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

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Environment Directorate
ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT
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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 22nd WPMN meeting (June 2022). 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.

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1 National developments on human health and environmental safety

1.1. Australia

1. Under the Australian Industrial Chemicals Introduction Scheme (AICIS), assessments of nanomaterials will follow the framework for conventional chemicals, using the internationally harmonised risk assessment paradigm. An introduction at the nanoscale (particle size range of 1 to 100nm) is considered a 'specified class of introduction'. Further details are available at https://www.industrialchemicals.gov.au/help-and-guides/extra-resources-help-you-categorise-your-introduction/categorisation-chemicals-nanoscale

2. AICIS issued two certificates to authorise the introduction of industrial nanomaterials within the last 12 months. One is to authorise introduction of single wall carbon nanotubes (with no assigned CAS number) and the other for multi-layer graphene (with the generic graphene CAS number). The certificate issued for the single wall carbon nanotube (SWCNT) included specific information requirements (SIR) that will be included with the inventory listing (after 5 years, or prior to that if early listing is requested by the applicant). Under SIR the introducers must advise AICIS within 20 working days if the circumstances of their introduction meet the legislated criteria of the SIR and AICIS will determine if a reassessment is required. A defined scope of assessment (DSA) and SIR were included in the certificate of multi-layer graphene. A DSA is a legal obligation for certificate holders to introduce a chemical within the DSA, without further assessment, and will be included in the inventory listing of the chemical. A DSA typically describes introduction volume, uses and concentrations of the chemical in end use products. 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 physical-chemical 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 (details available at Guide to categorising your chemical importation and manufacture | Australian Industrial Chemicals Introduction Scheme (AICIS)) into the appropriate introduction category (that is Exempted, Reported or Assessed), or apply to vary the term of the certificate or the inventory listing.

3. Due to the increasing number of stakeholder enquiries specific guidance was integrated into a decision tree on the AICIS website (available at: Step 4.1 Introductions that are always medium to high risk for human health | Australian Industrial Chemicals Introduction Scheme (AICIS) – See Section C) to assist stakeholders in determining if the chemicals they intended to introduce met the criteria for a 'specified class of introduction' and/or 'certain chemical at the nanoscale'. The guidance also aims to assist stakeholders in determining the level of proof needed to demonstrate their chemical in solid or dispersion form is not a specified class of introduction and/or a certain chemical at the nanoscale.

1.2. Austria

Highlight of developments since the last meeting of the WPMN

4. The 16th International Nano Authorities Dialogue will be hosted by the Austrian ministry for Climate Action, Environment, Energy, Mobility, Innovation and Technology in Vienna in 2023 (main language: German; participating countries: Germany, Liechtenstein, Luxemburg, Switzerland). Several members of Austrian authorities participated actively at the 15th International Nano Authorities Dialogue focusing on enforcement of nanoforms in Lucerne (12th to 13th of May 2022).

5. As a measure of implementation of the Austrian Nanotechnology Action plan (adopted on 2nd March 2010 by the Austrian government, an English and German version can be downloaded on http://www.lebensministerium.at/umwelt/chemikalien/nanotechnologie/nano-aktionsplan.html), the **national NANO Environment Health and Safety programme** (https://www.ffg.at/programme/nano-environment-health-and-safety) has been established which has been prolonged. The Nano-EHS programme is owned by the Austrian Federal Ministry of Climate Action, Environment, Energy, Mobility, Innovation and Technology (www.bmk.gv.at) and is handled by the FFG - Austrian Research Promotion Agency. The 9th call has been announced in December 2021 and has been closed in March 2022. Research focus has been laid on (1) safe-and-sustainable by design related to the European Chemical Strategy and (2) on the potentials of nanocarriers. A final decision can be expected before summer 2022. The transnational SAF€RA Joint Call for tenders has started recently. It is possible to submit innovative, cooperative R&D projects in the call for proposals “Industrial safety in the context of the sustainability imperative” and “Safety of advanced materials in energy conversion and storage applications”. Submission in the first stage is possible on a transnational level until September 5, 2022. In the second stage, submissions can be made at the transnational level by December 1, 2022.

National developments on human health and environmental safety

6. 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 2023) and consists of more than 30 members 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 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”. 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 are released: https://www.oeaw.ac.at/ita/publikationen/publikationsreihen/nanotrust-dossiers (german version) and https://www.oeaw.ac.at/en/ita/publications/publication-series/nanotrust-dossiers (english version). Recent publications are available on “Advanced Materials for innovative solar cell technologies” (part I and II, NanoTrust-Dossier Nos. 56 and 57) and “Advanced Materials” (NanoTrust-Dossier No. 58).This publication series will be continued. Several scientific papers (on nanoregisters and

the safe-by-design-concept) have been published by Nanotrust's co-worker Anna Pavlicek[1]. The project NanoTrust-Advanced and all its activities are accessible by its new website (landing page): https://www.oeaw.ac.at/ita/nanotrust.

7. NanoTrust-Advanced joined the **OECD-BNCT**[2] 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.

1.3. Belgium

8. 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.

9. The annual report for 2020 has been prepared and is already published. The 2021 report is now in preparation. A very short summary of the 2020 results is given in the next paragraph:

10. For the calendar year 2020, 661 registrations were submitted by 187 registrants. These registrations involve about 130 different chemical substances (based on CAS-number). In total, 96.867,42 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), sodium hydrogencarbonate, diiron trioxide and Pigment Blue 15. These numbers result only from the registrations submitted for nanomaterials, and placed on the market as substances.

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

1.4. Canada

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

12. The New Substances program is responsible for administering the New Substances Notification Regulations (Chemicals and Polymers) [NSNR(C&P)] of *the Canadian Environmental Protection Act* (CEPA). These regulations ensure that no new substances (chemicals or polymers) are introduced into the Canadian marketplace before undergoing ecological and human health risk assessments, and that any appropriate or required control measures have been taken. In total, Canada has assessed 20

[1] Pavlicek et al. (2021). Testing the Applicability of the Safe-by-Design Concept: A Theoretical Case Study Using Polymer Nanoclay Composites for Coffee Capsules. Sustainability 2021, 13, 1–21, doi:https://doi.org/10.3390/su132413951

Pavlicek et al. (2021). A European nano-registry as a reliable database for quantitative risk assessment of nanomaterials? A comparison of national approaches. NanoImpact Volume 21, January 2021, 100276; https://www.sciencedirect.com/science/article/pii/S2452074820300707

[2] OECD Working Party on Biotechnology, Nanotechnology and Ceonverging Technologies

nanomaterials and potential nanomaterials under the New Substances Program since WPMN21. In addition, six pre-notification consultations were initiated. Pre-notification consultations provide clarity on regulatory requirements prior to submission of a notification under the NSNR(C&P).

b. risk management approaches;

13. A form of graphene (Chemical Abstracts Service Registry Number [CAS RN] 1034343-98-0) was added to the Canadian Domestic Substances List (DSL) with significant new activity notification requirements. The Program used this opportunity to provide a compliance promotion letter to identified potential importers or manufacturers of carbon-based nanomaterials, informing them of this addition to the DSL as well as obligations to notify under the significant new activity provisions and the NSNR (C&P).

1.5. France

14. The **French government** has launched in May 2021 the fourth edition of its National Health and Environment plan (PNSE 4), which includes an action dedicated to nanomaterials. The action aims to better understand the health and environmental risks associated with these substances (uses, exposures and health and environmental effects). The objective is to better regulate these substances, if they do not have a strong utility and they may present risks. As part of that action, **the French Ministry for an ecological transition** (MTE) initiates an enforcement action on REACH registrations of nanomaterials to ensure dossiers are updated for substances in nanoform (as required by the Commission Regulation (EU) 2018/1881).

15. The fourth edition of the French National Health and Environment plan, available at https://www.ecologie.gouv.fr/gouvernement-lance-4eme-plan-national-sante-environnementenvironnement-sante, is currently in French. An English version will be available soon.

16. A study is underway between **LNE** and **ANSES** to develop and validate SOPs for food-grade TiO_2 low concentration in regulated food simulant by using sp ICP-MS to support containing nanoobjects-food packaging risk assessment. The study also aims to develop a software to harmonise the processing of sp ICPMS data and provide an evaluation of measurement uncertainties.

17. **LNE** contributed to the **NanoDeTox** project (French national funding / ADEME) to examine characteristics and toxicity of nanoparticles that remains within combustion residue after thermal degradation of nanocomposites.

18. **LNE** has contributed to the **MENBAT** project (ADEME funding) coordinated by CSTB, which aims to study nano-additive paints (TiO_2, Fe_2O_3) over a three-year period (2021-2024) and the emissions of nanoparticles associated with realistic mechanical stresses (use of commercial machine tools such as sanders and drills), taking into account the potential impact of product ageing. The project will lead to the production of two guides for the Construction industry on the analytical strategy to be implemented to assess the exposure of professionals, as well as on prevention in the workplace. **LNE** is contributing its expertise and cutting-edge analytical resources for the physicochemical characterisation of nanomaterials and the metrology of airborne nanoparticle.

1.6. Germany

Federal Institute for Risk Assessment (BfR)

19. The BfR is involved in the following national developments regarding human health: The Risk Assessment Committee (RAC) at ECHA adopted an Opinion on harmonized classification proposed by

Germany for rigid Multi-Walled Carbon Tubes, including Multi-Walled Carbon Nanotubes [MWC(N)T] as carcinogenic and chronically toxic to the lung via the inhalation route (Carc. 1B, H350i, STOT RE1, H372, lungs, inhalation). The classification is based on an asbestos-like mode of action, if the following dimensional boundary criteria are fulfilled: geometric tube diameter range ≥ 30 nm to < 3 µm and a length ≥ 5 µm and aspect ratio ≥ 3:1.

Federal Institute for Occupational Safety and Health (BAuA)

20. Germany proposed the harmonised classification of Multi-Walled Carbon Tubes (synthetic graphite in tubular shape) with a diameter range ≥ 30 nm to < 3 µm and a length ≥ 5 µm and aspect ratio ≥ 3:1, including Multi-Walled Carbon Nanotubes, MWC(N)T under the CLP regulation (EC No. 1272/2008) as Carc. 1B (H351i) and STOT RE1. After the discussion among member state experts the draft dossier was positively evaluated by the ECHA Risk Assessment Committee. The European Commission will include the substance to the CLP Annex VI upon a final decision of the European Council.

21. 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 are currently evaluated. Based on the results the different risk management options under REACH will be discussed. In the conclusion a justification will be given for the regulatory measure that will be pursued.

1.7. Italy

22. In January 2021, the Decree of the Italian Minister of Health (Article 3, paragraph 1, letter (f)) formalizes reconstitution of the Nanomaterials Working Group (NMWG) in the framework of the REACH Technical Coordination Committee referred to in Article 7 of the Interministerial Decree of Nov. 22, 2007 (O.J. Jan. 15, 2008, No. 12). The NMWG aims to promote activities in the framework of the REACH and CLP regulations to nanomaterials, ensure the protection of human health and the environment in relation to nanotechnology development, advanced materials production and manufacturing, placing on the market and use of nanomaterials and products containing them.

23. The NMWG is coordinated by two representatives designated by the Italian Ministry of Health and National Health Institute (ISS), respectively

Main tasks of the NMWG are:

- supporting the activities of European and international commissions as: EHS OECD program of the working group of national coordinators of the test guidelines program (WNT); OECD Working Party of Manufactured Nanomaterials (WPMN) and its steering groups; REACH and CLP competent authorities sub group on nanomaterials-CASG nano of the European Commission; expert group on nanomaterials of the European Agency for Chemicals-ECHA NMEG; REACH committee-ex art. 133 of REACH, the European Union Observatory for Nanomaterials (EUON);
- promote research activities, at the national and European level, to support the adaptation of current legislation on chemicals with regard to aspects relevant to nanomaterials and advanced materials;
- dissemination activities with national stakeholders and consumers related to nanomaterials.

24. The NMWG consists of members pertaining to the ministries participating in the REACH technical coordination committee and their technical bodies, regions and autonomous provinces of Trento and Bolzano, Italian Institute for Environmental Protection and Research (ISPRA), National Institute for

Insurance against Accidents at Work (INAIL), Italian National Agency for New Technologies, Energy and Sustainable Economic Development (ENEA), public and private bodies, trade associations, universities public and private research centers, ONGs.

25. Between September 2021 and June 2022, three update and implementation meetings were organized by the coordinators.

26. Furthermore, in June 2022, the Italian Ministry of Health, for the implementation of the interventions identified under the "Health-environment-biodiversity-climate" program of the National Plan for investments complementary to the National Recovery and Resilience Plan (PNRR), in order to develop a new institutional structure able to manage the health-environment-climate issue that can redesign and strengthen the National Health System – NHS finances n.14 programs included in two areas:

- AREA A - priority programmes for the health system (8 projects), in particular No 5 (Prevention and reduction of physical risks and risks associated with chemicals and processes)
- AREA B - programmes providing for actions with high synergy with other institutions/sectors (6 projects), in particular no. 14 (Applied research for the assessment of the impact on health of environmental risks).

27. The actions to be taken will have to be carried out through a holistic One Health approach, with the aim of strengthening the protection of citizens' health with respect to the currently known risks and the looming environmental-climate challenges and supporting sustainable development and safe economic growth, especially in relation to the green transition and digital transformation.

28. In the two areas described above, projects must be proposed and developed aimed at:

- Evaluate the potential toxic effects, for human health and the environment, of micro and nanoplastics through the development of advanced methodologies, which consider their peculiar chemical-physical characteristics, the main routes of exposure and environmental fate.
- Propose and test prevention models that provide for the implementation and adoption of the concept of Safe and Sustainable by Design in compliance with which the safety, for human health and the environment, of substances, materials, products and processes must be a fully integrated aspect in the development and design phase of an innovative product.

1.8. Japan

29. The Ministry of Economy, Trade and Industry (METI) publicized information on safety test data and management methods of manufactured nanomaterials, on METI's website firstly in 2010 (only in Japanese). Such information was voluntarily provided and annually updated by the manufacturers. METI publicised the updated information in 2021.

1.9. The Netherlands

30. The Netherlands volunteered to initiate **pilot inspections on REACH registrations of nanomaterials.** The main aim is to determine whether EU-wide enforcement action should be put in place to tackle the low level of information updates in dossiers for substances in nanoforms. ECHA will provide support together with the REACH Competent Authority in the Netherlands. Based on a list provided by ECHA, companies will be selected to gain insight in the type of information companies use in their considerations to register the substances with nanoforms or not. With the project the inspectors aim to build up knowledge and expertise on the (low number of) registrations of nanomaterials. France also showed interest in performing such pilot inspections. Depending on the results of the experiences in these

pilot inspections, the ECHA Forum may discuss potential further action related to nanomaterials at a later stage.

1.10. Slovak Republic

31. There exists the system of national legislation in Slovakia which protects the human health and environment from the negative impacts of products. These legally binding instruments are applied for protection of environment and human health in relation to nanomaterials and nanotechnology. Slovakia is a member country of the European Union and implements the Union legislation in the field of chemical substances including nanomaterials.

1.11. Sweden

SweNanoSafe

32. The Swedish National Platform for Nanosafety (SweNanoSafe) is a forum for knowledge exchange on the safe handling and use of engineered nanomaterials. The platform is commissioned by the Ministry of the Environment. Since 2019, the platform is hosted by the Institute of Environmental Medicine at Karolinska Institutet in Stockholm. SweNanosafe is comprised of a steering board including a representative from the Swedish Chemicals Agency and a coordination group as well as a scientific expert panel, a council of national government agencies, a national research network, and an education network, and organizes workshops, prepares or commissions reports, and maintains a website (www.swenanosafe.ki.se) to promote the dissemination of knowledge among stakeholders.

33. The platform has held annual meetings of the national research network (in English) since 2018. In November 2021, the 4th annual workshop (a hybrid meeting) focused on “measuring nanoparticles in occupational environments”. The keynote speakers were Dr. Hubert Rauscher, Joint Research Centre (JRC), European Commission, on Identification and measurements of nanomaterials, and Dr. Volker Bachmann, Federal Institute for Occupational Safety & Health (BAuA), Germany, on Occupational view on health and safety hazards. The next annual workshop of the research network will address “Risk assessment of advanced materials and mixtures of particles” (to be held in November 2022).

34. In January 2022, SweNanoSafe in collaboration with the Swedish Environmental Protection agency organized an online workshop on “Emissions of microplastics – measures to reduce environmental impact”. The workshop gathered representatives from academia, governmental agencies, industry and was intended to provide input on the consultation regarding Microplastics pollution – measures to reduce its impact on the environment. Presentations are available on the SweNanoSafe website.

35. In May 2021, SweNanoSafe published a report on Nanomaterials in the environment – an overview of the current state of knowledge and the knowledge gaps today (translation to English based on the report in Swedish). The report was compiled by Goodpoint AB, a Swedish consultancy firm in the field of sustainable development. The report identified several knowledge gaps (refer to the SweNanoSafe website).

36. In August 2021, SweNanoSafe published a report entitled “Nanosafety during chemical handling and in the work environment. Rules and recommendations on knowledge, risk assessment and risk management”. The report was written by Annika Nilsson, Professor of Public Law at the Faculty of Law, Lund University, with a special focus on chemicals legislation and legislation related to nanomaterials. The report mainly describes nanosafety in the “general” chemicals legislation, i.e., REACH and CLP, and legislation focusing on chemicals in the work environment. Cosmetics, food, medicines, and other product groups that are regulated by special legislation were not covered.

37. In October 2021, SweNanoSafe published a report entitled "Nanomaterials in the construction industry - a survey and inventory of knowledge and knowledge needs". Nanosafety in relation to the construction industry was identified as an area of particular interest and the platform therefore commissioned a report by an environmental consultant with extensive experience of chemicals in the construction industry to compile a pilot report in 2018. This was followed by a national workshop on nanomaterials in the construction industry in 2019 and the following year, a report on nanomaterials in the construction industry was commissioned. The final report describes an approach to find out to what extent nanomaterials are used in the construction industry today, awareness among companies regarding nanosafety, and an overview of research concerning applications of nanomaterials in the construction industry. The project is based on collaborations with representatives from several societal actors, agencies as well as industry organizations and companies in the construction sector.

38. In December 2021, SweNanoSafe published an executive summary report entitled “Toward Safe and Sustainable Nanotechnology Innovation”. The report is a summary of a research project conducted by Drs. Sari Scheinberg and Sverker Alänge from the Action Research Center based on in-depth interviews and workshops with actors in research and innovation (a total of 33 representatives from 26 organizations including 10 start-ups/SMEs and one large company were interviewed). In addition to the interviews, two online workshops (10 June 2020 and 9 September 2020) were conducted. A key question addressed in the study was: How can we create and maintain a sustainable workflow in industry, government, and academia that strengthens and integrates a safe and responsible process of research, innovation, and utilization at all stages of the ENM life cycle? The study also served to address ways to identify/develop a process that would contribute to the improved implementation of a responsible research and innovation (RRI) approach. The study has shown the urgency of establishing collaboration between stakeholders regarding nanosafety practices. The executive summary (available on the SweNanoSafe website) concluded with a series of recommendations.

