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## Developments in Delegations on the Safety of Manufactured Nanomaterials – Tour de Table

Series on the Safety of Manufactured Nanomaterials  
No. 102

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**SERIES ON THE SAFETY OF MANUFACTURED NANOMATERIALS**  
**NO. 102**

**Developments in Delegations on the Safety of Manufactured Nanomaterials –  
Tour de Table**

**IOMC**

**INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS**

A cooperative agreement among **FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD**

Environment Directorate  
ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT  
Paris 2021

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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.
2. In general, standard information requirements apply equally to bulk chemicals and nano-forms. An introduction at the nanoscale (particle size range of 1 to 100nm) is considered a 'specified class of introduction'. Such introductions may require additional or different information requirements when working out the category of introduction as well as additional record keeping obligations. Further details are available at <https://www.industrialchemicals.gov.au/help-and-guides/extra-resources-help-you-categorise-your-introduction/categorisation-chemicals-nanoscale>.
3. There were no new applications received for assessment of nanomaterials after the new Australian regulatory scheme (AICIS) commenced on 1 July 2020. Since the last WPMN meeting, AICIS issued a certificate to authorise introduction of multi-walled carbon nanotubes (MWCNT) using the generic CAS number for all carbon nanotubes. This chemical will be listed on the Australian Inventory of Industrial Chemicals, 5 years after issuing of the certificate, or prior to that if requested by the applicant.
4. Manufactured nanomaterials, including carbon nanotubes, assessed prior to introduction in Australia under *Industrial Chemicals Act, 2019* will include a defined scope of assessment (it is a legal obligation for certificate holders to introduce a chemical within the defined scope of assessment, unless further assessment is undertaken), which will be included in the inventory listing of the chemical.

## 1.2. Austria

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](http://www.bmk.gv.at)) and is handled by the FFG - Austrian Research Promotion Agency.
6. 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 most recent call addressed nanomaterials and “advanced materials” as potential materials for traceability.

7. Additionally, two international projects, **Sabattle** and **Safelibatt**, with Austrian partners recently started, funded under the ERA-net SAFERA are within the scope of the Austrian Nano-EHS program. Topic of the call was “**risk assessment of advanced and nanomaterials in batteries**”.

8. The **Austrian Nano Information Commission** (NIK; chair: André Gazsó) of the Austrian Federal Ministry of Social Affairs, Health, Care and Consumer Protection has entered its second function period (until 2023) and consists now of over 30 members coming from academia, regulatory authorities and non-governmental organisations.

9. 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. 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: <http://epub.oewar.ac.at/ita/nanotrust-dossiers>. Recent publications are available on Nanoregisters (No. 51), bioinspired nanomaterials (No. 54) and titanium dioxide as a food additive (No. 55). This publication series will be continued.

### 1.3. Canada

10. 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 outlines approaches and key considerations (e.g., unique properties of nanomaterials), and provides guidance to regulators on the assessment of environment and human health risk related to nanomaterials under CEPA. The draft has been shared with partners of the SGAP for peer-review and will be published in summer 2021 for a 60-day public comment period.

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

11. The New Substances program is responsible for administering the *New Substances Notification Regulations (Chemicals and Polymers)* [NSNR(C&P)] of CEPA. These regulations ensure that no new substances (chemicals or polymers) including nanomaterials are introduced into the Canadian marketplace before undergoing ecological and human health assessments, and that any appropriate or required control measures have been taken. In total, Canada has assessed four nanomaterials and potential nanomaterials under the New Substances Program since WPMN20. 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).

**c. Risk management approaches;**

12. A significant new activity notice was published on one new substance to require re-notification and assessment should the substance is used in any products available to consumers that are applied as a spray, mist or aerosol leading significant inhalation exposure and contain the substance at least 1%, or should the substance is used in a nanoform different from what was notified. The notice further requires

submission of relevant information such as characteristics and physical-chemical properties of the substance and for the assessment. Such significant new activity notice is one of the control measures available to minimize risk to the environment or human health when a new substance is suspected to be toxic or capable of becoming toxic under CEPA.

#### 1.4. Costa Rica

13. With the support of the National Nanotechnology Laboratory (LANOTEC), the National Technical Committee CTN 060 was created, this group works on a series of standards endorsed by the Costa Rican Institute of Technical Standards (INTECO)

14. This CTN 060 has developed 40 standards in the nanotechnology area that include definitions, characterization, manufacturing processes, risk assessment, health and safety practices in occupational settings, safety data sheets, toxicological evaluation, classification and categorization. In addition, Costa Rica is now officially a member of ISO International, in the ISO / TC 229 committee on Nanotechnology.

#### 1.5. European Union

15. The European Commission has in October 2020 adopted [Chemicals Strategy for Sustainability towards a toxic-free environment](#), a strategic vision towards 2030 as the principal contribution to the European Green Deal with respect to chemicals, in particular their safe use and management. It clusters more than 50 actions into 5 building blocks: the two mutually supportive objectives - boosting innovation for safe and sustainable chemicals (including also development of criteria for Safe and Sustainable by design chemicals) and increased protection of health and the environment, together with their three enablers – simplification, consolidation and coherence of legal framework, ensuring a comprehensive knowledge base, and international action. Nanomaterial are integrated in the common chemicals policy, addressed specifically only to ensure adequate risk assessment and management where necessary.

16. EU definition of nanomaterial in Commission Recommendation 2011/696/EU is presently under review. Targeted stakeholder consultation, identifying potential elements for the modification of took place from May-June 2021. Review will conclude in 2021, followed by the corresponding revision /replacement of the Recommendation, if so decided.

#### 1.6. France

17. Since 2004, France has drawn up a National Health and Environment Plan (PNSE) every five years. These successive plans have enabled significant progress to reduce the impact of the environment on health, better consideration of environmental health at all scales of the territory, and the development of structured research programs.

18. The French government has just 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. The objective is to better regulate these substances, if they do not have a strong utility and they may present risks.

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

20. The France's national metrology laboratory (**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'*:

- 1- 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)
- 2- 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.

21. A PhD study has been launched in 2020 between **LNE** and ANSES to develop and validate SOPs and software for the evaluation of sp ICP-MS uncertainties measurement applied on a case study dedicated to TiO<sub>2</sub> low concentration in regulated food simulant to support containing nanoobjects-food packaging risk assessment.

22. **LNE** led a proposal in the frame of a Call for tender organized by CEN/TC 352 *Nanotechnologies*. 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 whose aim is to develop a guidance document to harmonize the analytical methodologies and associated protocols to determine the nanofraction of chemicals integrated in food product by using electron microscopy (EM-EDX) and sp ICP-MS as complementary techniques. E551, E171, E172, E174, E175 additives are more particularly targeted and a focus will be made on the sample preparation step (extraction of additives from the food matrices) and validated through inter-laboratory comparison. The tender has been selected by CEN/TC 352 and EC. The work will begin in the next months.

23. **LNE** has contributed to a proposal led by NPL (UK) in the frame of a Call for tender organized by CEN/TC 352 *Nanotechnologies* to develop a Technical Specification on the agglomeration/aggregation topic. The tender has been selected by CEN/TC 352 and EC. The work will begin in the next months.

## 1.7. Italy

24. A virtual meeting on the outputs of project funded by the Italian Ministry of Health to support the OECD project on a new Guidance Document on intestinal fate of orally ingested nanomaterials (led by Italy) was held at ISS in March 2021. In the meeting were presented results obtained at ISS on the set-up of the advanced intestinal in vitro model together with the state-of-the-art analysis of simulated digestion protocols performed by EcamRicert and IIT. On this respect some improvements of the model are reported in the recent publication:

- Carnovale C., Guarnieri D., Di Cristo L., De Angelis I., Veronesi G., Scarpellini A., Malvindi M.A., Barone F.4, Pompa P.P. and Sabella S. 2021. Biotransformation of silver nanoparticles into oro-gastrointestinal tract by integrated in vitro testing assay: generation of exposure dependent physical descriptors for nanomaterial grouping. *Nanomaterials* 11, 1587. <https://doi.org/10.3390/nano11061587>

25. Outputs of the project on nano-pesticides characterization and determination (ISS-Italian Ministry of Health, 2018-2019) were published in *Food and Chemical Toxicology*:

- B. Bocca, F. Barone, F. Petrucci, F. Benetti, V. Picardo, V. Prota, G. Amendola. 2020 Nanopesticides: physico-chemical characterization by a combination of advanced analytical techniques. Food and Chem. Toxicol. 146 111816 <https://doi.org/10.1016/j.fct.2020.111816>

26. In the frame of the project “Nano and Key Enabling Technologies within the innovation processes: risk and opportunities in occupational settings by a Prevention-through-Design approach (NanoKey)” (2018-2020) funded by the Italian Workers’ Compensation Authority (INAIL) some scientific papers have been further published. The project was developed by INAIL in cooperation with the Italian Institute of Technology (IIT).

- F. Boccuni, R. Ferrante, F. Tombolini, C. Natale, A. Gordiani, S. Sabella, S. Iavicoli. 2020. Occupational exposure to graphene and silica nanoparticles. Part I: workplace measurements and samplings. Nanotoxicology, 14:9, 1280-1300. doi: 10.1080/17435390.2020.1834634
- C.L. Ursini, A.M. Fresegna, A. Ciervo, R. Maiello, V. Del Frate, G. Folesani, M. Galetti, D. Poli, G. Buresti, L. Di Cristo, S. Sabella, S. Iavicoli, D. Cavallo. 2021. Occupational exposure to graphene and silica nanoparticles. Part II: pilot study to identify a panel of sensitive biomarkers of genotoxic, oxidative and inflammatory effects on suitable biological matrices Nanotoxicology;15(2):223-237. doi: 10.1080/17435390.2020.1850903
- F. Tombolini, F. Boccuni, R. Ferrante, C. Natale, L. Marasco, E. Mantero, A.E. Del Rio Castillo, L. Leoncino, V. Pellegrini, S. Sabella, S. Iavicoli. 2021. An integrated and multi-technique approach to characterize airborne graphene flakes in the workplace during production phases. Nanoscale, 2021, 13, 3841. <https://doi.org/10.1039/D0NR07114E>

27. ISS, as part of the steering committee of the NANOINNOVATION 2021 Conference, Rome 21-24 September 2021, will organize three sessions: “*From life sciences to innovative materials: stories of successful integration of technology and nanoresearch*”, “*New drug delivery systems in biomedical applications*” and “*Nanosafety in food: Regulatory needs*”.

## 1.8. Japan

28. The Ministry of Economy, Trade and Industry (METI) publicised 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 2020.

## 1.9. Korea

29. The Act on the Registration and Evaluation, etc. of Chemical Substances is a legislation on a chemical registration and evaluation, and safety management. In this Act, the terminology of nanomaterials is defined, and nano risk assessment approaches will be provided. The Ministry of Environment (ME) has been conducting the project which is a voluntary survey on the production, use, import and export volumes and use patterns of manufactured nanomaterials since 2015.

### ***Estimation of human equivalent concentration of nanoparticles using Multiple-path particle dosimetry model (performed by Occupational Safety and Health Research Institute, OSHRI)***

30. The Multiple-path particle dosimetry model (MPPD) is a computation model mainly used to estimate the lung deposition fraction in humans and experimental animals. It is possible to calculate the clearance rate as well as deposition in recent version. Studies are underway to define exposure limit and

health effects of nanomaterials internationally, but there are not enough studies to conclude. However, it is believed that human equivalent concentration (HEC) can be estimated using the MPPD model, because the major exposure route of nanomaterials is inhalation. The installation and basic usage of the MPPD model that calculate lung deposition fraction and clearance rate was confirmed through a manual. MPPD model is an open-source program and anyone can use this model by installing the program. It was confirmed that HEC can be estimated by using the no observed adverse effect level (NOAEL) along with deposition and clearance rate in the existing literature. In the study by Lee et al. (2019), not only HEC but also occupational exposure limit (OEL) were derived based on the results of 13 weeks inhalation study. Research papers on in vivo inhalation toxicity of nanomaterials were reviewed, and papers with NOAELs were selected. This study can be used as basic data for the selection of exposure limits to prevent disease and maintain health of workers in the nanomaterial industry.

### 1.10. Malaysia

31. A National Nanotechnology Policy and Strategy 2021-2030 document is expected to be launched before end of the year. One of the strategic trust in this policy includes strengthening standards, safety and regulation on nanotechnology. The Ministry of Science, Technology and Innovation Malaysia will oversee the planning and implementation of strategies in the policy.

### 1.11. Netherlands

32. Several public institutes (i.e. RIVM, NWWA, and The Netherlands Nutrition Center) in the Netherlands harmonised their online communication to the public on new information on titanium dioxide. An update of information on the institutes' websites became necessary after the European Food Safety Authority (EFSA) published a new opinion on "[Safety assessment of titanium dioxide \(E171\) as a food additive](#)" in May 2021. In this opinion EFSA concludes that "[Titanium dioxide E171 is no longer considered safe when used as a food additive](#)". Experts from the Netherlands contributed to the EFSA opinion.

### 1.12. Sweden

33. SweNanoSafe - The Swedish National Platform for Nanosafety – is a forum for collaboration and knowledge exchange on nanosafety commissioned by the Swedish Ministry of the Environment. The platform was launched in 2016, and since 2019, the platform is hosted by the Institute of Environmental Medicine (IMM) at Karolinska Institutet in Stockholm. The platform continues to develop its website to promote knowledge exchange (<https://swenanosafe.ki.se>) (some content in English).

34. The objectives for the platform for 2021, as stipulated by the Ministry, are specifically to contribute to achieving the environmental quality goal of a non-toxic environment and the protection of human health. The assignment includes, amongst other things, to disseminate knowledge and provide support to government authorities in matters concerning the safe handling and use of nanomaterials.

35. SweNanoSafe recently compiled a report entitled "Proposals for national measures for safe use, handling and development of nanomaterials. SweNanoSafe Report 2020:3". The report was submitted to the Ministry of the Environment and is available to download on the website of the platform.

