingested silica nanomaterials via use of an integrated approach to testing and assessment to streamline risk assessment. Di Cristo L, Ude VC, Tsiliki G, Tatulli G, Romaldini A, Murphy F, Wohlleben W, Oomen AG, Pompa PP, Arts J, Stone V, Sabella S. Part Fibre Toxicol (2022), 2;19(1):68. doi: 10.1186/s12989-022-00508-4.
- How to formulate hypotheses and IATAs to support grouping and read-across of nanoforms. Murphy FA, Johnston HJ, Dekkers S, Bleeker EAJ, Oomen AG, Fernandes TF, Rasmussen K, Jantunen P, Rauscher H, Hunt N, di Cristo L, Braakhuis HM, Haase A, Hristozov D, Wohlleben W, Sabella S, Stone V. ALTEX (2023), 40(1):125-140. doi: 10.14573/altex.2203241

4.4 Sweden

BIORIMA

The H2020 project BIORIMA (“Risk Management of Biomaterials”) was concluded in January 2022. The “hazard” workpackage comprising 18 partner institutes working in the field of toxicology and ecotoxicology was coordinated by Karolinska Institutet (KI). IOM coordinated the overall project. The overall aim was to develop an integrated risk management framework for nano(bio)materials used in advanced therapy medicinal products and medical devices (see Giubilato et. al., Materials (Basel). 2020 Oct 13;13(20):4532) (and see https://www.biorima.eu/).

NanoSolveIT

Two Swedish partners have been involved in the H2020 project NanoSolveIT (“Innovative nanoinformatics models and tools: towards a solid, verified and integrated approach to predictive (eco)toxicology”) executing molecular simulations and development and application of omics data and predictive modelling to study the molecular mechanisms of toxicity and possible health effects of nanoparticles. The ambition is to advance and implement in silico IATAs for the environmental health and safety of nanomaterials. The project aims to develop a validated assessment e-platform to identify the critical characteristics of nanomaterials responsible for their adverse effects on human health and the environment and will

implement a nanoinformatics-driven decision-support strategy based on in silico methods, models, and tools.

HARMLESS

Two academic partners and one industrial partner from Sweden are involved in the H2020 project HARMLESS ("Advanced high aspect ratio and multicomponent materials: towards comprehensive intelligent testing and safe by design strategies") to develop and advance adverse outcome pathway (AOP)-driven IATAs based on new approach methodologies (NAMs). The overall ambition is to offer novel tools, guidance as well as decision support for balancing functionality versus risk to ensure that next-generation nanomaterials are safe by design.

4.5 United Kingdom

NanoSolveIT

This project is coordinated by Novamechanics with the University of Birmingham (Prof Iseult Lynch) as Deputy Coordinator. This will develop and deliver a validated, sustainable and multi-scale nanoinformatics IATA, tested and demonstrated via OECD style IATA case studies for assessment of potential adverse effects of nanomaterials on human and environmental health. The innovative nanomaterial fingerprint approach developed will be the core of the model integration, supporting the IATA by linking laboratory characterization data, computational characteristics, biological signatures and image analysis.

A first version of the NanoSolveIT IATA approach, linking three integrated computational approaches to generate data relevant to human health risk assessment based on inhalation of air-borne NMs has been presented. The IATA links the multi-box aerosol model for prediction of indoor air concentrations of NMs, a lung exposure model to determine the lung burden of NMs following acute exposures and a physiologically based pharmacokinetic (PBPK) model to determine the biodistribution of the NMs to other organs over longer timescales following inhalation (10.1039/D1EN00956G). The lung exposure application is based on empirical deposition equations for calculating the deposited mass in the human respiratory system. The PBPK model extends the lung exposure model by introducing clearance terms and translocation of the NMs to the systemic circulation after passage through the air-blood barrier in the alveoli. Several exposure scenarios with varying conditions were introduced in order to compare the models in relation to the accumulated mass of NMs in the alveolar, tracheobronchial and head airways regions of the respiratory system, thus exploring their capabilities and weaknesses, and potential contribution to a NM-specific IATA for occupational exposure.

Other work, currently being integrated into various modelling workflows include the recent experiment and theoretical demonstrations that the surface oxygen content (SOC) of graphene materials (GMs) determines their mode of interaction with bacteria and acts as a switch between the two main modes of action: parallel or perpendicular (10.1021/acsnano.2c10961). The data demonstrated that GMs with high SOC predominantly attach in parallel to the bacterial cell surface when in the suspension phase. The interaction mode shifts to perpendicular interaction when the SOC reaches a threshold of ～0.3 (the atomic percent of O in the total atoms). Such distinct interaction modes are highly related to the rigidity of GMs. Integrating these thresholds into the predictive models and IATA is a next step in terms of Safe By Design also.

Another highlight is the recent meta-analysis of a large collection of transcriptomics data from various engineered nanoparticle exposure studies, via which we identified common patterns of gene regulation that impact the transcriptomic response across species (10.1038/s41565-023-01393-4). Deregulation of immune functions was found to be a prominent response across different exposure studies, including multiple human and mouse cell types and tissues, both in vitro and in vivo, exposed to 103 ENMs varying in chemistry, geometry and size, and verified also in Danio rerio, Caenorhabditis elegans, Enchytraeus

albidus and Arabidopsis thaliana. Looking at the promoter regions of these genes, a set of binding sites for zinc finger transcription factors C2H2, involved in cell stress responses, protein misfolding and chromatin remodelling and immunomodulation, is identified. The model can be used to explain the outcomes of mechanism of action and is observed across a range of species indicating this is a conserved part of the innate immune system. This provides a new mechanistic insight and will be integrated into the AOP-based IATA.

RiskGone

RiskGone will develop regulatory-relevant guidance, addressing both human and environmental health prioritizing in vitro methods, based on an IATA framework. An initial decision support tool for screening potential ethical issues related to the manufacturing, transport or use of a product incorporating nanomaterials has been developed and implemented via a user friendly graphical intrefacce.

A freely available “in vitro dosimetry” web application is presented enabling users to predict the concentration of nanomaterials reaching the cell surface, and therefore available for attachment and internalization, from initial dispersion concentrations (10.3390/nano12223935). The web application is based on the distorted grid (DG) model for the dispersion of engineered nanoparticles in culture medium used for in vitro cellular experiments, in accordance with previously published protocols for cellular dosimetry determination. A series of in vitro experiments for six different NPs, with Ag and Au cores, were performed to demonstrate the convenience of the web application for calculation of exposure concentrations of NPs. The results show that the exposure concentrations at the cell surface can be more than 30 times higher than the nominal or dispersed concentrations, depending on the NPs’ properties and their behaviour in the cell culture medium. Therefore, the importance of calculating the exposure concentration at the bottom of the cell culture wells used for interpretation of in vitro assays is clear. Widespread application of this web tool will increase the reliability of subsequent toxicity data, allowing improved correlation of the real exposure concentration with the observed toxicity, enabling the hazard potentials of different NPs to be compared on a more robust basis. This model is now being integrated with the previously developed toxicity assessment models (e.g., from NanoSolveIT which are based on periodic descriptors, NMs facets and more, 10.1007/s11224-021-01869-w), and the recalculated dose-response curves can then be used to rank NMs and provide new insights on the actual toxicity of the NMs on a particle number basis rather than a mass basis.

4.6 The United States

The EPA and the Consumer Product Safety Commission are developing a case study for 3D printing which includes use of nanomaterials as well as other materials.

The Office of Research and Development at EPA will initiate development of a standardized approach to assessing risks for nanomaterials.

The National Nanotechnology Coordination Office (NNCO) and the Nanotechnology Environmental and Health Implications (NEHI) are updating the National Nanotechnology Initiative’s (NNI) 2011 Environmental, Health, and Safety (EHS) Research Strategy. Information about the public meeting (May 31-June 1) is available in link below as well as videos of the various presentations.

https://www.tvworldwide.com/events/nanotech/230531/default.cfm

4.7 Business at OECD (BIAC)

The NIA follows and contributes to discussions on IATAs through the OECD working group through activities under the WPMN SGTA group. Updates are shared and discussed with members at NIA-organised meetings. The NIA follows relevant projects either as a partner (iCare, nanoPASS, LEARN) or through the NanoSafety Cluster.

4.8 The International Council on Animal Protection in OECD Programmes (ICAPO)

As a follow up of a recommendation from an international expert workshop co-organised by PETA Science Consortium International and the US NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), PETA Science Consortium International is funding proof of concept testing to show the utility of *in vitro* approaches to assess respiratory toxicity. The results of testing on the first two chemicals (Triethoxysilane and Trimethoxysilane) were recently presented at the Society of Toxicology (SOT) conference, at a workshop organised by the American Cleaning Insititute, and at the Association of Inhalation Toxicologists (AIT) conference. A manuscript describing this testing is currently under review and includes results from testing in two biological systems—a human bronchial epithelial cell line (BEAS-2B) and a reconstructed human bronchial tissue model (MucilAir™, Epithelix)—exposed to the silanes as vapors at the air-liquid interface. Studies are underway to assess additional test chemicals (two surfactants) in both systems. The approaches developed are intended to be generally applicable to the testing of nanomaterials and other substances. More information on this project is available at: https://www.thepsci.eu/our-work/inhalation/

The PETA Science Consortium International e.V. provided funding to the Institute for In Vitro Sciences to assess the potential of cryopreserving human precision cut lung slices (hPCLS). Fresh and cryopreserved (~7 and ~34 weeks) hPCLS were cultured for 29 days and shown to have similar performance in terms of viability, biomass, cytotoxicity, and cytokine response. The highlights of this study were presented at the SOT and a manuscript was recently published in *Toxicological Sciences.*

Reference:

Vivek S Patel, Khalid Amin, Adam Wahab, Méry Marimoutou, Lindsey Ukishima, Jose Alvarez, Kelley Battle, Andreas O Stucki, Amy J Clippinger, Holger P Behrsing, Cryopreserved human precision-cut lung slices provide an immune competent pulmonary test system for "on-demand" use and long-term cultures, Toxicological Sciences, Volume 191, Issue 2, February 2023, Pages 253–265, https://doi.org/10.1093/toxsci/kfac136

PETA Science Consortium International e.V. and Epithelix announced an award to provide an opportunity for researchers worldwide to win three-dimensional (3D) reconstructed human respiratory tissues from Epithelix. Dr Suzanne Cloonan from Trinity College Dublin received tissues worth $15,000 redeemable for Epithelix tissues (MucilAir™, SmallAir™, or AlveolAir™) and/or primary human alveolar macrophages. More details on our awards related to 3D tissues and travel grants can be found here: www.thepsci.eu/funding/3d-tissue-awards/ and www.thepsci.eu/funding/travel-grants/

5 Developments and/ or considerations related to Advanced Materials (multicomponent / complex)

5.1 Austria

As a measure of implementation of the Austrian Nanotechnology Action plan the national NANO Environment Health and Safety programme (https://www.ffg.at/programme/nano-environment-health-and-safety) has been established. In the 9th call for proposals in 2021 the Project SiNa (*Sicherheit und Nachhaltigkeit von Nanomaterialien und anderen Advanced Materials*) is funded analyzing existing SSbD approaches and tools (project duration November 2022 – October 2023; The BOKU, Vienna (lead: Florian Part) cooperate with the Brimatech Services GmbH and Phornano GmbH. https://forschung.boku.ac.at/fis/suchen.projekt_uebersicht?sprache_in=de&menue_id_in=300&id_in=15029

5.2 Belgium

Over the last years, several contacts occurred from different partnerships, showing strong common interests in the development of harmonized extraction protocols (and/or an articulated set of them, similar to a decision tree) in complex matrices, in France, for example. A global initiative thus seems to be welcome and appropriate.

SMD is also part of the Euramet Advanced Manufacturing Network and its subgroup focusing on Advanced Materials.

5.3 Canada

Canada continues the risk assessment of ZnO and TiO_2 at the nanoscale that are in commerce in Canada, to evaluate their environmental and human health risks under the *Canadian Environmental Protection Act*. Progress has been made with the development of resources and databases in support of the science being undertaken for these assessments.