SIO Grafen

39. SIO Grafen is a national strategic innovation program designed to support industrial graphene development in Sweden. SIO Grafen is supported by the Swedish government agencies VINNOVA (Sweden’s innovation agency), the Swedish Energy Agency and the Swedish Research Council FORMAS (Sweden’s research council for sustainable development). The work in 2021 focused on establishing national priorities for international standardization of graphene and nanocellulose. The goal is that Sweden will be a driving force in the international standardization of nanomaterials, deploying a safe-by-design approach. The work is financed by VINNOVA, and Swedish Standards Institute, Chalmers Industriteknik, SIO Grafen, and RISE Research Institutes of Sweden are project partners.

1.12. United States

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

40. The U.S. Environmental Protection Agency (EPA) completed review of five low volume exemptions which included modified graphene materials and multi-walled carbon nanotube chemical substances. EPA granted one of the exemptions while the other four exemptions were denied or withdrawn before being denied EPA allowed the one exemption under conditions that limited human and environmental exposures to prevent unreasonable risks. Additionally, the EPA reviewed and completed six premanufacture notices for multi-walled carbon nanotube chemical substances. All six of the new chemical substances were regulated with a consent order due to limited available data on nanomaterials. The consent order limited uses and human and environmental exposure to prevent unreasonable risks.

c. risk management approaches;

41. Between June 2021 and June 2022, EPA received notification of 7 nanoscale substances based on amorphous silica 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 85. 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 was for metals or metal oxides.

42. Since January 2005, EPA has received and reviewed more than 255 new chemical notices for nanoscale materials under TSCA including fullerenes, quantum dots, 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.

43. 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.

d. any updates, including proposals, or modifications to previous regulatory decisions; and/ or

44. 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.

e. new regulatory challenge(s) with respect to any action for nanomaterials

45. Standards/methods for differentiating between different forms of the same chemical substance that is a nanomaterial.

46. Standardized testing for the physical properties that could be used to characterize/identify nanomaterials.

47. Differentiation between genuinely new nanoscale materials introduced in commerce and existing products which have been in commerce for decades or centuries.

1.13. European Union

48. European Commission has recently published revised **Recommendation on the definition of nanomaterial**, accompanied by the Staff Working document reporting on the review process, rationale for the choices made, and feedback to the targeted stakeholder review performed in 2021 as part of the review. Documents can be found here.

49. The Recommendation C(2022) 3689 is replacing the old Recommendation 2011/696/EU and will be used to provide a horizontal basis to identify nanomaterials and trigger nanomaterial-specific provisions in EU legislation across different sectors. Uptake of the definition in each sector, making it legally binding within its scope, will follow individual processes and timelines.

50. Implementation of the definition will be supported by guidance currently under preparation by the Joint Research Centre of the European Commission, to be published still in 2022.

51. Under **REACH**, compliance check processes addressing registrations of three substances in nanoform are ongoing; farthest is compliance check on multiwall carbon nanotubes (MWCNT), which targeted incompliances found in the set of nanoforms (Annex VI), where draft decision has already been sent to the registrants.

52. ECHA Guidance Appendix for nanomaterials applicable to Chapter R7a Endpoint specific guidance, is being updated and includes OECD recommendations, like the guidance documents 317, 318 and 342.

53. Under **Cosmetic Products Regulation (CPR)**, a targeted revision of the regulation is taking place. Proposal should be ready by the end of 2022 and is planned to address also nanomaterials.

54. Scientific Committee on Consumer Safety (SCCS) supporting implementation of CPR is presently re-evaluating Hydroxyapatite (nano), and has been also been tasked to evaluate four silica nanomaterials, fullerenes and hydroxylated fullerenes; all of the assessments are still to be concluded. SCCS also announced plans to revise its Notes of Guidance.

55. Within the food sector, European Food Safety Authority (EFSA) is implementing the new Nano Guidance documents published in 2021; the activity is mostly focused on novel foods and food and feed additives. In most cases there is a need for requesting additional information from applicants, to ensure that nanoscale considerations are addressed according to the new guidance. EFSA has organised a stakeholder event for facilitating the implementation of these new challenges, presentations and recordings are available here.

1.14. Malaysia

56. Malaysia's National Nanotechnology Policy and Strategy 2021-2030 (DSNN) was launched on November 15th, 2021. This policy consists of four strategic thrusts which includes strengthening standards, safety and regulation on nanotechnology. The Ministry of Science, Technology and Innovation Malaysia will oversee the planning and implementation of 32 initiatives under 15 strategies within this policy.

57. A National Nano Product and Technology Roadmap was recently launched on April 13th, 2022 to support DSNN. The nano ecosystem has been mapped towards these jumpstart sectors: Energy; Environment; Food and Agriculture; Medical and Well-being; Healthcare; and Electronics and Devices.

1.15. Thailand

58. National Nanotechnology Center (NANOTEC), Thailand and Department of Industrial Works (DIW) have a collaboration on the following projects:

- Guidelines for industrial workers on nanotechnology (published).
- Industrial training courses on the principles of nanotechnology, chemical management, and nanosafety.
- NANOTEC has developed Nanosafety checklist for DIW applications. The Nanosafety application is integrated under chemical safety concerns and used by the Department of Industrial Workers

- NANOTEC and 8 organizations in Thailand have signed the MOU to collaborate on the Nanosafety Development for Industry Network, so far have created 7 VDO episodes for e-learning under the scope of Nanosafety development for industry. All VDO clips are available for free at the Federal Thai Industries Academy (FTI Academy) platform, which is accessible to industries, businesses, and workers. The episode topics are as follows:

  Ep.1 Principle of Nanotechnology

  Ep.2 Fundamentals of Nanosafety

  Ep.3 Thai Industrial Standards and Nanotechnology

  Ep.4 Nanotechnology and metrology

  Ep.5 Improving nanosafety governance for industry employees and consumers

  Ep.6 Guidelines for Notifying Cosmetics Containing Engineered Nanomaterials in Thailand Before Manufacturing or Importing

  Ep.7 Guidelines for Applying for Voluntary Nano label (NanoQ)

2 Activities been initiated to implement the OECD Recommendation of the Council on the Safety Testing and Assessment of Manufactured Nanomaterials (e.g. regulatory changes, guidance, voluntary, etc.)

2.1. Austria

59. Austria plans to work 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 is co-funded by the EU Horizon 2020 Project Gov4Nano (see item 6 of this report).

60. 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.

61. In parallel the Department of Environmental Geosciences of the University of Vienna (Frank von der Kammer) works on the development of a technical guidance (TG) for the environmental transformation of nanomaterials and heteroagglomeration 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

62. The Government of Canada is developing a nanomaterial regulatory risk assessment framework to inform the assessment of manufactured nanomaterials under the *Canadian Environmental Protection Act, 1999* (CEPA), including existing nanomaterials in commerce in Canada, and new nanomaterials notified prior to being manufactured or imported into Canada. The framework describes how scientists at ECCC and HC conduct risk assessments on nanomaterials. With this document, the Departments of Environment and Climate Change Canada (ECCC) and Health Canada (HC) can communicate to industry and the public about the methods that are being used to make decisions under CEPA. The framework discusses in detail the nanomaterial-specific considerations for risk assessment, such as:

- the key physical and chemical properties specific for nanomaterial identification and used for grouping or classifying nanomaterials for information gathering;
- the data considerations used in a nanomaterial risk assessment such as test data or modeling;
- the behaviour of nanomaterials throughout the lifecycle of the nanomaterial (from production to disposal) and characterizing those potential effects on human health and the environment.

63. The draft has been shared with selected partners, including SGAP for peer-review, and was published on June 17, 2022 for a 60-day public comment period.

Link to the Landing Page[3]

Link to the Risk Assessment Framework[4]

2.3. France

64. France (**INERIS**) and Denmark (NRCWE) are leading the development of methods of measurement of dustiness of manufactured nanomaterials, and the use of dustiness results to assess occupational exposure and associated ATEX (Explosive atmospheres) hazardous zones. A TG on dustiness measurement methods and two GD (one on exposure modelling and one on associated ATEX zones for the case of combustible nanomaterials), are being proposed. The ILC involving 18 different international laboratories cover both granular and fibrous nanomaterials. ILC on granular materials is largely underway and analysis of ILC data is currently being performed. ILC on HARN is being started, for which morphological characterisation and data analysis are primarily made via electronic microscopy.

65. A poster presentation showing the proposed structure and first outcomes of the ILCs will be made at the NanoHamony/Nanomet joined conference (29th-30th June).

66. Spain (INIA) and France (**INERIS**) submitted last November a SPSF regarding the revision of Guidance Document 317 on Aquatic and Sediment Toxicological Testing of Nanomaterials to provide further guidance on conducting assays with manufactured nanomaterials according to OECD Test Guidelines 201, 202, and 203. The project has been adopted during the WNT meeting and is now included in the Work plan for the Test Guidelines Programme.

67. Within the framework of the EU project NanoHarmony, **INERIS** continued the technical work on the adaptations of OECD TG 201. Determination of the potential interferences of NMs with commonly used

[3] Also available in French : https://www.canada.ca/fr/sante-canada/services/substances-chimiques/nanomateriaux.html

[4] Also available in French : https://www.canada.ca/fr/environnement-changement-climatique/services/evaluation-substances-existantes/cadre-evaluation-risques-nanomateriaux-manufactures-lcpe-ebauche.html

methods to directly or indirectly count the algal cells was finalized including the optical density as an additional device to those already tested (*in vivo* algae autofluorescence, particle counter, hemocytometer…). Results were presented and discussed during the 2nd NH workshop that took place in November 2021.

68. Simultaneously, **INERIS** prepared a call for ecotoxicology laboratories to participate in the transferability study of proposed modifications to TG 201, scheduled for the last quarter of 2022.

69. France (**INERIS**) participates to the Ad hoc working group (grouping of nanomaterials) for the revision of section 6.9 of the OECD Guidance document on grouping of chemicals (GD 194).

70. France (**INERIS**) continues its participation the European project Gov4nano. Within the project, **INERIS** is in charge of a case study on the evaluation and reuse of ecotoxicity hazard data. The objective of the work undertaken in this case study is:

i. to improve and harmonize the data collection and metadata reporting for aquatic ecotoxicity studies and,

ii. to make the data quality assessment easier by considering relevant parameters to evaluate the ecotoxicity studies for nanomaterials.

71. Specific templates were developed which provide a structure to collect all relevant data and critical information that allow the assessment of the completeness and reliability of different aquatic ecotoxicity studies in microalgae, micro-invertebrates and fish including a quality criteria tool to ensure that data and metadata introduced in the database can be reused by others.

72. Templates were developed for the following tests:

- Algal growth inhibition test - OECD 201;
- Daphnia acute immobilization test - OECD 202;
- Fish acute toxicity test - OECD 203;
- Bioaccumulation in fish after aqueous and dietary exposures - OECD 305.

73. **LNE** will create the **NanoMesureFrance Center** (https://www.lne.fr/fr/communiques-de-presse/nouveau-centre-structurer-filiere-nanomateriaux-francaise) with the support of French Ministries and Industry (chemistry, cosmetics, plastics…). This Center will be a one-stop-shop structure in France for nanomaterials phys-chem characterization and evaluation (performances and exposure):

- to help in the identification of expert and infrastructures,
- to identify needs/build roadmaps & launched new services/studies to support safe(r) innovation approaches for nanomaterials,
- to share information (*regulation, standardisation, call for proposal, inter-laboratories comparisons*…),
- to offer a framework to validate proficiency of testing laboratories.

2.4. Germany

Federal Institute for Occupational Safety and Health (BAuA)

74. 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 two international virtual workshop to facilitate the needed exchange. It furthermore aims at supporting the TG development process by developing best practice guidance, training materials and a white paper on TG development for nanomaterials. NanoHarmony aims to continue the exchange between OECD, science and industry. A joint NanoHarmony and NANOMET workshop on TG development for nanomaterials will take place at OECD from 29.-30.06.22 directly after WPMN22. The Third NanoHarmony Online Workshop on TG Development for Nanomaterials will take place on 29.-30.11.2022 (registration via https://nanoharmony.eu/events/).

75. BAuA coordinates a workpackage in the EU-project Gov4Nano dedicated towards development of TGs and GDs for 7 nano-specific endpoints.

2.5. Italy

76. After a round of comments by Member States, the SPSF of the new Guidance Document on "*Integrated in vitro approach for intestinal fate of orally ingested Nanomaterials*", leaded by Italy, was approved in the last WNT meeting (April 2022).

77. ISS actively participates to the ad hoc group for updating section 6.9 on the OECD Guidance on grouping of chemicals.

2.6. Korea

78.

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

   Korea Research Institute of Standards and Science (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. Currently, this test guideline is being developed through expert circulation.

2) 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. Currently, this test guideline is being developed through expert circulation.

3) 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).

4) OECD test guideline development for surface analysis and, solubility and dissolution (OECD WNT project 1.5 and 1.6)

   KRISS will participate in round robin test for determination of solubility and dissolution using CFS. And another round robin test for developing test guideline of surface analysis of nanomaterials will be participated.

2.7. Slovak Republic

79. Most relevant activities for our country, which shall be implemented from the Council recommendation are following: Need to increase the science policy cooperation for better regulation in the

field of nanomaterials and closer cooperation with producers in safety and evaluation of risk assessment of products containing nanomaterials.

2.8. Switzerland

80. Ongoing consultation of the study report of the work on the WPMN/WNT project 4.133 DRP on the Applicability of the key event based Test Guideline 442D for in vitro skin sensitisation testing of nanomaterials by the OECD EG skin sensitization. This project is also part of the EU Horizon2020 project Gov4Nano.

81. Characterization and testing of OECD TG 442D with selected MNM has been finished. OECD TG 442D (ARE-Nrf2 luciferase KeratinoSensTM) is technically feasible. The in vitro to in vivo correlation exercise could only be performed in general terms (yes/no) due to the scarcity of data and the very limited and diverse information obtained from the literature. This did not allow producing conclusions on predictability of the assay. However, the study reports also includes recommendations for a future adaptation of KeratinoSensTM for nanomaterial testing. These recommendations are based on the results and discussion with experts of nanomaterials and/or skin sensitisation The recommendations included viability assessment of the cells, dispersion of nanomaterials, and use of DMSO during exposure of nanomaterials to the cell system, testing of leachates of nanomaterials, exposure time and endotoxin measurements of nanomaterials.

2.9. United Kingdom

NanoHarmony

82. The NanoHarmony (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 focussed 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. 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 November 2021 NanoHarmony hosted a further International Workshop to support TG and GD Development. The project has also hosted a number of webinar sessions exploring the OECD TG development process. Under Tasks 1.2 and 1.4 scientific papers relating to bioaccumulation and the use of single particle ICP-MS with biological samples were published.

RiskGone

83. 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.

84. Two main strands of activity have been progressing well:

I. Use of fish cell models, including Zebrafish embryo cells (ZF4) and rainbow trout gut cells (RTgut), to complement the existing OECD Test No. 249: Fish Cell Line Acute Toxicity which uses the rainbow trout gill cell line (RTgill-W1). RiskGONE is developing a suite of label-free assays for cytotoxicity (e.g., using the xCELLigence system (Agilent, US), which is a real-time impedance-based cell-analyzer), as well as assessing the applicability of the genotoxicity assay (Comet assay) to these cell lines, including developing additional image analysis tools for extracting information from the Comet images to enhance the understanding of the potential interference from NMs (e.g., non-symmetrical tail shape if NMs are physically present) – this should also help to overcome some of the objections to the Comet assay. An SPSF is being prepared for ZF4 and RTgut cells to extend the OECD249 to include these cells and additional endpoints, and confirm its suitability for use with NMs.

II. Based on extensive work on chronic reproductive testing with the indicator species Daphnia magna which responds to the presence of freshly dispersed NMs more dramatically than to environmentally aged NMs, displaying reduced growth, delayed maturation and delayed reproduction, induction of males and epigenetic changes passed from exposed mothers to their offspring, an SPSF is being prepared to adapt and extend the OECD211 test to include additional end-points and generations. RiskGONE's recommendations for adaption of the OECD 211 for testing of nanoscale particles are grouped into three broad categories:

    a. Adjustments to exposure conditions and duration, to allow for delays in maturation and brood timings, use of daphnia-conditioned media to disperse the particles and passivate the particle surfaces prior to exposure to the organisms, monitoring of the induction of males and the presence of fertilised eggs, and testing both freshly dispersed and medium-aged particles.

    b. Addition of particle-specific analyses to support determination of mode of action, including quantification of uptake dose before and after depuration, imaging of phenotypical changes and sub-cellular localisation of NM in the daphnia gut.

    c. Extension to additional generations and inclusion of additional stressors (e.g., temperature) to explore epigenetic effects of environmental exposures, including the potential for adaption to nanomaterials exposure and/or increased sensitization to nanomaterials of organisms whose parent or grandparent generations had been exposed to nanomaterials. This would require multi-generational assessment, over at least 2-3 generations.

85. An adverse outcome pathway for Daphnia reproduction is also being finalised, including dynamic energy budget modelling, which indicates that NMs accumulation in the gut leads to 5 interlinked processes, including oxidative stress, delayed carapace shedding leading to delayed reproductive maturity, induction of males, and reduced kairomone signalling leading to reduced mating success, that converge in impaired reproduction and overall population decline. This is currently being fully documented and will be published and submitted to the AOP-Wiki in the coming weeks.

TG305 Scoping Review

86. 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 progress report will be presented at WPMN22.

Project 4.095 Guidance Document on in Vitro Mammalian Genotoxicity for Manufactured Nanomaterials

87. 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 approval.

2.10. United States

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

2.11. European Union

89. Nothing specific to implementation of OECD guidance; work presented above however is considered to implement it.

2.12. Business at OECD (BIAC)

90. **NIA** supports the implementation of testing 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, NIA makes sure information is communicated to relevant stakeholders through the organisation of webinars and workshops, where updates regarding several Guidelines adaptations takes place. NIA also supports the dissemination of the information by broadly advertising those events and through member-only events.

91. **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. Austria

93. 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) in co-operation with NanoTrust, the University of Natural Resources and Life Sciences and BioNanoNet. The official document will be published later this year.

94. 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, sustainability, 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" (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).

3.2. Belgium

95. 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.

96. 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.

3.3. France

97. **LNE** contributed to two projects carried out under the auspice of CEN/TC 137 *Assessment of workplace exposure in order to produce standards* - WG 3 'Particulate matter':

i. Sampling and counting rules for the characterization of airborne NOAA in the workplace by scanning and transmission electron microscopy
   - Part 1: CEN/TS: Sampling of nano-objects and their agglomerates and aggregates in the workplace for electron microscopy
   - Part 2: EN: Counting rules for the characterization of airborne nano-objects and their agglomerates and aggregates for scanning electron microscopy (SEM) and transmission electron microscopy (TEM)

ii. Application of direct-reading low-cost sensors for measuring NOAA in the workplace
   - CEN/TS: The objective of this project is to develop a workplace monitoring strategy for measuring NOAA with low-cost sensors based on results of laboratory and workplace tests.