36. The platform comprises a steering group with participation from the Swedish Chemicals Agency (KEMI), a project team that manages the day-to-day activities, and an expert panel (established in 2016) consisting of experts from different universities in Sweden. The platform initiated a national network of nanosafety researchers and has hosted annual meetings of the research network since 2018. Furthermore, the platform recently launched a network for educational activities and several online meetings are planned

to consolidate the network and promote nanosafety in education. Hence, during the autumn of 2020, SweNanoSafe organised three workshops focused on education in nanosafety. The first workshop focused on the need for education in nanosafety. The second workshop dealt with available education in nanosafety in Sweden, and the third workshop discussed concrete opportunities of taking various education efforts one step further. The initiative brought together about 30 representatives from several different societal stakeholders, including government agencies, academia, companies, non-profit associations, and consultants with a common interest in the field of nanosafety. The joint discussions identified new opportunities for continued networking and plans for further development. The outcome from these workshops is summarized: [Nanosafety and Education – Report from workshop series with SwenanoSafe’s education network and Roadmap for 2021](#).

37. SweNanoSafe also hosted an online workshop for other national nanosafety initiatives in Europe in mid-September of 2020. The purpose was to discuss how to collaborate to better promote national and international initiatives for nanosafety, and the intention is to follow up with additional events.

38. Recently, SweNanoSafe has focused specifically on the use of nanomaterials in construction and a report from a recent workshop has been translated into English: “[Nanomaterials in the construction industry – a life cycle perspective. SweNanoSafe Report 2019:2](#)”. SweNanoSafe has subsequently up followed up with a more detailed evaluation and inventory of nanomaterials in construction. Findings were presented at a workshop end of March 2021 to be followed by a second report in late spring of 2021.

39. Another workshop held in the autumn of 2020, was “Nanomaterials in waste – a new challenge?”, co-arranged with Avfall Sverige and two research projects funded by Mistra and Vinnova. The workshop provided an overview of waste and nanomaterials, legislation, and recent research.

40. SweNanoSafe also commissioned a report on nanomaterials in the environment. The report, prepared by Goodpoint AB, is focused on the identification of knowledge gaps and proposals for research initiatives, with a focus on Swedish conditions. The report (to be translated to English) [Nanomaterial i miljön – en översikt av kunskap och av kunskapsluckor](#) – describes nanomaterial emissions to and accumulation in the environment, analytical methods for different matrices, how nanomaterials are transformed in the environment, toxicological effects in the environment, and environmental risk assessment. SweNanoSafe also organized an online workshop in the fall of 2020, “3rd Annual Workshop of the SweNanoSafe Research Network: Nanomaterials in the Environment”, where knowledge gaps in the area were discussed in the national research network, as a part of this effort.

41. Since 2019, standardization regarding nanomaterials and nanotechnology is of high national priority in Sweden. For reasons regarding safety, health and environmental issues, as well as for quality assurance and market introduction, accurate standards for characterization and materials’ definition are paramount. Swedish Standards Institute, Chalmers Industriteknik, SIO Grafen and RISE Research Institutes of Sweden are project partners in a project financed by the Swedish Government through Vinnova. To elaborate appropriate and standardised characterization methods, it is of utmost importance for Swedish stakeholders to engage in international work. This collaboration ensures that the developed standards are applicable and includes materials and technologies that are important to the Swedish market. The work is currently focused on [establishing national priorities for international standardization of graphene and nanocellulose](#) (in Swedish). The goal is that, within three years, Sweden will be a driving force in international standardization of nanomaterials (nanocellulose and graphene in particular), strategically implementing a safe-by-design approach.

42. Lund University recently launched a new nanosafety initiative called [NanoSafe4All](#) (in Swedish). This collaborative initiative in nanosafety includes not only researchers from various faculties at Lund University and from a number of local industry partners, but also researchers and experts representing external stakeholders such as the Mistra Environmental Nanosafety programme and SweNanoSafe. The intention is to discuss and identify needs in nanosafety with the widest possible perspective, identifying

possible interdisciplinary projects including funding opportunities and the possibilities of providing nanosafety services to ensure safe handling of nanomaterials and products.

### 1.13. Switzerland

43. The Action Plan on Synthetic Nanomaterials was completed at the end of 2019. A further extension was not necessary. The final report, approved by the Federal Council in September 2020, summarises the results, findings and further procedures. The report is available at [Action plan for synthetic nanomaterials \(admin.ch\)](#).

### 1.14. Thailand

44. National Nanotechnology Center (NANOTEC) has created a working group to work as Standards Development Organization (SDO) on behalf of Thai Industrial Standards Institute (STI) to lessen TISI workload and help speed up approval of industrial standards. The working group consisted of representatives from regulators, academia, and industries. For 2021 NANOTEC SDO team will push to complete the draft industrial standards for herb extract (Kaempferia extract) then submit to TISI for their final approval. The NANOTEC SDO team is looking to also work on 5 additional herbs extract for industrial standards within 2021-2025

45. A NANOTEC Nanosafety Alliance Section staff has also been invited to play the role of advisor to the Federation of Thai Industries (FTI) to help provide guidance to the FTI on nanosafety aspects.

### 1.15. United States

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

46. The U.S. Environmental Protection Agency (EPA) completed review of two low volume exemptions for a modified graphene substance and a modified titanium dioxide substance. EPA allowed the exemptions under conditions that limited human and environmental exposures to prevent unreasonable risks. Additionally, the EPA reviewed and completed a significant new use notice for a carbon nanotube substance. This new chemical substance was regulated with a consent order owing to limited available data on nanomaterials; the consent order limited uses and human and environmental exposure to prevent unreasonable risks.

47. The U.S. National Institute for Occupational Safety and Health (NIOSH) assessed potential health risk from occupational exposure to silver nanomaterials and derived a recommended exposure limit (REL) for silver nanomaterials ( $\leq 100$  nm primary particle size) of 0.9 micrograms per cubic meter ( $\mu\text{g}/\text{m}^3$ ) as an airborne respirable 8-hour time-weighted average (TWA) concentration. This assessment was published at <https://www.cdc.gov/niosh/docs/2021-112/default.html> in May 2021.

#### **c. Risk management approaches;**

48. Between September 2020 and May 2021, EPA received notification of 1 nanoscale substance 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 78. 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.

49. Since January 2005, EPA has received and reviewed more than 245 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.

50. 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***

51. 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***

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

# 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

52. 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](http://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).

53. The Department of Environmental Geosciences of the University of Vienna (Frank von der Kammer) started to work on the development of an OECD Test Guideline for the Solubility and Dissolution Rate of Nanomaterials under Environmental Conditions. The new project will combine 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.

## 2.2. Canada

54. The risk assessment framework for nanomaterials in Canada has adopted the Recommendation of the Council as one of the central pillars. The risk assessment framework builds on traditional chemicals frameworks, guidance documents and guidelines, and adapts existing knowledge to the particularities of the manufactured nanomaterials.

55. Canada is being fully adherent to the OECD Recommendation of the Council. To manage nanomaterials, Canada is making adaptations where necessary to take into account the specific properties of nanomaterials. For examples, revised guidance or adapted test guidelines specific to nanomaterials are recommended in risk assessment and regulation of nanomaterials to address nanospecific issues.

### 2.3. Chile

56. Collaborating with the National Institute of Standardisation (INN), initiatives have started for the generation, adaptation, and implementation of standards (including OECD recommendations as Test Guidelines, Guidance Documents and others) in fields such as nanomaterial terminology, labeling, testing, public health-, workplace- and environmental-safety.

### 2.4. Costa Rica

57. Costa Rica has a broad legal framework on registration, control, import, labelling and use of industrial chemicals controlled by the Ministry of Health; however, it doesn't include nanomaterials.

58. Currently, there is no specific legal framework for the registration of nanomaterials, the Ministry of Health will try to modify the regulations on the registration of chemical products to include them, so it is planned to create a working group considering representatives of government, academia and industry to work on the regulatory framework for nanomaterials.

### 2.5. Denmark

59. Denmark is leading three projects in the OECD Test Guidelines Programme as follows: i) 'Determination of solubility and dissolution rate of nanomaterials in water and relevant synthetic biologically mediums', ii) 'Identification and quantification of the surface chemistry and coatings on nano- and microscale materials', and iii) 'Determination of the dustiness of manufactured nanomaterials' although delayed by the Covid-19 pandemic.

60. In the solubility project, all key experimental work has been completed in order to develop test SOPs and benchmark data for interlaboratory comparison of test materials in biologically simulant fluids (lung-lining, phagolysosomal, and gastro-intestinal simulant media). For both projects, there will be a formal call for interlaboratory comparison (ILC) via OECD and NanoHarmony in the fall.

61. The work is being conducted by experts from the Danish National Research Centre for the Working Environment (NRCWE) and the German Federal Institute for Risk Assessment (BfR).

62. In the dustiness project, an international call for inter/intra laboratory comparison on non-HARN materials has been circulated via OECD and 18 partners have responded positively. Seven dustiness methods will be tested and include in the GD. Six non-HARN materials were selected for the dustiness tests and have been distributed to the partners. SOPs for each method have been discussed, written and shared between the members, and specific results templates provided to partners for test reports. Tests on rotating drums and small rotating drum techniques have already been started, and it is expected that tests with other techniques will be started before the end of year 2021. Regarding HARN materials, an international call for inter/intra laboratory comparison has been circulated via OECD, and 2-3 techniques will be retained for the round robin tests.

63. Experts from the Danish National Research Centre (NRCWE) and The French National Institute for Industrial Environment and Risks (INERIS) are leading the work.

64. Denmark is also active in the OECD Working Party on Manufactured Nanomaterials (WPMN), and has led the project 'Assessing the global readiness of regulatory and non-regulatory models for assessing occupational exposure to manufactured nanomaterials'. The report is expected to be published in September 2021. This report compiled 23 tools for occupational exposure assessment and evaluated for scope analysis, accessibility and sensitivity analysis. From these 23 tools, 15 were selected and assessed for performance testing. Based on the performance testing results guidance on potential usability of the tools is provided.

65. Experts from the Danish National Research Centre (NRCWE) and the National Institute For Occupational Safety And Health (CDC-NIOSH), with the close collaboration of Health Canada (HC) led the work.

## 2.6. European Union

66. No initiation of further activities, but a large number of EU projects are actively supporting OECD TG and GD development. More information also in contributions by EU countries and UK.

## 2.7. France

67. **INERIS** is leading and coordinating the development of a new TG and GD on the determination of dustiness and the use of dustiness in exposure modelling and in ATEX safety analysis.

68. This set of two documents will address the following:

- Identification of a set of measurands for dustiness indices to be used for ranking and exposure assessment in a regulatory context (e.g., the respirable mass fraction released, number of particles/fibers released, and dust particle morphology).
- Description of standard operating protocols (SOPs) and accepted methods for performing dustiness testing of powder materials and their application for safety purposes.
- Assessment of the applicability and limitations of the identified dustiness testing methods to support the current and foreseeable future regulatory needs and data requirements.
- Assessment of the applicability of different dustiness test methods to generate data for use in i) exposure categorization and quantitative exposure modelling, and ii) ATEX safety (explosion risks at the workplace) is planned to be part of the work in the GD development.

69. Within this project, **INERIS** is participating in the round robin tests on Vortex shaker dustiness technique. For this Malta project, **INERIS** is task leader in the dustiness tests development in the EU projects Gov4nano et NanoHarmony. **LNE** is also registered to participate to inter-laboratory comparison to validate OECD test guideline on dustiness measurement.

70. Within the framework of the EU project NanoHarmony, **INERIS** is involved with Spain (INIA) and Portugal (University of Aveiro) in the adaptation of OECD Test Guidelines 201, 202 and 203 for the determination of the ecotoxicity of manufactured nanomaterials. In this context, a SPSF, which aims at revising the GD 317 on Aquatic and Sediment Toxicological Testing of Nanomaterials in order to include detailed annexes providing technical recommendations for conducting assays according to TG 201, 202, and 203, will be submitted in November to WNT for inclusion in the workplan.

71. **LNE** participated to the inter-laboratory comparison organised in the frame of OECD to validate OECD test guideline on particle size distribution (contribution with 5 techniques: AFM, SEM, DLS, sp ICP-MS and ESI-DMA).

## 2.8. Germany

### a. **German Environment Agency (UBA)**

72. At WNT-32, a new OECD Guidance Document to guide on the investigation of nanomaterials using OECD TG No. 312 (“leaching in soil columns”) was adopted. The activity was led by Canada and Germany as WNT project 3.14 since April 2017. The objective of this activity was to improve the applicability of OECD TG 312 “leaching in soil columns” for the testing of mobility of nanomaterials in soils. As environmental behavior and fate of nanomaterials is subjected to kinetic processes (agglomeration, sedimentation) mainly, there is currently no method available to appropriately determine fate of nanomaterials in soils as current methods applied for conventional chemicals are either not applicable, not reliable or not yet advanced/available for nanomaterials. Thus, the use of OECD TG 312 for determining fate of nanomaterials in soil became particularly important and guidance for using the TG was needed. Elements which are considered in the new GD *inter alia* include the preparation of stock and test suspension, the application to the test system, choice of appropriate test duration and flow rate, reliable and robust (and cost-effective) analytics as well as appropriate data interpretation. The GD development was mainly executed by the support of an international core group of experts on a voluntary basis. A core element of GD development was an interlaboratory comparison (ILC) test which ran in 2019 (with 2 nanomaterials, 2 soils, data received from 7 labs from 4 countries). The first WNT commenting round of the draft GD took place in December 2020. In general, strong support for the proposed document was received and the comments on clarifications and editorial changes were considered in a final version of the draft document which was submitted to WNT for adoption in March 2021.

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

73. The draft TG on particle size and size distribution of nanomaterials (WNT project 1.4, led by Germany and the accompanying report on the interlaboratory test comparison that took place in 2019 was submitted to the Joint Expert Group on physical-chemical properties (JEG) of nanomaterials in summer 2020. More than 300 comments were received. The large majority of comments were of editorial nature or questions for clarifications within the paragraphs. There was no disagreement on the general technical performance of the TG. In November and December, the 2nd JEG meeting was executed in 4 online meetings to discuss the draft version of the TG revised based on the comments received to find approval by the JEG on the changes made (summary notes available on Clearspace: Expertise in Test Guidelines Development: <https://community.oecd.org/docs/DOC-168005>).