Where appropriate, the Program continues to provide a compliance promotion letters to identified potential importers or manufacturers of carbon-based nanomaterials, informing them of obligations to notify under the significant new activity provisions and the NSNR (C&P).

5.4 Germany

German Environment Agency (UBA)

On 14 -15 June 2023 the SG AdMa held its 2nd AdMa Workshop on Advanced Materials with focus on nanocarrier. The workshop gave an overview on types and applications of nanocarrier based on a current survey commissioned by UBA and presented the current state of the art on nanocarriers used in pesticides, cosmetics, and medicinal products as well as the current knowledge on potential safety and sustainability issues of these application types. Furthermore, the regulatory challenges associated with the application of nanocarrier were presented. Based on the current version of the Early4 AdMa scheme (tier 2), dedicated discussions in break out groups took place to support the formulation of recommendations, e.g., with regard to SSbD and regulatory preparedness based on example cases of previously mentioned application types. These break out group discussions were also used to further promote the Early4AdMa scheme by providing specific remarks to its applicability.

German Environment Agency (UBA)

New publication on advanced material medicinal products/nanomedicine:

- Berkner, S., Schwirn, K. & Voelker, D. Too advanced for assessment? Advanced materials, nanomedicine and the environment. Environ Sci Eur 34, 71 (2022). https://doi.org/10.1186/s12302-022-00647-7

Federal Institute for Risk Assessment (BfR)

The BfR is involved in the following advanced materials activities:

- RIVM has developed together with the German higher authorities BAuA, BfR and UBA a proposal for an early warning system to provide a common perspective on the responsible use of advanced materials. (Towards Safe and Sustainable Advanced (Nano)materials: A proposal for an early awareness and action system for advanced materials (Early4AdMa) https://www.rivm.nl/documenten/Early4AdMa-brochure.
- The OECD Steering group Advanced Materials selected case studies to test, verify, and improve safe-by-design and safe innovation approaches in different industrial sectors. One of the selected case studies is performed together with the EU project HARMLESS (https://www.harmless-project.eu/case-studies/), in which the BfR is involved. HARMLESS organised a workshop together with the OECD WPMN SG AdMa on 15 November 2023 to discuss this case study. The report is currently being finalised. The BfR will also contribute via studies to the nanocarrier case study.
- A review on risk assessments of 3D printing emissions has been published (https://doi.org/10.1016/j.atmosenv.2022.119501)

5.5 Italy

A case study on Ag nanoparticles (AgNPs) based composites made of AgNPs core nucleated over different bio-molecular shell has been proposed by the ASINA EU H2020 project (Anticipating Safety Issues at the Design Stage of NAno Product Development, https://www.asina-project.eu/) in the AdMa working group. The AgNPs primary particles, ranging in size from 5 to 20 nm, are embedded in a bio- (polymeric) molecular shell of vegetable source. The design alternatives will regard the synthesis variables (reagents weight ratios) and the composition of the organic shell. The material is used to produce antimicrobial textile

coatings that find application as protective clothing and in general personal protective equipment (masks, gloves). Nevertheless, it can also be investigated as an active ingredient for the formulation of cosmeceuticals or medical products.

5.6 The Netherlands

The **new European project** MACRAMÉ is aligned with the EU ambitions to secure the safety and sustainability of new chemicals, materials, products and processes in order to strive for zero pollution and toxic-free environments. The project concentrates on **methodologies that are applicable to nanomaterials and widens them to advanced materials in commercialised products**. Within the project five advanced materials (products) are selected for sampling and characterisation during the life cycle. Three of these are based on graphene, one is based on carbon nanotubes and one is a nanomedicine. Furthermore, potential impacts on (human) health and the environment in intended or unintended exposure situations in the product value-chain will be assessed. The developed and improved methods and techniques are further advanced for OECD test guidelines and standardization (CEN/ISO). Within the project RIVM will use air liquid interface (ALI) models developed and used within previous EU projects to assess potential hazard of the selected advanced materials after inhalation. In order to advance the best models towards OECD test guidelines and standards, there will be an exchange of ALI models. Both the chemical and medicine domain are represented in the selected materials and RIVM will help promote coordination between these regulatory frameworks in the field of advanced materials. As co-lead of WP1 on Bridging Communities & Refining MACRAMÉ Strategies RIVM will assess the needs of regulatory and policy frameworks.

5.7 Sweden

HARMLESS

The project HARMLESS includes testing the performance of the safe-by-design frameworks and tools developed for nanomaterials with respect to high aspect ratio and multicomponent materials.

SweNanoSafe

The 5th Annual Workshop of the National Research Network covered aspects of particle mixtures and advanced materials with plenary speakers from Sweden, Greece, Holland, and UK.

5.8 United Kingdom

In April 2021, the UK held a UK workshop on Advanced Materials. The workshop served to create a UK knowledge sharing community to share views on the benefits of this new technology, including societal benefits and potential obstacles to the wider adoption of advanced materials. This meeting included perspectives from organizations developing advanced materials, business manufacturing, academics and regulators. Following the success of the first workshop, the UK held another workshop in February 2023 co-organized by Defra, NPL, HSE, BSI, ISO, UKHSA, BEIS focusing on challenges faced by those working with at different points in the supply chain, and how to incorporate safety by design and considering end-of-life of advanced materials.

Health and Safety Executive (UK) Advanced Materials project

This is a national project which aims to understand occupational risks to health from exposure to carbon based materials, including composite materials and graphene, used in new manufacturing processes. NPL (UK) leading and contributing to the development of ISO documents for the characterisation of graphene and graphene platelets. This is an ongoing project focussed on workplace settings. The Health and Safety Executive Science Division is now working closely with the University of Manchester.

SUNSHINE

This project is coordinated by the University of Venice with two UK based work-package leads: Swansea University (WP2) and Herriot-Watt University (WP4). SUNSHINE is focused on developing and implementing simple, robust, and cost-effective Safe and Sustainable by Design (SSbD) strategies for materials and products incorporating advanced multi-component nanomaterials. The aspects of work being led by the UK include the development of experimental methods and the generation of human and environmental hazard data on multi-component nanomaterials to support the development of SSbD strategies and their validation (WP2). The UK is also leading the development and application of grouping and read-across strategies for the SSbD of multi-component nanomaterials (WP4). Since the last meeting, in collaboration with HARMLESS and DIAGONAL, methods have been generated to compare the leaching of different metals from multicomponent nanomaterials using quantum dots as a case study and then being able to use this data to assess their similarity for grouping. We have also extended the grouping hypothesis template to include enhanced features and mixture effects that could be associated with MCNMs.

5.9 Malaysia

Under the National Advanced Materials Technology Roadmap 2021-2030, four game-changers have been identified - graphene, nitinol, rare earth, and microcrystalline cellulose polymer – with specially designed programmes towards developing the advanced materials ecosystem in Malaysia.

5.10 Business at OECD (BIAC)

For example, this could include information related to initiatives, workshops, publications. Whether these are based on new compositions, combinations of existing materials, materials with unique properties.

The NIA actively contributes to the discussion on Advanced Materials through its participation at the OECD WPMN Steering Group on Advanced Materials. In this reporting period, a thorough insight of foresight tools took place, including Early4AdMa, and recommendations for improvement have been circulated.

6 Developments in policy context for Advanced Materials

6.1 Austria

In September 2022, the three-year project "Examination and further development of strategic approaches for dealing with novel materials in chemical safety - study on nanocarriers and their environmental behaviour" started (contact: Bernd Giese, Institute for Safety and Risk Sciences, BOKU). The BOKU Institutes of Waste Management and Circularity as well as Synthetic Bioarchitectures are also involved. The project is funded by the German Federal Environment Agency (UBA) and considers "nanocarriers" as a case study of "advanced materials" that pose challenges for chemical regulation and regulatory risk assessment. However, chemical safety is not only about the risk assessment of substances or newly developed systems such as "nanocarriers", but also about sustainability aspects that need to be looked at more closely along the entire product life cycle up to waste and circular economy (in the sense of "safe and sustainable by design"). The above mentioned BOKU-institutes contribute also to an OECD activity to develop an “Early awareness and action system for advanced materials (Early4AdMa)” as a pre-regulatory strategic approach to advanced materials. The approach provides an assessment of potential risks based on properties of the material and information on its context of use, which is available at early stages of material development (e.g., through its physico-chemical properties). To this end, the BOKU team will contribute its experience from the “nanocarrier” project to case studies on nanocarriers with relevance for applications in the medical, agricultural, and cosmetic sectors. The corresponding workshop of the OECD WPMN Steering Group on Advanced Materials will take place on 14 and 15 June 2023.

The University of Natural Resources and Life Sciences (BOKU; contact: Florian Part) is partner of the H2020 project “SAFEGRAPH – Regulatory Pathway and Safety Assessment of Graphene-based products” (project duration 2020 – 2023). This project aims to conduct quantitative risk assessment of graphene-based products (water filters, deicing systems for aircrafts, smart textiles etc.) that has been developed in the framework of the “Graphene Flagship” (http://graphene-flagship.eu/). BOKU focuses on exposure scenarios at the end of the life cycle and the recyclability of products, Empa on exposure during product use and on human toxicity. The University of Triest (UNITS) is responsible for ecotoxicity testing and the UCLM for graphene detection. TEMAS Solutions GmbH is responsible for the regulatory pathway that should be followed for product approval coordinates the project.

The SAF€RA project SafeLiBatt (11/2020-10/2023) addresses the safety and sustainability assessment of second life lithium-ion batteries (2ndL-LIBs) derived from e-vehicle LIBs (first life). The project is coordinated by BOKU (lead: Florian Part). BAM and INERIS are aging first life LIBs to simulate a second life and then test thermal runaways whether there are differences in their behaviour. The BOKU uses the obtained data on nano-/particle and gas emissions for risk assessment and additionally performs a life cycle assessment (LCA) to evaluate the environmental benefits of 2ndL-LIBs. BRIMATECH GmbH and ITA-OeAW are responsible for social-economic assessment of potential 2ndL applications, such as energy storage systems. Three stakeholder workshops will be held, and project results will be presented to the appropriate standardization working groups.

Its sister project SABATLE (01/2021-03/2023) aimed to investigate the safety and (nano)toxicity aspects of current and emerging electrolytes in redox flow batteries as well as the corresponding environmental impacts by performing a life cycle assessment (University of Graz) of the whole life cycle from resource extraction to the end-of-life. During the course of the project, electrolytes from commercially available RFB technologies were investigated and compared to emerging electrolytes developed by the Technical University of Graz, based on organic compounds derived from lignin, provided by MONDI AG. The Austrian partner BNN (contact: Clemens Wolf) contributed by creating and implementing a Safe- and Sustainable-by- Design concept (SSbD) concept guiding the development.

The national projects NanoSyn3 (April 2022 - March 2023) and NanoSny4 (April 2023-March 2024) coordinated by BNN (contact: Andreas Falk), funded by the Ministry for Climate Action, Environment, Energy, Mobility, Innovation and Technology (BMK), identified potentials and are lifting synergies at national and international level towards collaboration in the field of nanotechnology – expanding to advanced materials in NanoSyn4; more specific, in the Safety and Sustainability area. The collaboration with Austrian technology platforms (e.g., SusChem-AT, NanoMedicine-AT, Advanced Microfluidics) as well as with public financed activities (e.g., NanoTrust), strengthens the national and international interaction (e.g., within the EU NanoSafety Cluster (NSC), the INISS-nano, PARC, OECD, ISO, CEN, ETP Sustainable chemistry, Microfluidics community) related to nanotechnologies and advanced materials.