98. **LNE** started a project within the CEN/TC 352 Nanotechnologies to develop a CEN Technical Specification entitled "Guidelines for sample preparation, detection, identification and characterization by spICP-MS and EM-EDX of nano-objects in inorganic additives incorporated in food matrices". E551 (SiO2), E171 (TiO2) & E172 (Iron Oxides) food additives are more particularly targeted, with a focus on the sample preparation step (extraction of additives from the food matrices) and validation of SOPs through inter-laboratory comparison. Official control laboratories for food products from different EU Member States (SCL / FR, Sciensano / BE, DTU / DK, WFSR / NL & HSE / IRE) are involved in the project.

99. **LNE** started with partners to work on the development of a CEN Technical Specification entitled "*Guidance on the determination of the aggregation and agglomeration state of nano-objects*" within CEN/TC 352 *Nanotechnologies.*

100. **LNE** with its European partners (BAM, PTB, LGC, VSL, SMD) work within the **nPSize** EMPIR project which aims to assess the performances of various measurement techniques (SEM, SAXS…), deliver to users reference materials and develop methods and models to improve the metrological traceability chain and comparability of nanoobjects size distribution characterization. Methodologies will be further assessed through a VAMAS interlab study in 2022.

101. **LNE** is associated with NPL (UK) in the **ISO-G-Scope** EU project to develop ISO/PWI 23879 'Nanotechnologies - Structural characterisation of graphene oxide flakes: thickness and lateral size measurement using SEM and AFM' in order to better characterize graphene.

102. As part of the European **NanoFabNet** project, **LNE** coordinated the drafting of two public reports on validation, harmonisation and standardisation issues regarding the implementation of sustainable nanofabrication. EHS issues are considered together with Advanced Materials characterisation topic:

- Challenges & Opportunities of Validating, Harmonising & Standardising industrial-scale Nanofabrication;
- Validation, Harmonisation & Standardisation Action Plan for sustainable Nanofabrication

103. **LNE** initiated in 2021 within the French standardisation Committee dedicated to nanotechnologies/nanomaterials (AFNOR/X457) the development of a guidance to help industry choosing the most relevant analytical strategy identifying nanoforms (EC Recommendation for the definition of nanomaterial) according to key phys-chem properties.

3.4. Germany

Federal Institute for Risk Assessment (BfR)

104. NanoHarmony has started a new series of interactive webinars covering the journey of an OECD Test Guideline through the initiation, development and eventual use phases to understand the challenges and barriers that need to be addressed at each stage. Six webinars have been held since the last WPMN.

The latest workshop/webinar will be conducted back-to-back following the 22nd OECD WPMN, 29-30 June.

105. In the context of the activities of NanoHarmony mentioned above, last year a survey on identifying difficulties arising during the development process of OECD Test Guidelines (TGs) and Guidance Documents (GDs) was successfully conducted. The questionnaire tried to identify barriers and challenges that may result in delays in the process towards approved TGs/GDs.

Max Rubner Institute (MRI)

106. As a member of the "Nano in food expert group" coordinated by the Joint Research Centre (JRC) of the European Commission, the German Max Rubner-Institut (MRI) is involved in the investigation, development and interlaboratory testing of methods for the characterisation of nanomaterials in food. The group recently published an interlaboratory comparison study on determination of the transport efficiency in spICP-MS analysis (https://doi.org/10.3390/nano12040725).

Fraunhofer Institute for Molecular Biology and Applied Ecology IME

107. Publication on the testing of particles in the nano- and micro-size range using the algal growth inhibition test (OECD TG 201) demonstrating the suitability of the in vivo chlorophyll fluorescence measurements (https://doi.org/10.1186/s12302-022-00623-1):

108. Chlorophyll fluorescence measurements are recommended for the testing of particles. The analysis of in vivo fluorescence is the simplest and fastest approach, but is only suitable if there is no interference with the materials. Therefore, in vitro fluorescence analysis is often preferred. For this method chlorophyll is extracted before the measurement. Therefore, this approach is more labour-intensive and time-consuming compared to the in-vivo approach.

109. A comparative study was performed considering a wide range of particles such as inorganic and organic particles (including alloys and polymers), ion releasing and non-releasing materials, and particle sizes in the nanometer to micrometer range with a variety of shapes (spherical, flaky and fibrous). The in vitro method used was that developed in the EU's MARINA project. In this approach particles are separated using locust bean gum before chlorophyll is extracted.

110. The in vivo approach was a suitable and time-saving method for all tested particles. All tests were valid, whereas the validity criteria listed in OECD test guideline 201 were not always fulfilled by the in vitro measurements.

111. The authors conclude that the in vivo-method can be recommended as suitable approach and should be considered in the revision of the OECD TG 201. As they cannot completely exclude the possibility that some particles may interfere with fluorescence measurement, pre-tests with simple measurements are therefore recommended to avoid false assessments.

112. The work was carried out within the framework of a project funded by the German Federal Ministry of Education and Research.

German Environment Agency (UBA), Federal Institute for Occupational Safety and Health (BAuA) and Federal Institute for Materials Research and Testing (BAM)

113. At WNT-34, a new Test Guideline on particle size and size distribution of nanomaterials was adopted (OECD TG 125). The activity was led by Germany as WNT project 1.4 since April 2018. The objective of this activity was to provide standardised methods for determining size and size distribution for both particles and fibres at the nanosize. It provides standardised protocols for seven methods to determine

particle size and size distribution and standardised protocols for two methods to determine fibre diameter and length distributions.

114. The activity was supported by intensive exchange and contribution of an international expert group as well as 31 labs worldwide contributing to the international validation of the draft Test Guideline which took place in 2019.

115. A draft Test Guideline together with the validation report presenting the results of the comprehensive interlaboratory comparison was submitted for the first WNT commenting round in July 2021. This was followed by a second WNT commenting round starting in November 2021. In general, strong support for the proposed document was received and the comments on clarifications and editorial changes were considered for revision, which supported clarity and accuracy of the document. The final version of the draft Test Guideline was submitted to WNT in March 2022 for adoption in April 2022.

German Environment Agency (UBA)

116. In autumn 2021, UBA launched a new research project which intends to develop and validate a harmonised test method to determine abiotic transformation of nanomaterials under environmental conditions. This project is intended to supplement the current WNT project 3.16 on an OECD Guidance Document on the respective endpoint and to provide the technical and methodical addition to allow to the development of an OECD Test Guideline in addition to the OECD Guidance Document underway. The project includes the experimental and conceptual work for method development, the establishment of an expert group, validation testing as well as the processing of WNT commenting rounds.

117. In addition to the development of an OECD Test Guideline on abiotic transformation of nanomaterials, conceptual and experimental work on method development for determining dispersion stability based on heteroagglomeration of nanomaterials under environmental relevant conditions is executed within this project. Based on the experimental procedure of OECD TG 318, it is planned to provide a protocol which allows to also determine dispersion stability based on heteroagglomeration. For this, within the project, interlaboratory comparison studies will be performed to both validate the test performance to determine heteroagglomeration but also to provide a standard protocol for synthesis of artificial suspended particulate matter for the interaction with nanomaterials. As a follow up to this research project, the outcomes might be used as expansion to the current OECD TG 318 or as addition to the current OECD GD 318.

https://www.umweltbundesamt.de/en/topics/chemicals/nanotechnology/research-development-projects-on-nanomaterials#oecd-test-guideline-development-for-nanomaterials-transformation-of-nanomaterials-under-environmental-conditions

Federal Institute for Occupational Safety and Health (BAuA)

118. BAuA initiated a project for the development of an OECD Guidance on Release Test for Manufactured Nanomaterials. The project will be presented at WPMN22. All partners (BAuA, UBA, BfR (Germany), NRCWE (Denmark) and ECHA) met in spring 2022 for the kick-off meeting in which the objectives and the scope of the guidance document were defined. 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 spring 2023.

3.5. Japan

119. The Japanese Industrial Standards Committee (JISC), which is the national member body participating as a P-member in ISO/TC229 (Nanotechnologies), 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 group 21 "Measurements of particle size and shape distributions by scanning electron microscopy" (IS 19749), and now IS19749 has been published. JISC leads "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 discussion. 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.

3.6. Korea

120. In November 2021, the 'High throughput screening method for nanoparticles toxicity using 3D model cells' proposed by Korea Institute of Toxicology (KIT) has been published in the International Standard for Nanotechnology (ISO/TC 229). ISO TR 22455 document approved as international standards provide a method for high throughput evaluation of cytotoxic response of 3D model cells exposed to nanoparticles (NPs) without optical interference. The methods in this document are intended to be used in biological testing laboratories that are competent in the culture and growth of cells and the evaluation of cytotoxicity of NPs using 3D-model cells. The described method applies to materials that consist of nano-objects such as NPs, nanopowders, nanofibers, nanotubes, and nanowires, as well as aggregates and agglomerates of these materials. This work was supported by Nano safety metrology center of KRISS funded by the Ministry of Science and ICT, Republic of Korea.

121. ISO TR 22455 Nanotechnologies - High throughput screening method for nanoparticles toxicity using 3D model cells - https://www.iso.org/standard/73244.html

122. Nano safety metrology center of KRISS is additionally proposed 4 new items for the development of the International Standard for Nanotechnology (ISO/TC 229).

- ISO/AWI 4962 - In vitro 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)

3.7. The Netherlands

123. The OECD WNT Project 4.146 on **toxicokinetics** of nanoparticles is led by the Netherlands (RIVM) and co-led by the UK (UKHSA). The current OECD TG 417 on toxicokinetics was identified as not

applicable to nanomaterials. WNT Project 4.146 therefore aims to develop a new TG on *in vivo* toxicokinetic testing of nanoparticles following the inhalation and oral route. Korea and Australia are contributing by providing studies, and the EU contributes via accommodating work in the H2020 project NanoHarmony. A literature overview was compiled for the model substances titanium dioxide, cerium dioxide, and silicon dioxide. This overview identified some knowledge gaps for the appropriate design of a toxicokinetics study. These can partly be addressed with recently finalised study from EU projects (e.g. PATROLS), and some limited experimental work in NanoHarmony. An important starting point in the development of the new test guideline is the dissolution rate of nanomaterials that may help to estimate the necessary test duration to enable monitoring the distribution of a nanomaterial inside an organism. Test development for dissolution rate is ongoing in OECD WNT Project 1.5 and supported by EU projects Gov4Nano and NanoHarmony. Another important issue in toxicokinetics is the ability to measure nanomaterial inside an organism without (large) interference from tissues or other substances. UK is developing an OECD Guidance Document (WNT Project 1.10), also supported by the NanoHarmony project. Within NanoHarmony close collaborations between the different projects are optimised to ensure exchange of information and optimal use of each other's expertise.

124. Within the context of CEN TC352, TNO is involved in developing a Quick start guide entitled "Nanotechnologies - Conduct of inhalation risk management of nano-objects and their aggregates and agglomerates (NOAA) and nanoparticulate substances, for the proximity occupational hygienists". The purpose of this document is to provide a quick start guide to structure the approach to be taken by health and safety professionals when they wish to **manage the occupational health and safety risks of manufactured NOAA** greater than 100 nm. All routes of exposure are taken into account: inhalation, dermal or ingestion. The objective is to help the reader to build a first approach in terms of identification, risk assessment, risk mitigation and control methodology. Relevant documents and tools will be provided.

125. RIVM continues the efforts in the EU project NanoHarmony to help further optimise the processes for guideline development. Workshops have been and will be held for various stakeholders to inform them on optimizing options for guideline development. The NanoHarmony and NANOMET will have their first face-to-face joint workshop on OECD Test Guideline (TG) Development for nanomaterials back-to-back with the WPMN at the OECD Conference Centre in Paris. Recordings of past NanoHarmony workshops are still available for viewing. These include webinars on identifying ways to improve the different phases of the OECD Test Guidelines process, e.g. on using TGs, on technical development and commenting rounds, and on submitting project proposals to WNT.

3.8. Slovak Republic

126. In Slovakia we are not in a position to develop good practice documents such as standards concerning manufactured nanomaterials, which needs more specific knowledge, information exchange and international cooperation, but such internationally accepted guidance's are needed for our decision making process and we are opened for share our experiences and for international cooperation in this field.

3.9. Spain

127. The Spanish National Institute of Health and Safety (INST) published a technical guidance on safety measures at research laboratories using nanomaterials. The guidance is available in Spanish at https://www.insst.es/documents/94886/566858/NTP+1172+Nanomateriales.+Medidas+preventivas+en+laboratorios+de+investigaci%C3%B3n+-+A%C3%B1o+2022.pdf

3.10. United Kingdom

128. **HSE Science and Research Centre** leading on the revision of ISO/TS 12901:2012 (Nanotechnologies — Occupational risk management applied to engineered nanomaterials Part 1: Principles and approaches is a general document. The revision of this document is progressing well.

Graphene Standardization

129. Graphene Standardization work. NPL (UK) leading and contributing to the development of ISO documents for the characterisation of graphene and graphene platelets, and this work is currently ongoing.

130. The following article was published: Paper - *Towards health-based nano reference values (HNRVs) for occupational exposure: Recommendations from an expert panel*. Maaike Visser, Ilse Gosens, Delphine Bard, Pietervan Broekhuizen, Gemma Janer, Eileen Kuempel, Michael Riediker, Ulla Vogel, Susan Dekkers. **NanoImpact**, Volume 26, April 2022, 100396

NanoCommons

131. 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.

132. The cumulative learnings from NanoCommons, based on its research, its Transnational Access activities supporting the research community with their data management needs, and the demonstration case studies to explore the applicability of the NanoCommons tools, approaches and solutions as applied in real-world situations (e.g., academic versus industry labs) is being captured into our NanoCommons Data Shepherd User Guidance Handbook.

133. The handbook (which is a living document and will continue to be maintained and updated beyond the funded project lifetime, contains sections on data management, FAIRification, Nanoinformatics, Safe-and-Sustainable-by-Design, Nanofabrication, Training courses, descriptions of the demonstration cases including:

- ELNs for data collection and annotation
- Protein corona modelling
- Data management concept NanoFASE
- Study design documentation
- SOP development documentation
- SbD, risk governance and nanofabrication
- Grouping and read-across
- Nanomaterial risk assessment
- Building regulatory acceptance
- Development of NInChI

RiskGONE

134. RiskGONE is finalising a guidance document covering all aspects of NMs safety assessment (deliverable report D3.1) based on the insights gained across the project and linking to the adapted SOPs developed within the project. This also includes also a guidance document / set of recommendations

regarding Good Laboratory Practice (GLP) as applied to nanomaterials. The complete document will be submitted shortly for publication in the Open Access journal F1000Research.

3.11. United States

135. In 2021 and 2022, researchers at the U. S. National Institute for Occupational Safety and Health (NIOSH) published or contributed to major reports:

- Utilizing literature-based rodent toxicology data to derive potency estimates for quantitative risk assessment. Boots TE; Kogel AM; Drew NM; Kuempel ED. Nanotoxicology 2021, 15(6):740-760. https://doi.org/10.1080/17435390.2021.191827
- Towards health-based nano reference values (HNRVs) for occupational exposure: Recommendations from an expert panel. Visser M; Gosens I; Bard D; van Broekhuizen P; Janer G; Kuempel E; Riediker M; Vogel U; Dekkers S. NanoImpact 2022, 26:100396. https://www.sciencedirect.com/science/article/pii/S2452074822000180?via%3Dihub
- Occupational Exposures to Engineered Nanomaterials: a Review of Workplace Exposure Assessment Methods. McCormick S; Niang M; Dahm MM. Current Env. Health Reports 2021, 8:223-234. https://link.springer.com/article/10.1007/s40572-021-00316-6

3.12. European Union

136. Technical committee **CEN/TC 137** of the European Committee for Standardization, working on Nano-objects and their aggregates and agglomerates (NOAA) in the workplace, is identifying potential for collaboration with OECD WPMN on Project 1 (Sampling and counting rules for the characterization of airborne nano-objects and their agglomerates and aggregates by electron microscopy).

137. Very notable **developments within the OECD** itself, to which EC contributed:

138. The JRC-led new OECD TG 124 on determination of Volume Specific Surface Area (VSSA) was adopted by WNT-34, just in time for the revised Commission Recommendation on the Definition of Nanomaterial. The JRC has already started the work to prepare updated guidance for the implementation of this Recommendation.

139. Guidance Notes on Genotoxicity of Nanomaterials were also adopted by WNT-34. This work was initiated and pursued by JRC and finalised thanks to the timely the collaboration of UK and DE.

140. We also welcome de adoption of OECD TG 125 on Nanoparticles Size and Size Distribution led by German, in which JRC had the pleasure to significantly contribute. It is also very much timely in view of the new Recommendation.

141. Finally, several **relevant JRC scientific publications** in this period:

- Mech, A., Gottardo, S., Amenta, V., Amodio, A., Belz, S., Bowadt, S., Drbohlavova, J., Farcal, R., Jantunen, A.P., Malyska, A., Rasmussen, K., Riego Sintes, J. and Rauscher, H., *Safe- and Sustainable-by-Design: the Case of Smart Nanomaterials. An outlook based on a European Workshop*, Regulatory Toxicology and Pharmacology, 2021. Accepted. JRC125986.
- Jeliazkova, N., Bleeker, E., Cross, R., Haase, A., Janer, G., Peijnenburg, W., Pink, M., Rauscher, H., Svendsen, C., Tsiliki, G., Zabeo, A., Hristozov, D., Stone, V. and Wohlleben, W., *How can we justify grouping of nanoforms for hazard assessment? Concepts and tools to quantify similarity.* NANOIMPACT, ISSN 2452-0748 (online), https://doi.org/10.1016/j.impact.2021.100366, 2021, JRC126283.