74. Nearly all comments were clarified during the meeting and revisions were agreed by the JEG. Open discussion points included (i) the application of terms related to nanomaterials which should follow the objective for unambiguous understanding throughout the draft TG and (ii) the applicability of the draft TG to meet EU regulatory needs. Both issues are currently addressed by the leads. Submission of a revised version of the draft TG as well as the validation report to WNT for the 1st commenting round is anticipated for late spring/early summer.

## 2.9. Italy

75. Italy is coordinating the WPMN project on a new Guidance Document on “*Integrated in vitro approach for intestinal fate of orally ingested Nanomaterials*”. The SPSF draft has been submitted to WPMN. Comments are expected from WPMN delegations in order to submit to WNT an agreed version of the SPSF (November 2021).

- ISS participates to the WNT project 4.095 for developing a Guidance Document on the Adaptation of the “*In Vitro Micronucleus assay (OECD TG 487) TG for Testing of Manufactured Nanomaterials*” (led by JRC) supporting the writing of the GD.

## 2.10. Korea

76. The Ministry of Environment (ME) has modified OECD TG 318 for further testing dispersion stability of nanomaterials in simulated environmental media by using different exposure methods and testing conditions (static, semi-static, flow-through).

## 2.11. Switzerland

77. Ongoing 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. This project is also part of the EU Horizon2020 project Gov4Nano.

78. Characterization and testing of OECD TG 442D with selected MNM has been finished. OECD TG 442D (ARE-Nrf2 luciferase KeratinoSens™) is technically feasible. The work about *in vivo/ in vitro* correlation using existing literature is ongoing.

## 2.12. United Kingdom

### a. **NanoHarmony**

79. The NanoHarmony ([www.nanoharmony.eu](http://www.nanoharmony.eu)) project (2020 – 2023) supports the development of a set of scientifically reliable test methods and good practice documents, based on the translation of existing scientific knowledge and data into a form that has regulatory relevance. NanoHarmony is 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 2020 NanoHarmony hosted an International Workshop on Gap Analysis and Data Requirements to support TG and GD Development which included sessions related to all the scientific projects and reported the outcome at a webinar on 16 December 2020. Under Tasks 1.2 and 1.4 scientific papers relating to bioaccumulation and the use of single particle ICP-MS with biological samples were submitted for publication.

### b. **RiskGone**

80. 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. Currently, 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.

81. Focussing on *Daphnia* reproductive toxicity, RiskGONE are working to establish an AOP for chronic (reproductive) toxicity including induction of males, building on existing AOPs on endocrine disrupting chemicals leading to induction of males (AOP 201: Juvenile hormone receptor agonism leading to male offspring induction associated population decline), on the impact of excessive oxidative stress on oocyte apoptosis (AOP 216: Excessive reactive oxygen species production leading to oocyte apoptosis-associated reproduction decline) and on the role of chloride channels in acute mortality which is also linked with impaired reproduction pathways (AOP 113: Glutamate-gated chloride channel activation leading to acute mortality). Identifying 5 interconnected end-points related to reproduction (decreased growth, decreased fertility, induction of males, reduced mating success all leading to decreased reproduction) a first set of key events (KEs) and their interconnections have been established. The Molecular Initiating Event appears to be gut blockage / gut overload leading to reduced calorific uptake and thus reduced energy availability for growth and diversion of energy to fighting ROS rather than to reproduction (as per the Dynamic Energy Budget model). Given the strong link to reduced calorific uptake, the limited nanomaterials literature is being supplemented by the extensive literature on daphnia adaption to low food availability / competitive interactions to document the KEs and their interconnections. A number of key genes involved in carapace shedding (an essential step in growth and development), maturation, induction of males and sex communication have been identified, and utilising an extensive chronic toxicity dataset from UoB based on 11 silver and titanium dioxide nanomaterials, exposed according to the OECD 211 protocol extended over 5 generations in a pair-wise continuously exposed versus parent only exposure and recovery of the offspring (F1-F4) generations is now being mined (in collaboration with NanoSolveIT) to supplement the AOP. Lessons from the OECD NanoAOP working group on how to define the plausibility, measurability, and regulatory relevance of each potential KE are being integrated also. From the data analysis, a set of assays to supplement the OECD 211 test are being proposed, to build the evidence base for the AOPs and to enable manufacturers and regulators to confirm whether a specific nanomaterial or nanoform induces a specific KE or not. These additional end-points (including the extension to multiple generations to assess adaption and/or enhanced sensitivity to reproduction failure) are also being integrated into the revision of the test guidelines being developed as a part of the project. AOP presentations have been made on both the human and *Daphnia* AOPs at NanoSafe conference. For the *Daphnia* AOP, a workshop is planned after the summer to get feedback on the AOP itself and the assays identified to support each KE and the MIE. For the *Daphnia* AOP, a workshop is planned after the summer to get feedback on the AOP itself and the assays identified to support each KE and the MIE.

### **c. TG305 Scoping Review**

82. 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. The UK has developed a scoping review to consider how to trigger or waiver the TG 305 Bioaccumulation fish test for nanomaterials. 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 are being formulated for next steps in developing tools and guidance to support decision making in triggering or waiving TG 305 for nanomaterials.

### 2.13. United States

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

# 3

## Developments related to good practice documents

### 3.1. Austria

84. The federal **standardisation committee on “Nanotechnology” (ASI 052.73)** continued observing and commenting the international standardisation activities (CEN/TC 352, ISO/TC 229) and 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. The Austrian standardisation committee is chaired by “NanoTrust” (contact: André Gzásó).

### 3.2. Canada

85. Two papers have been published on an interlaboratory comparison that provides supporting data for an ISO standard: TS 23151 Nanotechnologies - Particle Size Distributions for Cellulose Nanocrystals.

- Meija, J., Bushell, M., Couillard, M., Beck, S., Bonevich, J., Cui, K., Foster, J., Will, J., Fox, D., Cho, W., Heidelmann, M., Park, B. C., Park, Y. C., Ren, L., Xu, L., Stefaniak, A., Knepp, A. K., Theissmann, R., Purwin, H., Wang, Z., de Val, N., Johnston, L. J. Particle size distributions for cellulose nanocrystals measured by transmission electron microscopy: An interlaboratory comparison, *Anal. Chem.*, 92, 13434-13442, 2020.
- Bushell, M., Meija, J., Chen, M., Batchelor, W., Browne, C., Cho, J.-Y., Clifford, C. A., Al-Rekabi, Z., Vanderfleet, O., Cranston, E., Lawn, M., Coleman, V. A., Nyström, G., Arcari, M., Mezzenga, R., Park, B. C., Ren, L., Saito, T., Kaku, Y., Wagner, R., Johnston, L. J. Particle size distributions for cellulose nanocrystals measured by atomic force microscopy: An interlaboratory comparison, *Cellulose*, 28,1387-1403, 2021.

### 3.3. Costa Rica

86. Two papers have been published in the field of the physicochemical characterization of metallic nanoparticles, development of statistical, web applications for characterization, and manufacturing of stable nanoparticles that provides supporting data of the development of nanoparticles reference materials (RMs), and explore their role as a metrological mechanism to improve the quality and comparability of NP measurements.

- Calderón-Jiménez, B., Johnson, M. E., Bustos Montoro, A. R., Murphy, K. E., Winchester, M. R., & Vega Baudrit, J. R. (2017). Silver nanoparticles: technological advances, societal impacts, and metrological challenges. *Frontiers in Chemistry*, 5:6.

- Calderón-Jiménez, B, Sarmanho GF, Murphy KE, Montoro Bustos AR, Vega-Baudrit JR. (2017). NanoUV-VIS: An Interactive Visualization Tool for Monitoring the Evolution of Optical Properties of Nanoparticles throughout Synthesis Reactions. Journal of Research of National Institute of Standards and Technology. Volume 122, Article No. 37.

### 3.4. European Union

87. As further support to the [registration of substances in nanoform under REACH](#) (link to ECHA site covering legal provisions and implementation support including guidance), in mandatory application since 1 January 2020, the European Chemicals Agency (ECHA) is presently updating its REACH guidance. The update to the Guidance on information requirements and chemical safety assessment related to human health is expected in autumn 2021, while the revision of the part of the guidance covering environmental aspects is also planned but has not yet been launched (discussion on combining the work with related EFSA revision, see below). Update of the Guidance on registration and Substance Identification (incl. support on nanoforms) and the development of an extended Q&A document supporting implementation of obligations of downstream users are also well in progress.

88. European Food Safety Authority (EFSA) has finalized the work on Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain Part 1: human and animal health, first [published in 2018](#), and since recently under review. The re-publication is planned in July 2021. Work on the Part 2, focusing on environmental assessment, is ongoing and may potentially result in joint ECHA/EFSA guidance. EFSA has also finalized related Guidance on technical requirements for regulated food and feed product applications to establish the presence of [small particles including nanoparticles](#). It is also planned for publication in July this year. The general page to follow work by EFSA on nanomaterials (including publication of guidance) is <https://www.efsa.europa.eu/en/topics/topic/nanotechnology>

### 3.5. France

89. LNE contributed to the drafting of ANSES (French Agency for Food, Environmental and Occupational Health & Safety) [Opinion and Report on nanomaterials in food products](#) (in French) and to the [ANSES Scientific and technical support report on the review of analytical methods available for characterising nano-objects and their aggregates and agglomerates in order to meet regulatory requirements](#) (in French).

90. A- Scientific publications regarding:

- **Food grade TiO<sub>2</sub> exposure:** Basal Ti level in the human placenta and meconium and evidence of a maternofoetal transfer of food-grade TiO<sub>2</sub> nanoparticles in an ex vivo placental perfusion model, Guillard et al., Particle and Fibre Toxicology (2020) 17:51 <https://doi.org/10.1186/s12989-020-00381-z>
- **Nanomaterials at workplace:** Engineered nanomaterials at workplace: An overview of the state of the art, K. Chami et al., Archives des Maladies Professionnelles et de l'Environnement 82 (2021) 51—68
- **Interlab on size measurements:** Size measurement of silica nanoparticles by Asymmetric Flow Field-Flow Fractionation coupled to Multi-Angle Light Scattering: a comparison exercise between two metrological institutes, Alasonati et al., Journal of Chromatography A, Volume 1638, 2021, 461859, ISSN 0021-9673, <https://doi.org/10.1016/j.chroma.2020.461859> as an output of an inter-laboratory comparison carried out in the frame of the French network Club nanoMétrologie ([www.club-nanometrologie.fr](http://www.club-nanometrologie.fr))

- **SEM data processing:** Deep Learning Based Instance Segmentation of Titanium Dioxide Particles in the Form of Agglomerates in Scanning Electron Microscopy, Monchot et al., *Nanomaterials* 2021, 11, 968. <https://doi.org/10.3390/nano11040968>
- **sp ICP-MS characterization:** Titanium dioxide nanoparticles in food: comparison of detection by triple-quadrupole and high-resolution ICP-MS in single-particle mode, Noireaux et al., *J Nanopart Res* (2021) 23:102, <https://doi.org/10.1007/s11051-021-05198-1>
- **New approach for NPs shape characterisation:** A novel approach for 3D morphological characterization of silica nanoparticle population through HAADF-STEM, Crouzier et al., *Measurement* 180 (2021), <https://doi.org/10.1016/j.measurement.2021.109521>
- **New route to calibrate SEM for dimensional measurement:** Influence of electron landing energy on the measurement of the dimensional properties of nanoparticle populations imaged by SEM, Crouzier et al., *Ultramicroscopy* 226 (2021), <https://doi.org/10.1016/j.ultramic.2021.113300>

91. B- **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 transferred in 2021 to European standardization body CEN/TC 352 Nanotechnologies.

92. C- **LNE** is associated with KRISS (Korea) in a Preliminary Work Item entitled 'Nanotechnologies – Determination of size and size distribution of nano-objects in liquid using aerosolization differential electron mobility analysing system' to develop a new Technical Specification (TS) within ISO/TC 229 Nanotechnologies

93. D- **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.

94. **INERIS** is contributing to the development of a FAIR (Findable, accessible, interoperable, and reusable, phys-chem and (eco)tox data base for nanomaterials, via the project the EU project Gov4nano. A paper detailing the methodology has been accepted in 2021:

- Towards FAIR nanosafety data, Nina Jeliaskova et al.: *Nature Nanotechnology*. 16, 644–654: <https://doi.org/10.1038/s41565-021-00911-6>.

### 3.6. Germany

#### a. **Federal Institute for Occupational Safety and Health (BAuA)**

95. From 2020 when the nano-specific information requirements of REACH have become mandatory for the registration of nanoforms of a substance, registrants have faced major challenges. These concern all areas of a registration, such as reference to existing data, data sharing, calculation of tonnage. But also completely new requirements for characterisation and formation of categories of similar nanoforms have to be met. An edition of the Helpdesk Focus series deals with questions arising in the registration of nanoforms of a substance and tries to clarify them in a broader context (in German). <https://www.baua.de/DE/Angebote/Publikationen/Fokus/Stoffe-in-Nanoform.pdf>

**b. Federal Institute for Materials Research and Testing (BAM)**

96. The SEM-Standard on nano particle size & shape distribution ISO 19749, *Nanotechnologies — Measurements of particle size and shape distributions by scanning electron microscopy*, developed within ISO/TC 229, is currently being prepared for publication. Supposed publication date: 2021-05.

**c. Federal Institute for Materials Research and Testing (BAM)**

97. The Versailles Project on Advanced Materials and Standards (VAMAS) has started an Inter-Laboratory Comparison '*Surface Analysis of Oxide Nanoparticles by Secondary Ion Mass Spectrometry (SIMS)*', organized by BAM. Results of the participants are submitted to BAM and the final report is being prepared by BAM and BfR to be published in the next months.

**d. Federal Institute for Materials Research and Testing (BAM)**

98. The German standardization project *AQuaFunkNano* (BMW; programm WIPANO) was initiated with the goal to identify, develop, optimize, and validate analytical methods which are able to quantify the total number of carboxyl and amino groups on nanoparticles and the number of these groups accessible for further conjugation reactions. The methods which should reveal traceability to metrological standards should be eventually developed into normative standards. The focus lays on organic and inorganic nanoparticles with applications in the life science and material sciences. The identified methods will be further developed and introduced to ISO/TC 229 "*Nanotechnologies*" or IEC/TC 113 "*Nanotechnology for electrotechnical products and systems*". This project is carried out in cooperation with two companies and will also involve a collaboration with BfR.