6.2 Germany

German Environment Agency (UBA)

In March 2023, UBA published a position paper on advanced materials and the field of tension between their promising use and possible challenges for environmental and health protection and other sustainability dimensions. Advanced materials may play an important role for the transition to a more sustainable society. The position concentrates on topics in the remit of UBA, such as the energy transition, circular economy and chemical safety. The position paper describes opportunities, challenges, and conflicting goals for safety and sustainability that might go hand in hand with the use of advanced materials. This is shown in more detail for three types of advanced materials. The position describes cornerstones that UBA believes are essential for dealing with these conflicting goals in order to promote safe and sustainable material innovations and their applications.

https://cms.umweltbundesamt.de/publikationen/advanced-materials

Max Rubner Institute (MRI)

MRI is a member of the German Interagency Group „Advanced Materials“ headed by the German Federal Institute for Risk Assessment. The aim of the group is a cross-departmental mutual information with the aim of identifying possible health and environmental risks of innovative materials and substances at an early stage and to enable an initial assessment.

6.3 The Netherlands

With Germany as chair, the Netherlands co-chaired the OECD Steering Group on Advanced Materials (AdMa). Monthly meetings were organised in which the activities were presented and discussed with the experts. The Netherlands has chaired a subgroup working on the OECD Strategic Approach for AdMa by **updating the Early4AdMa system** using feedback from cases (MXenes, fibre-aerogel-mats). The updated Early4AdMa system aims to address Regulatory Preparedness and Safe-and-Sustainable-by-Design of AdMa. It provides a system that facilitates timely identification of potential safety and/or

sustainability issues of AdMa, and whether current regulatory frameworks and test methods are adequate. Furthermore, the Netherlands coordinated the writing of the report from the subgroup on the updated Early4AdMa system. Several presentations on the Early4AdMa system to the AdMa community were given.

6.4 United Kingdom

PATROLS

The H2020 project PATROLS started in January 2018 and is led by Swansea University (Prof Shareen Doak). This project was aimed at establishing and standardizing a battery of next generation physiologically anchored, hazard assessment tools that more accurately predict adverse human and environmental effects caused by long-term, low dose nanomaterial exposure to support regulatory decision making. The project was finalised in Sept 2021, achieving significant innovative developments that involved adapting & further advancing cell based ENM hazard testing systems by 1) enhancing their physiological relevance through increased biological complexity; 2) extending their culture time whilst maintaining normal cell function and viability, to better support more realistic longer-term, repeated dosing scenarios; 3) development of a suite of diseased-state models. Ecological assays have also been improved to better support long-term ENM exposures, through generation of novel systems to both support chronic environmental exposure and detect new hazard endpoints with greater sensitivity. Since the project completed, many of the SOPs developed within PATROLS have been passed to other ongoing Horizon 2020 and Horizon Europe projects for further application in evaluating the safety of nanomaterials (e.g. RiskGONE), advanced materials (e.g. SUNSHINE) and for application in aligned areas of research such as carcinogenicity testing (e.g. CutCancer).

UK Involvement in PARC

The €400 Million PARC project, which started on 1st May 2022 and will run for 7 years, while focusing on chemicals more broadly, has a significant cohort of nanosafety experts and will include at least 1 cross-cutting case study / project on nanomaterials safety. The UK have strong involvement in PARC (funded via UKRI) including Co-Leading WP7 on FAIR data management (Iseult Lynch, UoB) and as a WP Co-Lead also have a set a at the Management Board, as well as on the Governance Board (Ovnair Sepai, PHE). UoB are the largest UK partner in PARC, being involved in WPs 2-7, with a strong emphasis on environmental aspects / ecotoxicity and New and Alternative Methods (NAMs).

The first round of substance prioritisation in June 2022 was jointly with the final prioritisation round of the EU-funded project HBM4EU (Human Biomonitoring for EU) and as such had a strong focus on chemicals in homes and for which biomonitoring was being performed. As such, NMs/AMs were not on the first list of prioritised substances. That said, there is broad recognition within PARC that the nanosafety field have really been leading in terms of SSbD approaches and FAIR data, and as such there is consensus that NMs/AM should be included in the 2nd round prioritisation activity, planned for Autumn 2023. The various nano-interested partners (UK and EU-wide) will organise to have some specific prioritisation of exemplar NMs/AM families to nominate and why. There is also an opportunity to drive NM/AM in via the SSbD case studies / demonstrations – there is an internal PARC survey open currently that I have fed into highlighting NMs/AMs.

University of Birmingham (Iseult Lynch) is Co-WP lead for WP7 on FAIR data, as well as co-task lead for Task 7.1 / 7.3 (Luke Slater/George Gkoutos). Year 1 has been focused on mapping the FAIR landscape across the different domains within the remit of PARC, and training the FAIR Implementation Team (via the sub-contracted GO FAIR Foundation's 3 Point FAIRification Framework (3PFF), including development of FAIR implementation profiles, development of tools to make metadata machine-actionable (beyond just

being machine readable) including harmonised vocabularies and integrated ontologies. Two levels of data stewards have also been (and continue to be) trained, with Data Champions in every task/project within PARC and Data Liaisons from WPs assigned to guide each PARC project through the FAIRification steps and identify gaps and development needs in terms of tooling, vocabularies etc. A roadmap for FAIRification is currently being developed, including integration with IPCHEM and the forthcoming Commons Open Platform for Chemicals Safety, and will be supplemented with the PARC-developed and recommended tools and supports to operationalise the roadmap.

Environmental Exposures and Health (EEH)

The UK National Institute of Health Research's Health Protection Research Unit (NIHR HPRU) on Environmental Exposures and Health (EEH) (2020-2025), a partnership between the UK Health Security Agency, Imperial College London, King's College London, University of Leicester, MRC Toxicology Unit, and UK Health and Safety Executive, includes projects on exposures from nano consumer spray products, 3D printing, toxicity of micro/nano plastics, particulate (+nano) effects on asthma/allergic airway disease and the use of aerosol exposure air liquid interface (AE-ALI) systems for nanomaterial toxicity assessment. In the last year we have completed a study on the aerosols produced by metal-containing 'colloidal' consumer spray products (presented at IAC2022) and finalised the characterisation of AE-ALI system for nanoparticle toxicity studies (paper currently in draft). A new activity on the neurotoxicological impacts of inhaled particles has also commenced. (https://eeh.hpru.nihr.ac.uk/)

6.5 European Union

There are different activities across chemicals related policies which include consideration of advanced materials; an extensive information on the EU support of research and innovation for chemicals and advanced materials is provided on the dedicated DG R&I website that also contains a list of relevant key legislation.

6.6 Business at OECD (BIAC)

As a partner of the OECD SG AdMa, the NIA takes part in these discussions; the group is currently setting up the "playing field" for AdMa, which is essential in the scope of future policy developments.

7 Research programmes or strategies designed to address human health and/ or environmental safety aspects of (advanced) (nano) materials

7.1 Austria

PARC (EU-Partnership for the Assessment of Risk from Chemicals) is an EU Horizon Europe partnership to support research and innovation in EU and national chemical risk assessment and risk management bodies with new data, knowledge, methods, networks and skills to address current, emerging and novel chemical and nanosafety challenges. It will facilitate the transition to next generation risk assessment to better protect human health and the environment, in line with the Green Deal's zero-pollution ambition for a toxic-free environment, and will be an enabler for the EU Chemicals Strategy for Sustainability. The Austrian Environment Agency is co-leading work package 2 ("A common science policy agenda"). BNN is involved in Task 8.1 ("Safe-and-Sustainable-by-Design (SSbD)"). PARC is funded by the European Commission together with member states.

The University of Natural Resources and Life Sciences (BOKU; contact: Florian Part) is partner of the Horizon Europe project "Depolymerizable bio-based multifunctional closed loop recyclable epoxy systems for energy efficient structures" (www.repoxyble.eu; coordinated by AVANZARE (Spain); duration from 12/22-05/26). The project, a consortium of 10 project partners, aims to develop a new class of high-performance materials – bio-based epoxy composites – targeting cost and energy effectiveness, recyclability and sustainability. REPOXYBLE assumes an upstream approach more efficient and effective than having to address deficiencies at the end of the product development process. This approach integrates product performance, multifunctionality, sustainability, safety and potential legal concerns, while there is still time to act, on the monomers' synthesis, the resin formulation and the future composite design. REPOXYBLE is driven by two complementary market applications in the aerospace and automotive sectors. Experimental toxicity tests on the novel nanoformulations, material tests on the epoxy-based products including life cycle assessment and the evaluation of the chemical recyclability (solvolysis) at a laboratory scale circularity (by the BOKU) will be carried out according to the SSbD principle.

In the H2020 project NanoCommons (start: January 2018) BNN (contact: Andreas Falk) and University of Salzburg (contact: Albert Duschl) are partners and work package leader. The project brings together academia, industry and regulators to facilitate pooling and harmonising of methods and data for modelling, Safe-by-Design product development and regulatory approval purposes, thereby driving best practice and ensuring maximum access to data and tools (https://www.nanocommons.eu/). NanoCommons developed a sustainability plan, integrating all three dimensions of sustainability and creating a long-term supporting infrastructure in Europe and globally. The project concluded in June 2022.

Furthermore, BNN (contact: Susanne Resch) was beneficiary its H2020 NMBP-13 sister project "Gov4Nano - Implementation of Risk Governance: meeting the needs of nanotechnology", which recently ended in February 2023. BNN was work package leader and main responsible for stakeholder engagement and, the co-organization of interdisciplinary User Committee dialogues where new potential risks arising from advanced materials were discussed with international experts. Next to that, public risk perception, risk governance, dissemination, as well as training & education were key tasks of BNN.

Within the H2020 project "NextGenMicrofluidics - Next generation test bed for upscaling of microfluidic devices based on nano-enabled surfaces and membranes" (start: April 2020), coordinated by JOANNEUM RESEARCH Forschungsgesellschaft mbH and by the project established Open Innovation Test Bed "Microfluidic Innovation Hub", BNN (contact: Andreas Falk) is responsible for the evaluation of potential hazards and safety issues in all Demo Cases as well as raising awareness on potential regulatory issues. By implementing its safety strategy, the overall aim of BNN's nanosafety team is to ensure that all aspects of the involved processes will be conform to the "Safe-by-Design" concept for the technological development.

In the H2020 NMBP-15 project "SABYDOMA - SAfety BY Design Of nanoMAterials" (start: April 2020), BNN (contact: Andreas Falk) contributes to the integration of the methodology developed in the project into a decision tree model, through the use of SbD guidance documents for the assessment of potential risks and benefits early in the development of innovative nanomaterials.

Within the second H2020NMBP-15 project "SbD4Nano - Safe-by-Design for Nano" (start: April 2020), BNN (contact: Susanne Resch) is involved as work package leader coordinating the stakeholder engagement, communication, dissemination & exploitation activities, thus supporting the international collaboration in the field of SbD-tools development.

The H2020 project "HI-ACCURACY – High-ACCuracy printed electronics down to µm size, for Organic Large Area Electronics (OLAE) Thin Film Transistor (TFT) and Display Applications" (start: April 2020; coordinator: JOANNEUM RESEARCH Forschungsgesellschaft mbH) aims to produce printed, thin, flexible displays using nano-inks and cutting-edge technologies. BNN (contact: Susanne Resch) is leading the health and safety task, focusing on potential nanosafety issues, and supports the project partners to consider and address sustainability principles within the SSbD framework.

In the H2020 project "SIXTHSENSE - Smart integrated extreme environment health monitor with sensory feedback for enhanced situation awareness" (start: May 2020), as task leader for 'safety', BNN (contact: Andreas Falk) contributes to the WP 'co-development, safety and experimental deployment'. In addition, safety evaluation will be performed in collaboration with the relevant practitioner groups throughout the development cycle (e.g., safety evaluation of bioinks, etc.).

In the H2020 project "NanoPAT - Process Analytical Technologies for Industrial Nanoparticle Production" project (start: June 2020), BNN (contact: Andreas Falk) is leading the Safe-by-Design task, being in charge of developing a SbD concept for the project, supporting the development of responsible and safer innovations with special focus on nano-related safety issues. The Medical University of Graz (MUG; contact: Christian Hill) and Brave Analytics GmbH (contact: Gerhard Prossliner) are also partner in the project, providing their knowledge of inline and real-time sample characterisation of particle streams based on the innovative technology OptoFluidic force induction (OF2i).