- Jeliazkova, N., Apostolova, M.D., Andreoli, C., Barone, F., Barrick, A., Battistelli, C.L., Bossa, C., Botea-Petcu, A., Châtel, A., De Angelis, I., Dusinska, M., El Yamani, N., Gheorghe, D., Giusti, A., Gomez-Fernandez, P., Grafström, R., Gromelski, M., Jacobsen, N.R., Jeliazkov, V., Alstrup Jensen, K., Kochev, N., Kohonen, P., Manier, N., Mariussen, E., Mech, A., Navas, J.M., Paskaleva, V., Precupas, A., Puzyn, T., Rasmussen, K., Ritchie, P., Rodríguez Llopis, I., Rundén-Pran, E., Sandu, R., Shandilya, N., Tanasescu, S., Haase, A. and Nymark, P., *Towards FAIR Nanosafety Data*, NATURE NANOTECHNOLOGY, ISSN 1748-3387 (online), 16 (6), 2021, p. 644–654, JRC121321.
- Cross, R., Bossa, N., Stolpe, B., Loosli, F., Mønster Sahlgren, N., Clausen, P.A., Delpivo, C., Michael, P., Valsesia, A., Ponti, J., Mėhn, D., Ag Seleci, D., Mueller, P., Lawlor, A., Von Der Kammer, F., Rauscher, H., Spurgeon, D., Svendsen, C. and Wohlleben, W., *Reproducibility of methods required to identify and characterize nanoforms of substances*, NANOIMPACT, ISSN 2452-0748 (online), 2021, JRC126869.
- Loosli, F., Rasmussen, K., Rauscher, H.,Cross, R., Matzke, M., Svendsen, C., Spurgeon, D., Bossa, N., Peijnenburg, W., Arts, J., Clausen, P.A., Wohlleben, W., Ruggiero, E. and Von Der Kammer, F., *Refinement of the selection of Physicochemical Properties for Grouping and Read Across of Nanoforms*, NANOIMPACT, ISSN 2452-0748 (online), 2021 JRC126623.
- Basei, G., Zabeo, A., Rasmussen, K., Tsiliki, G. and Hristozov, D., *A Weight of Evidence approach to classify nanomaterials according to the EU Classification Labelling and Packaging regulation criteria*, NANOIMPACT, ISSN 2452-0748 (online), 24 (100359), 2021, p. 1-13, JRC125664.
- Jantunen, A.P., Rauscher, H., Riego Sintes, J. and Rasmussen, K., *Commentary on "Safe(r) by design implementation in the nanotechnology industry" [NanoImpact 20 (2020) 100267] and "Integrative approach in a safe by design context combining risk, life cycle and socio-economic assessment for safer and sustainable nanomaterials"* [NanoImpact 23(2021) 100335], NANOIMPACT, ISSN 2452-0748 (online), 24, 2021, p. 100356, JRC125848.
- Allan, J., Belz, S., Hoeveler, A., Hugas, M., Okuda, H., Patri, A., Rauscher, H., Silva, P., Slikker, W., Sokull-Kluettgen, B., Tong, W. and Anklam, E., *Regulatory landscape of nanotechnology and nanoplastics from a global perspective*, REGULATORY TOXICOLOGY AND PHARMACOLOGY, ISSN 0273-2300 (online), 122, 2021, p. 104885, JRC123848
- Tschiche, H., Bierkant, F.S., Creutzenberg, O., Fessard, V., Franz, R., Giese, B., Greiner, R., Haas, K., Haase, A., Hartwig, A., Hesse, B., Hund-Rinke, K., Iden, P., Loeschner, K., Mutz, D., Rauscher, H., Rakow, A., Rasmussen, K., Richter, H., Schoon, J., Schmid, O., Som, C., Tovar, G., Wohlleben, W., Westerhoff, P., Luch, A. and Laux, P., *Nanotechnology: A current overview of research, applications, and regulatory perspectives*, ENVIRONMENTAL SCIENCE-NANO, ISSN 2051-8153 (online), 2021, JRC123949.
- 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*, Submitted to ENVIRONMENTAL SCIENCE-NANO, 2021.
- Mėhn, D., Gilliland, D., Mech, A., Rauscher, H. and Rasmussen, K., *Chapter 23. Challenges encountered in the size characterization of nano particulate systems*, In Contado, C. (editor) Particle separation techniques – Fundamentals, instrumentationand selected applications., Elsevier, 2021, JRC124195
- Harald R. Tschiche, Frank S. Bierkandt, Otto Creutzenberg, Valerie Fessard, Roland Franz, Bernd Giese, Ralf Greiner, Karl-Heinz Haas, Andrea Haase, Andrea Hartwig, Kerstin Hund-Rinke,

Pauline Iden, Charlotte Kromer, Katrin Loeschner, 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, Peter Laux, *Environmental considerations and current status of grouping and regulation of engineered nanomaterials*, Environmental Nanotechnology, Monitoring & Management, Volume 18, 2022, 100707, ISSN 2215-1532

- Basei G, Rauscher H, Jeliazkova N, Hristozov D. *A methodology for the automatic evaluation of data quality and completeness of nanomaterials for risk assessment purposes.* Nanotoxicology. 2022 Mar;16(2):195-216. doi: 10.1080/17435390.2022.2065222.

3.13. Malaysia

142. Department of Standards Malaysia (DSM) continue to participate in ISO/TC 229 Nanotechnology standardization meetings. Malaysia now 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 makes reference 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)

143. A new proposal titled Radiotelemetry-Spectral-Echocardiography Based Real-time Surveillance Protocol for In Vivo Toxicity Detection and Monitoring of Engineered Nanomaterials has been registered as a Preliminary Work Item (PWI 4963) under Project Group No. 35 (PG35).

3.14. Thailand

144. NANOTEC as a Standard Developing Organization (SDO) has collaborated with the Thailand Industrial Standard Institute (TISI) to develop new Thailand National Standards Guidelines, as shown below.

- Turmeric extract nano-encapsulated particles
- Centella extract nano-encapsulated particles
- Black ginger extract nano-encapsulated particles

145. These extract of nano-encapsulated particles are currently in high demand for using in cosmetics commercial products both domestically and export internationally.

3.15. Business at OECD (BIAC)

146. **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 NIA. As part of NanoHarmony, NIA will be contributing to the development of best practice guidelines for developers of future Test Guidelines.

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

147. PETA Science Consortium International e.V., a member of the International Council on Animal Protection in OECD Programmes (ICAPO), co-authored a publication describing an adverse outcome pathway (AOP) network evaluating the major processes known to be involved in regulating efficient mucociliary clearance (MCC) following exposures causing oxidative stress. The AOP network is under development on AOP-Wiki platform (AOP 411, 424, and 425).

Reference:

Luettich K, Sharma M, Yepiskoposyan H, Breheny D, Lowe FJ. An adverse outcome pathway for decreased lung function focusing on mechanisms of impaired mucociliary clearance following inhalation exposure. Front Toxicol. 2021;3:750254.

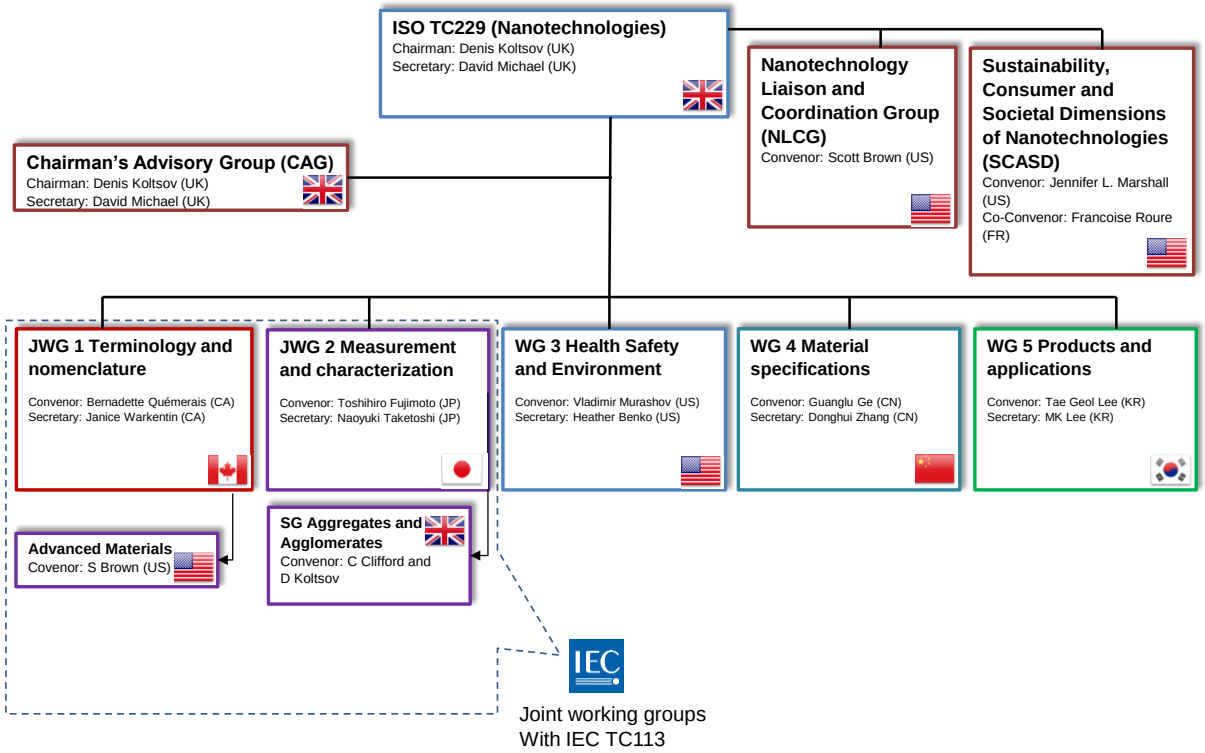
3.17. The International Organization for Standardization Technical Committee 229 (ISO TC229)

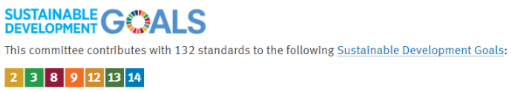
148. Scope: Standardization in the field of nanotechnologies that includes either or both of the following:

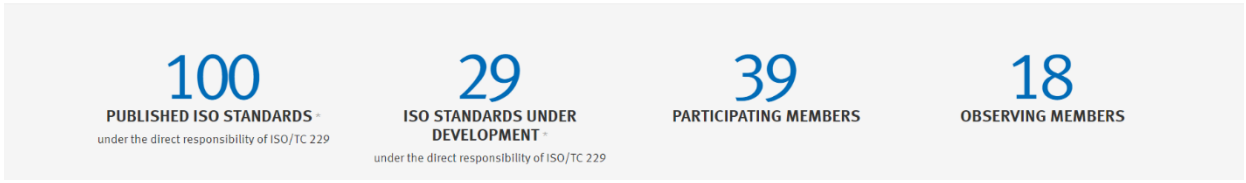
I. Understanding and control of matter and processes at the nanoscale, typically, but not exclusively, below 100 nanometres in one or more dimensions where the onset of size-dependent phenomena usually enables novel applications,

II. Utilizing the properties of nanoscale materials that differ from the properties of individual atoms, molecules, and bulk matter, to create improved materials, devices, and systems that exploit these new properties.

149. Specific tasks include developing standards for: terminology and nomenclature; metrology and instrumentation, including specifications for reference materials; test methodologies; modelling and simulation; and science-based health, safety, and environmental practices.







a. Work Programme of ISO/TC 229 Nanotechnologies - May 2022

JWG 1 Terminology and nomenclature

TS 4958	Nanotechnologies — Liposomes terminology
TS 20477 (Rev)	Nanotechnologies — Standard terms and their definition for cellulose nanomaterial
ISO 80004-1	Nanotechnologies – Vocabulary — Part 1: Core terms and definitions
TS 80004-13 (Rev)	Nanotechnologies — Vocabulary — Part 13: Graphene and related two-dimensional (2D) materials
PWI 5341	Nanotechnologies — Nomenclature — Part 1: General nomenclature

JWG 2 Measurement and characterization

TR 18196 (Rev)	Nanotechnologies —Measurement technique matrix for the characterization of nano-objects
TS 19590 (Rev)	Nanotechnologies — Size distribution and concentration of inorganic nanoparticles in aqueous media via single particle inductively coupled plasma

	mass spectrometry
TS 21356-2	Nanotechnologies – Structural characterization of graphene – Part 2: chemical vapour deposition (CVD) grown graphene'
ISO 21362	Nanotechnologies – Analysis of nanoobjects using asymmetrical-flow and centrifugal field-flow fractionation
TS 23359	Nanotechnologies – Chemical characterisation for graphene in powders and suspensions
TS 23361	Nanotechnologies - Crystallinity of cellulose nanomaterials by powder Xray diffraction (Ruland- Rietveld analysis)
TS 23690	Nanotechnologies – Carbon nanotubes -- Determination of amorphous carbon content by thermogravimetric analysis
TS 23878	Nanotechnologies – Positron annihilation lifetime measurement for nanopore evaluation in materials
ISO/NP TS 23879	Nanotechnologies – Structural characterization of graphene oxide flakes: thickness and lateral size measurement using AFM and SEM
TR 24672	Nanotechnologies — Guidance on the measurement of nanoparticle number concentration
IEC 62565-3-1	Nanomanufacturing – Material specifications – Part 3-1: Graphene – Blank detail Specification
PWI 3181	Nanotechnologies — Total and free drug quantitation in doxorubicin hydrochloride liposomal formulations
PWI 4961	Nanotechnologies — Determination of size and size distribution of nano-objects in liquid using aerosolization differential electron mobility analysing system
PWI 17530	Measurement of polyaromatics and other surface organic contaminants in carbon nanomaterials using Soxhlet extraction, UV-Vis, and GC/MS

WG 3 Health, Safety and Environmental

ISO 4962	Nanotechnologies — In vitro nanoparticle phototoxicity assay
TS 5094	Nanotechnologies — Assessment of peroxidase- like activity of metal and metal oxide nanoparticles
TR 5387	Nanotechnologies: Lung burden measurement of nanomaterials for inhalation toxicity studies
TS 7833	Extraction method of nanomaterials from organs by the proteinase K digestion
TS 11353	Nanotechnologies — Test method for detection of nanoobject release from respiratory masks media under different working conditions
TS 12901-1 (Rev)	Nanotechnologies — Occupational risk management applied to engineered nanomaterials — Part 1: Principles and Approaches
TS 12901-2 (Rev)	Nanotechnologies — Occupational risk management applied to engineered nanomaterials — Part 2: Use of the control banding approach
TR 13329 (Rev)	Nanomaterials — Preparation of safety data sheets (SDS)
ISO 19337 (TS Rev)	Nanotechnologies — Characteristics of working suspensions of nano-objects for in vitro assays to evaluate inherent nano-object toxicity
TR 23463	Nanotechnologies — Characterization of carbon nanotube and carbon nanofibre aerosols in relation to inhalation toxicity tests
PWI 4963	Nanotechnologies — Radiotelemetry-spectralechocardiography based real time surveillance protocol for in vivo toxicity detection and monitoring of engineered nanomaterials (ENM)
PWI 5265	Nanotechnologies — Method for characterizing and quantifying nanomaterials released from wood products
PWI 7666	Evaluation method for chronic inhalation toxicity based on lung burden of nanomaterials
PWI 12769	Nanotechnologies — Toxicity assessment of manufactured nanomaterials in soils using plant Arabidopsis thaliana

WG 4 Material specification

TS 22298	Nanotechnologies — Silica nanomaterials — Specifications of characteristics and measurement methods for nanostructured porous silica samples with ordered nanopore array
PWI 4966	Nanotechnologies — Nanostructured porous silica microparticles for chromatography
PWI 9651	Nanotechnologies — Classification framework for commercial graphene
PWI 12948	Nanotechnologies — Nanocomposite materials for insulating — Specification of characteristics and measurement methods

WG 5 Products and applications

TS 4971	Nanotechnologies –Performance evaluation of nanosuspensions containing clay nanoplates for quorum quenching
TS 10818	Nanotechnologies — Textiles containing nanomaterials and nanostructures — Superhydrophobic characteristics and durability assessment
TS 23366	Nanotechnologies — Performance evaluation requirements for quantifying biomolecules using fluorescent nanoparticles in immunohistochemistry
TS 23367-1	Nanotechnologies — Performance characteristics of nanosensors for chemical and biomolecule detection — Part 1: Detection performance
TR 23652	Nanotechnologies — Considerations for radiolabelling methods of nanomaterials for performance evaluation
PWI 10689	Nanotechnologies —Superhydrophobic surfaces and coatings: characteristics and performance assessment
PWI 23653	Nanotechnologies — Experimental considerations when evaluating nanoparticle performance of cellular uptake

150. For all published documents under ISO TC229 please follow this link: https://www.iso.org/committee/381983/x/catalogue/p/1/u/0/w/0/d/0

4 Information on any developments related to Integrated Approaches to Testing and Assessment (IATA)

4.1. Belgium

151. 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.

152. 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.

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

- nPSize (2018-2021): Improved traceability chain of nanoparticle size measurements. This project aims to develop methods, reference materials and modelling to improve the traceability chain, comparability and compatibility of nanoparticle size measurements.
- EMUE (2018-2021): Examples of Measurement Uncertainty Evaluation. This project provides a comprehensive set of worked examples illustrating how the principles of measurement uncertainty can support and give added value to normative and related practices. In particular our goal is to provide metrological traceability for nanoscale measurements and support instrument' users with comprehensive guidance on uncertainty evaluation.
- 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 (will start in 2022): 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.

4.2. Canada

154. Canada is developing a nanomaterial database containing information on both human health hazard and physical-chemical endpoints, in an attempt to predict genotoxicity of nanomaterials using machine learning techniques. Currently this database has been shared with NanoSolveIT, a project on introducing IATA for the environmental and human health and safety of nanomaterials, and further collaboration is ongoing.

155. Canada has initiated a program of work to develop the use of the in vivo zebrafish embryo platform for determination of toxic effects of nanomaterials in collaboration with Dr. Lee Ellis of the National Research Council of Canada. When validated this platform will allow for high-throughput whole-organism exposures at a fraction of the cost of traditional rodent assays and will reduce the need for animal testing. Current development of this platform is focused on ensuring that there is no interference from nanomaterials, that results can be accurately interpreted, and that the procedures can precisely control the dosimetry. Work will be ongoing through 2022/2023.

4.3. Germany

Federal Institute for Risk Assessment (BfR)

156. The BfR is involved in the following developments related to IATA: The EU H2020 project GRACIOUS, developing a grouping framework for nanomaterials, ended in September 2021. Two new publications on IATA have been published since the project ended, a general inhalation IATA (DOI: 10.1089/aivt.2021.0009) and an IATA for assessing genotoxicity (DOI: 10.1186/s12989-022-00476-9).

4.4. Italy

157. Nine IATAs to group ingested NMs following predefined hypotheses were presented in the paper *Grouping Hypotheses and an Integrated Approach to Testing and Assessment of Nanomaterials Following Oral Ingestion*, published by 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. *Nanomaterials* (Basel), 2021, 11(10):2623. doi: 10.3390/nano11102623.

158. The study was developed in the framework of H2020 EU projects GRACIOUS.

4.5. Korea

159. KATS(Korea Agency for Technology and Standards) developed two standards under ISO TC229 WG3 (Health, Safety and Environmental Aspects of Nanotechnologies).

160. The standards under development by KATS;

1) ISO/WD TR 5387 Nanotechnologies: Lung burden measurement of nanomaterials for inhalation toxicity studies
2) ISO/WD TS 7833 Extraction method of nanomaterials from organs by the proteinase K digestion.

4.6. The Netherlands

161. The EU project REFINE has ended March 1, 2022. The project delivered a regulatory framework for the risk benefit analysis of nanomedicinal products. The framework was built upon the Decision Support System as developed within the previous EU project SUN. The Decision Support System will be used to identify the most effective way to deliver the data required by regulation using the best fitting methods for registration of nanomedicinal products. The project produced a white paper on regulatory aspects and needs, and safety testing of nanomedicinal products. Based on regulatory requirements, the project further identified methodological gaps in the assessment of physicochemical parameters, kinetics (absorption, distribution, metabolism, and excretion – ADME), and immunotoxic effects of nanomedicines. Part of these gaps were experimentally addressed in the project. This experimental work included several animal toxicokinetic studies, as well as work on kinetic modelling at the cellular and organ level to potentially replace or limit animal testing. In addition, the applicability of a series of assays for nanomedicine characterisation and determination of potential immunotoxicity was tested for two nanomedicines.