### 3.7. Italy

99. Two papers were published from Italian research groups on importance of harmonized *in vitro* approaches for nanomaterials testing and characterization:

- Zijno A., Cavallo D., Di Felice G., Ponti J., Barletta B., Butteroni C., Corinti S., De Berardis B., Palamides J., Ursini C.L., Fresegna A.M., Ciervo A., Maiello R., Barone F. 2020. Use of a common European approach for nanomaterials' testing to support regulation: a case study on titanium and silicon dioxide representative nanomaterials. *J. Appl. Toxicol.* 40(11), 1511-1525. <https://doi.org/10.1002/jat.4002>
- Andreoli C., Prota V., De Angelis I., Facchini E., Zijno A., Meccia E., Barletta B., Butteroni C., Corinti S., Chatgialloglu C., Krokidis M.G., Masi A., Condello M., Meschini S., Di Felice G., Barone F. 2021. A harmonized and standardized in vitro approach produces reliable results on silver nanoparticles toxicity in different cell lines. *J. Appl Toxicol.* May 12. doi: 10.1002/jat.4178.

### 3.8. Korea

100. In 2020, Korea Institute of Toxicology (KIT) and Korea Research Institute of Standards and Science (KRISS) joined the Horizon 2020, NanoHarmony project consortium as associate partners to develop test guidelines and guidance documents for nanomaterials.

101. KRISS has developed the Certified Reference Materials (CRMs) of different types according to the size, morphology, physical properties for reliable nanosafety evaluation. As internationally agreed reference, CRMs are used to provide metrological traceability and the international equivalence of measurement results. In addition, it is playing an important role in ensuring the quality control in physical

and biological measurements and testing. KRISS contributes to developing OECD test guide (TG110) by participating in a comparison study and providing certified reference materials (20, 50 nm SiO<sub>2</sub> nanoparticles). In addition, KRISS are involved as partners in the NanoSolveIT consortium and provided certified reference materials (20, 50, 90 nm SiO<sub>2</sub> nanoparticles, 30, 90 nm Au nanoparticles). This work was supported by Nano Safety Metrology Center funded by the Ministry of Science and ICT, Republic of Korea.

102. In April 2021, the ‘High throughput screening method for nanoparticles toxicity using 3D model cells’ proposed by KIT has been adopted in the International Standard for Nanotechnology (ISO/TC 229). FDTR 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 funded by the Ministry of Science and ICT, Republic of Korea. FDTR 22455 : Nanotechnologies — High throughput screening method for nanoparticles toxicity using 3D model cells

### 3.9. Malaysia

103. 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. 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).

### 3.10. Netherlands

104. EFSA published an [overview by RIVM](#) of relevant information for **environmental risk assessment (ERA) of nanomaterial use in the food and feed sector**. This overview – commissioned by EFSA – has been compiled to support EFSA in preparing guidance aimed at ERA of the application of nanoscience and nanotechnology in the food and feed chain. Such guidance will complement EFSA’s existing [guidance on human and animal health](#) aspects of nanomaterial risk assessment. The report highlights areas in the ERA where specific adaptations may be needed for nanomaterials and provides directions towards development of Guidance to support ERA of nanomaterials. The focus is on ERA in the food and feed sector, but most topics addressed are also applicable in ERA for other applications. Overall, collaboration with other EU agencies (e.g. ECHA, EMA) and organisations on method developments (e.g. OECD, ISO) is advised to avoid duplication of work and contradictory recommendations in ERA guidance for nanomaterials.

105. The OECD WNT project “Development of new Test Guideline on **toxicokinetics** to accommodate testing of nanoparticles” is led by the Netherlands (RIVM) and co-led by the UK (PHE). Korea and Australia are contributing by providing studies, and the EU contributes via accommodating work in the H2020 project [NanoHarmony](#). The OECD project aims to develop a new TG on *in vivo* toxicokinetic testing of nanoparticles following the inhalation and oral route. The current OECD TG 417 on toxicokinetics was identified as not applicable to nanomaterials. In December 2020, the project was discussed in an OECD WPMN WNT Joint Expert Group online meeting. Major topic was the approach taken to identify data gaps with respect to the minimum requirements of the study design of *in vivo* toxicokinetic studies with respect

to the dosing regimen (dose levels, exposure frequency and duration), the duration of the post exposure period, the time points for determining tissue and organ burdens and the key tissues and organs to be analysed. Experts provided valuable input on data gaps and their prioritisation, as well as on other relevant topics (e.g. analytical methods, mode of administration).

### 3.11. Sweden

106. Swedish scientists contributed to the World Health Organization (WHO) International Programme on Chemical Safety (IPCS) report on “Principles and methods to assess the risk of immunotoxicity associated with exposure to nanomaterials. Environmental Health Criteria Document No. 244” published in April 2020. This report provides an overview of the current knowledge on principles and basic mechanisms of immunotoxicity caused by engineered nanomaterials, and how to test for such effects.0

### 3.12. United Kingdom

107. 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) under ISO TC 229. Revision progressing to reflect the development in science and knowledge in last 9 years. It is a relatively high-level document. ISO/TS 12901-1 is and will continue to be complementary to ISO/TR 12885:2018 (Nanotechnologies — Health and safety practices in occupational settings).

108. UK Nanosafety group is starting to update its national guidelines for working safely with Nanomaterials.

#### **a. Graphene Standardization**

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

#### **b. NanoCommons**

110. 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.

111. Significant progress on consensus building related to metadata standards for nanosafety – data to describe the datasets and thus to make it more re-usable by others. A first paper has been published, introducing the concept of Scientific FAIR principles, for which experimentalists (data generators) are responsible, to complement the more technical FAIR principles which are perceived by the data generators as being the responsibility of database owners and managers (see Papadiamantis et al., 2020, <https://www.mdpi.com/2079-4991/10/10/2033>). Further demonstration cases for specific types of data, including dissolution data, protein corona data and nanomaterials characterisation data are being developed, along with so-called instance maps to document the experiments, including the nanomaterials, their surroundings and their effects on the target organisms (see Martinez et al., 2020, <https://www.mdpi.com/2079-4991/10/10/1936>, for an example of an instance map, which was then linked to the data capture template via an Electronic Lab notebook, and the data integrated into the NanoCommons KnowledgeBase for further modelling and re-use.

112. Developed a first (alpha) version of an extension of the InChI chemical identifier to cover also nanomaterials, which has been really well received by the international community. The paper describing the concept is here: Lynch et al., 2020, <https://www.mdpi.com/2079-4991/10/12/2493/htm>. Iseult Lynch has been invited by the IUPAC InChI Trust to chair a working group on NanoInChI to further develop it into an official InChI standard. This will have a number of important impacts, including facilitating distinction of nanoforms as per the ECHA guidance, harmonised integration of datasets related to similar nanomaterials, grouping and read-across of nanomaterials are more. Anyone interested to join the NanoInChI working group can contact Iseult ([i.lynch@bham.ac.uk](mailto:i.lynch@bham.ac.uk)).

113. An integrated Risk Assessment decision support tool for nanomaterials has been developed. For estimating the hazard Reference Points (RPs), the NanoCommons Risk Assessment workflow includes three hazard quantification approaches:

- The Benchmark Dose (BMD) modelling approach, that can be applied to available dose-response data;
- The Read-across and/or nano Quantitative Structure Activity Relationship (QSAR) approach assuming the availability of relevant fully validated predictive models;
- The GUIDENano similarity module and reference database, which provides a list of Final Safety Limit Values (FSLVs), which depend on the exposure setting and the RA hypothesis.

114. Using publicly available data, a PBPK biokinetics model for describing the biodistribution of TiO<sub>2</sub> after inhalation in rats was developed and extrapolated to mice. A dose-response methodology was applied to determine the BMDL values of 20 nm TiO<sub>2</sub> NMs in mice for AOP-173 (“Substance interaction with the resident lung cell membrane components leading to lung fibrosis”) and for all associated pathways. Multiple external exposure scenarios were formulated in the GUIDENano tool and were transformed to internal biodistribution using the PBPK model. Risk quotients were computed by comparing internal concentrations in the lower respiratory tract with the pathway and the AOP-173 BMDL values. The complete NanoCommons Risk Assessment decision support workflow can be accessed via: <http://enaloscloud.novamechanics.com/nanocommons/exposure/>. A publication on the tool is currently in preparation and will be reported subsequently.

### 3.13. United States

115. In 2020, the U. S. National Institute for Occupational Safety and Health (NIOSH) published two good practice documents for the use of 3D printers in the workplace. “3D Printing with Filaments: Health and Safety Questions to Ask” (<https://www.cdc.gov/niosh/docs/2020-115/default.html>) and “3D Printing with Metal Powders: Health and Safety Questions to Ask” (<https://www.cdc.gov/niosh/docs/2020-114/default.html>) posters cite health and safety questions with different control options and information to reduce exposure to potential hazards.

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

116. PETA Science Consortium International e.V., a member of the International Council on Animal Protection in OECD Programmes (ICAPO), co-authored a publication with scientists from the National Institute of Standards and Technology, the U.S. Consumer Product Safety Commission, the National Institute of Environmental Health Sciences, and the Swiss Federal Laboratories for Material Testing and Research. Published in a peer-reviewed scientific journal, the paper explains how to choose a positive control chemical for *in vitro* methods.

Reference:

- Petersen EJ, Nguyen A, Brown J, Elliott JT, Clippinger A, Gordon J, Kleinstreuer N, Roesslein M. Characteristics to consider when selecting a positive control material for an in vitro assay. *ALTEX*. 2021;38(2):365-376.

117. PETA Science Consortium International e.V. collaborated with scientists from German Federal Institute for Risk Assessment (BfR) and two U.S. federal agencies (the National Institute of Standards and Technology and the Consumer Product Safety Commission) on a publication on standardizing *in vitro* methods used for inhalation toxicity testing. The manuscript has been accepted for publication and describes the use of cause-and-effect analysis to maximize the reliability of *in vitro* inhalation toxicity measurements using an air-liquid interface.

Reference:

- Petersen E, Sharma M, Clippinger AJ, Gordon J, Katz A, Laux P, Leibrock L, Luch A, Matheson J, Stucki A, Tentschert J, Bierkandt F. Use of cause-and-effect analysis to optimize the reliability of *in vitro* inhalation toxicity measurements using an air-liquid interface. *Chem Res Toxicol*. 2021; *In press*.

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

## 4.1. Canada

118. 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.

## 4.2. Germany

### a. *Federal Institute for Risk Assessment (BfR)*

119. Within the EU-H2020 project GRACIOUS, a grouping framework for nanomaterials has been developed. The underlying IATAs, covering different routes of exposure (inhalation, oral, dermal), are currently being evaluated in multiple case studies. The HARN IATA has already been published and can be accessed via doi. <https://doi.org/10.1016/j.impact.2021.100314>. A final workshop is scheduled for September 2021.

## 4.3. Japan

120. 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 is under publication process. JISC leads “Analysis of nano-objects using asymmetrical-flow and centrifugal field-flow fractionation” (IS 21362), and now this is under discussion. JISC leads a project group 25 “Characterization of individualized cellulose nanofibril samples” (TS 21346), and now TS 21346 has been published. JISC leads “Measurement of film thickness of nanomaterials by using ellipsometry” (TS 23397), now TS 23397 has also been published. JISC leads “Positron annihilation lifetime measurement for nanopore evaluation in materials” (PWI TS 23397), now this goes to project stage. In TC229/WG3 (Health, Safety and Environmental Aspects of Nanotechnologies), JISC leads “Method for quantification of cellular uptake of carbon nanomaterials by using optical absorption measurement” (TS 23034), and now TS 23034 has been published. JISC leads a project group 39 “Lung burden measurement of nanomaterials for inhalation

toxicity tests" (PWI TR 5387), now this is under discussion. In TC229/WG4 (Material specification), JISC leads a project group 17 "Silica nanomaterials -Specifications of characteristics and measurement methods for nanostructured porous silica samples" (AWI TS 22298), now this is under discussion.

#### 4.4. Korea

121. Korea Agency for Technology and Standards (KATS) developed two standards under ISO TC229 WG3 (Health, Safety and Environmental Aspects of Nanotechnologies), in vivo toxicity assessment of nanomaterials using dechlorinated zebrafish embryo and ISO TC229 WG4 (material specifications), Nano-object-assembled layers for electrochemical bio-sensing applications-specification of characteristics and measurement methods.

122. The standards under development by KATS;

1. High throughput screening method for nanoparticles toxicity using 3D cells
2. Testing of the Photocatalytic Activity of Nanoparticles for NADH oxidation
3. Characterization of carbon nanotube and carbon nanofiber aerosols in relation to inhalation toxicity tests
4. Performance Characteristics of Nanosensors for Chemical and Biomolecule Detection
5. Considerations for Performance Evaluation of Radiolabeling methods for Nanomaterials
6. The Overview of Methods to Evaluate the Nanoparticle in Cellular Uptake Between 2-dimensional and 3-dimensional cell cultures

#### 4.5. Netherlands

123. The main goal of the EU project **GRACIOUS** ([www.h2020gracious.eu](http://www.h2020gracious.eu)) is to generate a science-based framework to enable practical application of grouping and read-across of nanomaterials. In 2018 a first draft framework was presented at a workshop at the OECD and discussed with regulatory (ECHA, EFSA, OECD delegations), industrial and academic stakeholders. The comments were used to adapt and publish the framework (doi: [10.1016/j.nantod.2020.100941](https://doi.org/10.1016/j.nantod.2020.100941)) and target further research. The GRACIOUS Framework is underpinned by scientific hypotheses identifying endpoints relevant to grouping and read-across. The use of IATA facilitate effective data gathering to justify the grouping and read-across. Application of the Framework helps in moving away from the case-by-case risk assessment paradigm, thereby improving the efficiency of risk analysis and decision making for safer design of quality nanomaterials. The project will end in September 2021. Current efforts focus on publishing the individual IATAs with supportive case studies, and a "user guide" for the framework, accompanied by a "blueprint" that will allow a user-friendly software environment to further facilitate the use of the framework seek input from stakeholders to ensure that the framework effectively meets the needs of both regulators and industry. Outputs from the project can provide valuable input for an update of the section on nanomaterials in the [OECD Guidance on Grouping of Chemicals](#). RIVM is a main partner in this project, as work package lead and playing a crucial role in the development of the Framework and engagement of stakeholders.