The H2020 NMBP-16-project "HARMLESS - Advanced high aspect ratio and multicomponent materials: towards comprehensive intelligent testing and Safe-by-Design strategies" (start: January 2021), is supported by BNN (contact: Susanne Resch) with contributing to the Safe Innovation Approach and S(S)bD implementation specifically for multicomponent and High Aspect Ratio Nanomaterials.

Next to that, BNN (contact: Susanne Resch) is involved in its sister H2020 NMBP-16-project "DIAGONAL - Development and scaled Implementation of sAfe by design tools and Guidelines for multicOmponent aNd

hArn nanomateriaLs" (start: May 2021) with the role to mainstream sustainability into Safe-by-Design, liaison management, stakeholder engagement, communication & dissemination.

The H2020 project DeDNAed (start: March 2021) develops a novel sensor based on a DNA-origami template that offers unparalleled sensitivity, versatility and speed. BNN (contact: Susanne Resch) contributes to this project by leading the Safe-by-Design task, ensuring that potential nano-related safety hotspots are identified early in the development phase at low technology readiness level and "designed-out" during the innovation process.

The H2020 project BreadCell (start: April 2021) develops a pioneering technology to produce porous lightweight low-density materials that are massively used in industries and mainly consist of non-degradable polymers. The technology includes a foaming process that creates products from new and existing raw materials from pulping and converts them into high-value, energy-absorbing and lightweight composites. The consortium includes the Technical University of Graz as well as the University of Vienna. Austrian partner BNN (contact: Clemens Wolf) leads the task Safety and sustainability assessment of the BreadCell manufacturing process to guide the development of the production of sustainable and safe products by implementing Safe-and sustainable-by-Design principles.

The H2020 project "PHOENIX – Pharmaceutical Open Innovation Test Bed for Enabling Nano-pharmaceutical Innovation Products (start: March 2021) aims to enable the seamless, timely and cost-friendly transfer of nano-pharmaceuticals from lab bench to clinical trials by providing the necessary advanced, affordable and consolidated network of facilities, technologies, services and expertise for all the technology transfer aspects, covering characterisation, testing, verification up to scale up, GMP compliant manufacturing and regulatory guidance. The consortium includes RECENDT, RCPE and BNN (contact: Johanna Scheper) as Austrian partners. BNN's role was to develop the business concept and overall sustainability of the project and the future OITB, and leads the communication, dissemination and exploitation activities of the project. The project has already established the single entry point of the OITB, the Phoenix gGmbH. Within the service portfolio of the test bed, BNN offers innovation and guidance on and implementation of the SSbD approach.

The HORIZON EUROPE project "IRISS – accelerating the transition to Safe-and-Sustainable-by-Design" (start: June 2022) aims to connect, synergize and transform the Safe-and-Sustainable-by-Design community in Europe and globally towards a lifecycle approach, with a holistic integration of safety, climate neutrality, circularity and functionality already in an early stage of designing and manufacturing materials, products and processes. In close collaboration with industry, a number of roadmaps will be developed to implement research and innovation, but also to demonstrate needs that exist in the policy area. Focus is on the value chains for textiles, construction, electronics, energy, automotive and packaging. BNN (contact: Johanna Scheper) supports in the mapping of SSbD methods and criteria, liaison and stakeholder engagement, communication, dissemination and consultation and takes a key role in the definition and testing of services to key targets.

The recently started HORIZON EUROPE project "NABIHEAL – ANTIMICROBIAL NANOSTRUCTURED BI.OMATERIALS FOR COMPLEX WOUND HEALING" (start: January 2023) will develop multifunctional biomaterials to improve wound management, by using quatsomes nanovesicles (QS) with demonstrated inherent antimicrobial properties as alternative to silver. BNN (contact: Johanna Scheper) supports and guides the research and innovation partners in addressing the SSbD principles and will develop a project- and application-tailored SSbD concept as well as specific implementation guidelines.

A project that was recently funded via the Austrian nanoEHS programme is CHEMSAVE (start: October 2022). Coordinated by JOANNEUM RESEARCH Forschungsgesellschaft mbH, together with BNN (contact: Susanne Resch), the project aims to elaborate the role of the EU Chemicals Strategy for Sustainability and the SSbD framework on national level and its potential impact for Austrian industry. An important outcome of CHEMSAVE will be a roadmap identifying possible next steps to further support SSbD implementation in innovation processes.

The Austrian Federal Economic Chamber organizes on a regular basis so called “Chemicals Evening Talks” (Chemische Abendgespräche). The objective of these events is to offer different Stakeholders a platform to discuss up-to-date topics around chemicals policy.

On 8th March 2023 on Evening Talk focused on Safe and Sustainable by Design (SSbD). The two presentations showed the perspective of the Austrian competent authority for chemicals legislation and a larger Austrian company. The objective to trigger a fruitful discussion was achieved and the audience had an intense debate of the pros and cons of SSbD, but also what potential hurdles are and what potential support measures could be. Some additional documents on the event are available here: https://www.wko.at/service/umwelt-energie/chemisches-abendgespraech.html

Since 2017, the BioNanoNet Forschungsgesellschaft mbH (short: BNN) (contact: Andreas Falk) is part of the EU NanoSafetyCluster coordination team. Within this function, BNN contributed to the further shaping of the S(S)IA and SSbD-developments and co-coordinates the “international network initiative on safe and sustainable nanotechnologies” (INISS-nano), a global collaboration initiative towards “co The concept paper for an “International network initiative on safe and sustainable Nanotechnology” (INISS-nano) had been elaborated by international experts on Nanosafety under the lead of the BNN and the Austrian Federal Ministry of Climate Action, Environment, Energy, Mobility, Innovation and Technology (bmk). The actual and updated version is public available:

Andreas Falk, Pogany, Alexander, Aungkavattana, Pavadee, Bañares, Miguel A., Beitollahi, Ali, Bim, Vinicius, Briffa, Sophie, Bochon, Anthony, Cassee, Flemming, Doridot, Fernand, Exner, Thomas, Farias, Patricia M.A., Favre, Georges, Franzese, Giancarlo, Friedrichs, Steffi, Hristozov, Danail, Hunt, Neil, Indaraprasirt, Ramjitti, Karim, Md. E., … Wilkens, Terence A. (2022). INISS-Nano: revised concept and action plan (International Network Initiative on Safe and Sustainable Nanotechnologies) (Version_03). Zenodo. *https://doi.org/10.5281/zenodo.7877359*

The concept shows 4 pillars: (i) Harmonisation, (ii) Support industrial understanding, (iii) Sharing / facilitate sharing of resources / infrastructures, and (iv) International collaboration on ethical and societal aspects of nanotechnology. The next activity is the 6th EU-Asia Dialogue on NanoSafety, which will be held on June 21st 2023, in Berlin, Germany.

The MSCA-ITN “Directing the immune response through designed nanomaterials (DIRNANO)”, started in 2020. Jutta Horejs-Höck (University of Salzburg) is a partner in this project, that will develop biocompatible nanopharmaceuticals with either “super”-stealth or immune-specific behavior for cancer immunotherapy and vaccination by mapping nanoparticle-immune interactions through two core approaches: 1) inception of novel surface engineering approaches, based on new organic polymers, zwitterionic lipids, and conjugation chemistry strategies, 2) engineering of host or microbial-derived modulators of innate immunity (e.g. complement system). BNN (contact: Andreas Falk) is partner organization of the project, hosting ESRs for secondments to enable and train them in the field of networking, stakeholder interaction and SSbD-elements relevant for nanomedical applications.

7.2 Belgium

Case studies on silver and titanium dioxide nanoparticles in face masks were performed in Belgium. The projects have now run out of resources. Final report on silver-based biocides and titanium dioxide particles in face masks for general use is now available on Sciensano’s website.

The AgMask project aimed to clarify the possible risks linked to the use of face mask treated by silver-based biocides. The first report AgMask COVID-19 (phase 1) was already published by Belgium in September 2021. Phase 1 was used to characterize the fibers and the type of silver present in masks Avrox. Nanosilver and titanium dioxide were also identified. As it was unknown if and how these nanoparticles can be inhaled, exposure scenarios were developed.

TiO2-Mask COVID-19 project has also analysed several facemasks (in paper and in textile) in order to identify as well as to conduct a physicochemical characterisation of TiO2 nanoparticles.

7.3 Germany

German Environment Agency (UBA)

In autumn 2022, UBA launched a new research project entitled “Examination and further development of strategic approaches for dealing with advanced materials in chemical safety - Study on nanocarrier and their environmental behavior”

The project considers nanocarrier as a case study for advanced materials that pose challenges for chemical regulation and regulatory risk assessment. In the project, extensive investigations are carried out on existing nanocarrier and those under development and their (potential) applications. From the overview obtained in this way, those nanocarrier will be selected for further investigation that are expected to pose particular challenges for environmental assessment with regard to their appearance or their application. For the selected nanocarrier, test strategies will be developed and applied, which enable an investigation of their environmental behavior and the possible release of the transported active substance under environmentally relevant conditions. Under investigation are the mobility of the nanocarrier, possible unintentional release of the active substance, as well as degradability of the remaining carrier. In this way, the influence of encapsulation on the change of the environmental behavior of active substances will be determined as an example. The implications of the encapsulation for an appropriate assessment of the environmental behavior within the framework of risk assessment will be described in more detail.

Duration: September 2022 to August 2025

https://www.umweltbundesamt.de/en/topics/chemicals/nanotechnology/research-development-projects-on-nanomaterials#standardisation-of-methods-regarding-fate-and-behaviour-of-nanomaterials-in-environmental-media-solubility-and-dissolution-rate

Federal Institute for Risk Assessment (BfR)

The BfR is involved in the following research programmes:

- The BfR is currently involved in the EFSA funded project NAMS4NANO - Integration of New Approach Methodologies results in chemical risk assessments: Case studies addressing nanoscale considerations.
- This effort is subdivided in three lots with a four-year duration. LOT 1 and 2 are coordinated by the BfR as well as several other partners (ANSES, ISS, Sciensano, WUR, ISS and LIST. The Italian national Institute of health (ISS) is coordinating LOT 3 and the partners listed above participate.
- LOT 1 (Review of tools and developing a ‘Qualification System for NAMs’) focuses on (i) complementing the EFSA NAMs roadmap with a review of available NAM-based tools and methods for assessing the toxicity of nanoparticles, in particular those developed by recent EU Research projects, and (ii) developing and implementing a proposal for a “fit for purpose qualification system for NAMs” aimed at facilitating the regulatory use of NAM tools and methods.
- LOT 2 (Risk assessment case studies) focuses on five case studies using NAMs in IATAs to address nanoscale considerations and integrates the information obtained by NAMs with existing information and knowledge for risk assessments.
- LOT 3 (Methodological and generic case studies) focuses on five methodological and cross-cutting case studies. These case studies aim to advance the methodology and provide input to EFSA, which could be used in future guidance documents for risk assessment. One of the case studies

in LOT 3 is coordinated by the BfR and aims to develop a methodology for assessing human health risks of nanocarriers loaded with known active substances (for pesticides).