4.7. Sweden

BIORIMA

162. Karolinska Institutet (KI) participated in the H2020 project BIORIMA ("biomaterial risk management") (2018-2021) and coordinated the workpackage on hazard assessment of nanobiomaterials (NBMs) comprised of 18 partner institutes. The BIORIMA project aimed to develop an integrated risk management framework for NBMs used in advanced therapy medicinal products (ATMP) and medical devices (MD). The risk management framework was conceptualized in the following publication: Giubilato E, et al. Materials (Basel). 2020;13(20):4532. The collection/generation of data for safety assessment of NBMs is based on integrated approaches to testing and assessment (IATAs).

4.8. United Kingdom

GRACIOUS

163. The GRACIOUS project started in January 2018, and will run until the end of September 2021. GRACIOUS has generated a Framework (Stone et al., NanoImpact 2020) to support the grouping and read-across of nanoforms, in order to streamline regulatory risk assessment and to support safe(b) by design processes during innovation. The Framework has been well received by regulatory stakeholders, with interest from ECHA, US NIOSH and Health Canada. ECHA and NIOSH are currently testing the framework with case studies. Industry case studies are also underway for consultants and industry group representatives.

164. The GRACIOUS Framework is now feeding into the work at OECD to update the Guidance on grouping of chemicals. Section 6.9 specifically addresses nanomaterials and currently states that grouping for nanomaterials has not yet been demonstrated. So far we have added a definition for nanomaterials, a historical and state of the art review of various projects including GRACIOUS. We have conducted a systematic analysis of the other sections of the guidance to identify where the guidance should differ to address nano-specific issues. We have also generated a list of current limitations that remain around the grouping of nanomaterials. The systematic analysis currently exists as a long table, which needs to be discussed with members to identify which elements are most important to include. An update will be provided in June in Paris. We hope to finish the work before the end of the year.

NanoSolveIT

165. 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.

166. The first integrated exposure and PBPK modelling has been developed and extension to include also toxicity impacts / adverse outcomes is underway. NanoSolveIT has integrated computational approaches which can be used to generate data relevant to human health risk assessment, namely the multi-box aerosol model for prediction of indoor air concentrations of NMs, the 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. 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 are 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. The full paper is here: https://doi.org/10.1039/D1EN00956G. The link to the models are here:

- Multi-box aerosol application: https://aerosol.cloud.nanosolveit.eu/
- Lung exposure: https://lungexposure.cloud.nanosolveit.eu/
- PBPK: https://exposurepbpk.cloud.nanosolveit.eu/

167. Complete documentation of the IATA hypothesis, the underpinning data, and the results are being written up and will be submitted for consideration as an OECD IATA Case study.

168. Work is also at an advanced stage on the daphnia reproduction IATA, integrating prediction of the acute toxicity, the DeepDaph image analysis tool to quantify morphological defects (e.g., changes in eye-tail length, tail length, lipid deposits, etc.), as well as a PBPK model and the Dynamic Energy Budget model and AOP developed within RiskGONE. Complete documentation of the IATA hypothesis, the underpinning data, and the results are being written up and will be submitted for consideration as an OECD IATA Case study.

RiskGone

169. 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.

170. RiskGONE is developing an in vitro NMs dosimetry application for the numerical transport modeling of NMs settling during cellular exposure to predict the real exposure dose. Using the approach of De Loid et al. (2018) who developed a multi-step in vitro dosimetry methodology to quantify delivered dose metrics as a function of time which consists of three interconnected parts: 1) ENM dispersion preparation; 2) ENM dispersion characterization; 3) numerical transport modeling to derive the delivered dose metrics. Our work falls into the category of the numerical transport modeling to derive dose metrics. We developed a user-friendly web-based application, termed as “NMs in vitro dosimetry application”,

designed especially for non-expert users based on the distorted grid (DG) fate and transport model. The DG model used in the in vitro dosimetry application requires user-input of ENM size and effective density, and is based on differential-equations. The solution of these equations provides both deposition and concentration metrics, and concentration profiles of ENMs across the experimental well (e.g., in a 96-well plate) as a function of the exposure time. The model was paramterised using seven different NPs, including two different gold NPs, coated with cysteine (CYS) and glutathione (GSH), and four different silver NPs (AgNPs), coated with CYS, GSH, bis(2-ethylhexyl)sulfosuccinate (AOT), and poly-L-lysine (PLL), and cytotoxicity data in human keratinocytes (HaCaT cell line) by means of cell viability using the MTT assay and oxidative stress response using 2′ ,7′ -dichlorofluorescein diacetate (DCFH-DA) staining. Based on the dosimetry modelling, the actually dose reaching cells is much higher than the stated dose based on the average solution concentration as a result of particle settling, which has consequences for the ranking of the NMs toxicity, and interpretation of dose-response curves.

171. Extensive work has been performed to compile and evaluate all of the potential interferences of NMs with different cytotoxicity assays, and the dependence of this on the NM physicochemical characteristics, the exposure conditions and the cell type (where this is known), which is now being utilised to develop a decision support tool to guide users towards the most suitable cellular assay for the particular end-point in question based on the specific NM properties. This will be part of the overall good practice guidance also.

4.9. European Union

172. As part of EFSA roadmap on new approach methodologies (NAMs), EFSA will launch in June 2022 a large project for implementing IATA based case studies demonstrating that NAMs can replace animal testing for the assessment of nanoscale considerations for food and feed safety assessment.

4.10. Business at OECD (BIAC)

173. **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.

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

174. PETA Science Consortium International e.V. is co-editing a Research Topic in *Frontiers in In Vitro Toxicology* together with the US Environmental Protection Agency, Japan Tobacco International, Corteva Agriscience, and The Acta Group. The aim of the Research Topic on 'Chemical Testing Using New Approach Methodologies (NAMs)' is to highlight innovative NAM research, elucidate how NAMs can be used in an integrated approach to provide information that answers regulatory questions to protect humans and the environment, and overall increase confidence in NAMs. Seven articles from academia, industry, and government agencies have already been published and a couple more are currently in the reviewing process. More information about the Research Topic and the published manuscripts can be found here: https://www.frontiersin.org/research-topics/19075/chemical-testing-using-new-approach-methodologies-nams

175. Following up on the recommendations from 2016 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 this testing on the first set of chemicals (Triethoxysilane and Trimethoxysilane) were presented at the Society of Toxicology (SOT) conference, at a webinar organized by ScitoVation, and at the Lung In Vitro event (LIVe2022) organised by Epithelix Sarl and Altertox. The initial phase of the project used BEAS-2B cells (a human bronchial epithelial cell line) and reconstructed tissue model (MucilAir™, Epithelix) to assess the ability of silanes to cause portal-of-entry effects on the human respiratory tract. 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/

176. 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 (~8 months) hPCLS were cultured for 28 days and showed to have similar performance in terms of viability, biomass, cytotoxicity, and cytokine response. The highlights of this study were presented at the SOT and LIVe2022, and a manuscript is under preparation to be submitted soon.

177. In 2021, PETA Science Consortium International e.V. and MatTek announced an award to provide an opportunity for researchers worldwide to win three-dimensional (3D) reconstructed human respiratory tissues from MatTek. Dr. Eleonore Fröhlich from the (Medical University of Graz, Austria) and Dr. Elizabeth McInnes (Syngenta Ltd, UK) received tissues worth $10,000 (first place) and $5,000 (runner-up) redeemable for EpiAlveolar™ and EpiAirway™ tissues. The two awardees are using the tissues to assess the respiratory toxicity of carbon nanotubes and pesticides, respectively. 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

178. 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 2020 one project (SolarCircle) is funded dealing with the role of nanomaterials and „advanced materials“ in the circular economy (project duration September 2020 – September 2021; The BOKU, Vienna (lead: Eva-Kathrin Ehmoser) cooperated with the Institute of Physical Chemistry and Linz Institute for Organic Solar Cells as well as with the Energieinstitut at the JKU Linz.

https://forschung.boku.ac.at/fis/suchen.projekt_uebersicht?sprache_in=de&menue_id_in=300&id_in=13572.

5.2. Belgium

179. Over the past few years, numerous discussions, within different partnerships, have highlighted the need to develop 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 therefore seems welcome and appropriate on this subject.

180. The FPS Economy, Service of Metrology – National Standards (SMD) is part of the EURAMET Advanced Manufacturing Network and its subgroup focusing on Advanced Materials.

5.3. Canada

181. Canada has done some preliminary work to identify advanced materials relevant for our activities and better understand advanced materials and their status in Canada and the Canadian market. Work involves defining, grouping and characterizing advanced materials, as well as conducting a market scan and collecting information on the use of advanced materials in Canada.

5.4. France

182. **LNE** helped set up the **European Metrology Network** on *Advanced Manufacturing* (EMN for Advanced Manufacturing / https://www.euramet.org/european-metrology-networks/advanced-manufacturing/?L=0), in which it is responsible for leading the *Advanced Materials* pillar. The main objectives of this network are:

- to improve coordination of European actions in the field of metrology to address Advanced Manufacturing & Advanced Materials issues;
- to set up a Single Entry Point to access the NMI (National Metrology Institute) community; and
- to draw up a Strategic Research Agenda (SRA) based on interested stakeholders consultations with a view to providing input for future European calls for proposals (including those under the new *European Partnership on Metrology* EPM / https://www.metpart.eu/).

183. **LNE** continued its participation in the ***Validation Service*** within the **EU Graphene Flagship**. It aims at offering industry high metrological quality services regarding characterization of Graphene-Related Materials features and behaviour (in particular ageing and released during the life cycle of product). LNE is finally involved in the EMPIR project **ISO-G-Scope**, entitled “Standardisation of structural and chemical properties of graphene”, aiming at developing a harmonized reference method to reliably characterize graphene properties.

184. **LNE** has been asked by the French Ministry of Health to characterise the graphene contained in masks. The results obtained were used to publish the corresponding ANSES opinion (https://www.anses.fr/en/node/152312).

5.5. Germany

Federal Institute for Risk Assessment (BfR)

185. BfR is involved in the following advanced materials activities:

- The German authorities BAuA, BfR and UBA drafted a framework document on advanced materials “Risk Governance of Advanced Materials”. This includes, among other things, an early warning system to identify "materials of concern" as well as a presentation on the implementation of "regulatory readiness", for which the concept of "regulatory readiness levels" is introduced. The document was published in December 2021 and can be accessed via the UBA Homepage (https://www.umweltbundesamt.de/publikationen/risk-governance-of-advanced-materials)
- The EU HARMLESS project case studies on advanced materials were presented at the OECD Steering Group Advanced Materials meeting. The case studies intend to test, verify and improve Safe-by-Design and Safe Innovation Approaches in different industrial sectors, i.e. papermaking, paint formulation, catalysts, façade insulation, and agriculture. A detailed overview of the case study materials is provided on the HARMLESS Project homepage (https://www.harmless-project.eu/case-studies/).

German Environment Agency (UBA)

186. From December 2019 until June 2020, UBA executed a series of thematic conferences to initiate international stakeholder exchange on challenges of advanced materials for chemical safety and sustainability. At the conferences the heterogeneity of the field, approaches to cluster the broad field but also proposals to priorities advanced materials based on concerns regarding safety, insufficient regulation or impacts for sustainability were discussed. Examples of advanced materials were presented which were

already identified to pose challenges to current risk assessment tools, chemical regulations or might hamper circular economy of products. In the final conferences, considerations and options for actions on advanced materials were discussed from different stakeholder perspectives. The final report describing the execution and outcomes of the thematic conference is now available at: https://www.umweltbundesamt.de/en/publikationen/thematic-conferences-advanced-materials

German Environment Agency (UBA), Federal Institute for Occupational Safety and Health (BAuA) and Federal Institute for Risk Assessment (BfR)

187. The German higher federal authorities Federal Institute for Occupational Safety and Health (BAuA), the German Federal Institute for Risk Assessment (BfR) and the German Environment Agency (UBA) have issued a joint paper with recommendations for the responsible use and appropriate governance of advanced materials.

188. This includes, among other things, an early warning system to identify materials that give cause for concern. The authorities also see the need to review and, if necessary, to adapt existing laws, regulations and assessment methods in a timely manner. Only in this way the legal framework can keep pace with technical innovation.

189. This joint perspective also takes up the on current discussions about concepts for safe and sustainable design ("Safe and Sustainable by Design") of chemical substances, materials and products. In doing so, it offers recommendations regarding what needs to be considered in order to apply these concepts to advanced materials.

190. In view of the interdisciplinary nature of the subject and the diversity of the interest groups concerned, the paper emphasises the importance of establishing dialogue mechanisms. In addition, future research needs are also determined. In particular, preliminary research should be intensified in order to support safe and sustainable early-stage development of material innovations. Research accompanying regulation is also required, examining the need for specific regulatory measures and developing adapted test and assessment methods.

191. The paper, which summarises current activities, considerations and recommendations of BAuA, BfR and UBA, is intended to serve as a basis for discussion at national, European and OECD level. It picks up the discussions that were held in a series of three international thematic conferences organised by the UBA on advanced materials and their challenges. It can be found at the webpage of UBA: https://www.umweltbundesamt.de/en/publikationen/risk-governance-of-advanced-materials

5.6. Italy

192. ISS in collaboration with the Italian Ministry of Health is organizing the second national conferences on AdMa (October 2022). Main conference purpose is to stimulate a national dialogue among Academia, Industry and Regulators on AdMa. The outputs of the OECD' activities will also be mentioned. The establishment of an Italian task force is the main objective of the meeting, in order to strengthen the national position hopefully through the development of a position paper.

193. Case studies developed in the ASINA EU H2020 project (*Anticipating Safety Issues at the Design Stage of NAno Product Development*, https://www.asina-project.eu/) have been included in the work plan of the WPMN ad hoc group on AdMa.

5.7. The Netherlands

194. In collaboration with BfR, BAuA and UBA RIVM developed a novel early warning system – named **Early4AdMa** (formerly EWARN) - to identify emerging safety and sustainability issues of advanced nanomaterials. This system can be applied by regulators, risk assessors, as well as innovators. Details of how this system works are described in a brochure. The system aims to provide an anticipatory risk governance approach and to proactively avoid the occurrence of potential unexpected risks of advanced (nano)materials. Addressing safety and sustainability issues early in the innovation chain can support innovation by preventing problems later on. The brochure of the proposed Early4AdMa system can be regarded as a thought starter. The main purpose of this brochure is to receive input on the structure and content of the proposed Early4AdMa system for advanced nanomaterials. The system was discussed in a workshop by the OECD Steering Group on advanced materials in February 2022, in which hands-on experience with a case study was achieved. The input and feedback received will be used to further improve the Early4AdMa system in the coming year, facilitate discussions at an EU level, and to use as input for the development of the strategic approach for advanced materials by the OECD WPMN Steering Group on Advanced (nano)Materials (SG-AdMa).

5.8. Slovak Republic

195. The Slovak Academy of Sciences organized conference dealing with nanocomposites in plastics and workshops solving the problematic of nano-coatings and nano-fillings.

5.9. United Kingdom

196. In April 2021, the UK held a UK workshop on Advanced Materials co-organized by (Defra, NPL, HSE, BSI, ISO and PHE). 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. The UK is planning to expand the series with another workshop in 2022 focusing on identifying case studies and best practice.

Health and Safety Executive (UK) Advanced Materials project

197. 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. Graphene Standardization work. NPL (UK) leading and contributing to the development of ISO documents for the characterisation of graphene and graphene platelets.

198. HSE Advanced Materials project. Main objectives to be delivered in 2021/2022 include:

- **O1** To collect and disseminate information on advanced carbon based materials in manufacturing, the processes that release hazardous particles that can enter the lungs and good working practices.
- **O2** To gather and disseminate knowledge on practical methods for sampling, quantifying and characterising exposure to airborne hazardous particles from the use and handling of advanced carbon based materials.
- **O3** Stakeholder engagement and communications.

SUNSHINE

199. 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).

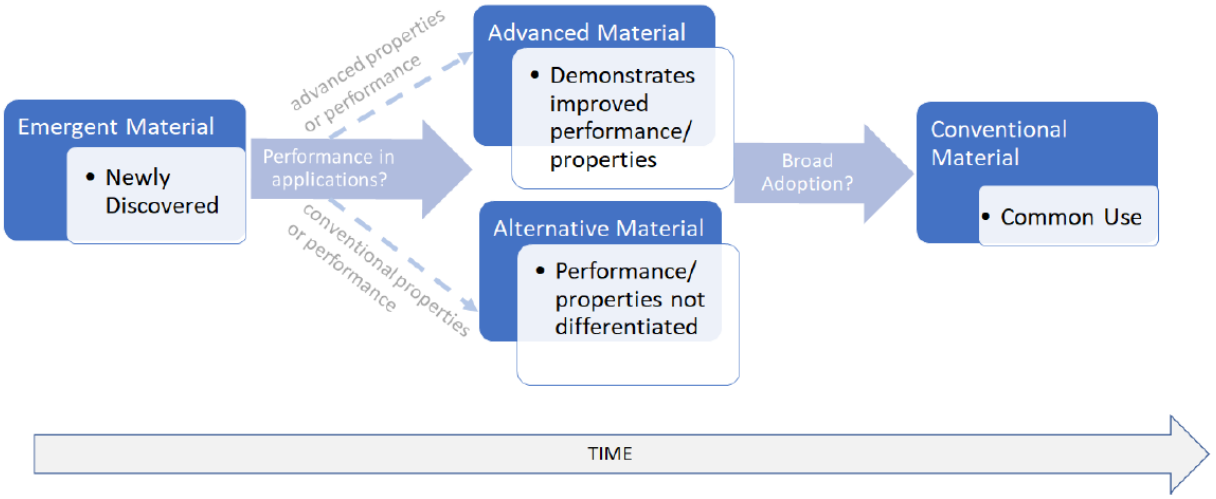
5.10. Business at OECD (BIAC)

200. **NIA** actively contributes to the discussion on Advanced Materials through its participation at the OECD WPMN Steering Group on Advanced Materials.

201. **The American Chemical Council** (ACC) members have been working diligently to reach their 2030 and 2050 sustainability goals. Achieving these goals require the use of advanced technologies including nanotechnology. The ACC has been active in the development of voluntary standards in parallel and in support of the work in the OECD WPMN. The ACC through the American National Standards Institute (ANSI) led ISO TC 229 study group efforts on the topic of advanced materials. This study group involved over 13 countries and received input from industry, government, academia and non-governmental organizations. The study group is in the process of submitting a pre-work item (PWI) to ISO TC 229 as a potential future technical specification covering terminology related to innovations in technology and materials. This document is intended to provide consensus driven definitions of terms and will include a definition for 'advanced materials'. The ACC also worked with the US Nanotechnology Standards Panel to develop a two-day web-conference on advanced materials. ACC members have also been active participants in inter-laboratory studies in support of Test Guideline development within the OECD related to nanotechnologies.