124. The EU project [REFINE](#) will deliver a regulatory framework for the risk benefit analysis of nanomedicinal products. The framework will be 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, ADME, and immunotoxic effects

of nanomedicines. Part of these gaps are experimentally addressed in the project. This experimental work includes 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.

#### 4.6. Sweden

125. Swedish scientists participate in the Horizon 2020 (H2020) project, BIORIMA ('biomaterial risk management'), a large nanosafety/nanomedicine project in which one of the objectives is to develop IATAs specifically for nanobiomaterials (NBMs) deployed in advanced therapy medicinal products and medical devices. This work is conducted in collaboration with the H2020 project GRACIOUS, also with participation from Sweden. Both projects are coordinated by UK partners. The toxicology and ecotoxicology work in BIORIMA is coordinated by Karolinska Institutet in Sweden. The project will conclude in 2021. In the H2020 project NanoSolveIT (Innovative Nanoinformatics models and tools), Sweden has one partner executing molecular simulations for studies of the molecular mechanisms of toxicity and possible health effects of nanoparticles. NanoSolveIT's ambition is to advance and implement *in silico* IATAs for the environmental health and safety of nanomaterials. The project aims to develop a validated assessment e-platform to identify the critical characteristics of nanomaterials responsible for their adverse effects on human health and the environment and will implement a nanoinformatics-driven decision-support strategy based on innovative *in silico* methods, models, and tools.

#### 4.7. United Kingdom

##### a. GRACIOUS

126. 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.

127. ECHA requires an evidence based hypothesis to explain why nanoforms can be grouped. The Framework includes 40 pre-defined hypotheses to support grouping, which cover both human and environmental hazards. Testing of these grouping hypotheses is supported by tailored Integrated Approaches to Testing and Assessment (IATAs). These IATAs are decision trees which support the user to identify the relevant information needed to assess whether the grouping hypothesis should be accepted or rejected for the nanoforms under consideration. Each decision node of the IATA is supported by a tiered testing strategy, which encourages use of existing data, and where testing is required it prioritises use of non-animal testing where appropriate. The Framework provides advice on how to use lower tier (e.g. *in vitro*) data to justify the use of *in vivo* data for source nanoforms and non-nanoforms in order to fill data gaps for target nanoforms. ECHA requires demonstration of similarity between the nanoforms within a group, and so we have generated protocols for assessing similarity either property by property, or in a multidimensional approach. We have extended nanomaterial databases (using enanmapper) by generation of new templates for physicochemical characterisation and for exposure assessment – previously templates existed only for hazard. The exposure assessment data has been gathered into an exposure library for open access use. Quality and completeness scores are being incorporated into these

templates – a workshop with stakeholders to discuss this methodology will be held in June. The Framework is being delivered as a guidance document but also a software blueprint that can be incorporated into risk assessment software. Finally, the Framework will be extended by new projects such as SUNSHINE, HARMLESS and DIAGONAL, for application to multicomponent nanomaterials.

**b. *NanoSolveIT***

128. 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.

129. A broad range of tools and predictive models have been developed and/or provided with graphical user interfaces to make them available to the wider community so far in NanoSolveIT, ranging from human and environmental exposure models, to QSAR models for physicochemical endpoints such as zeta potential or biological end-points such as cytotoxicity, a deep learning model for prediction of chronic daphnia toxicity, and omics workflows, as shown in the table below with the relevant links to the models. Additionally, the first version of the IATA, integrating exposure models with PBPK models has also been implemented for inhalation / occupational exposure in indoor settings.

Category	Description	URL
Exposure (Occupational)	Multi-box aerosol occupational exposure model	<a href="https://aerosol.cloud.nanosolveit.eu/">https://aerosol.cloud.nanosolveit.eu/</a>
Exposure (Environmental)	NanoFase WSO Environmental exposure model	<a href="https://nanofase.cloud.nanosolveit.eu/">https://nanofase.cloud.nanosolveit.eu/</a>
Deep Learning / Image Analysis	Deep Learning model to predict NM exposure effects on Daphnia Magna	<a href="https://deepdaph.cloud.nanosolveit.eu/">https://deepdaph.cloud.nanosolveit.eu/</a>
Biokinetics	Human Inhalation Model	<a href="https://lungexposure.cloud.nanosolveit.eu/">https://lungexposure.cloud.nanosolveit.eu/</a>
QSAR/Read-across	Cytotoxicity (Cell Viability) Prediction for Metal Oxide NPs	<a href="https://cellviability.cloud.nanosolveit.eu/">https://cellviability.cloud.nanosolveit.eu/</a>
QSAR/Read-across	Read-Across Model for Zeta Potential Prediction	<a href="https://zetapotential.cloud.nanosolveit.eu/">https://zetapotential.cloud.nanosolveit.eu/</a>
QSAR/Read-across	MS <sup>3</sup> bD Zeta Potential Predictive Model	<a href="https://mszeta.cloud.nanosolveit.eu/">https://mszeta.cloud.nanosolveit.eu/</a>
QSAR/Read-across	Vythos (Gold NM cell association, CNT absorption coefficients)	<a href="https://vythos.cloud.nanosolveit.eu/">https://vythos.cloud.nanosolveit.eu/</a>
QSAR/Read-across	NanoPot (logP, Zeta Potential in water, Cellular Uptake of A549 of Gold ENM)	<a href="https://nanopot.cloud.nanosolveit.eu/">https://nanopot.cloud.nanosolveit.eu/</a>
Omics Analysis	eUTOPIA - Preprocessing and analysis of omics data	<a href="https://eutopia.cloud.nanosolveit.eu/eUTOPIA/">https://eutopia.cloud.nanosolveit.eu/eUTOPIA/</a>
Omics Analysis	FunMappOne - Visualisation of molecular biology experiments	<a href="https://funmappone.cloud.NanoSolveIT.eu/">https://funmappone.cloud.NanoSolveIT.eu/</a>
QSAR/Read-across	Cytotoxicity (Cell Viability) Classification Model	<a href="https://cytotoxicity.cloud.nanosolveit.eu/">https://cytotoxicity.cloud.nanosolveit.eu/</a>
Biokinetics/ Integrated Application	NanoSolveIT IATA: PBPK models and integration with the occupational exposure model	<a href="https://exposurepbpk.cloud.nanosolveit.eu/">https://exposurepbpk.cloud.nanosolveit.eu/</a>

130. IATA case studies on genotoxicity and reproductive toxicity to daphnids are in development and will be submitted to the OECD IATA Case study group for evaluation and feedback.

### c. **RiskGone**

131. 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 interface. This screening tool should be used during the pre-assessment step of the Risk Governance process. It is accessible at: <http://enaloscloud.novamechanics.com/riskgone/thresholdanalysis/>

132. Further extensions to develop decision support tools for Environmental Impact Assessment, and for AOP tools are under development.

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

133. PETA Science Consortium International e.V. co-authored a publication with the Environmental Protection Agency (EPA) and others that describes a tiered strategy (aimed at reducing the use of animals) to facilitate EPA's review of pre manufacture notices for new chemicals under general surfactant category. The manuscript has been accepted for publication.

*Reference:*

- Henry T, Salazar K, Jarabek A, Price O, Hayes M, Kennedy W, Keene A, Moors S, Jovanovich L, Rose J, Tveit A, Tremblay R, Becker R, Osman-Sypher S, McMullen P, Slattery S, Irwin W, Odin M, Melia J, Sharma M, Stucki AO, Clippinger AJ, Stedeford T. Surfactants Category: An Integrated Approach to Testing and Assessment (IATA) Including Application of New Approach Methods (NAMs) for Assessing Inhalation Risks under the Toxic Substances Control Act (TSCA). *Chem Res Toxicol.* 2021; *In press.*

134. PETA Science Consortium International e.V. and MatTek announced an award to provide an opportunity for researchers worldwide to win three-dimensional reconstructed human respiratory tissues from MatTek. The two awardees will receive tissues worth \$10,000 (first place) and \$5,000 (runner-up) redeemable for EpiAlveolar™ and EpiAirway™ tissues. The award winners from international institutions were selected based on their proposal's scientific merit and potential to replace animal testing. More details on this award can be found here: <https://www.thepsci.eu/mattek-award/>

135. In collaboration with EPA, Syngenta, and Unilever, PETA Science Consortium International e.V. co-organised a three-part inhalation webinar series on 'Using *In Silico* and *In Vitro* Approaches for Next Generation Risk Assessment of Potential Respiratory Toxicants'. Each two-hour long public webinar featured three presentations and discussions. More information and the recordings of the webinars can be found here: <https://www.thepsci.eu/inhalation-webinars/>

136. PETA Science Consortium International e.V. is co-editing a Research Topic in *Frontiers in In Vitro Toxicology* together with the EPA, 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. More information about the Research Topic can be found here: <https://www.frontiersin.org/research-topics/19075/chemical-testing-using-new-approach-methodologies-nams>

# 5

## Developments and/ or considerations related to “advanced” materials (multicomponent / complex)

### 5.1. Austria

137. NanoTrust organised several events and conferences on “Advanced Materials”. (1) A workshop on **Advanced Materials** in Vienna on 10<sup>th</sup> of May 2020 and (2) a “**Workshop on Advanced Materials and Emerging Issues**” as part of the 17<sup>th</sup> **Asian Nanoforum Summit** on 4<sup>th</sup> of October 2020. This workshop has been held in cooperation with the National Institute for Materials Science (NIMS), Japan

138. 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 most recent call addressed nanomaterials and “advanced materials” as potential materials for traceability. The EHS programme is owned by the Austrian Federal Ministry of Climate Action, Environment, Energy, Mobility, Innovation and Technology ([www.bmk.gv.at](http://www.bmk.gv.at)) and is handled by the FFG - Austrian Research Promotion Agency.

139. The Erwin Schroedinger Society for Nanosciences (ESG) organized an exploratory meeting on the subject of “Material Innovations for Medicine, Technology and Environmental protection” on March 9<sup>th</sup>, 2020 in Vienna. The aim of this event, which united several disciplines and institutes, was the critical examination of the topic “advanced materials” and intended to clarify the question of what the research landscape of the future should look like that enables productive and creative research in terms of sustainable development for the environment and the society. <http://esg-nano.ac.at>.

### 5.2. European Union

140. In September 2020, the European Commission’s Joint Research Centre (JRC) hosted a virtual event “[EC Workshop on Safe and Sustainable Smart Nanomaterials](#)”. A synopsis of the contribution from the authors from the European Commission organizing the event can be found [here](#). The workshop was focused on a specific group of advanced materials: smart (i.e. responsive, multi-functional) nanomaterials, which are developed for application in industrial sectors such as agriculture, food, packaging and cosmetics. The objectives of the workshop were to

- identify specific safety and sustainability aspects in the development of smart nanomaterials, current tools and their use and adequacy to assess safety and sustainability of smart materials,
- the needs and challenges in adequately addressing the safety and sustainability of smart nanomaterials by both industry and legislation,
- research needs to fill in the gaps in knowledge and methodology,
- directions and actions for the way forward to meet the identified challenges towards safer and more sustainable smart nanomaterials,
- the way forward towards the adoption of Safe-and-Sustainable-by-Design approach in line with the Chemicals Strategy for Sustainability.

The report is in preparation (publication scheduled for July 2021).

### 5.3. France

141. **LNE** worked within the *NanoFabNet* Hub project (EU-funded CSA / [www.nanofabnet.net](http://www.nanofabnet.net)) to build an **European Metrology Network (EMN) within EURAMET** to support Advanced Manufacturing. A proposal has been submitted over the last weeks by PTB (German National Metrology Institute) to EURAMET with LNE in charge of the **section dedicated to Advanced Materials** (with a link to VAMAS).

142. **LNE** put in place with NPL (UK) and University of Saragossa (SP) the *Validation Service* within the Graphene Flagship in order to offer industry high metrological quality services regarding characterization of graphene features and behaviour (in particular ageing and released during the life cycle of product). **LNE** is finally involved in the new 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.

143. An expert group dedicated to graphene was created at the initiative of the **LNE** within the French standardisation committee dedicated to nanotechnologies/nanomaterials (AFNOR/X457) and is chaired by LNE’s expert.

144. Regarding ecotoxicity of nanomaterials, the ongoing research of **INERIS** is focusing on:

- the NMs accumulation and elimination dynamics in waterborne and foodborne exposure scenarios on freshwater microcrustaceans (finally, modelling these dynamics is aimed);
- the usefulness of *Caenorhabditis elegans* and *Ceriodaphnia dubia* in the assessment of ecotoxicity of nanomaterials.

### 5.4. Germany

#### a. **German Environment Agency (UBA)**

145. Within the research project “Advanced materials - Thematic conferences: Assessment of needs to act on chemical safety” (interim report available at <https://www.umweltbundesamt.de/publikationen/advanced-materials-overview-of-the-field-screening>), the third and final thematic conference was executed as online conference on 14 June 2021. The first conference (Dec 2019, UBA Germany) focused on gaining an overview of the heterogenous field of advanced materials. The 2<sup>nd</sup> conference (executed as two online meetings in June and September 2020) concentrated on (i) approaches to cluster the field advanced materials and approaches to prioritise those to assess their relevance for chemical safety and discussed (ii) challenges of (types of) advanced materials with regard to chemical safety, as well as examples of advanced materials already identified of potential concern for chemical safety and/or circular economy.

146. Objective of the third thematic conference was the discussion of governance options for advanced materials. For this aim, the German higher federal authorities developed a draft joint perspective (“Risk Governance of Advanced Materials: Consideration from the joint perspective of BAuA, BfR and UBA”) which guided through the discussions. *Inter alia*, the document includes considerations on the application of an early warning system including the identification of “materials of concern”, options to improve regulatory readiness with respect to material innovations, and considerations to promote safe and sustainable by design of advanced materials. Furthermore, it highlights the current situation and needs for both preparatory, but also regulatory motivated research and outlines the need for exchanges and mechanisms of interactions with relevant stakeholders.

147. Based on input from this perspective, areas of discussion at the thematic conference included “(i) early warning and systematic approaches to identify and prioritize advanced materials, (ii) regulatory action needs, and (iii) the application of safe and sustainable-by-design principles. During the conference, these considerations were complemented by presentations and alternative views of different stakeholders. It is intended to consider outcomes and learnings from the conferences for the finalisation of the joint perspective document and transfer it to WPMN to support its future work on advanced materials.