- The BfR is a partner in the EU H2020 projects POLYRISK (POLYRISK - Understanding human exposure and health hazard of micro- and nanoplastic contaminants in our environment). Together with the projects AURORA, IMPTOX, PlasticHeal, PlasticsFatE, the project established the collaborative European research cluster CUSP to understand the health impacts of micro- and nanoplastics (https://cusp-research.eu/). As part of CUSP's aim to investigate and discuss the applicability of existing risk assessment frameworks related to micro- and nanoplastics (MNPs), the CUSP Working Group on Risk Assessment together with the CUSP member projects, has been organising a series of online thematic workshops in spring 2023 under the theme "Human Risk assessment of Micro- and Nanoplastics (MNPs)".
- The first workshop, organised by CUSP and PlasticHeal, focused on regulatory insights and knowledge gaps (07 February 2023). The second workshop within the series was about risk assessment frameworks and was organised by CUSP and PolyRisk (14 March 2023). The third workshop, organised by CUSP and PlasticsFatE, took place on 21 April 2023 and focused on data and information gaps.
- The BfR was a partner in the EU H2020 project NanoInformaTIX, Development and Implementation of a Sustainable Modelling Platform for NanoInformatics, for risk management of engineered nanomaterials (ENM) in industrial manufacturing. The following two scientific articles were published with BfR participation. NanoInformaTIX concluded end of February 2023.
- Amorim, M. J. B., Peijnenburg, W., Greco, D., Saarimäki, L. A., Dumit, V. I., Bahl, A., ... & Scott-Fordsmand, J. J. (2023). Systems toxicology to advance human and environmental hazard assessment: A roadmap for advanced materials. Nano Today, 48, 101735. https://doi.org/10.1016/j.nantod.2022.101735
- Bahl, A., Ibrahim, C., Plate, K., Haase, A., Dengjel, J., Nymark, P., & Dumit, V. I. (2023). PROTEOMAS: a workflow enabling harmonized proteomic meta-analysis and proteomic signature mapping. Journal of Cheminformatics, 15(1), 1-17. https://doi.org/10.1186/s13321-023-00710-2

- The BfR was also part of the EU H2020 project Gov4Nano (Project end: February 2023). Here, the AdvancedNano GO FAIR Implementation Network (https://www.go-fair.org/implementation-networks/overview/advancednano/) was initiated. The Action Plan of the Implementation Network was published:
- Dumit, Verónica I., Ammar, Ammar, Bakker, Martine, Bañares, Miguel A., Bossa, Cecilia, Costa, Anna, Cowie, Hilary, Drobne, Damjana, Exner, Thomas E., Farcal, Lucian, Friedrichs, Steffi, Furxhi, Irini, Grafström, Roland, Haase, Andrea, Himly, Martin, Jeliazkova, Nina, Lynch, Iseult, Maier, Dieter, Noorlander, Cornelle W., … Nymark, Penny. (2023). From Principles to Reality. FAIR Implementation in the Nanosafety Community (Version v1). Zenodo. https://doi.org/10.5281/zenodo.7614989

- On initiative of the German Federal Ministry of Food and Agriculture and of the German Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection, the BfR is working on the development of a risk assessment of tattoo ink pigments. In this context, a BfR statement on minimum requirements and test methods with emphasis on necessary tattoo ink specifications has been published (https://mobil.bfr.bund.de/cm/349/tattoo-inks-minimum-requirements-and-test-methods.pdf). The document is being developed further in the frame of the newly established BfR Commission for Tattoo Inks. Furthermore, a cooperation with the Fraunhofer Institute for Microengineering and Microsystems IMM was established to investigate the dynamic dissolution of tattoo ink pigments.

7.4 Italy

ISS (Environment and Health Dept.) and ISPRA (Section of Hazardous Substances) provided support for the presentation of the four-year project approved by the Ministry of Health, as part of the National Plan for Complementary Investments (PNC) for Health, Environment, Biodiversity and Climate. The contribution to the project, entitled "Biomonitoring of biodegradable micro and nanoplastics: from the environment to man in a one health perspective (BioPlast4SAFE), AREA B 14. Applied research for the assessment of the impact of environmental risks on health" provides the evaluation of the environmental risks of chemical substances and the evaluation of the health risk derived from the indirect human exposure through the environment, in accordance with the European Regulations: Reg. (CE) n. 1907/2006 (REACH) and Reg. (CE) n. 1272/2008 (CLP), in particular related to the emerging risks associated with the micro- and nano-forms of plastics. The project is coordinated by the Campania region and includes the participation of University Federico II of Naples, Stazione Zoologica Anton Dohrn, NCR-IPCB, and the Italian regions Lazio and Emilia Romagna.

ISS (Enviroment and Health Dept.) participated in the EU project Gov4nano, particularly in activities addressing the challenge of advancing nanosafety data FAIRness, for maximizing their availability, understanding, exchange and ultimately their reuse. The final consortium meeting of the project was hosted by ISS (Rome 14-15 February 2023) Moreover, in the context of Gov4nano, ISS participated in the development of policy briefs, in particular on "Implementation of FAIR Principles in Nanosafety Data Management".

ISS is collaborating in AdvancedNano Implementation Network initiative, whose main objectives are described in the paper: “From principles to reality. FAIR implementation in the nanosafety community” Dumit V.I. et al, NanoToday 2023; https://doi.org/10.1016/j.nantod.2023.101923

ISS collaborated in the organization of the workshop "Current status and future challenges of genotoxicity test guidelines (TGs) for nanomaterials”, 24th January 2023, OECD (Paris)", and related publication: “Current status and future challenges of genotoxicity OECD Test Guidelines for nanomaterials: a workshop report” Doak S.A. et al. Mutagenesis 2023; https://doi.org/10.1093/mutage/gead017.

The Italian Workers’ Compensation Authority (INAIL) is coordinating the research project on “Training on emerging risks in R&D and production of nanomaterials and advanced materials: providing systematic approaches to deal with uncertainties (Nano-AM OSH Training)”, co-funded by the Partnership for European Research in Occupational Safety and Health (PEROSH). The project activities produced a first deliverable entitled “Training practices on nanomaterials and advanced materials for workers safety and health: stakeholders consultation report”, available at https://perosh.eu/repository/training-practices-on-nanomaterials-and-advanced-materials

At ISS (Food Safety, Nutrition and Veterinary Public Health Dept) were concluded experiments related to the NANOPERSIST project, an ISS-EC JRC collaboration under the Framework for access to the Joint Research Centre physical Research Infrastructures of the European Commission (Research Infrastructure Access Agreement N 35050/5). The project was focused on the NPs persistence after gastrointestinal digestion. Its main outputs are reported in the paper: “Agglomeration Behavior and Fate of Food-Grade Titanium Dioxide in Human Gastrointestinal Digestion and in the Lysosomal Environment”. Ferraris F., Raggi A., Ponti J., Mehn D., Gilliland D., Savini S., Iacoponi F., Aureli F., Calzolai L. and Cubadda F. Nanomaterials (2023), 13: 1908. https://doi.org/10.3390/nano13131908

The project NANOCELLUP - Use of New Approach methodologies (NAMs) for the hazard assessment of nanofibers - funded by EFSA (European Food Safety Authority), has recently been completed. ISS leaded the Lot 1 on “Nanocellulose oral exposure: gastrointestinal digestion, nanofibers uptake and local effects”. Goal and results of this unit are available at https://www.iss.it/en/progetto-nanocellup.

The ISS - Food Safety, Nutrition and Veterinary Public Health Dept – coordinates the Lot 3 of the EFSA project: NAMS4NANO - Integration of New Approach Methodologies results in chemical risk assessments: Case studies addressing nanoscale considerations. In particular, the Lot 3 - Methodological and generic case studies - focuses on five methodological and cross-cutting case studies. They do not cover a full risk assessment for a specific material; rather they aim to methodological progress and update of the EFSA guidance documents on nanospecific risk assessment. More information is available at: https://www.iss.it/en/nams4nano-il-progetto.

Italian research and industrial groups continue their efforts in the following ongoing EU projects: ASINA (NRC-ISTEC, University Milano Bicocca, Colorobbia, Warrant Hub, Angel-consulting), NanoHarmony (ISS, EcamRicert, IIT), SAbyNA (CNR-ISTEC), CHALLENGES (La Sapienza Università di Roma coordinator, NRC-IMM, Applied Materials Italia, beWarrant), CHARISMA (Università degli Studi di Milano), LightMe (Politecnico of Milan, coordinator, IRIS, MBN Nanomaterialia, STAM), SbD4Nano (AcZon, Ambrosialab, NanoVector, ART-ER)

7.5 Korea

Ministry of Environment (MOE)

A research project on the environmental monitoring, exposure, and toxicity of tier-wear nanoparticles, including carbon black, was initiated in 2022 in the National Institute of Environmental Research (NIER) within the MOE. The expected outcome of this project is to estimate the potential human health impacts resulting from inhalation exposure, as well as direct and indirect ecological impacts. Additionally, the project aims to set out a plan on strategies for health and safety management concerning road-wear nanoparticles exposure in South Korea. This year, NIER is evaluating acute inhalation toxicity and exploring alternative methods to animal experiments for assessing a mixture of tire-wear particles and heavy metals in the atmosphere.

MOE has established the 3rd master plan of nano-safety management, which provides support to the comprehensive national plan for nano-technology development since 2012. The 2nd master plan was jointly established at an inter-ministerial level. The 2nd plan was established jointly at an inter-ministerial level in 2017. According to these plans, the guideline on national nanomaterial definitions was developed. After the year 2015, three Acts were enacted to regulate the definition of nanomaterials: the Act on the Registration and Evaluation, etc. of Chemicals (K-REACH), the Consumer Chemical Products and Biocides Safety Control Act (K-BPR), and the Chemical Substances Control Act (CSCA). Under K-REACH, nanomaterials are substances that are subject to a government-led hazard assessment.

There are ongoing activities, such as the investigation of regular distribution inventory, the development of nano-registration guidance, and the registration of nanomaterials. Under K-BPR, nanomaterials are included in statistical surveys with a two-year cycle of distribution survey. The CSCA implements a reporting system for nanomaterials present in consumer chemical products and requires nanomaterial labelling.

MOE is currently working on revising the definition of nanomaterials within the three Acts, as well as establishing nano-safety management (‘24~’26), for priority nanomaterials and consumer chemical products including monitoring nanomaterials in the environment and products, assessing exposure, characterizing nanomaterial properties, and conducting comprehensive risk assessment within the domestic circumstances of South Korea.

Ministry of Food and Drug Safety (MFDS)

MFDS plans to conduct the immunotoxicity study on nanomaterials in food and drug from 2022 to 2024, evaluates the damage to the immune system when exposed to nanomaterials to propose guidelines for immunotoxicity of nanomaterials based on specific considerations.

MFDS conducted international joint research of "Scientific document to support OECD activities on the development of TG on toxicokinetics of ENMs", an OECD WPMN NanoHarmony project hosted by Netherland and United Kingdom and participated by Germany and Italy, for three years from 2020 to 2022. Through the international joint research, the results of the toxicokinetic study by oral administration of silica dioxide nanomaterials were derived, and this was provided to the OECD WPMN NanoHarmony. Based on this, the final report of NanoHarmony D1.6/7 is scheduled to be completed in August 2023.

7.6 The Netherlands

In close collaboration, the three H2020-projects Gov4Nano, NANORIGO and RiskGONE have gained a tremendous **knowledge on risk governance and risk assessment of nanomaterials**, including meaningful insights about risk governance challenges and issues. These insights are considered relevant for efficient and effective risk governance of advanced (nano)materials. They are reported in a memorandum on risk governance of advanced materials that suggests four lines of policy actions to fill gaps regarding knowledge, connection with innovation policies and regarding harmonization and standardization. With this memorandum the projects aim to raise awareness that the specific issues regarding safety (and sustainability) of advanced (nano)materials are not automatically covered in projects and activities under the European Green Deal - Chemicals Strategy for Sustainability (CSS). Furthermore, the projects aim to gain active support for the identified lines of action from stakeholders, including the European Commission, Member States, industry, the research community, and NGOs. The memorandum served as a key background document for the projects' **joint conference in Paris**. For this conference, the projects gathered a broad range of different experts and stakeholders to discuss the key results. Four multistakeholder roundtables were organised here to discuss different thematic areas: 1) Harmonisation & Standardisation, where we need to reduce the pacing problem of test methods by fostering early awareness and harmonisation and standardisation, 2) Risk Governance Portal and Tools, where there is a need for a common platform to find developed and emerging tools that can support a sustainable future, 3) Data Management, where data/knowledge sharing, ontologies and platforms need to be in place for future development of FAIR data, and 4) Organisation of Risk Governance, where there is a need to choose the appropriate organisational form to support the implementation of various initiatives for advanced materials and foster co-creation among stakeholders. Outcomes of the projects and the Paris discussions were presented in an online event on "Future-proof Approaches for Risk Governance". A summary document will be published shortly. In addition, a publication will be prepared for a special issue of NanoImpact towards the end of 2023.