5.11. The International Organization for Standardization Technical Committee 229 (ISO TC229)

202. ISO TC229 (Nanotechnologies) JWG1/SG (Study Group on Advanced & Emerging Materials). Study group was led by USA since 2020 and has now produced a set of terms and definitions that may help us to clarify what we mean by emerging technologies and advanced materials.



203. The focus for the definition of the term “Advanced Materials” (after a great number of meetings) was on the actual performance and enhancement brought worth by the use of AdMa. It was also clearly stated that advanced materials of today may become conventional materials tomorrow.

204. The following terms were proposed at the working group level at ISO TC229/JWG1 (Terminology). These terms have not yet been balloted widely but represent ISO TC229/JWG1 current consensus. These terms will be included in a newly proposed terminology document (Nanotechnologies — Vocabulary — Innovations in Materials and Technology).

205. NOTE: OECD is a liaison organisation with ISO TC229 and therefore has full capacity to send in comments on any of these terms. Please contact us with your comments.

206. The newly proposed document:

Nanotechnologies — Vocabulary — Innovations in Materials and Technology

Scope:
This document lists terms and definitions related to advanced technologies and materials related to nanotechnologies.
It is intended to facilitate communications between organizations and individuals research, industry and other interested parties and those who interact with them.

Key terms:
advanced technology
technology that uses highly sophisticated equipment and engineering techniques

Note 1 to entry: Sophisticated equipment and engineering techniques apply more recent advances in science or are more complex than others.

conventional technology
technology in common use for a given purpose

Example:

emergent technologies
any new technology or an existing technology applied for new unconventional purposes

conventional material
material in common use for a given purpose, or material having typical properties for a given measure.

Example: copper metal used as a conductor; silicon used as a semiconductor

advanced material
material (4.1) with significant improvements in properties or performance **(4.3)** for a specific application
Note 1 to entry: Some advanced materials gain their improved properties through modification of their internal or surface structure.
Note 2 to entry: Some but not all advanced materials are created by Advanced Technologies (4.2).
Note 3 to entry: Some but not all nanomaterials are advanced materials.
Note 4 to entry: Advanced materials can be, but are not always ***complex / highly engineered*** ***materials*** *(4.3).*
Note 5 to entry: Materials that are considered to be advanced materials today are anticipated to be displaced or to become conventional materials in the future.
Note 6 to entry: Might include new functionality or emergent properties of a material
Note 7 to entry: significant improvements in performance and properties relate to conventional materials (when they exist)
Note 8 to entry: Used in advanced technologies or specialty applications

emergent material
any new material, or a material applied for new purposes

Note to entry: emergent materials might not have emergent properties

Example of a new material: Replacing silicon with gallium arsenide in electronic devices

Example of material applied for a new purpose: Quantum dots in televisions

207. These terms (and a few others) will form the basis of the new Preliminary Work Item (PWI) under consideration in ISO TC229/JWG1.

6 Research programmes or strategies designed to address human health and/ or environmental safety aspects of (advanced) (nano) materials (e.g. investigation in safety aspects, case-studies, pre-regulatory strategies)

6.1. Austria

208. 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, networksand 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 workpackage 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.

209. 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.

210. 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-OeW 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.

211. It's sister project **SABATLE** aims 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 are investigated and compared to emerging electrolytes developed by the **Technical University of Graz**, based on organic compounds derived from lignin, provided by **MONDI AG** Austrian partner **BNN** (contact: Clemens Wolf) contributes by implementing a Safe and Sustainable by Design concept (SaSb) guiding the development.

212. The project **PLASTMARK** (lead: Florian Part; running from 11/2021 to 12/2022), which is funded by the NANO EHS program, aims to integrate special markers into thermoplastics in order to improve the detectability and thus recyclability of engineering plastics. This approach is also known as marker- or tracer-based sorting, in which automated sensor systems are used to sort our recyclable plastics. BOKU, in cooperation with POLYMERWERKSTATT GmbH, is selecting three candidate markers based on their unique properties (e.g. fluorescence) and toxicity profiles in the sense of the safe- and sustainable-by-design concept. For the proof-of-concept on a laboratory scale, these markers are incorporated into polyoxymethylene (POM), which is known as problematic plastic waste stream because it is immiscible with other thermoplasts and can lead to formaldehyde emissions during extrusion.

213. The Institute of Technology Assessment is partner in the EU-Projekt "REconciling sCience, Innovation and Precaution through the Engagement of Stakeholders" (RECIPES; lead: University of Maastricht. 2020-2022). The project **RECIPES** aims to analyse how the precautionary principle is applied in the European Union and improve its future application with recourse to participatory methods. The precautionary principle has been recognised as a general principle in EU law and in various EU regulations and directives. The Project RECIPES has been completed with an international conference on the applicability of the precautionary principle in May 2022.

214. The project **NanoSyn3**, coordinated by **BNN** (contact: Andreas Falk), funded by the Ministry for Climate Action, Environment, Energy, Mobility, Innovation and Technology (BMK), started in April 2022 and shall be finalized by in March 2023. Core activities will be to lift the identified potentials and synergies at national and international level towards collaboration in the field of nanotechnology, more specific in the Safety and Sustainability area. The collaboration with Austrian public financed activities (e.g., NanoTrust), as well as technology platforms (e.g., SusChem-AT, NanoMedicine-AT, Advanced Microfluidics) shall strengthen the national and international interaction (e.g., within the EU NanoSafety Cluster, the INISS-nano, PARC, OECD, ISO, CEN, ETP Sustainable chemistry, Microfluidics community) related to nanotechnologies and advanced materials.

215. The **H2020 project GRACIOuS**: Grouping, Read-Across, CharacterIsation and classificatiOn framework for regUlatory risk assessment of manufactured nanomaterials and Safer design of nano-enabled products finished end of 2021. The **University of Vienna** (Department of Environmental Geosciences, contact **Frank von der Kammer**) participates in this project and acts as co-leader of WP 3 Intrinsic Properties of Nanomaterials. The project aims to develop grouping and read-across strategies and tools for nanomaterials. http://cordis.europa.eu/project/rcn/212339_de.html

216. The **H2020 project ACEnano** concluded in June 2021 and developed analytical tools for nanoparticle testing and risk assessment. The **University of Vienna** (Department of Environmental Geosciences, contact **Frank von der Kammer**) is scientific co-coordinator of the project and leads WP1,

technical innovation. Specifically in WP1 the outcomes of the NanoEHS project DetectNano will be further developed into an instrumentation to identify ENPs based on their elemental fingerprints in collaboration with the producer and the ETH Zurich. **BNN** (contact: Andreas Falk) joined in 2020 as partner to strengthen the consortium with its innovation support expertise. BNN developed **Guidelines for SMEs** for the ACEnano tools; furthermore collaborating in WP5 (guidelines, standardisation) and WP6 (dissemination, workshops).

217. **ENDONANO** (Albert Duschl and Jutta Horejs-Höck, **University of Salzburg**) is a European Industrial Doctorate (EID) that aims at developing new concepts and methods for the evaluation of bacterial endotoxin in complex matrices. The goals of ENDONANO include: 1. Investigating the capacity of endotoxin to specifically inducing inflammatory reactions in human primary blood cells; 2. Developing new methods based on endotoxin capture by metal nanoparticles in complex matrices; 3. Designing and implementing signal generation and detection methods for the quantitative endotoxin measurement in NP formulations; 4. Planning assay prototypes to be developed and validated for commercial purposes.

218. 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.

219. The EU funded **H2020 Research and Innovation action BIORIMA - Biomaterial Risk Management** (start: November 2017) finally ended after more than four successful years in January 2022. The project aimed to develop an integrated risk management framework for nano-biomaterials used in advanced therapeutic medicinal products and medical devices. **BNN** (contact: Susanne Resch) and **JOANNEUM RESEARCH - HEALTH** (Thomas Birngruber) were part of the BIORIMA consortium.

220. In the **H2020 project NanoCommons** (start: January 2018) **BNN** (contact: Andreas Falk) and **University of Salzburg** (contac:Albert Duschl) are partners and work package leader in this project. 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 is developing a sustainability plan, integrating all three dimensions of sustainability and creating a long-term supporting infrastructure in Europe and globally. The project shall conclude in June 2022.

221. In the EU-funded H2020 NMBP-13 project **NanoRigo** (start: January 2019) the **University of Salzburg** (contact Albert Duschl and Martin Himly) are responsible for performance of case studies and training activites on the currently ongoing development of a nanorisk governance framework. Training activities include further stakeholder engagement (researchers, industry, regulators, insurances, NGOs, policy makers, open public) for the establishment of a pan-European NanoRisk Governance Council.

222. Furthermore, Austrian organisation **BNN** (contact: Susanne Resch) is beneficiary of project **Gov4Nano - Implementation of Risk Governance: meeting the needs of nanotechnology** (start: January 2019), the second of the three NMBP-13 projects. Within the project, BNN is work package leader and responsible for Stakeholder engagement, Organization of interdisciplinary User Committee dialogues, Public risk perception, Risk governance, Dissemination, as well as Training & Education. The Department of Environmental Geosciences of the University of Vienna (Frank von der Kammer) is also involved in Gov4Nano, specifically in the OECD related activities of WP2 and as leader of task 2.7 on the environmental transformation of nanomaterials.

223. 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 (Austria), and the 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.

224. In the H2020 project **SABYDOMA - SAfety BY Design Of nanoMAterials** – (start: April 2020), the Austrian partner **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 nanomaterials.

225. Within the EU-H2020-funded NMBP-15-project **SbD4Nano - Safe-by-Design for Nano** (start: April 2020), **BNN** (contact: Susanne Resch) is involved as partner contributing in the Stakeholder engagement, Communication, Dissemination & Exploitation, thus supporting the international collaboration in the field of SbD-tools development.

226. 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.).

227. In the EU funded H2020 Research and Innovation action **NanoPAT - Process Analytical Technologies for Industrial Nanoparticle Production** – project (start: June 2020), **BNN** (contact: Andreas Falk) is leading the "safety" task, being in charge of developing a SbD concept for the project, supporting the development of responsible and safer innovations by assessing safety aspects, 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).

228. The EU-H2020-funded 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 Safe Innovation Approach, Stakeholder engagement, Graphic Design, Communication & Dissemination.

229. Complementary to this, **BNN** (contact: Susanne Resch) is involved in the EU-H2020 project **DIAGONAL - Development and scaled Implementation of sAfe by design tools and Guidelines for multicOmponent aNd hArn nanomateriaLs** (start: May 2021) in its role to work on Mainstream Sustainability into Safety-by-Design, Liaison management, Stakeholder engagement, Communication & Dissemination.

230. Next to that, 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.

231. The EU-funded 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: Susanne Resch) contributes to develop the production of sustainable and safe products by implementing Safe-by-Design principles guiding the entire process chain.

232. **Martin Himly**, University of Salzburg is since Apr 2020 chair of the EU NanoSafety Cluster Working Group A on Communication, Training and Education) organizes project-overarching webinars and training sessions in nanosafety assessment (www.nanosafetycluster.eu).

6.2. Belgium

233. Case studies on silver and titanium dioxide nanoparticles in face masks ongoing in Belgium.

234. The AgMask project aims 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. TiO2 seems to be embedded in the mask fibers while silver is found on the surface of the textile. At the moment, it is unknown if and how these nanoparticles can be inhaled and if users of Avrox masks have been exposed to them. Investigations are ongoing to create exposure scenarios and calculate the risk.

235. TiO2-Mask COVID-19 will analyze several facemasks (in paper and in textile) and identify as well as conduct a physicochemical characterisation of TiO2 nanoparticles. Investigations are ongoing to create exposure scenarios and calculate the risk.

6.3. Canada

Listing of internally funded projects undertaken by Environment and Climate Change Canada on engineered nanomaterial (ENM) include environmental toxicity testing, fate studies and health research on amorphous silica, zinc oxide and titanium dioxide nanoforms.

236. As part of Canada's Chemicals Management Plan, the Government of Canada has the responsibility to assess nanoscale forms of several metal oxides on the Domestic Substances List. Environment and Climate Change Canada researchers are investigating the relationship between dissolution behaviour and toxicity of eight metal oxide nanomaterials that are currently in commerce in Canada.

- Investigating the environmental background of nanomaterials in Canada, including areas expected to have high and low anthropogenic release.
- Developing sampling and pretreatment strategies for nanoparticles in natural samples.

237. Developing analytical techniques using isotope and elemental ratios to distinguish manufactured nanomaterials from natural colloids in the Canadian environment. This research approach will be helpful to determine fate of nanoparticles, including those that are potentially soluble in Canadian natural waters with varying pH, dissolved organic matter, etc.

Publications:

- Jreije I, Hadioui M, Wilkinson KJ. 2022. Sample preparation for the analysis of nanoparticles in natural waters by single particle ICP-MS. Talanta. 238:123060. doi:10.1016/j.talanta.2021.123060.

- Auclair J, Peyrot C, Wilkinson KJ, Gagné F. 2022. The Influence of Silver Nanoparticle Form on the Toxicity in Freshwater Mussels. Applied Sciences. 12(3):1429. doi:10.3390/app12031429.
- Azimzada A, Jreije I, Hadioui M, Shaw P, Farner JM, Wilkinson KJ. 2021. Quantification and Characterization of Ti-, Ce-, and Ag-Nanoparticles in Global Surface Waters and Precipitation. Environ Sci Technol. 55(14):9836–9844. doi:10.1021/acs.est.1c00488.

238. Evaluation of fate, bioaccumulation, and toxicity of CuO nanomaterials to soil invertebrates in soil and biosolid-amended soil. CuO nanomaterial toxicity was predicted by the soluble Cu ion in soil, with time and biosolid amendment affecting the rate of dissolution. Although not significantly bioaccumulative, Cu nanoparticulates were detectable in tissues. Soluble Cu was also predictive of plant toxicity in the same exposure scenarios, although minimal impact to soil microbial communities and their activity was observed.

Publications:

- Velicogna, J., Schwertfeger, D., Jesmer, A., Beer, C., Kuo, J., Scroggins, R., DeRosa, M., Smith, M., Princz, J. 2021. Soil invertebrate toxicity and bioaccumulation of nano copper oxide and copper sulphate in soils, with and without biosolids amendment. Ecotoxicology and Environmental Safety 217: 11222. DOI: 10.1016/j.ecoenv.2021.112222
- Samarajeewa, A., Velicogna, J., Schwertfeger, D., Princz, J., Subasinghe, R., Scroggins, R., Beaudette, L. 2021. Ecotoxicological effects of copper oxide nanoparticles (nCuO) on the soil microbial community in a biosolids-amended soil. *Science of the Total Environment*. DOI: 10.1016/j.scitotenv.2020.143037

239. Evaluation of the fate and removal of metal (CuO, Ag) nanomaterials during chemical conditioning of anaerobically digested sludge, and their impact to soil bacteria after land application. Rapid physical and chemical transformations were evident following conditioning, with significant accumulation in sludge. CuO nanomaterials exerted greater effects on soil bacterial endpoints, relative to Ag; effects varied, depending on bacterial community and activity studied. Study was a collaboration between Government of Canada researchers and Carleton University researchers.

Publications:

- Abdulsada, Z., Kibbee, R., Schwertfeger, D., Princz, J., DeRosa, M., Örmeci, B. 2021. Fate and removal of silver nanoparticles during sludge conditioning and their impact on soil health after simulated land application. Water Research 206(1): 117757. DOI: 10.1016/j.watres.2021.117757
- Abdulsada, Z., Kibbee, R., Princz, J., DeRosa, M., Örmeci, B. 2021. Transformation of silver nanoparticles (AgNPs) during lime treatment of wastewater sludge and their impact on soil bacteria. Nanomaterials 11(9): 2330. DOI: 10.3390/nano11092330
- Abdulsada, Z., Kibbee, R., Örmeci, B., DeRosa, M., Princz, J. 2021. Impact of anaerobically digested silver and copper oxide nanoparticles in biosolids on soil characteristics and bacterial community. Chemosphere 263:128173. DOI: 10.1016/j.chemosphere.2020.128173

240. Ongoing evaluation of metal solubility for CuO nanomaterials in soil, using nanomaterials with different coatings (e.g., PVP, stearic acid, mineral oil) and sizes (e.g., 10 and 25-55 nm), and resultant impacts on soil invertebrate and microbial health. Current research also includes an evaluation of the influence of soil pore water, derived from different soil types, on dissolution.

241. Assessment of the fate of nanomaterials, such as silver nanoparticles (Ag NP) released from municipal wastewaters. Silver nanoparticles and transformation products were evaluated in Canadian municipal wastewater effluents as potential additional silver sources in natural waters. Studies reported the presence of Ag NP in all effluent samples with concentrations reaching 0.5 ng/L on a mass basis. However, on a particle number basis, Ag NP concentrations (expressed in particle/mL) in the 20-34 nm small fraction were much more abundant (>700%) than in the >35 nm larger fraction. The proportion of Ag at the nanoscale (1-100 nm) represented less than 8% of the total suspended Ag for all effluent samples.

Because Ag nanotoxicity is size dependent, the determination of size distribution and exposure concentration on a particle number basis (i.e., number instead of mass) is needed for risk assessment of this class of nanomaterial.

Publication:

- Gagnon C, Turcotte P, Gagné F, Smyth SA. 2021. Occurrence and size distribution of silver nanoparticles in wastewater effluents from various treatment processes in Canada. Environ Sci Pollut Res. 28 : 65952–65959. doi: 10.1007/s11356-021-15486-x

242. The projects undertaken by Environmental Health Sciences and Research Bureau (EHSRB), Health Canada on engineered nanomaterial (ENM) toxicity testing for health and safety aspect include work on amorphous silica, zinc oxide and titanium dioxide nanoforms (Dr. Prem Kumarathasan, Dr. Dalibor Breznan, Dr. Azam Tayabali), and have internal funding. These research projects are also relevant to IATA (4- as identified in OECD-WPMN template) based on the integrated nature of toxicity testing and can also be applicable to the development and consideration related to multicomponent/complex advanced materials (5- as identified in OECD-WPMN template). These projects will generate information on relative in vitro potencies of these nanoforms, toxicity mechanisms and identify physico-chemical determinants of toxicity of these ENMs. These projects are conducted in collaboration with ECCC, NRC and academic partners and the work is on-going.

Amorphous Silica nanoforms

243. In this project, a set of custom-synthesized amorphous nonporous silica nanoparticles (SiNPs) including pristine and surface-modified NPs of varying sizes for in vitro cytotoxicity. We have examined internalization of SiNPs into phagocytic cells by TEM analyses and localization of these NPs and assessed cellular structural changes. We are also developing high-throughput high content proteomic analysis based on mass spectrometry methods to assess nanoform specific protein-level changes to understand toxicity mechanisms and as part of a New Approach Methodology (NAM) development for nanaomaterial toxicity testing. In vitro cell culture exposure experiments were carried out with these SiNP variants using multiple cell lines (human lung epithelial cells-A549; mouse monocyte/macrophage cells-J774) 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) construction.