#### **b. Federal Institute for Risk Assessment (BfR)**

148. The BfR is involved in the following advanced materials activities:

- The BfR has established a governmental interagency working group on “advanced materials”. At the kick-off meeting in November 2020, ten different higher German federal authorities from a wide range of fields were represented, including two ministries (Federal Ministry of Economics and the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety). A second meeting was held in March 2021.
- A framework document on advanced materials was drafted by the following three higher federal authorities: BAuA, BfR and UBA. It was developed within the framework of the research project “Advanced materials - Thematic conferences: Assessment of needs to act on chemical safety” and served as a basis for discussion for the third thematic conference (June 2021).
- The BfR is a member of the ISO TC 229 study group “advanced materials” chaired by Scott C. Brown. The study group conducted two surveys and discussed draft definitions for advanced materials.
- The Federal Institute for Materials Research and Testing (BAM) and the BfR coordinate a VAMAS (Versailles Project on Advanced Materials and Standards) activity in the technical working area 2 on the analysis of titanium dioxide. This working area is chaired by I. Gilmore from the National Physical Laboratory and supported by CEN.
- The BfR was involved in an ISO TC201 activity on advanced materials (ring trial to distinguish nanoparticles coated with different peptides) using artificial intelligence. The results have been published and can be accessed via DOI: 10.1021/acs.analchem.0c04577.
- The BfR is a partner in the new EU H2020 Projects HARMLESS (Advanced High Aspect Ratio and Multicomponent materials: towards comprehensive intelligent Testing and Safe by design Strategies). The project aims to investigate the role of next-generation nanostructures related to human health and environment concerns, with a focus on high-aspect-ratio nanomaterials (HARN) and multicomponent materials.

#### **c. Federal Institute for Materials Research and Testing (BAM)**

149. The EMPIR-Graphen-Project 19NRM04 ISO-G-Scope ‘Standardisation of structural and chemical properties of graphene’ started in September 2020. BAM is involved with the methods SEM, EDX und XPS. The project includes Inter-Laboratory Comparisons under the umbrella of VAMAS and ISO.

## 5.5. Italy

150. To introduce and discuss this relevant topic at national level ISS in collaboration with the Italian Ministry of Health is organizing the first Italian conference on advanced materials in October 2021.

## 5.6. Netherlands

151. The Netherlands (RIVM) is part of the core group that developed a draft work plan on Advanced Materials for OECD WPMN. The draft work plan was discussed with an ad hoc expert group in May 2021 and will be further discussed at WPMN 21. The work plan includes objectives of the work and proposes next steps.

152. RIVM gave presentations on advanced materials at several internal meetings (UBA workshop, safe and sustainable smart nanomaterials workshop). A systematic approach to identify emerging safety and sustainability issues of advanced materials was presented in combination with case studies, e.g. bionanomaterials and nano-carbon-metal hybrids for application in the energy sector.

153. By elucidating the role of nanostructures, their transformation and initiation of adverse outcome pathways, the EU project **HARMLESS** will provide novel tools, guidance and decision support for balancing functionality versus risk to ensure that the next generation advanced nanomaterials will be harmless. **HARMLESS** will develop a novel, multifaceted Safe Innovation Approach (SIA) to nanomaterials and high aspect ratio nanomaterials (HARNs). This involves integrating a tool-box of New Approach Methodologies (NAMs), which can test key data, according to latest scientific insights into multicomponent nanomaterials and HARNs. HARMLESS has been designed as an industrially oriented project. 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 work package 5 on Tool Development, which aims to build a user friendly SbD Decision Support System for complex HARNs and multi-component NMs. The support system applies modelling tools and bioinformatics tools (e.g. machine learning) to allow ranking and prioritization of available and newly generated. The HARMLESS SbD decision support system builds on the NanoRisk Governance Portal that was developed in the caLIBRAte project and currently used in the Nano Risk Governance projects Gov4Nano, NanoRIGO and RiskGONE.

## 5.7. Sweden

154. The 10th International Conference on Nanotoxicology, was organized jointly by the EU-funded projects BIORIMA, GRACIOUS and PATROLS, and addressed not only nanomaterials but also advanced materials, reflecting the increased interest in multi-component/multi-functional materials. The conference took place online in April 2021. The conference counted more than 380 participants.

155. Scientists from Chalmers Technical University and the Technical University of Denmark (DTU) in the MISTRA Environmental Nanosafety consortium recently published an evaluation of the risks of nanorobots, i.e., active, nano-sized devices designed to perform a specific task (Arvidsson R, Foss Hansen S. Environmental and health risks of nanorobots: an early review. Environ Sci Nano. 2020;7:2875–2886).

## 5.8. United Kingdom

### a. *UK Workshop on Advanced Materials*

156. 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 workshop hosted presentations from a variety of fields on different areas of advanced materials including terminology, the importance of advanced materials, the interface between regulators and materials technology as well sustainability and recyclability of these materials. Break out sessions included questions such as if advanced materials are eco-friendly and how they could be incorporated into a circular economy as well addressed the barriers and the benefits to commercialization of advanced materials and if they could contribute to a net zero economy.

**b. Health and Safety Executive (UK) Advanced Materials project**

157. 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.

158. HSE Advanced Materials project. Main objectives to be delivered in 2020/2021 include:

- To update HSE's review on "Occupational risks from advanced carbon-based materials".
- To engage with stakeholders.
- To draft joint industry article with Advanced Materials Research Centre (AMRC, UK) on composites and workplace safety approach.

To draft biannual short summary of current new health and safety research and commercial development of graphene.

## 5.9. Business at OECD (BIAC)

159. VCI has organised several workshops with its member companies and with scientific organisations as well as German Federal authorities reflecting the issue of advanced materials. These activities have started already three years ago within the "Nano Dialogue" of the German Federal Ministry of environment. VCI committees are discussing a way forward to a position on advanced materials as discussed on national, European, and international level.

# 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

160. PARC (EU-Partnership for the Assessment of Risk from Chemicals) is an EU Horizon Europe partnership to support research and innovation in EU and national chemical risk assessment and risk management bodies with new data, knowledge, methods, networks and skills to address current, emerging and novel chemical and nanosafety safety 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 Memberstates.

161. The project **SolarCircle** (duaration 2020 – 2021, <https://projekte.ffg.at/projekt/3828182> ) aims to qualitatively assess the potential environmental risks and the recyclability of advanced materials, such as perovskite semiconductors, quantum dots, CIGS or organic dyes, that are used for "emerging" photovoltaic technologies. The project is coordinated by the University of Natural Resources and Life Sciences (BOKU; contact: Eva-Kathrin Ehmoser). Partners are the Johannes Kepler Universität Linz (JKU), Institute of Physical Chemistry and Linz Institute of Organic Solar Cells as well as the Energieinstitut of the JKU.

162. In the project **NANO CYCLE** (project duration 2018 – 2019), manufactured nanomaterials (MNM) and advanced materials (AM) in waste streams shall be quantified and effects of MNM and AM on the recycling process analysed. The exposure of MNM and AM in a circular economy will be described and visualised, and methods for recycling of MNM and AM are tested. The project is led by AIT Austrian Institute of Technology (contact: Manuela Kienegger), partners are Environment Agency Austria and Austrian Society for Environment and Technology (ÖGUT).

163. 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 Trieste (UNITS) is responsible for ecotoxicity testing. The TEMAS AG coordinates the project.

164. The ERA-net project **SafeLiBatt** (11/2020-10/2023) has started with an initial stakeholder workshop in March 2021. The project is a cooperation between the University of Natural Resources Vienna (lead, Dr. Florian Part), the Institute of Technology Assessment, the German BAM and INERIS (F). The main goal of the project “SafeLiBatt” is to provide a scientific basic for the safe and sustainable development and use of second life lithium-ion batteries (2ndL-LIBs). In the next few years, there will be a tremendous increase worldwide of these applications coming from different sources, mainly from electric vehicles. Consequently, highly potential alternative markets will soon emerge, such as reuse for residential, distribution or off-grid systems. To gain market’s acceptance of 2ndL-LIBs, potential risk and safety issues must be assessed to ensure sustainability. The safe use of 2ndL-LIBs is therefore essential to foster reuse applications and avoid negative impacts for the environment and society. Key factors are technical performance standards, battery liability, improved workplace safety in industrial settings and sustainability performance.

165. The Institute of Technology Assessment is partner in the EU-Projekt "REconciling sScience, 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.

166. The Horizon2020 project **GoNano** (Governing nanotechnologies through societal engagement; lead by the Danish Board of Technology) has been completed in December 2020 after 36 months. The Institute of Technology Assessment of the Austrian Academy of Sciences has been responsible for several work packages.

167. The project **NanoSyn2**, coordinated by **BNN** (contact: Andreas Falk), funded by the Ministry for Climate Action, Environment, Energy, Mobility, Innovation and Technology (BMK), started in February 2021 and shall be finalized by January 2022. Core activities will be the further development of the nano-community including stakeholders from the three main networks in Austria, BNN, Nanonet-AT and ESG-Nano, to connect this with other Austrian initiatives (e.g. NanoTrust), to strengthen the national and international interaction (e.g. within the EU NanoSafety Cluster, the INISS-nano, ETP Sustainable chemistry, Microfluidics community) related to nanotechnologies and advanced materials.

168. 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 started in January 2018. 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](http://cordis.europa.eu/project/rcn/212339_de.html)

169. The **H2020 project ACEnano** started in January 2017 and develops 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 expertise to develop Guidelines for SMEs for the ACEnano tools; furthermore collaborating in WP5 (guidelines, standardisation) and WP6 (dissemination, workshops). The project ends in June 2021, running training activities in May 2021, as well as the final conference on June 21<sup>st</sup>, 2021 (online).

170. **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.

171. 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.

172. The EU funded **H2020 Research and Innovation action BIORIMA - Biomaterial Risk Management** (start: November 2017). The project aims 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) are part of the BIORIMA consortium.

173. In the **H2020 project NanoCommons** (start: January 2018) **BNN** (Andreas Falk) and **University of Salzburg** (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.

174. In the EU-funded H2020 NMBP-13 project **NanoRigo** (start: Jan 2019) the **University of Salzburg** (contact Albert Duschl and Martin Himly) are responsible for performance of case studies and training activities 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.

175. 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.

176. 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), **BNN** (contact: Andreas

Falk) is responsible for the evaluation of potential hazards and safety issues in all Demo Cases as well as 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.

177. 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.

178. 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.

179. 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.).

180. 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).

181. 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.

182. 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.

183. **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](http://www.nanosafetycluster.eu)).

## 6.2. Canada

184. Environmental fate and bioaccumulation of metal-based (CeO<sub>2</sub>, CuO, Ag, ZnO) nanomaterials were evaluated in natural waters by Government of Canada researchers. Following bioavailability assessments, their toxicity to exposed fish and bivalves were evaluated. The bioavailability and toxicity of nanoparticles (NPs) and transformed products to aquatic organisms were characterized as influenced by the nature and size of particles, but also the chemical properties of waters.

**Publications:**

- Gagnon C. 2020. Fate, transformation and bioavailability of metal-based nanoparticles (NP Bi<sub>2</sub>O<sub>3</sub>, CeO<sub>2</sub>, CuO, MnO<sub>2</sub>, NiO, Ag, ZnO, ZrO<sub>2</sub>) in the aquatic environment. Annual Report. Chemical Management Plan. Gov. of Canada. 20 p.
- Auclair, J., Turcotte, P., Gagnon C., Peyrot, C., Wilkinson KJ, Gagné F. 2020c. Toxicological effects of inorganic nanoparticle mixtures in freshwater mussels. *Environments* 7, 109; doi:10.3390/environments7120109
- Auclair, J., Turcotte, P., Gagnon C., Gagné F. 2020b. Toxicity of copper oxide nanoparticles to rainbow trout juveniles. *Current Topics Toxicol.* 16: 1-11.
- Auclair, J., Turcotte, P., Gagnon C., Peyrot, C., Wilkinson KJ, Gagné F. 2020a. Comparative toxicity of copper oxide nanoparticles and dissolved copper to freshwater mussels. *Intern. J. Zool. Invest.* 6 (1): 135-147, doi.org/10.33745/ijzi.2020.v06i01.001.

185. A publication was prepared on the release of NP Ag from municipal wastewater effluents in Canada. Silver nanoparticles and their transformation products were analysed in Canadian municipal wastewater effluents as potential additional silver sources in natural waters. Results showed the presence of Ag NP in all samples with concentrations reaching 0.5 ng/L on a mass basis. The proportion of Ag at the nanoscale (1-100 nm) represents less than 8% of the total suspended Ag for all effluent samples, regardless of their origins.

**Publication:**

- Gagnon C, Turcotte P, Gagné F, Smyth SA. Occurrence and size distribution of silver nanoparticles in wastewater effluents from municipal plants in Canada (submitted).

186. To address gaps, collaborative research projects are well underway developing characterization methods following ISO/TC 229 procedures using commercial pristine/surface coated silver and zinc oxide nanoparticles (NP's) by complementary techniques (e.g. SP-ICP-MS, TEM, Zeta DLS, Sed-FFF, MALS) under ISO 17025 requirements.

187. Priority is to further develop the single particle ICP-MS method by conducting inter-lab comparisons for refinement and to standardize known results reporting challenges using different instrument systems (e.g. transport efficiency) in order to provide reliable measurement data (size distribution by number, shape, surface chemistry, agglomeration/aggregation state) listed as data needs in the GoC's regulatory risk assessment framework.

188. A key area of success is development of a silver nanoparticle reference material, in different sizes, coated in proteins present in foods as a strategy to improve stability of the particles in dry powder form and are readily dispersible in water to be used for instrument calibrations, validations and scale up.