PeroCUBE brings together top experts and pioneers in upscaling of the LED and PV technology and the top groups in perovskites materials and perovskite processing for device manufacturing. TNO (The Netherlands) leads WP7 'Human Health Risk assessment and LCA' to assess the potential human health risks. This WP also will provide a **life cycle assessment to balance the risks and benefits of the application of nano-perovskites in lighting and energy harvesting applications**. WP7 followed a Tiered Risk Assessment approach that started with a qualitative assessment at the start of the project, while the LED and PV devices were still in early development stages. Currently the project moves towards its final year in which the devices are being fabricated and tested and hence a quantitative human health risk assessment and LCA are being performed.

Initiated by RIVM, an international team of experts in the field of occupational risk assessment for nanomaterials explored the possibilities to derive **health-based nano reference values (HNRVs) for the**

workplace. Discussions involved experts from the Netherlands (RIVM and University of Amsterdam), Denmark (NRCWE), Spain (LEITAT), United Kingdom (HSE), USA (NIOSH), and Switzerland (SCOEH). In addition, written feedback was provided by experts from UK (HSE), USA (NIOSH), Spain (INSHT), Switzerland (SUVA), Germany (BAuA and DGUV/IFA), Norway (NLIA) and Belgium (VITO). The discussion sessions resulted in a proposal for categorization of nanomaterials in six categories: (1) WHO-fibre-like high-aspect ratio nanomaterials (HARNs), (2) other non-spheroidal nanomaterials, (3) readily soluble spheroidal nanomaterials, (4) biopersistent spheroidal nanomaterials with unknown toxicity and (5) biopersistent spheroidal nanomaterials with and (6) without substance specific toxicity. Details on the categorisation and recommendations for deriving HNRVs are described in an open access scientific paper. RIVM is currently preparing follow-up actions to work out the recommendations of this paper, starting with deriving HNRV values for categories 5 and 6. The same approach of discussions in an international team of experts will be used to achieve this. In addition, a joint workshop with scientific experts and policy makers is foreseen to discuss the support and practicability of the derived values.

In April 2023 the EFSA project **NAMS4NANO** has started. The project aims to facilitate the routine use of **New Approach Methodologies (NAMs) in the (next generation) risk assessment of nanomaterials**. This is a 4-year project divided into three LOTs. LOT1 focuses on (i) complementing the EFSA NAMs roadmap with a review of available NAM-based tools and methods for assessing the toxicity of nanoparticles, in particular those developed by recent EU Research projects, and (ii) developing and implementing a proposal for a "fit for purpose qualification system for NAMs" aimed at facilitating the regulatory use of NAM tools and methods. LOT2 focuses on five case studies using NAMs for addressing the nanoscale considerations and integrating this information with existing information and knowledge for conducting a risk assessment for consumers. LOT3 focuses on five methodological and cross-cutting case studies. These do not cover a full risk assessment for a specific material, rather they aim at methodological progress and update of the EFSA guidance documents on nanospecific risk assessment. Core partners involved in the project are from Germany (BfR), Italy (ISS), the Netherlands (RIVM, WFSR), Belgium (Sciensano, Hasselt University), France (ANSES), and Luxemburg (LIST).

7.7 Sweden

Graphene Flagship

The Graphene Flagship (2013-2023), an EU-funded Future Emerging Technologies (FET) project, is coordinated by Chalmers Technical University in Gothenburg, and the consortium comprises 170 academic and industrial partners. Karolinska Institutet (KI) is engaged in the workpackage on Health & Environment. Recent work in the Flagship has addressed the biocompatibility of 2D materials beyond graphene including transitions metal dichalcogenides (TMDs) such as MoS2 and WS2, as well as hexagonal boron nitride (hBN) (sometimes referred to as "white graphene"). The Flagship has also launched a project called SafeGraph under the so-called spearhead project initiative, and the objective of the latter project is to bring graphene-based products to the market in compliance with regulatory requirements and standard practices. The work is led by TEMAS, a regulatory consultancy company based in Switzerland.

MISTRA

The Swedish Foundation for Strategic Environmental Research (MISTRA) has supported the MISTRA Environmental Nanosafety consortium over the past 8 years through two consecutive grants. The project is coordinated by Lund University and comprises five Swedish and one Danish university, along with industry partners. The project aims to develop research, knowledge and best practices on risks associated with nanomaterials and their impact on the (aquatic) environment. Special focus is dedicated to the role of

the so-called eco-corona on the surface of nanomaterials. Recent work has addressed emerging nanomaterials such as the transition metal carbides and nitrides (also known as MXenes), an emerging class of 2D materials, with respect to its potential ecotoxicological impact (no adverse effects noted thus far).

NanoLund

The NanoLund network at Lund University recently launched the initiative NanoSafe4All (2021-2023) which strives to bring researchers and industry together to address issues related to nanosafety. Other activities include the organization of EuroNanoForum 2023 in connection with the Swedish the presidency of the Council of the European Union. The conference will bring various stakeholders together to discuss developments in nanotechnologies. The event is scheduled to take place from June 11 to June 13, 2023. Session topics include advanced materials and manufacturing, graphene and other 2D materials, safe-and-sustainable-by-design.

7.8 United Kingdom

SUNSHINE

SUNSHINE is a new project that started Jan 2021, and is coordinated by Ca'Foscari University Venice. The project is focused on generating protocols and tools to support safe and sustainability by design (SSbD) of multi-component nanomaterials (or advanced materials). The existing projects GRACIOUS and PATROLS will feed into this project. The GRACIOUS Framework for grouping and read-across will be further developed to allow consideration of potential grouping and read-across of multi-component nanomaterials, including development of the Integrated Approaches to Testing and Assessments (IATAs) that support tailored identification and generation of the information needed. SUNSHINE has so far adapted the GRACIOUS grouping hypothesis template for simple nanomaterials to make it suitable for multicomponent nanomaterials. In addition, more detail has been added to the template, to help the user generate a clear hypothesis wording, as well as design the IATA to test the hypothesis. Most of the case studies in SUNSHINE are either a core material with a coating, or a mixture of components throughout the nanomaterial structure. In collaboration with HARMLESS, the suitability for this template may be considered for a wider array of advanced materials.

The UK Nanosafety group is reviewing its guidelines: "Working safely with Nanomaterials in Research & Development".

7.9 European Union

Horizon Europe Strategic Plan 2025–2027 Analysis: published on 25 May 2023, highlights the importance to continue strengthening the EU's capacity to ensure adequate reskilling/upskilling of the workforce; to support socioeconomic transformations in a fair manner; to develop and implement advanced materials, technologies, and processes; and to stay competitive and avoid future strategic dependencies. Detailed information about advanced materials gap analysis within Cluster 4 – digital, industry and space of Horizon Europe is provided in Table 19 (starting on p. 137).

Horizon Europe Cluster 4 Work Programme:

In 2023-2024, the work programme had 3 dedicated topics on **advanced materials** (and nanomaterials) as well as a coordination and support action, all of which refer to the **SSbD** framework.

- Bioinspired and biomimetic materials for sustainable textiles
- Smart sensors for the Electronic Appliances market
- Advanced (nano and bio-based) materials for sustainable agriculture
- Coordination and knowledge sharing across materials development communities

Moreover, there are 3 dedicated topics for the development of **SSbD tools.**

- Innovative methods for safety and sustainability assessments of chemicals and materials
- Integrated approach for impact assessment of safe and sustainable chemicals and materials
- Computational models for the development of safe and sustainable by design chemicals and materials

In 2024 there will be a call with 2 topics on advanced materials (Advanced biomaterials for the Health Care and Biodegradable polymers for sustainable packaging materials) and 1 topic on SSbD (Development of safe and sustainable by design alternatives).

There are 5 new projects funded under the topic **HORIZON-CL4-2022-DIGITAL-EMERGING-01-35**: Advanced characterisation methodologies to assess and predict the health and environmental risks of nanomaterials (RIA), which will:

- develop high-resolution imaging methods;
- increase availability of validated protocols to advance both nanosafety studies and material characterization;
- ensure appropriate control experiments and more realistic in vitro models;
- deliver reliable data and improved data reporting guidelines, supported by computational modelling;
- develop harmonized standardized test methods;
- and increase the efficiency and effectiveness of materials and product development by reducing costs and time for product design, time-to-market and regulatory compliance.

The funded projects are:

- ACCORDs: tested material is graphene as representative of 2D material.

  Major expected outputs: decision support framework and guidance; reference 2D nanomaterials and reference tests; atlas with reference images for decision making; and proposal for standards and guideline.
- iCARE: test materials include graphene, graphene oxide, silver, silicon oxide, etc.

  Major expected outputs: realistic and high-throughput in vitro models for neuro-nanosafety studies, in vitro and in vivo; bridging models for neuro-nanotoxicity in human and environmental health; comprehensive in silico framework for data consolidation, analysis, and read-across methods.
- MACRAME: materials selection includes graphene-related material, carbon nanofibres, and nanotubes, poly lactic-co-glycolic acid (nano)particles.

  Main expected outputs: proposals for harmonisation and (pre-)standardisation projects to be provided to and further elaborated with the relevant bodies, (i.e., OECD, VAMAS/CEN/ISO).
- nanoPASS: test materials include 40+ benchmark nanomaterials with in vivo data from previous EU projects and 5 industrial materials: cement, plastics, electronics, catalysis, medical.

  Main expected outputs: new in vitro models of key events; new detection of key event dynamics; new outcome prediction algorithms; calibration against in vivo data; and validation with industrial cases.

- POTENTIAL: test materials include graphene, perovskites, advanced polymer/lipid nanoparticles with encapsulated metal/metal oxide nanoparticles, micro-and nano-plastics.

  Main expected outputs: harmonization of protocols; advance analytical and imaging-based approaches for detection and quantification.

7.10 Malaysia

Malaysia's four-year nationwide project to benchmark risks of nano-based products is due to end in 2023. An inventory of locally available nano-based products has been established. Primary data of physical-chemical, toxicology, ecotoxicology, environmental effects and life cycle assessment (LCA) studies on selected products, based on specific criteria including product category, nanomaterial in use and exposure risk are being compiled. These studies were conducted in accredited laboratories and GLP certified facilities according to OECD Test Guidelines and ISO standards. The safety data will be uploaded into an online Nanosafety Referral System (NRS) as reference for regulators, industries, academicians, and the public. From this study, NNC will propose the development of a new Malaysian Standard (MS) on the technical verification of products with 'nano' claims.

NNC will seek collaborations with related national departments and agencies to expand NRS through the inclusion of nano-products within the ASEAN region.

NNC has approached UNITAR to jointly organize a Nanosafety Course, almost similar to the one held in Putrajaya in 2018. Participations will be extended to neighbouring countries.

7.11 Business at OECD (BIAC)

As part of the MALTA Initiative and on behalf of its members, the **NIA** has provided comments to the European Commission on the lack of funding in the first and upcoming Horizon Europe Work Programmes to help support developing future Test Guidelines. The NIA has also consistently linked this issue to the broader policy and regulatory debate (e.g., revision of the REACH or Cosmetic Products Regulations, implementation of the Safe- and Sustainable-by-Design Framework), noting how nano-adapted TGs will be essential to facilitate compliance as well as to ensure the sustainability transition of European industry.

The NIA has also been participating in the International Network Initiative on Safe and Sustainable Nanotechnologies (INISS-nano), aimed at fostering global collaboration in areas of relevance to nanomaterials including standardisation and TGs development.