Zinc oxide nanoforms

244. In this work, well characterized pristine and surface-modified zinc oxide NPs are screened for in vitro toxicity. In vitro toxicity testing is done using multiple cell lines (human lung epithelial cells-A549; mouse monocyte/macrophage cells-J774) using integrated toxicity testing approach for multiple cytotoxicity endpoints (e.g. viability, cell metabolism, membrane integrity). Cellular oxidative stress and protein level changes are examined for secreted protein changes (e.g inflammatory cytokines, growth factors). Testing of association between physicochemical properties and cellular cytotoxicity endpoints are carried out to identify physicochemical characteristics influencing cytotoxicity. Also, cells were exposed to reference particles to understand the nature of contribution of ionic and particulate forms of Zn towards cytotoxic responses. In addition, high content proteomic analyses for exploration of toxicity mechanisms in support of adverse outcome pathway (AOP) construction is planned in this project.

Titanium dioxide nanoforms

245. In this project, pristine and surface-modified TiO2 nanoforms with known physicochemcial properties (e.g. ICP-MS, DLS, etc.) from various sources are screened for in vitro toxicity. In vitro exposure

experiments are carried out using multiple cell lines (human lung epithelial cells-A549; mouse monocyte/macrophage cells-J774, and human monocytes-driven macrophages THP-1). Integrated toxicity testing approach is applied with multiple cytotoxicity endpoints testing (e.g. viability, cell metabolism, membrane integrity). Cellular oxidative stress levels and secreted protein changes (e.g inflammatory proteins) are analyzed, after NP exposures. Testing of association between physicochemical properties and cytotoxicity is conducted to identify determinants of toxicity. In addition, high content cellular proteomic analyses for exploration of toxicity pathways is planned to support increase resolution and confidence on adverse outcome pathway (AOP) analysis.

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.

Scientific journal publications:

- Prem Kumarathasan, Nazila Nazemof, Dalibor Breznan, Erica Blais, James Gomes, Renaud Vincent, Mohan Babu and Sadhna Phanse. Amorphous silica nanoparticle exposures can lead to mitochondrial proteomic changes. Analyst (in Review)

Presentations at Scientific meetings:

- N. Nazemof, D. Breznan, Y. Dirieh, E. Blais, Linda Johnston, A. Tayabali, J. Gomes and P.Kumarathasan. Exposure of mouse monocyte/macrophage (J774) & human lung epithelial (A459) cells to ZnO nanoforms, and in vitro cytotoxic responses. NanoTox 2021-virtual meeting, April 20-22.
- N. Nazemof, D. Breznan, E. Blais, Y. Dirieh, A. Tayabali, Linda Johnston, J. Gomes and P.Kumarathasan. In vitro toxicity screening of TiO2 nanoforms. IUPAC/CCCE virtual meeting. 2021 August 13-20.
- P.Kumarathasan, N. Nazemof, D. Breznan, Y. Dirieh, E. Blais, Linda Johnston, A. Tayabali, H. Aoki, S. Phanse, M. Babu and J. Gomes. Cellular protein perturbations identify toxicity pathways associated with ZnO nanoform exposures. HUPO Human Proteome Organization World Congress 2021 (virtual meeting). Nov 15-19.
- N. Nazemof , D. Breznan, E. Blais, Y. Dirieh, A. Tayabali, J. Gomes, L. Johnston, P. Kumarathasan. Cellular cytotoxicity and protein-level changes after metal oxide nanoparticle exposures. The Society of Toxicology Canada 53rd Annual Symposium. 2021 November 29-December 01.
- 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.

246. The team has found significant differences in the dissolution behaviour of nano-ZnO, nano-MnO2, nano-CeO2, nano-Al2O3, and nano-Fe2O3 in distilled water compared to cell culture medium and/or simulated lung fluids. The results demonstrated that dissolution behaviour of metal oxide ENMs should be evaluated using aqueous media representative of the exposure pathway being considered (paper in preparation). The team also demonstrated that dissolution behaviour of metal oxide ENMs should be studied at toxicological relevant concentrations, as dissolution behaviour in cell culture media varied depending on initial nanomaterials concentration. This observation is relevant for the interpretation of toxicity results as increased nanomaterial solubility also affects toxicity. The results of the toxicological investigation showed that for toxicity induced by some soluble metal oxides, exposure to particulate form is essential and for others, ion species is the main determinant of toxicity. While toxicity showed dependence on dissolution, endpoint specific effects were also observed. These results suggest careful review of current read across practices before their application to nanomaterials.

Publication:

- Boyadzhiev, A.; Solorio-Rodriguez, S.A.; Wu, D.; Avramescu, M.-L.; Rasmussen, P.; Halappanavar, S. The High-Throughput In Vitro CometChip Assay for the Analysis of Metal Oxide Nanomaterial Induced DNA Damage. Nanomaterials 2022, 12, 1844. https://doi.org/10.3390/nano12111844

6.4. France

247. Through NanoFabNet and the NanoSafety Cluster, **LNE** co-authored the concept paper on an **'International Network Initiative on Safe and Sustainable Nanotechnologies (INISS-nano)'**, which has been pre-published for comments on ZENODO: http://doi.org/10.5281/zenodo.5004929.

6.5. Germany

Federal Institute for Materials Research and Testing (BAM)

248. BAM takes part at the EU Horizon 2020 Project ACEnano "Analytical and characterisation excellence in nanomaterial risk assessment: a tiered approach" led by the University of Birmingham. The aim was to develop new techniques, instrumentation and equipment for nanomaterial analysis which were into a quality assurance and risk assessment framework. It could be shown that secondary ion mass spectrometry (TOF-SIMS) is a suitable method for investigating nanoparticles. Video protocols for the preparation of nanoparticles were published with open access. For the further development of surface analytical techniques, BAM organised an interlaboratory comparison about the surface analysis of oxide nanoparticles in the framework of the Versailles Project on Advanced Materials and Standards (VAMAS) together with the German Federal Institute for Risk Assessment (BfR). First results show that the contamination of the nanoparticles by environmental effects in the laboratory must be taken into account in the data analysis. Guidance for this data treatment will be developed.

Max Rubner Institute (MRI)

249. MRI is a member of the "International Nano-Authorities Dialogue" which is a transnational platform of the German speaking environment, health and safety authorities for the safe and sustainable use of nanotechnology.

Federal Institute for Risk Assessment (BfR)

250. The BfR is involved in the following research programmes:

- The BfR is currently preparing a contract for a research project on nano-specific adaptions with regard to acute inhalation test guidelines, notably OECD TG 433. This project is funded by the German Federal Ministry for the Environment (BMUV). It includes sample preparation and administration optimisation, in vivo studies with extended histopathology, and (further) development of alternative methods to standardise, reduce, and ultimately replace animal testing.
- The BfR is partner in the new EU H2020 Projects POLYRISK (POLYRISK - understanding human exposure and health hazard of micro- and nanoplastic contaminants in our environment). The Project, together with the projects AURORA, IMPTOX, PlasticHeal, PlasticsFatE, established the collaborative European research cluster CUSP to understand the health impacts of micro- and nanoplastics (https://cusp-research.eu/). The CUSP cluster consists of 75 organisations from 21 countries working within the five large-scale research projects mentioned above.

- The BfR is 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 final project meeting is foreseen for February 2023.

6.6. Italy

251. ISS is strongly involved in advancing nanosafety data FAIRness, for maximizing their availability, understanding, exchange and ultimately their reuse. In this area several activities are underway:

- in the Gov4Nano project several case studies have been performed to demonstrate the reusability of nanosafety data, progressing from data quality assessment and curation to translation of data into formats suitable for specific purposes (e.g., for reuse in (Q)SAR based approaches and/or in risk assessment tools) In particular, ISS is carrying out a case study on reuse of *in vitro* Comet test data available in the Nanosafety Data Interface (https://search.data.enanomapper.net/). Problems related to quality assessment, curation and translation are analysed and addressed together with FAIRification needs, with a view to reuse data in predictive toxicology and risk assessment. Results of the case study were reported (via a poster and a short pitch) in the Nanoweek meeting (Cyprus[5], June 2022);
- in the framework of the AdvancedNano Implementation Network initiative, implementation of the FAIR principles in the current nano-EHS databases are pursued;
- in the PARC partnership, as a part of WP8 activities (dedicated to the development and consolidation of concepts and tools for SSbD of chemicals and materials, and their operationalisation), ISS contributed to the series of online seminars organized in the context of Task 8.1.

252. 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).

253. The project is developed in partnership with other European OSH Institutes such as INSST (Spain), NRCWE (Denmark), STAMI (Norway) and TNO (The Netherlands) and in cooperation with other partners, such as the Italian Industrial Association (AIRI - Italy), the Interuniversity Microelectronics Centre (IMEC - Belgium), the Nanotechnologies Industries Association (NIA), Scuola Normale Superiore of Pisa (SNS – Italy) and Tyndall National Institute (Ireland).

254. After a comparative analysis of existing EU approaches on training practices on NMs and AM, the project consortium is starting a stakeholder consultation by conducting a survey on gaps, needs and barriers for an effective training for workers' safety and health. Further details are available in the project website https://perosh.eu/project/nanomaterials-training-project/.

255. ISS coordinates the **Nanocellup** projects (GP/EFSA/SCER/2020/0374/Lot1) – *Use of New Approach methodologies (NAMs) for the hazard assessment of nanofibers*, funded by EFSA (European

[5] Note by the Republic of Türkiye: The information in this document with reference to "Cyprus" relates to the southern part of the Island. There is no single authority representing both Turkish and Greek Cypriot people on the Island. Türkiye recognises the Turkish Republic of Northern Cyprus (TRNC). Until a lasting and equitable solution is found within the context of the United Nations, Türkiye shall preserve its position concerning the "Cyprus issue".

Note by all the European Union Member States of the OECD and the European Union: The Republic of Cyprus is recognised by all members of the United Nations with the exception of Türkiye. The information in this document relates to the area under the effective control of the Government of the Republic of Cyprus.

Food Safety Authority). The project is aimed to understand the influence of the nanoscale characteristics of nanocellulose (NC) on its toxic kinetic behaviour. It aims to design and conduct a set of NAM-based studies for addressing the current knowledge gaps on NC hazards.

256. Italian research groups continue their activities in the following ongoing EU projects: **ASINA** (NRC-ISTEC, University Milano Bicocca, Colorobbia, Warrant Hub, Angel-consulting), **Gov4Nano** (ISS, AIRI, EcamRicert), **GRACIOUS** (Italian Institute of Technology, GreenDecision), **NanoExplore** (University of Turin), **NanoHarmony** (ISS, EcamRicert, IIT) **RiskGONE** (University Ca'Foscari Venice), **PATROLS** (CNR-ISTEC, University of Pisa), S**AbyNA** (CNR-ISTEC).

6.7. Japan

257. 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 will be published to support voluntary safety assessment in CNF-related companies.

258. 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 2022, one 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.

259. 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 2021-22 MOE continues collecting and reviewing existing literature on ecotoxicity of manufactured nanomaterials including TiO2, silver and CNTs to identify any harmful effects attributed to their particle sizes.

6.8. Korea

The research projects of MOTIE (Ministry of Trade, Industry and Energy)

260. A research project on the lung burden measurement of reduced graphene nanomaterials was initiated in 2020. The resultant outcomes are the following ISO projects: (1) ISO/WD TR 5387 Nanotechnologies: Lung burden measurement of nanomaterials for inhalation toxicity studies and (2) ISO/WD TS 7833 Extraction method of nanomaterials from organs by the proteinase K digestion

261. A research project on the behavior and biotransformation of nanomaterials in the biological system was initiated in 2022. The expected outcome will be the ISO standard to measure the biotransformation of nanomaterials in an inhalation setting.

The research projects of Ministry of Environment (MOE)

262. A research project on the environmental monitoring, exposure and toxicity of tier weard nanoparticles including carbon black is being initiated in 2022 in the National Institute of Environmental

Research (NIER) in the MOE. The expected outcome will be able to estimate human health impacts by inhalation route as well as ecological impacts directly and/or indirectly and set out plans for developing health and safety management related to those nanoparticles exposure in the roads in South Korea.

263. MOE has established the mater plan of nano-safety management supporting to the comprehensive national plan of nano-technology development since 2012. In a straight line with the master plan, MOE is now consider the 3rd mater plan of nano-safety management ('22~'26) including monitoring nanomaterials in environment and products, exposure and characterizing nanomaterial properties, and comprehensive risk assessment in South Korea.

6.9. The Netherlands

264. In September 2021 the European GRACIOUS project has ended. The project has developed a highly innovative science-based framework that supports the assessment of risk posed by the ever-increasing array of nanomaterials on the market and under development. The framework streamlines the process for assessing their risk by logically grouping nanomaterials thereby allowing extrapolation between (read-across) nanomaterials and reducing the need to assess exposure to and toxicity on a case-by-case basis. To facilitate the use of the Framework, an extensive guidance document was published, together with a guidance in a nutshell that provides a brief introduction. Further details on the different aspects of the framework are published in scientific literature. Output from the project forms an important foundation in the currently ongoing update of the section on nanomaterials in the OECD Guidance on Grouping.

265. 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.

266. The European Gov4Nano project organised a second Trans-Regulatory Risk Analysis Summit (RRAS) on 24-26th of January 2022. The online meeting aimed to raise awareness for (new) challenges for risk analysis of nanomaterials posed by the goals and ambitions of the Green Deal (GD) and underlying relevant strategies from a trans-regulatory perspective. Emphasis lay on the potential impact of the Chemical Strategy for Sustainability (CSS). Moreover, specific topics from the CSS, e.g. "one substance, one assessment", and new toxicological endpoints to be addressed (like endocrine disruption) were discussed. Major outcomes include the continuous need for (1) a structural way of trans-regulatory sharing of lessons (including those learned in the nanosafety community), knowledge and information to address the goals and ambitions of the CSS, (2) prioritisations in the 87 actions of the CSS and frequent updates of regulatory and research roadmaps for nanomaterials, and (3) promotion of harmonization to enable risk (and sustainability) governance to deal with the ambitious policy goals and dynamic character of a transition, in which sharing state-of-the art information is critical. A report on the RRAS will be published at the Gov4Nano website.

267. The coordination team of the NanoSafety Cluster (NSC) is in constant contact with representatives of the European Commission regarding development of new calls for proposals as well as contributions to Safe-by-Design activities at DG Research and Innovation. After many months, the NSC met in person during the "Nano-Week" in Limassol, Cyprus, where NanoCommons has its final conference, several

projects organized their consortium meeting, NanoHarmony arranged a training session on OECD guideline development and the NSC and the EU-US Communities of Research met to discuss progress on various working groups and the future of the community.

268. The EU project PeroCUBE brings together top experts and pioneers to merge the 3 different technologies of lighting, energy harvesting and light communication. This includes uses of OLED technology, perovskites materials and their processing for device manufacturing. The project will develop new nano-characterization tools, while theoretical studies will significantly contribute to development and upscaling of the perovskite technology. All advancements will be demonstrated at TRL 5 for printed, large area (> 10 cm^2) devices for lighting, photovoltaic and light fixture applications, and also wearables. Robust commercializing channels of the PeroCUBE developments are guaranteed by the involvement of industry partners. TNO leads WP7 'Human Health Risk assessment and LCA'. The objective of WP7 is to assess the potential human health risks and to provide a life cycle assessment to balance the risks and benefits of the application of nano-perovskites in lighting and energy harvesting applications.

6.10. Slovak Republic

269. There no exists joint governmental strategy for nanomaterials in Slovak Republic or specific overall research programmes in this area. However, several governmental strategies deals partly with nanomaterials such as Economic Development Strategy, Health Care Strategy, Research Strategy and Sustainable Development Strategy was created.

6.11. Sweden

Graphene Flagship

270. The Graphene Flagship, an EU-funded Future Emerging Technologies (FET) project, is coordinated by Chalmers Technical University in Göteborg, Sweden, and the consortium comprises 170 partner institutes. Karolinska Institutet (KI) is engaged in the workpackage on Health & Environment (2013-2023). Recent work in the Flagship has addressed the issue of hazard assessment of graphene-enabled composites from a life cycle perspective and this multi-laboratory study, coordinated by EMPA in Switzerland, was recently published in the Journal of Hazardous Materials 2022;435:129053.

MISTRA

271. The Swedish Foundation for Strategic Environmental Research (MISTRA) has supported the MISTRA Environmental Nanosafety consortium through two consecutive grants (for a total of 8 years). The project is currently coordinated by Lund university and comprises of 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. The project partners recently published a paper on "nanomaterials in the European chemicals legislation – methodological challenges for registration and environmental safety assessment" (Environ. Sci. Nano. 2021;8:731-747). The study aimed to assess the availability and suitability of methods needed to comply with the new regulatory provisions on nanomaterials. The authors concluded that a targeted effort should be made to develop protocols and guidelines to determine nanomaterial adsorption/desorption, degradation, exposure scenarios and ability to cross biological membranes.

NanoLund

272. In addition, Lund university also coordinates a new collaboration to ensure that products based on nanotechnology can be developed and handled in a safe way. The initiative NanoSafe4All (2021-2023) intends to bring researchers and industry together to address issues related to nanosafety.

PARC

273. The Institute of Environmental Medicine (IMM), a department at Karolinska Institutet and a national institute for risk assessment, contributed to the planning of the Partnership for the Assessment of Risk from Chemicals (PARC) in Horizon Europe and now participates as a member of the PARC consortium. The Swedish Chemicals Agency represents Sweden in PARC's Managing Board. Although specific projects (working packages) are not clearly related to nanomaterials at present such developments in the future may become tangible

SweNanoSafe

274. The platform and research network are represented in the steering group for safe(er) innovation approaches (SG-SIA) and the steering group for advanced materials (SG-AdMat) with the OECD WPMN.

6.12. United Kingdom

275. 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, achieveding 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. A summary of the PATROLS achievements in relation to supporting the European Commissions Green Deal and Chemicals Strategy for Sustainability has recently been published:

- Doak SH, et al. The Road to Achieving the European Commission's Chemicals Strategy for Nanomaterial Sustainability-A PATROLS Perspective on New Approach Methodologies. Small. 2022 Apr;18(17):e2200231. doi: 10.1002/smll.202200231.

UK Involvement in PARC

276. 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).

Environmental Exposures and Health (EEH)

277. 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. Recent results of aerosol exposure measurements from nano-enable consumer spray products will be presented at the11th International Aerosol Conference, Athens, Sept 2022.

6.13. European Union

278. See information on SRIP under Point 7 below.

6.14. Malaysia

279. Malaysia has embarked on a four-year nationwide project to benchmark risks of nano-based products. The first step towards establishing an inventory of nano-based products available in the local market has been established. An online system is being developed to make this data available as reference to the general public. Physical-chemical, toxicology, ecotoxicology, effects on the environment and life cycle assessment (LCA) studies are being carried out on selected products, based on specific criteria including product category, nanomaterial in use and exposure risk. Studies are conducted according to OECD Test Guidelines and ISO standards in ISO 17025 accredited laboratories and GLP certified facilities.