189. 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. Government of Canada researchers are investigating the relationship between dissolution behaviour and toxicity of eight metal oxide nanomaterials that are currently in commerce in Canada. The team has found significant differences in the dissolution behaviour of nano-CuO, nano-NiO and nano-TiO<sub>2</sub> in distilled water compared to cell culture medium. The team has also demonstrated that the composition, size and purity of commercially-available engineered nanopowders must be independently confirmed by researchers, as they found that several nanoforms of the eight studied metal oxides did not meet the manufacturers' claims. Related research is determining the degree to which observed toxicity is caused by metal oxide nanoparticles, by aggregates/agglomerates, or by the release of dissolved metal ions. In this context, transcriptomics tools were applied to investigate 1) whether genome-wide gene expression profiles can be used to understand the role of particulate and the ionic forms of metal oxides in toxicity and 2) if

transcriptomic dose response information can be used to rank the potency of different metal oxides exhibiting different dissolution rates. This research has been published for nano-CuO<sub>2</sub> and is underway for other metal oxides. This work contributes to the current debate as to whether toxic effects are due to nanoparticles themselves or to the released ions.

### **Publications:**

- Boyadzhiev, A, Avramescu, M-L., Wu, D., Williams, W., Pat Rasmussen. P.E., Sabina Halappanavar, S. (2021) Impact of copper oxide particle solubility on lung epithelial cell toxicity: response characterization using global transcriptional analysis. *Nanotoxicology* 15(3):380-399.
- Bushell M, Beauchemin S, Kunc F, Gardner D, Ovens J, Toll F, Kennedy D, Nguyen K, Vladisavljevic D, Rasmussen PE, Johnston LJ. Characterization of Commercial Metal Oxide Nanomaterials: Crystalline Phase, Particle Size and Specific Surface Area. *Nanomaterials*. 2020 Sep;10(9):1812
- Avramescu, M-L., Chénier, M., Palaniyandi, S., Rasmussen, P.E. (2020) Dissolution behaviour of metal oxide nanomaterials in cell culture medium versus distilled water. *J. Nanoparticle Research*, 22 (8),222).

190. Results for the physical chemical characterization of a set of metal oxide nanoparticles (Al<sub>2</sub>O<sub>3</sub>, CuO, TiO<sub>2</sub>, ZnO) have been published. The paper highlights potential limitations of the characterization data provided by the manufacturer for commercial nanomaterials. This work supports studies of the human health effects of metal oxide nanoparticles and the development of a regulatory framework for their use.

- M. Bushell, S. Beauchemin, F. Kunc, D. Gardner, J. Ovens, F. Toll, D. Kennedy, K. Nguyen, D. Vladisavljevic, P. Rasmussen, L. J. Johnston, Characterization of commercial metal oxide nanomaterials: crystalline phase, crystallite and particle size and specific surface area, *Nanomaterials* 10, 1812, 2020.

191. Nanotoxicology projects (funded by CMP, CRA -NSACB-EHSRB) that are currently underway at EHSRB in our research group (Dr. Prem Kumarathanan, Dr. Dalibor Breznan, Dr. Azam Tayabali) to obtain toxicity information on amorphous silica, titanium dioxide, and zinc oxide nanoforms is continuing. Also, effort is made to explore the association between physico-chemical properties of these nanoforms and relative potency values. These research projects are also relevant to IATA (4- as identified in OECD-WPMN template) due to the integrated nature of toxicity testing and can also be applicable to the developments and consideration related to multicomponent/complex advanced materials (5- as identified in OECD-WPMN template), in the context of understanding the toxicology of these nanoforms and relationship between physchem properties and associated toxicity. These projects are conducted in collaboration with ECCC, NRC and academic partners.

### **a. Amorphous Silica nanoforms**

192. In this project, a set of custom-synthesized amorphous silica nanoparticles (SiNPs) including pristine and surface-modified NPs (n=25) are screened for in vitro toxicity. Currently, we have analysed the internalization of these SiNPs into phagocytic cells by TEM analyses, have identified subcellular localization of these NPs and assessed structural changes in cellular organelles. We have also, exposed mitochondrial fractions to these SiNPs at different doses and screened for high content proteomic changes to assess the feasibility of this test method for toxicity screening of SiNPs and perhaps other NPs. 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 testing (e.g. viability, cell metabolism, membrane integrity), functional assays as well as testing of association with physicochemical properties using statistical and bioinformatic approaches and analysis of molecular levels changes (e.g protein changes)

are underway . In addition, exploration of toxicity mechanisms in support of adverse outcome pathway (AOP) construction is another aspect of this project. (please see some relevant KTE below)

### **b. Titanium dioxide nanoforms**

193. In this project, a set of pristine (anatase, rutile and mixtures) and surface-modified TiO<sub>2</sub> nanoforms are screened for in vitro toxicity. This work also includes, some physicochemical characterization (e.g. ICP DLS, etc.), and in vitro cell culture exposure experiments 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). Also, cellular oxidative stress and secreted proteins (e.g. inflammatory proteins) were analyzed. Testing of association between physicochemical properties and toxicity characteristics is on-going using statistical and bioinformatic approaches. In addition, high content proteomic analyses for exploration of toxicity mechanisms in support of adverse outcome pathway (AOP) construction is also an aim of this project. (please see some relevant KTE below)

### **c. Zinc oxide nanoforms**

194. In this project, set of well characterized pristine and surface-modified zinc oxide NPs are screened for in vitro toxicity. Additional physicochemical characterization (e.g. ICP-MS) was done under this project. In vitro cell culture exposure experiments using multiple cell lines (human lung epithelial cells-A549; mouse monocyte/macrophage cells-J774) are done using integrated toxicity testing approach for multiple cytotoxicity endpoints (e.g. viability, cell metabolism, membrane integrity). Also, cellular oxidative stress and secreted proteins (e.g. inflammatory proteins) were analyzed. Testing of association between physicochemical properties and toxicity characteristics is on-going using statistical and bioinformatic approaches. In addition, high content proteomic analyses for exploration of toxicity mechanisms in support of adverse outcome pathway (AOP) construction is on-going in this project. (please see some relevant KTE below)

195. **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.

KTE activities:

Scientific publications:

- Prem Kumarathanan, 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. (In internal review)

### **Presentations at Scientific meetings:**

- 2020 N. Nazemof, D. Breznan, E. Blais, J. Gomes, M. Babu and R. Vincent, P. Kumarathanan. Effects of exposure to pristine and surface-modified amorphous SiO<sub>2</sub> nanoparticles on mitochondrial proteins from macrophage cells. Health Canada Science Forum, January 20-21. Ottawa, Canada.
- 2020 P.Kumarathanan, D. Breznan, N. Nazemof, E. Blais, A. Tayabali, J. Gomes, M. Babu and R. Vincent. Nanomaterial toxicity in vitro and impacts of physicochemical properties: SiO<sub>2</sub>, TiO<sub>2</sub>, ZnO nanoforms. Technological Advances in Science, Medicine and Engineering Conference and Workshop-Virtual meeting 2020, August 22-23.
- 2020 Prem Kumarathanan, Nazila Nazemof, Dalibor Breznan, Erica Blais, James Gomes, Renaud Vincent and Mohan Babu. Proteomics in in vitro toxicity screening of amorphous silica

nanoforms. 19th Human Proteome Organization (HUPO) World Congress- Virtual meeting HUPO connect 2020, October 19-22.

- 2020 N. Nazemof, N. Assudani, D. Breznan, Y. Dirieh, E. Blais, Linda Johnston, A. Tayabali, J. Gomes and P.Kumarathasan. In vitro cytotoxicity characteristics of ZnO nanoforms. Society of Toxicology Canada 52<sup>nd</sup> Annual Meeting-virtual meeting, Nov 30-Dec 02.
- 2021 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.

### 6.3. Chile

196. Collaborating with the Public Health Institute (ISP), monitoring of nanomaterial exposition in workplace environments will be started inside companies that produce and/or make use of nanotechnology.

197. In coordination with the Chilean Laboral Safety Association (ACHS), nanotechnology and nanomaterial workplace safety training of operators will be started.

198. Collaborating with the Chilean Government's Environmental Department, data will be produced regarding first measurement of airborne environmental nanomaterials.

### 6.4. Costa Rica

199. LANOTEC has begun to develop studies of the impact of different incubation times and different concentrations, environmentally of silver nanoparticles on the communities of fungi and bacteria in tropical agricultural soils and in semi-arid Mediterranean soils, evaluating the effect on microbial biomass, the Extracellular Enzyme Activities and Microbial Diversity Using Next Generation Sequencing.

200. These studies are carried out with the Segura Center for Soil Science and Applied Biology, the Higher Council for Scientific Research (CSIC), Murcia, Spain, and the School of Biological Sciences of the National University of Costa Rica.

201. As a result, of these investigations, by 2020, two articles were published:

- Montes de Oca-Vásquez, Gabriela; Solano-Campos, Frank; Vega-Baudrit, José; López-Mondéjar, Rubén; Vera, Alfonso; Moreno, José Luis; Bastida, Felipe. (2020). Organic amendments exacerbate the effects of silver nanoparticles on microbial biomass and community composition of a semiarid soil. *Science of the Total Environment*, 744, 140919.
- Montes de Oca-Vásquez, Gabriela; Solano-Campos, Frank; Vega-Baudrit, José; López-Mondéjar, Rubén; Odriozola, I; Vera, Alfonso; Moreno, José Luis; Bastida, Felipe. (2020). Environmentally relevant concentrations of silver nanoparticles diminish soil microbial biomass but do not alter enzyme activities or microbial diversity. *Journal of Hazardous Materials*, 391, 122224.

### 6.5. European Union

202. The European Commission has recently adopted [Horizon EU](#), a principal multiannual programme for research and innovation in EU, and it work programme for 2021-22 (14.7 billion to help accelerate the green and digital transitions and contribute to sustainable recovery from the coronavirus pandemic and to

EU resilience against future crises). More information available also through the dedicated [Info days Horizon EU](#).

203. Several calls dedicated to work on advanced materials including nanomaterials:

1. [HORIZON-CL4-2021-RESILIENCE-01-08](#): Establishing EU led international community on safe- and sustainable-by-design materials to support embedding sustainability criteria over the life cycle of products and processes (CSA) 110
2. [HORIZON-CL4-2021-RESILIENCE-01-11](#): Safe- and sustainable-by-design polymeric materials (RIA) 115
3. [HORIZON-CL4-2021-RESILIENCE-01-12](#): Safe- and sustainable-by-design metallic coatings and engineered surfaces (RIA) 116

## 6.6. France

204. **LNE** has initiated the NanoDeTox project (French national funding / ADEME) to examine characteristics and toxicity of nanoparticles that remains within combustion residue after thermal degradation of nanocomposites. **LNE** is also working with IGFL regarding the development of a stable and validated aerosol generation system to support *in vivo* toxicity study of nano-pesticides (Paraquat + TiO<sub>2</sub>) by the inhalation route.

205. **LNE** has launched a new project aiming to assess metrological performances and compare results provided by different techniques (SEM, SAXS, DLS, XRD) to characterize size parameters of nanoparticles in complex media (biological sample, consumer products, soot).

206. **LNE** launched a new topic on nanoaerosol characterization and metrology issues within the Club nanoMétrologie with INRS, IRSN and CEA.

## 6.7. Germany

### a. **Max Rubner Institute (MRI)**

207. As 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 a study on particle size analysis of pristine food-grade titanium dioxide and E 171 in confectionery products (<https://doi.org/10.1016/j.foodcont.2020.107550>).

### b. **Federal Ministry of Education and Research (BMBF)**

208. The Federal Ministry of Education and Research (BMBF) funds national research and development projects on the topic of "Reliable material innovations - Nano Care4.0" within the framework of its materials research programme "From Material to Innovation" (2015-2025). During the cluster meeting on the 26th of November 2020 the latest results of the funded projects were presented as talks.

209. Further information on the funded projects is available on the web-based knowledge and data platform DANA ([www.nanopartikel.info/www.nanoobjects.info](http://www.nanopartikel.info/www.nanoobjects.info)). “DaNa4.0 - Data on new, innovative and safe application” related materials is a science communication project funded by the BMBF in the context of material’s safety (Grant No.: 03XP0282; Duration: 01.03.2020 – 28.02.2023). The project deals with questions whether certain materials could be harmful to humans and/or the environment or whether and how humans and the environment could come into contact with these materials. Complex, toxicological questions from current materials research are prepared in a generally understandable way.

**c. Federal Institute for Risk Assessment (BfR)**

210. The BfR is involved in the following research programs:

- The BfR is a partner in the new EU H2020 Projects HARMLESS (Advanced High Aspect Ratio and Multicomponent materials: towards comprehensive intelligent testing and Safe by design Strategies). The project started in February 2020 focusing on high-aspect-ratio nanomaterials (HARN) and multicomponent materials. HARMLESS will develop integrated testing and assessment strategies (IATAs) considering relevant adverse outcome pathways.
- 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 started in April 2021. It investigates possible human health and environmental risks of microplastic and nanoplastic particles (MNP). POLYRISK aims to develop corresponding IATAs, including grouping and read-across strategies, to facilitate the assessment of hazards, exposures, and risks posed by MNPs.

**d. Federal Institute for Materials Research and Testing (BAM)**

211. The new project SIREN financed by the German Research Council will develop and characterise nanoparticles for fluorescence imaging in the spectral range > 1000 nm (short-wave infrared, SWIR). As part of this project, the BAM Biophotonics Department, together with the French research group of Dr. X. Le Guevel from Grenoble will develop optical contrast agents utilizing gold nanoclusters of atomically precise composition and heavy metal-free semiconductor quantum dots such as Ag<sub>2</sub>S QDs with optimized optical properties. The new materials will be characterized spectroscopically in solution, in tissue models, and in small animals.