8 Developments and/ or research related to Safe(r) and Sustainable Innovation Approaches, Safe-by-Design and/or other anticipatory strategies relevant for (advanced) (nano) materials

8.1 Germany

Federal Institute for Risk Assessment (BfR)

The BfR is involved in the following developments or research related to SIA or other anticipatory strategies relevant:

- The German Higher Federal Authorities BAuA, BfR and UBA contributed to the brochure prepared by RIVM regarding a proposal for an early awareness and action system for advanced materials. The proposed system is intended to identify, describe, and prioritise warnings related to safety and sustainability of advanced materials, but also to inform decision makers, policy makers, and regulators so that timely action can be taken to prevent or mitigate safety and/or sustainability issues. (DOI: 10.21945/brochure-advanced-materials).
- NanoHarmony, NanoMet contribute to the interlaboratory comparison (ILC) for the OECD projects 1.5 "Determination of solubility and dissolution rate of nanomaterials in water and relevant synthetic biological media" and 1.6 "Identification and quantification of surface chemistry and coatings on nanoscale and microscale materials". For project 1.5, the first ILC round is currently underway with four different solubility/dissolution experiments (inhalation and oral route; static/dynamic approach); the second round is planned for summer 2023. For project 1.6, the first round of ILC has been completed, and data evaluation and the second round of ILC has started.

8.2 Italy

The EU Horizon 2020 project SUNSHINE (GA No. 952924) aims to develop and implement Safe and Sustainable by Design (SSbD) strategies for products enabled by (advanced) multi-component nanomaterials (MCNM). Currently, GreenDecision srl (Italy) collaborates with EMERGE (Bulgaria) in coordinating the task related to the development of a tiered approach for SSbD to promote the design of safer and more sustainable MCNM-based materials and products. This approach uses screening-level qualitative (Tier 1) and semi-quantitative (Tier 2) methods to assess safety, functionality and sustainability

at the early stages of product development, and quantitative (Tier 3) assessment methods for the later stages. Tier 1 is a self-assessment methodology for industries (esp. SMEs) targeting the initial R&D steps, where quantitative information along the material/product lifecycle is partial or even missing. The goal is to identify potential safety and sustainability concerns, information gaps and regulatory needs to inform more detailed analysis in the higher tiers.

Early4AdMa and the SUNSHINE TIER 1 methodology are complementary but share common elements. It has been discussed and agreed to work on common application of the two methodologies to 2 case study materials from the SUNSHINE project to identify similarities and complementarities, better target the two approaches to relevant users and identify future areas for collaboration within the frame of the OECD WPMN. This joint work is planned in the period of July 2023 to April 2024.

8.3 The Netherlands

The first web application prototype for the **SUNSHINE e-infrastructure** is completed. The e-infrastructure brings together results from several EU research projects and integrates functionality, and data and models related to safety (risk) and sustainability. The data are linked to external sources such as E-NanoMapper and NanoPharos databases, and to internal sources including the SUNSHINE open & FAIR database. Blockchain is used for secure /controlled date exchange. The models used include those from the NanoInformatix platform and SUNDS. The assessments in the e-infrastructure include stage-gate approach, lifecycle thinking approach, safety (risk) assessment, sustainability assessment, and comparison of SSbD alternatives. A deliverable (D4.2) was completed with an inventory of relevant properties and interactions that arise or are enhanced due to multicomponent nature of the materials (functionality). There were 21 properties identified which were relevant to new or enhanced properties. The deliverable shows whether these **properties and interactions affect their EHS risks** qualitatively assesses by investigating impact ‘release’, ‘where they go’ and ‘what they do’. This work is ongoing and assessment is informed by evidence of mechanisms and examples. Finally, the deliverable identifies how information can be used in risk assessment, as well as grouping, read-across, and similarity assessment of multi-component nanomaterials. Some general observations include that mechanical properties can have large impact on ‘where they go’, reactive properties can have large impact on ‘what they do’. Optical properties have limited impact, except for increased reactivity (‘what they do’) in case of exposure to light. A publication of this work is in progress.

A **SUNSHINE-HARMLESS-DIAGONAL collaboration** is ongoing on grouping hypotheses for multicomponent nanomaterials and development of IATAs to generate the data needed for hypothesis-driven grouping of these types of materials. An important discussion is the absence of a formal definition of the term multicomponent nanomaterial within any global regulation or other legislative tool. Identified related terms include hybrid nanomaterial, nanohybrids, nanocomposites, multifunctional nanoparticles, multicomponent nanostructure, smart multifunctional nanoparticles, and advanced material. But also for these formal definitions are generally lacking. A deliverable is now completed evaluating how MCNMs are addressed/covered by EU regulations and guidance documents.

In the InteRnational Safe and Sustainable by design materials ecosystem (**IRISS**), a mapping assessment and **gap analysis** was done for: i) methods and criteria of existing safe and sustainable by design (SSbD) approaches, covering safe materials, processes and products, including environmental impact, lifecycle costing and social impact; ii) alternative business models and service/functioning to reduce flows of materials, processes and products including their diversity, complexity, and dynamics in space and time; iii) tools for developing products and processes, considering sustainability and system approaches to achieve safer, functional, recyclable or degradable products, maximising lifetime and minimizing energy use; and iv) criteria and methods of applying circular economy to recycling, specifically mapping methods for improving recycling, performance and product use longevity, including proposals for products that

cannot be circulated where concepts such as (bio)degradability and non-ecotoxicity could play an important role. **Value chain perspectives** with regards to SSbD were obtained during several IRISS workshops in 2022 and 2023 with the following value chains: Packaging (IPC; Industrial Technical Centre for Plastics and Composites); Textiles (ETP; EU Technology Platform for the Future of Textiles & Clothing); Construction (EFCC; European Federation for Construction Chemicals); Automotive (CLEPA; European Association of Automotive Suppliers); Energy materials (EMIRI; Energy Materials Industrial Research Initiative); Electronics (INL; International Iberian Nanotechnology Laboratory); and Fragrances (IFRA, International Fragrance Association). The main workshop was held online on 25 November 2022 where 417 registrants attended. This resulted in the development of a **draft SSbD generic roadmap** with agendas on needs for research, skills, competence and education and knowledge sharing. Seven **value chain specific SSbD draft roadmaps** have also been developed. Since January 2023, a RTD-JRC-IRISS-PARC expert group was established to create effective synergies around SSbD activities (for instance for supporting the EC JRC SSbD framework and the Commission Recommendation on Safe and sustainable by design).

SbD4Nano is an industrially oriented project, where recognized research and technology organisations in Nanosafety cooperate with SMEs and large industries to validate specific case studies, used in the implementation of new Safe-by-Design (SbD) approaches and tools. TNO (the Netherlands) is involved in almost all work packages and leads WP4 'Safe by process design: exposure assessment and risk management'. In this WP we develop a newly tested and calibrated cost driven exposure model to **predict the effectiveness of Risk Management Measures** (RMM) to design a safe process with a data e-infrastructure with updated databases consisting of release, exposure and RMM effectiveness information that will support an exposure-driven safe-by-process-design modelling framework as key outcome. Other WPs in which TNO is involved are: WP1 Data management and nanosafety resources integration, WP3 Safe by material design, WP5 SbD computing infrastructure design and development, WP6 Industrial implementation and validation, WP7 Stakeholder engagement.

HARMLESS provides novel tools, guidance and decision support for balancing functionality versus risk to ensure that the next generation nanomaterials will be harmless. TNO (the Netherlands) leads WP 5 on 'Tool Development', which aims to build a user friendly SbD Decision Support System (DSS) for complex High Aspect Ratio Nanomaterials (HARNs) and multi-component Engineered NanoMaterials (ENMs). TNO integrates HARMLESS methods and components developed in other WPs of the project into a **user-friendly SbD decision support system** (DSS), which builds on the NanoRisk Governance Portal that was developed in the caLIBRAte project and used in the NMBP-13 Nano Risk Governance projects. TNO applies artificial intelligence (AI) and bioinformatics tools, such as machine learning for purposes such as ranking and prioritization. We use the data generated with New Approach Methodologies (NAMs) to build and improve models for the more complex HARNs and multi-component ENMs.

In May 2019, **SPINE**, the Safe-and-Sustainable-by-Design (SSbD) Policy International Network, was established by the Dutch Ministry of Infrastructure and Water Management. A SSbD network for policy makers is important to facilitate knowledge sharing and exchanging expertise between European policy makers on the development of the SSbD, also in order to establish a safe and circular economy. SPINE will focus on **further development and implementation of SSbD within several domains**. Currently participating countries are Austria, Denmark, Estonia, Germany, Netherlands, Spain, Sweden, Switzerland, and the UK. Other countries are invited to join the SPINE network. For now, SPINE serves as an ad hoc network, without formal status. In July 2021, SPINE was asked to join IRISS as an associated partner. The scope of the InteRnational Safe and Sustainable by design materials ecosystem (IRISS) is to establish a self-sustained international and inclusive network of experts and stakeholders in the materials community. This aims to enable multidisciplinary design processes, map skills mismatches and competence gaps, to allow transition towards an overarching framework in which sustainability is the essential entry point into markets. Furthermore, SPINE is connected with the OECD WPMN, DG RTD, DG

ENV, PARC, AMI2030 and other relevant organisations and initiatives to exchange information regarding the SSbD actions on an international level. SPINE is in contact with the European Commission (DG RTD).

As acknowledged again in a recent comparative analysis of SSbD frameworks performed in the IRISS project (Apel et al., under review); education remains a strong potential source of inertia around the implementation of SSbD. The RIVM invests in developing attention for SSbD in higher (vocational) education to resolve this potential source of inertia and several significant developments have been made over the last 2 years with regard to this aim. Several academic and applied science universities have (expressed interest to) adopt(ed) attention for SbD within ongoing or new programs around, biotechnology, (sustainable) chemistry or multidisciplinary programs around emerging technologies. Often alongside attention for green chemistry, benign by design, sustainable and circular by design. The University of Delft will organize the third consecutive SbD PhD course in collaboration with the RIVM which attracts a multi-disciplinary audience from materials, biotechnology and engineering disciplines. From 2023 onwards SbD should be an established, albeit limited, part of curricula in at least 6 institutes. The RIVM itself has further developed a teaching materials portfolio that consists of animations, exercise and short video lectures introducing the general ideas behind SbD. Domain specific materials tailored to SbD in biotechnology and in nanotechnology development are available as well, including reading materials, case study exercises and a serious game. A recent addition to this portfolio resulted from the development of insights from the NanoReg2 project into several nanotechnology SbD case study exercises. Within a European context the RIVM contributes to education work packages in both IRISS and PARC which currently emphasises mapping of needs, inventorying relevant teaching programs and establishing an SSbD learning agenda. From 2024 onwards focus is likely to move towards development of a learning infrastructure and teaching programs tailored specifically to SSbD.

The EU-project **SAbyNA** focusses on the implementation of safe-and-sustainable-by-design (SSbD) for nanoforms (NF), nano-enabled products (NEPs), and processes. To this end, a user-friendly e-infrastructure is developed that assists developers and innovators (from industry) in a tiered approach to **identify and implement SSbD interventions** for their material, product or process. An important part of SSbD principles involves hazard assessment. A hazard assessment strategy is developed that can be used at an early stage of product innovation.

The **hazard assessment strategy** consists of 2 parts. Part 1 gathers basic information on the NF or NEPs, including physicochemical properties and intended application, and aligns this with potential exposure routes and environmental compartments. Clear hazard concerns are identified as red flags. In Part 2 the user will be guided through a stepwise approach to gather information from data sources and/or to generate new hazard data specific for the exposure routes/environmental compartments of concern. A testing strategy is suggested to help the user generate missing data. For **human health**, data on dissolution rate in physiological fluids, cytotoxicity, genotoxicity, oxidative potential and inflammation are gathered. For **environmental safety**, data on biodegradation, bioaccumulation, acute and chronic toxicity to aquatic and terrestrial organisms are gathered. Guidance is provided on which assays to use, including standard operation procedures (SOPs) for testing NEPs and how to interpret data for SSbD. Finally, SSbD interventions/design changes are proposed to reduce potential hazard.

8.4 Sweden

SweNanoSafe

SweNanoSafe has published two reports in 2022 related to sustainability and the SSbD concept:

- SweNanoSafe Report 2022:01 “Safe-and-Sustainable-by-Design: a prerequisite for achieving a circular economy - a report from SweNanoSafe’s workshop”

- SweNanoSafe Report 2022:02 “Nanosafety, the Sustainable Development Goals and meeting EU policy ambitions”

IRISS

The H2020 project IRISS (“The international ecosystem for accelerating the transition to safe-and-sustainable-by-design materials, products and processes”) was launched in 2022 and is coordinated by the Swedish Environmental Research Institute (IVL). The stated aims are to connect, synergize, and transform the safe-and-sustainable-by-design community in Europe and globally towards a lifecycle approach, with a holistic integration of safety, climate neutrality, circularity, and functionality at an early stage of designing and manufacturing materials, products, and processes. The planned work includes case studies on value chains relevant to nanomaterials and advanced materials, such as packaging, textiles, and energy materials.