6.15. Business at OECD (BIAC)

280. As part of the MALTA Initiative and on behalf of its members, 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.

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

7.1. Austria

281. 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 intiative 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. The first version is public available here: *DOI: 10.5281/zenodo.5004929*

282. 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 publication of the revision of the concept paper, including action plans for the four pillars shall be expected in summer 2022.

7.2. Canada

a. Background:

283. The current pace with which advanced technology is being developed (e.g. nanotechnology) provide promising opportunities to address issues relevant to human and non-human health, and safety of the environment. However, such rapidly evolving innovations pose challenges to the existing system in terms of the growing demands and needs for suitable risk assessment tools and measures. In this context, a potential approach to minimize the risks and uncertainties of such technologies could be the implementation of the ‘Safe-and-Sustainable-by-Design’ concept (SSbD). Specifically, SSbD highlights the importance of making anticipatory assessments of the end product early on, starting with the research and

development phase, through the manufacturing process with considerations to a life cycle assessment. In order to achieve the best outcomes of the SSbD principles, collaborations between industry partners and regulators is critical in mitigating the challenges of novel products through responsible and safer innovation approaches (SIA).

b. OECD Steering Group on SIA[6]:

284. A Steering Group on SIA (WPMN21) was established in June 2021 with an aim to:

(i) support innovation (nanomaterials and advanced materials) using safe and Sustainable methodologies to align with circular economy approaches.

(ii) foster working collaborations between regulators and innovators (industry and academia) by facilitating the development of trusted environment platforms.

285. Canada co-leads this newly established Steering Group and is supported by experts from other participating countries/organizations.

c. Implementation:

286. The SIA WPMN work goals are divided into four parallel activities, of which activity 4 is led by Canada with the support from Austria, Netherlands, United Kingdom, and BIAC.

- Activity 1: SSbD: Working description Sustainable-by-Design, Sustainability, integrating SSbD to SIA.
- Activity 2: Develop an inventory of frameworks, methods, aspects/ parameters, and tools/toolboxes for SSbD and RP
- Activity 3: Bring SIA closer to practical applicability (TE, dealing with Barriers and Constraints)
- **Activity 4 (led by Canada): Platform for Sharing Knowledge, learning from industry and regulator's experiences**

287. The first SIA teleconference was held in September 2021 to review recommendations and plan roadmap. Since then, several teleconferences have been conducted to review activities and suggestions for milestones.

d. Work plan and Achievements under Activity 4 (led by Canada):

288. This activity led by Canada aims to facilitate communication and collaboration between innovators and regulators at the early stages of product concept design. To begin with, Canada prepared a survey questionnaire, which was hosted by the OECD and sent out to OECD WPMN members to obtain their response. The survey comprised of questions to assess trusted environment (TE) requirements and characteristics, barriers in establishing trusted platforms and satisfaction of respondents based on their experience collaborating with partners through existing platforms.

289. The purpose of this survey was to gather information, feedback and opinion from OECD stakeholders to enrich our understanding on a suitable platform for industry/academia/-regulator and/or regulator-regulator interactions. Based on the responses and input received, a first scan of existing platforms has been compiled.

[6] OECD (2020) Moving Towards a Safe(r) Innovation Approach (SIA) for More Sustainable Nanomaterials and Nano-enabled Products: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2020)36/REV1&doclanguage=en

290. In brief, this preliminary scan has indicated that:

(i) 100% participants indicated that existing TE platforms do not fulfil all the characteristics (e.g. governance agreements on confidentiality statements, etc.) as specified in the survey.

(ii) 57% participants indicated that lack of existing TE platforms is one of the major barriers in establishing collaborations between regulators and innovators.

(iii) 86% participants expressed dissatisfaction with availability of human resources and financial resources available to carry out the work.

291. Below are a few noteworthy opinions and learnings collected from this survey:

(i) Trusted Environment is a new concept in the context of SSbD.

(ii) Willingness to share information should be channeled through an agreement between collaborating partners.

(iii) Collaboration will enrich understanding of the innovative product in question and international consensus on the acceptance of the product.

(iv) In the agreement, increase the frequency of communication with collaborating partners and clearly list out roles, rules and conditions for sharing information and knowledge between participating groups.

(v) The level of importance of the SSbD for the two parties should be defined at a preliminary stage. This is the basis on which to build the trusted environment.

(vi) Exploring why there are difficulties in establishing collaborations is more informative (e.g. lack of trust, lack of platforms, lack of agreements, etc.).

e. Next steps:

292. The SSbD concept is gaining attention from different member countries.

293. As one of the activities (activity 4 detailed above) under the OECD delegations, Canada aims to:

(i) analyse the potential benefits and pitfalls of platforms for industry/academia/- regulator and/or regulator-regulator interactions in sharing knowledge.

(ii) use this baseline understanding to identify relevant criteria for establishing terms of reference to launch a SIA-trusted environment platform.

(iii) propose the use of the selected platform to run a pilot case study based on Canadian government priorities (e.g. 'Finding safer and sustainable alternatives to traditional fossil fuel-based Plastics') for developing a trusted environment platform.

7.3. Germany

Federal Institute for Risk Assessment (BfR)

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

- The German Federal Authorities BAuA, BfR and UBA contributed to the brochure prepared by RIVM regarding a proposal for an Early WArning, pRioritisation and actioN system (EWARN) for AdMa. The proposed system is intended to identify, describe, and prioritize 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).

- G4Nano, 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 biologically mediums', and 1.6 'Identification and quantification of the surface chemistry and coatings on nano- and microscale materials'. The first ILC round is currently ongoing; the second round is planned for fall 2022.

Federal Ministry of Education and Research (BMBF)

295. Focusing specifically on materials research topics, the M.ERA-NET Call 2022 will set various thematic priorities. The international projects provide important findings in areas such as functional materials, high-performance composites and materials for energy. More than 30 different funding organizations are participating in this call with a budget of approximately 25 million euros.

296. In addition, as a science communication project, the DaNa4.0 platform (Data on New, Innovative and Application-Safe Materials) provides various information on the safety of novel materials for humans and the environment.

7.4. Italy

297. In the framework NANOINNOVATION conference (the largest event on nano and enabling technologies in Italy), Rome 19-23 September 2022, ISS and AIRI (Italian Association for Industrial Research) will organize a symposium on: *Beyond state of the art, through Safe and Sustainable Development approaches for materials development*. The symposium will reflect on the recent policy discussion at EU and at national level and will provide examples and case studies from research and production processes. Two sessions are scheduled: 1) *Practical implementation of Safe and Sustainable by Design approaches in applied and industrial research* and 2) *Frameworks and criteria for Safe and Sustainable Development.*

7.5. The Netherlands

298. The EU project SbD4Nano has been designed as an industrially oriented project. Recognized research and technology organisations in Nanosafety cooperate here with SMEs and large industries to validate specific case studies. These case studies are used in the implementation of new Safe-by-Design (SbD) approaches and tools. TNO is involved in almost all work packages and leads WP4 'Safe by process design: exposure assessment and risk management'. The objective of this WP is to develop a newly tested and calibrated cost driven exposure model to predict the effectiveness of Risk Management Measures (RMM) to design a safe process. The model builds on a data e-infrastructure with updated databases consisting of release, exposure and RMM effectiveness information. This will then support an exposure-driven safe-by-process-design modelling framework as key outcome. Topics of other WPs include data management/integration, material design, computing infrastructure design/development, and industrial implementation/validation.

299. The EU project SUNSHINE aims to develop and implement Safe & Sustainable by Design (S&SbD) strategies for products enabled by multi-component (advanced) nanomaterials (MCNM), including high aspect-ratio nanomaterials (HARNs). Currently, work on the operationalisation of safe-and-sustainable-by-design (SSbD) for multi-component materials (MCNMs) is ongoing. An industry user committee was set-up consisting of experts in human and environmental toxicology, material scientists, safe-by-design, sustainability and regulatory. This user committee supports the five case studies in the

operationalisation of SSbD. A methodology on how to integrate safety and sustainability throughout the innovation process is now being developed and tested in the case studies. RIVM is coordinating the work package on regulatory preparedness that performed an analysis on how to define multicomponent nanomaterials from a regulatory (REACH only) viewpoint. An overview was also made of the different types of MCNMs and a matrix was developed with the different characteristics of MCNMs. RIVM is also involved in adapting grouping and read-across approaches to multi-component nanomaterials. Properties related to the new or enhanced functionality of multi-component nanomaterials are considered for their potential impact on risk and how this information can be used in risk assessment and grouping and read-across approaches. SUNSHINE is a sister project of the HARMLESS project.

300. The EU project HARMLESS will provide novel tools, guidance and decision support for balancing functionality versus risk. This aims to ensure that the next generation advanced nanomaterials will be harmless. HARMLESS will develop a novel, multifaceted Safe Innovation Approach (SIA) to nanomaterials, including high aspect ratio nanomaterials (HARNs). This involves integrating a toolbox of suitable New Approach Methodologies (NAMs). In HARMLESS a number of recognized research institutions in nanosafety will cooperate with several enterprises (SMEs) to implement and validate new SbD approaches and tools. TNO leads the work package on Tool Development, which aims to build a user friendly SbD Decision Support System for complex HARNs and multi-component NMs. The HARMLESS SbD decision support system builds on the NanoRisk Governance Portal that was developed in the caLIBRAte project and currently further developed in the governance projects Gov4Nano, NanoRIGO and RiskGONE. HARMLESS is a sister project of the SUNSHINE project.

301. Since May 2019, **SPINE**, the Safe-by-Design Policy International Network, has been established by the Dutch Ministry of Infrastructure and Water Management. A Safe-by-Design network for policy makers is important to facilitate knowledge sharing and exchanging expertise between European policy makers on the development of the Safe-by-Design concept, also in order to establish a safe and circular economy. SPINE will focus on further development and implementation of Safe-by-Design within several domains. Currently participating countries are Austria, Denmark, Estonia, Germany, Netherlands, Spain, Sweden, Switzerland, and UK. Since April 2021, the EEA (European Environmental Agency) is also involved. For now, SPINE serves as an ad hoc advisory board, without formal status. A report regarding Safe-by-Design best practices on a national level has been written in March 2022. 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 gender balanced and inclusive network of experts and stakeholders in the materials community to enable multidisciplinary design processes, map skills mismatches and competence gaps, to enable transition towards an overarching framework in which sustainability is the essential entry point into markets. IRISS has had its kick-off meeting in June 2022 and SPINE will be connected from September 2022. Furthermore, SPINE is connected with the OECD WPMN, OECD WPHROB, PRAC, SIA and other relevant organisations and initiatives to exchange information regarding the Safe-by-Design actions on an international level.

7.6. Slovak Republic

302. In the field of research the Ministry of Environment and Slovak Academy of Sciences prolonged the agreement between both organisations for cooperation of created expert group for nanomaterials as an advisory body for research development in this area. Research institutions and universities have issued a series of projects addressing aspects of further research on nanomaterials, including their health and environmental risks. One of the most important part of research in the field of nanomaterials is construction ceramics, such as silicon nitride, titanium nitride, boron nitride, silicon carbide and titanium nitride and colour pigments. Ultra fine nano-scale powders for construction ceramics are prepared by chemical vapour deposition or sol – gel methods. Expert group for nanomaterials offers exchange of knowledge and further cooperation between national authorities and producers of nanomaterials in Slovak republic.

7.7. Sweden

SweNanoSafe

303. SweNanoSafe has been exploring to what extent responsible research and innovation (RRI) is implemented in Sweden with respect to nanomaterials and how RRI is managed in practice, for example, in terms of concepts such as the precautionary principle and safe-by-design. The work was accomplished through interviews with stakeholders followed by two feedback workshops, and information was gathered on how companies and other actors work with nano-innovation and nanosafety. The project has been finalized and an executive summary was published (see above).

304. In Nov 2021, SweNanoSafe organized an online workshop entitled “Safe and Sustainable by Design: a prerequisite for achieving a circular economy” aimed to orient government agencies in the ongoing development and implementation of SSbD and regulatory challenges related to nano- and advanced materials. The workshop gathered participants from several government agencies, academic researchers, industry participants in Sweden as well as more than 20 other European and non‑European countries. The presentations are available on the SweNanoSafe YouTube channel. The workshop was summarized in a report that was published on the SweNanoSafe website in March 2022. In addition, SweNanoSafe published a report in May 2022 entitled “Nanosafety, the Sustainable Development Goals and meeting EU policy ambitions”. The SweNanoSafe focus areas include sustainable development of nanotechnology and the report aims to describe the alignment between the United Nations’ Sustainable Development Goals (SDGs) and the objectives and activities of SweNanoSafe, and how SweNanoSafe activities contribute to the European Union policy ambitions, including the EU Green Deal and Chemicals Strategy for Sustainability. The report was prepared by SweNanoSafe and reviewed by Lya Soeteman-Hernandez (RIVM – National Institute for Public Health and the Environment) and by several experts at the Swedish Chemicals Agency (KemI).

7.8. United Kingdom

305. 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.

7.9. European Union

306. Implementing its 2020 Chemicals Strategy for Sustainability, the European Commission is pursuing two initiatives, addressing chemicals in general but relevant for (advanced)nanomaterials:

- the ‘Strategic Research and Innovation Plan for chemicals and materials (SRIP)’
- ‘Safe and Sustainable by Design (SSbD) framework’

307. For both, a Commission publication is expected in October 2022. For SRIP, a consultation survey is currently open[7]. The SSbD framework is planned to be published as a Commission Recommendation. The 3rd SSbD stakeholder workshop to discuss case studies will be held in Q3 2022.

308. The JRC, in collaboration with DG RTD, has been working on the development of *a Framework for the definition of criteria for Safe and sustainable by design chemicals and materials*. A first JRC Technical report *Safe and Sustainable by Design chemicals and materials - Review of safety and sustainability dimensions, aspects, methods, indicators, and tools* was published (doi 10.2760/879069 (online)) early this year. Several meetings and webinars with stakeholders were held to present and discuss early draft versions of the framework and received good and relevant feed-back. After addressing the feed-back, the JRC Report with a proposed framework should be published by the time of the WPMN-22.

7.10. Business at OECD (BIAC)

309. **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.

310. NIA is co-author in the following publications: "*Safe(r)-by-design guidelines for the nanotechnology industry*[8] and *Safe(r) by design implementation in the nanotechnology industry*[9] which represent unique efforts to SbD implementation at industrial level. 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 throughout the process and feedback on the adaptability of the proposed framework to nanomaterials.

[7] Please read full draft SRIP before replying, document attached to the survey in Section 1. Please note you must follow the survey format for your answers to be taken into account. Attachments or input via email will not be considered. For questions, contact the European Commission via RTD-E3-CHEMICALS-MATERIALS@ec.europa.eu

[8] Sanchez-Jimenez et al. Safe(r)-by-design guidelines for the nanotechnology industry. NanoImpact, Volume 25, 2022, 100385.

[9] Sanchez-Jimenez et al Safe(r) by design implementation in the nanotechnology industry. NanoImpact Volume 20 2020, 100267

8 Additional Information

8.1. Canada

311. 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.

312. A voluntary questionnaire was sent to previously identified importers/manufacturers of ZnO and TiO_2 to have up-to-date information relevant to support this risk assessment activity.

313. The Important Issues on Risk Assessment of Manufactured Nanomaterials document was published in 2022 providing relevant updates since the initial publication in 2012. The document identifies advancements in the main topics of regulatory risk assessments, and research needs to support decision-making. These research needs have been used to guide Canadian research teams.

Link to the Important Issues on Risk Assessment of Manufactured Nanomaterials.

8.2. France

314. **LNE** organized the fourth session of a training aiming at helping industry choosing the most suitable characterization technique to determine number size distribution of particles and reliably classify chemicals as nanomaterial according to EC recommendation of definition (EC/2011): overview of available analytical techniques and corresponding application range/limitations.

315. **LNE** co-chaired with BNN (Austria) a break-out session dedicated to the issues of harmonisation/standardisation and validation of characterization methodologies during the 2nd *NanoFabNet* Development Workshop (January 2021).

316. **INERIS** is involved in Nanoharmony and Gov4nano and technically supporting the development of OECD TGs and GDs, as well and identifying potential barriers in the development of such documents.

8.3. Germany

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

317. Since 2006, the NanoDialogue (stakeholder dialogue) has been conducted as part of the German government's Nano Action Plan under the lead responsibility of the Federal Ministry for the Environment (now: BMUV). Due to the Covid19-pandemic the NanoDialogue paused in 2020 and 2021 and is continued in 2022. It will conclude with an international conference in cooperation with OECD, which will take place on 22 and 23 June 2023 in Berlin.

8.4. European Union

318. EUON – European Observatory for Nanomaterials, has published a report in November 2021, entitled “Study on the Product Lifecycles, Waste Recycling and the Circular Economy for Nanomaterials”.

8.5. Malaysia

319. NanoVerify Sdn Bhd (Pvt. Ltd), a subsidiary of NanoMalaysia Berhad (Ltd.) is developing a Nano Product Certification Scheme under the purview of Department of Standards Malaysia. Such a scheme provides public assurance on the added-value of nano products in the market.

8.6. Business at OECD (BIAC)

320. **NIA** has published an Opinion through the EU Observatory on Nanomaterials (EUON) on the need to adapt terminology by encouraging the use of the term “Nanoform” whenever possible, to help implementing the term at industrial level and to better reflect the evolution in thinking demonstrated by the adoption of specific information requirements in the submission of REACH dossiers for (sets of) nanoforms.

321. The NIA is also involved in stakeholder groups such as the Nano Safety 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.

8.7. Environmental NGO

322. As relevant civil society stakeholders in Europe working in the fields of both standardisation and nanotechnologies, ECOS (Environmental Coalition on Standards) and BUND (Bund für Umwelt und Naturschutz Deutschland) are conducting the project NanoTG - Nanomaterialien auf dem Prüfstand - Methoden, Richtlinien und transparente Informationen für eine sicherere Nutzung. Or, in English, NanoTG, putting nanomaterials to the test: methods, guidelines and transparent information for safer use. The project runs from March 2021 to March 2023.

323. The project contributes to:

- Supporting the robust development and amendment of OECD TGs for nanomaterials, and facilitating their integration into EU and national policies regulating the use of nanomaterials in food, cosmetics, and other high-exposure applications;
- Supporting greater inclusion and impact of socio-environmental interests in the development of the regulatory framework for nanomaterials in Europe, through the participation of civil society organisations.

324. ECOS is also an active member in standardisation committees and workgroups at European (CEN/TC 352) and international level (ISO/TC 229).

8.8. The International Organization for Standardization Technical Committee 229 (ISO TC229)

325. ISO TC229 has a Task Group 2 with a title: “Sustainability, consumer and societal dimensions of nanotechnologies”. It is lead by USA and has conducted a number of surveys in its field.