PARC

The Institute of Environmental Medicine (IMM), a department at Karolinska Institutet and a national institute for risk assessment, is involved in the H2020 project “Partnership for the Assessment of Risk from Chemicals” (PARC). Contributions include activities relating to nanosafety, e.g., developments in findable, accessible, interoperable, and reusable (FAIR) data, as well as tools and approaches applicable to safe-and-sustainable-by-design (SSbD) processes.

8.5 European Union

The **Commission Recommendation 2022/2510** (EUR-Lex - 32022H2510 - EN - EUR-Lex (europa.eu) proposed a European ‘safe and sustainable by design’ framework for chemicals and materials (including advanced materials). This framework is to be used as a reference point by Member States, academia industry and research and technology organisations.

The Recommendation has announced a **testing phase** of the framework, which will be run during 2023-2024. This will take the form of voluntary reporting process. Feedback collected during these testing phases will help the Commission to assess additional safety and sustainability elements and improve the relevance, reliability, and operability of the framework.

The **first reporting period** of the testing phase is underway (until 30 June 2023 - EUSurvey - Survey (europa.eu)). The Commission encourages all relevant stakeholders (including the ones working on advanced materials or nanomaterials to contribute to the testing phase with case studies. A second reporting period will take place in 2024.

JRC published **Technical Reports** on the development of a framework for achieving Safe and Sustainable by Design chemicals as announced in the EU Chemicals Strategy for Sustainability:

- EC-JRC, **Safe and sustainable by design chemicals and materials: review of safety and sustainability dimensions, aspects, methods, indicators, and tools**, Publications Office of the European Union, March 2022, https://data.europa.eu/doi/10.2760/879069
- EC-JRC, **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, July 2022, https://data.europa.eu/doi/10.2760/487955

The EC Recommendation “establishing a European assessment framework for ‘safe and sustainable by design’ chemicals and materials” (C(2022) 8854 final) published on 8 December 2022 is based on the JRC Technical Reports mentioned above. The recommendation sets a two year testing period of the framework.

It also invites member states, industry, academia and RTOs to test the framework and provide feedback to be able to improve its relevance, reliability and operability in order to stablish the framework in R&I activities.

Since then, the JRC has been working on the application/implementation of the framework on real case studies. **The technical report on the case studies will be published soon**.

The JRC developed a **reporting template** that is now **available in** the SSbD website Safe and sustainable by design (europa.eu).for the collection of feedback during the testing period which started on the 5th of May and will last till the 28th of July.

The JRC is supporting and **collaborating with PARC and IRISS in the operationalisation of the SSbD** framework. In this context the JRC is in collaboration with PARC for the development of a **SSbD training school** programme.

8.6 Business at OECD (BIAC)

The NIA contributes to the development of SbD strategies through its participation at the WPMN SG on Safer Innovation Approach, where NIA actively participates in three out of 4 tasks. The NIA then collects and shares information with its members at dedicated webinars and through surveys. In this reporting period we collected from members their views on the Early4AdMa scheme as well as on Trusted Environments in collaboration with the HE project SUNSHINE.

The NIA has also been involved in the ongoing European Commission and JRC's work on the development of SSbD criteria for the chemicals sector, providing comments as requested by the JRC on the adaptability of the proposed framework to nanomaterials.

9 Additional Information

9.1 Austria

The 16th International Nano Authorities Dialogue ("Behördendialog") will be hosted by the Austrian Ministry for Climate Action, Environment, Energy, Mobility, Innovation and Technology in Vienna on 15th September 2023 (main language: German; participating countries: Germany, Liechtenstein, Luxemburg, Switzerland).

The 15th NanoTrust annual conference in Vienna under the central topic "Technology Assessment and Governance of Emerging Technologies)" will be organised by NanoTrust in the new premises of the Austrian Academy of Sciences ("Academy Campus", Bäckerstraße 13, 1010 Vienna) on 14th September 2023. In the evening of the 14th of September NanoTrust will celebrate the 15th anniversary and 10 years existence of the Austrian Nanoinformation Commission.

9.2 Germany

Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection (BMUV)

International Conference "How the world deals with materials on the nanoscale"

On 22 and 23 June 2023 the German Ministry of the Environment hosted an International Conference on Nanomaterials that was organised in cooperation with the OECD. With this Germany ended the NanoDialogue - a national stakeholder dialogue to discuss the introduction of nanotechnologies into products and processes, that has been started in 2006. The conference facilitated an exchange about successes and limitations of governance approaches and sustainable uses of nanomaterials. To this end, speakers and audience explored how to address the benefits and risks of nanomaterials by discussing examples from all over the world, including legislative approaches, standardisation, and stakeholder engagement. The background documents and a final documentation will be published here:

https://www.bmuv.de/en/topics/health-chemicals/nanotechnology/the-nanodialogue

EU-Asia-Dialogue on Nanosafety

The German Federal Ministry of Environment hosted the 6th EU-Asia-Dialogue on Nanosafety, that is organised by INISS-nano with the EU NanoSafetyCluster and the Asia Nano Forum. This globally open communication event was held on 21st of June 2023 in Berlin, Germany. Speakers and audience discussed the progress of the actions planned in the INISS-nano-initiative and focused particularly on the role of characterisation. To this end the experts exchanged their views on characterisation items in standardisation, industrial characterisation needs, characterisation facilities and infrastructures, and considered societal and ethical implications.

Malta Initiative

The Malta Initiative has published a Position Paper advocating a European Test Methods Strategy that ensures continuous financial support for the systematic (further) development of OECD TGs. The signatories emphasize that this strategy should also consider and promote international cooperation in the spirit and context of the OECD collaborative effort.

The Malta Initiative Position Paper is publically available on the new website www.malta-initiative.org. The website of the test guideline network has launched it in March 2023 to increase international visibility.

9.3 Italy

On September 2023, INAIL, in cooperation with the Italian Institute of Technology (IIT), will organize a seminar on “Prevention-through-design in the industrial scale up of nanomaterials and advanced materials” during the Nanoinnovation 2023 Conference, to be held in Rome (19-22 September 2023). Main results will be reported of the Prevention-through-Design approach developed in the framework of “Nanokey Advanced” National research project and applied to the manufacturing of graphene and boron nitride case studies at BeDimensional company pilot plant, including promising application in the industrial scale up of such innovation processes.

9.4 European Union

As in previous times, just to raise general awareness on the European Union Observatory for Nanomaterials (EUON), managed by the European Chemicals Agency, with a host of information regarding different aspects: news, nanomaterial market survey, EU regulatory overview, database of substances in nanoform, nanopinions (reflections by different experts from the field) etc.

9.5 Malaysia

The NANOVerify Programme is fostering trust, facilitating trade, and driving nanotechnology growth in Malaysia and the ASEAN region. Through new schemes, strategic thrusts, collaborations, international accreditation, and setting a regional "Gold Standard", the programme is paving the way for a robust nanotechnology landscape. Key highlights of the programme's achievements include: Role in the National Nanotechnology Policy and Strategy 2021-2030 (DSNN)

- The NANOVerify Programme, integral to DSNN's Strategic Thrust 4, Strategy 4.3, provides facilitation to companies producing nano-related products. The medium-term target is to certify an additional 100 products and expand the certification programme into the ASEAN region.
- Introduction of NANOTrust and GRAPHENEVerify Schemes

  Launched on 15th May 2023, these schemes have significantly advanced Malaysia's nanotechnology landscape. NANOTrust expedites verification for Micro, Small and Medium enterprises (MSMEs), while GRAPHENEVerify ensures the quality of graphene in products.
- Pursuit of ISO 17065 Accreditation

  The NANOVerify Programme applied for ISO 17065 accreditation with Standards Malaysia on 8th February 2023. This international standard will enhance the programme's credibility and recognition.
- Establishing a Gold Standard in ASEAN

The collaboration between NANOVERIFY SDN. BHD. (NVSB) and PT NANOTECH INDONESIA GLOBAL (NIG), formalised on 6th June 2023, aims to establish a regional "Gold Standard" in nano product certifications.

9.6 Business at OECD (BIAC)

The NIA has published an Opinion on the SSbD strategy from the Commission and a joint call with a member company for the development of a protocol for the degradation of carbon nanotubes.

The NIA is also involved in stakeholder groups such as the NanoSafety Cluster and the INISS-Nano network, which bring together actors in the nano ecosystem to discuss relevant topics and to promote collaboration and information exchange. Through its “Nano in Action” and “Nano in Business” webinar series, the NIA also organizes events to raise awareness of the enabling potential of nanotechnologies in different application sectors, as well as aspects related to their commercialization.

The NIA is also completing research work on the challenges related to the identification and safety assessment of nanomaterials present in consumer products available to European consumers.

9.7 The International Council on Animal Protection in OECD Programmes (ICAPO)

PETA Science Consortium International e.V. provided funding to the Luxembourg Institute of Science and Technology (LIST) to transition A549 cells, a human lung alveolar-like cell line commonly used in respiratory research, from a culture medium containing fetal bovine serum (FBS) to media without FBS. To demonstrate successful transitioning of cells, their genotype, morphology, and functionality were assessed by monitoring the expression of gene markers for lung cell types, surfactant production, cytokine release, the presence of multilamellar bodies, and cell viability following sodium dodecyl sulphate exposure. Several researchers have expressed interest and are testing the transitioned cells for their work. The manuscript describing the results of this study has been published.

Reference:

Chary, A., Groff, K., Stucki, A. O., Contal, S., Stoffels, C., Cambier, S., Sharma, M., Gutleb, A. C., & Clippinger, A. J. (2022). Maximizing the relevance and reproducibility of A549 cell culture using FBS-free media. Toxicology in vitro: an international journal published in association with BIBRA, 83, 105423. https://doi.org/10.1016/j.tiv.2022.105423

Current processes to validate new approach methodologies (NAMs) are costly, time-consuming, and do not necessarily produce methods that are fit for regulatory purposes. The PETA Science Consortium International e.V. published a paper—with co-authors from the EU Joint Research Centre (JRC), OECD, National Institutes of Health (NIH), US Consumer Product Safety Commission (CPSC), and US Environmental Protection Agency Office of Pesticide Program (OPP) and Office of Pollution Prevention and Toxics (OPPT)—outlining a framework for establishing scientific confidence in testing approaches. The paper builds on previous efforts from the OECD and the International Cooperation on Alternative Test Methods (ICATM) to propose a modern, flexible framework comprising five essential elements to establish scientific confidence in NAMs for regulatory use: fitness for purpose, human biological relevance, technical characterization, data integrity and transparency, and independent review. The framework provides a robust process for evaluating and assessing confidence in new and existing test methods, and its application will accelerate industry uptake and regulatory acceptance of relevant and reliable NAMs, thereby providing better protection of human health.

Reference:

van der Zalm AJ, Barroso J, Browne P, Casey W, Gordon J, Henry TR, Kleinstreuer NC, Lowit AB, Perron M, Clippinger AJ. 2022. A framework for establishing scientific confidence in new approach methodologies. Arch Toxicol. 96(11):2865–2879. https://doi.org/10.1007/s00204-022-03365-4

9.8 UNITAR

In 2022, UNITAR finalised a new version of its e-Learning course on “Nanomaterials safety”. The course is self-paced, takes approximately 30-40 hours to compete and includes videos, interactive lessons, reading materials and quizzes. The three modules cover: Introduction to Manufactured Nanomaterials, Hazard assessment, safety and risks of manufactured nanomaterials, and Risk management of manufactured nanomaterials, including societal dimensions - global approaches. It can be accessed at https://cwcourses.unitar.org/.