## 6.8. Italy

212. Italy is involved in Gov4Nano project, in collaboration with the two other NMBP-13 projects NANORIGO and RiskGONE, which aims to develop an efficient and effective risk governance process for nanotechnologies. The improvement of FAIRness (i.e., Findability, Accessibility, Interoperability, and Reusability) of nanosafety data is a specific goal of Gov4Nano. One of the pillars in this work is the reusability of existing nanosafety data. For a number of diverse case-studies a harmonized workflow is applied, going from data quality assessment and curation, to translation of data, to be fit for purpose e.g. for reuse in (Q)SAR based approaches and/or in user-friendly risk assessment tools. In this context, ISS is carrying out an in-depth study regarding the reuse of genotoxicity data, to highlight the most important needs in the FAIRification process. On this respect the following scientific papers were produced:

- C. Bossa, C. Andreoli, M. Bakker, F. Barone, I. De Angelis, N. Jeliaskova, P. Nymark and C.L. Battistelli. 2021. QSAR approaches for safety assessment of nanomaterials: how FA(I)R are we? (2021) 328, Abstract to 19th International Workshop on (Q)SAR in Environmental and Health Sciences. QSAR 2021
- Jeliaskova N., Apostolova M.D., Andreoli C., Barone F., Barrick A., Battistelli C, Bossa C., Botea-Petcu A., Châtel A., De Angelis I., Dusinska M., El Yamani N, Gheorghe D., Giusti A., Gómez-Fernández P., Grafström R., Gromelski M., Raun Jacobsen N., Jeliaskov 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. 2021. Towards FAIR nanosafety data. Nature Nanotechnology 16, 644–654, <https://doi.org/10.1038/s41565-021-00911-6>

- Giusti, A. Atluri R., Tsekovska Gajewicz A, Apostolova MD, Battistelli C.L., Bleeker E., Bossa C., Bouillard J., Dusinska M., Gómez Fernández P., Grafström R., Gromelski M., Yordan Handzhiyskid Nicklas Raun Jacobsenb Paula Jantunenm Alstrup Jensen K., Mech A., Navas J.M., Nymark P, Oomeng AG, Puzyn T., Rasmussen K., Riebeling C., Rodriguez-Llopis I., Sabellao S., Riego Sintes J., Tanasescu S., Håkan Wallinb H. 2019. Nanomaterial grouping: existing approaches and future recommendations. *NanoImpact* 16, 100182, <https://doi.org/10.1016/j.impact.2019.100182>

213. In the frame of Gov4nano, NANORIGO and RiskGONE joint activities AIRI (Italian Association for Industrial Research) coordinated the webinar *“How to govern risks of particles and nanomaterials in the work environment - precautionary approaches and threshold values to assess exposure”* (June 2021). This workshop is the first of a series of events organized by the Gov4Nano Project, in cooperation with RiskGone and NanoRigo, to discuss governance issues in the development of NMs, with the goal to promote the safety and sustainability of innovation in NMs in Europe. Outcomes will inform the implementation of the new NMs Risk Governance Council (NRGC) developed by these projects.

214. Italian research groups continue their activities in the following ongoing EU projects: RiskGONE (University Ca'Foscari Venice), PATROLS (CNR-ISTEC Faenza and University of Pisa), GRACIOUS (Italian Institute of Technology), BIORIMA (CNR, University of Turin, University Tor Vergata Rome, University CàFoscari Venice, Warrant Group srl, Nanovector srl, Colorobbia Consulting srl, Fin-Ceramica Faenza spa, GreenDecision), and NanoHarmony (ISS, EcamRicert, IIT).

## 6.9. Japan

215. 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.

216. 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 2021, five research projects, including a basic research on development of methods for evaluating hazard and adverse effect of nanomaterials on human health, are progressing.

217. 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 2020 MOE continued collecting and reviewing existing literature on ecotoxicity of manufactured nanomaterials including TiO<sub>2</sub>, silver and CNTs to identify any harmful effects attributed to their particle sizes.

## 6.10. Korea

218. Ministry of Trade, Industry and Energy (MOTIE) launched research programs titled

1. Development of hazard test evaluation of carbon based nanomaterial (graphene) to respond to international regulation

2. Development of performance and safety evaluation techniques for nano-products to support the nano-products industry

219. The Ministry of Food and Drug Safety (MFDS) has been conducting joint research from 2018 to the present to revise the application of nanomaterials to the OECD skin sensitization test method (OECD TG 442) organized by Switzerland. In order to prepare guidelines(draft) when applying nanomaterials, the test results will be shared among countries for joint research. In addition, international joint research has been conducted from 2020 to the present to develop a test method for applying nanomaterials to the OECD toxicokinetics(TK) study under the supervision of the Netherlands.

### 6.11. Malaysia

220. Malaysia has embarked on a four-year nationwide project to benchmark risks of nano-based products. The first step towards establishing a 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.

### 6.12. Netherlands

221. **Gov4Nano** ([www.gov4nano.eu](http://www.gov4nano.eu)) is a European research project that develops, in collaboration with sister projects [RiskGONE](#) and [NANORIGO](#), a concept for a Nano Risk Governance Council (NRGC) which brings together the elements of innovation and regulation, including regulatory preparedness for new innovations and developments. Gov4Nano is coordinated by the RIVM. After 18 months the process of defining the nature of the Council, its mandate, its potential members, how to ensure credibility and establish itself within existing groups and organisations is the major joint activity, involving close collaboration of Gov4nano with NANORIGO en RiskGONE. Over the past year this collaboration matured which was visible during the positive received joint conference in April 2021 and in the outcomes of joint Core Groups and a collective Blueprint for the Council. Within Gov4Nano RIVM developed [a video on Gov4Nano FAIR data](#), which explains the guiding principles of FAIR data and how to join the AdvancedNano Implementation Network. Gov4nano also develops science to support seven ongoing OECD WNT projects towards development or adaptation of test guidelines and guidance documents. Here close collaborations with the projects NanoHarmony and NANOMET are established.

222. The EU **NanoSafety Cluster** (NSC, [www.nanosafetycluster.eu](http://www.nanosafetycluster.eu)) maximises the synergies between European research projects addressing the safety of materials and technologies enabled by the use of nanoparticles. The NSC is crucial in preserving the legacy of the many projects that the EU has funded and offers a great portal for information needs from a wide range of stakeholders. The Netherlands (RIVM) supports the NanoSafety Cluster by providing one of the 3 members of the coordination team. The (coordination team of the) NSC has collected an overview of the various [safe-by-design activities](#) that are ongoing or initiated by a range of EU funded projects. This overview contributed to the European Commission's study on the state-of-the-art and ongoing research in the field of safe-and-sustainable-by-design. Safe-and-sustainable-by-design was further discussed in a recent NSC workshop on "[The delivery/usability of S\(S\)bd for science, regulators and the industry](#)", which was organised back to back with EuroNanoForum 21. Videos from the workshop are available from Youtube: <https://www.youtube.com/playlist?list=PLDBSs2loZJ38RAZ7usEYvIM0h0H5J5bHr>.

223. The Netherlands (RIVM) contributes to the newly started European H2020 **SUNSHINE** Project. The project started on 1 January 2021 and focuses on Safe and sUustainable by designN Strategies for High performance multi-component NanomatErials (SUNSHINE). It is an industry-oriented project, where leading research and technology organisations cooperate with Small and Medium Enterprises (SMEs) and large industries. The aim is to develop and implement simple, robust and cost-effective Safe & Sustainable by Design (SSbD) strategies for materials and products incorporating Multi-component Nanomaterials (MCNMs). SUNSHINE will generate essential new knowledge, tools and data to fill the gaps in the current understanding of the exposure, hazard and functionality characteristics of these materials, especially those arising from their unique properties and interactions.

224. In April 2020 the EU project **PeroCUBE** was launched. The project brings together top experts and pioneers in upscaling of the OLED technology, namely partner FRAUNH and VTT, and the top groups in perovskites materials (partners UOXF and UPAT) and perovskite processing for device manufacturing (CSEM). Due to its ambitious, but feasible goals, new nano-characterization tools are developed (TUW and ALPES) while theoretical studies will significantly contribute to development and upscaling of the perovskite technology (CNRS). Any human health and environmental issues, along with LCA is studied by TNO while robust commercializing channels of the PeroCUBE developments are guaranteed by the involvement of AURA, a pioneer in the lighting market, and also VBC. Finally, partners OM, EULAM and VODAF will develop and demonstrate communication applications (LiFi) of the new devices. All advancements will be demonstrated at TRL 5 for printed, large area (> 10 cm<sup>2</sup>) devices for lighting, PV and LiFi applications and also wearables. 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.

225. The **NanoHarmony** project ([www.nanoharmony.eu](http://www.nanoharmony.eu)), funded through Horizon 2020, has the mission to support the development of OECD Test Guidelines and Guidance Documents via the [Malta Initiative](#). The focus will be on eight endpoints where nanomaterial-adapted test methods have been identified as a regulatory priority. NanoHarmony will coordinate the collection and use of available data and information to support the finalisation of the test method development and to organise a sustainable network for the needed exchange, also for future regulatory development needs. The three year project brings together expert partners from European Countries and will work alongside OECD and ECHA to establish maximum synergy of actions across industrial sectors and international cooperation. The Netherlands/RIVM is leading a task contributing to the development of an OECD TG for biodistribution/toxicokinetics and leads the work package 'from science to regulation'. This includes optimising communication between science and regulation, which may include a further improved streamlining of scientific knowledge flows towards the OECD test guideline programme. As part of its activities and in close collaboration with OECD (via the [NANOMET](#) project), NanoHarmony organises regular webinars to disseminate work from the project and related work from OECD. Video recordings of past webinars remain [available](#).

226. TNO developed the **LICARA Innovation Scan**. The LICARA Nano Scan was originally developed in the EU LICARA project by TNO and EMPA to guide companies through their decision-making process for the sustainable development of new innovative nano-enabled products and has now been extended. The [LICARA Innovation Scan](#) is a web-based tool that guides companies through their decision-making process for the sustainable development of new innovative products. It uses the principles of Life Cycle Assessment, Risk Assessment and Multi-Criteria Decision Assessment to evaluate product benefits and specific risks for consumers, workers, the public and the environment. The final outcome supports product manufacturers and their stakeholders in their decision-making process.

227. The aim of the EU project **PATROLS**, is to establish and standardise methods for the next generation of advanced, physiologically anchored, hazard assessment tools. [PATROLS](#) has been working to help deliver better models and test methods that can be used to help address concerns over the use of

animals in chemical testing and to provide quicker and efficient tests that are accessible for use in industry. The project is well positioned to help deliver some of the key components of the European Commission's chemicals strategy for sustainability and project outcomes will be able to address some of the key components to deliver safe and sustainable chemicals. PATROLS (co-)organized 2 successful digital events in April 2021. A [stakeholder workshop](#) was held to showcase the tools and advanced methods that have been developed within the project. The workshop highlighted the projects developments in nanomaterial characterisation in biological systems, the *in silico* hazard models, the advanced *in vitro* human tissue models, as well as ecotoxicity testing systems. The workshop helped stakeholders from industry, regulatory bodies and policy makers to understand how they can access and use these methods and tools in their work. The workshop welcomed 122 attendees from 25 countries. The [10th International Conference on Nanotoxicology](#) was jointly organised by three leading EU Horizon 2020 Projects, BIORIMA, GRACIOUS, and PATROLS. The focus on the event was on the development of novel tools for evaluating human and environmental hazard, and strategies for nanomaterial characterization, grouping, and read-across for risk analysis. The conference not only showed the outputs and results from those three projects, but also showcased the latest trends and developments in the field of nanosafety. Overall, the conference welcomed 361 members of academia, research institutions, industry, governmental institutions and NGOs from 33 countries.

228. In the Netherlands, Nano Reference Values (NRVs) can be used for risk assessment in the workplace in absence of OELs for nanomaterials ([vanBroekhuizen et al 2012](#); [SER 2012](#)). The NRVs were established in 2011 as a pragmatic tool and are not health-based. In 2017, the NRVs were evaluated and compared to available threshold levels for specific nanomaterials and were found not to be protective enough in all cases ([Buistet et al 2017](#); [VanBroekhuizen2017](#)). As a follow-up of this evaluation, RIVM initiated discussions among an international team of experts in the field of occupational risk assessment for nanomaterials. Discussion explored the possibilities to derive health-based nano reference values for the workplace. Experts from the following countries and affiliations contributed: Netherlands (RIVM and Bureau KLB), Denmark (NRCWE), Spain (LEITAT and INSHT), United Kingdom (HSE), USA (NIOSH), Swiss (SCOEH and SUVA), Germany (BAuA and DGUV/IFA), Norway (NLIA) and Belgium (VITO). The experts contributed in kind in online discussion sessions and provided feedback on written proposals. The discussion sessions resulted in a proposal for categorization of nanomaterials into health-based NRVs, which is described in a scientific paper. Publication is expected in 2021.

### 6.13. South Africa

229. The launch of the Nanotechnology Health, Safety and Environment (HSE) Risk Research Platform by the Department of Science and Innovation (DSI) in 2015 in South Africa has created awareness in research laboratories and also in nanotechnology industries to be cognisant of the HSE aspects of nanotechnologies. The research centres involved in this platform include the National Centre for Occupational Health (NIOH), Northwest University (NWU), and the Council for Scientific and Industrial research (CSIR). The platform was established to support the implementation of the National Nanotechnology Strategy (NNS), by developing expertise for the assessment, identification and mitigation of health, safety and environmental (HSE) risks associated with nanotechnology.

230. The work conducted involved the generation of data from occupational, environmental, and consumer-based nanotechnology industries and products as well as the development of predictive tools for the risk assessment of engineered nanomaterials. The generation of data includes exposure assessment and hazard identification data ranging from short-term acute toxicity to potential long term health effects. The development of predictive models i.e., *in silico* (QSARs/AOPs) and cellular (ALI) modelling systems have also aided in the human and environmental risk assessment of nanomaterials synthesised in South Africa and therefore assist in the registration and exportation of South African-based nanotechnology products. Lastly, based on the data generated, a Safe(r) Innovation Approach is presently

being developed together with a stakeholder engagement plan that will span throughout the lifespan of the platform. As for environmental aspects of nanomaterial HSE, it is now possible to determine the bioavailability of metal-based nanomaterials in environmental media, to determine the biodistribution of metal based nanomaterials in selected terrestrial and aquatic organisms and to perform the bioaccumulation model validation. Moreover, it is now possible to assess the levels of release of nanoparticles from commercially available nano-enabled products as potential sources of environmental water pollution. The information drawn from such activities is aimed at providing the foundation for the prioritisation/ranking of local nanopollution sources, thus enabling a close estimation of the “real world” environmental implications.

231. Most importantly, an Industry Engagement Plan has just been initiated with a strategic relationship with role players in the value chain of nanomaterial manufacturing, and nano-enabled products (NPEs) formulation and their commercialization. It is in this context that the Industry Engagement Plan is formulated in order to serve as a roadmap that facilitates a mutually beneficial relationship with various industry role players. In advancing the research agenda, the Nano HSE Risk Research Platform aimed to identify local sources of emissions of nanomaterials (nanopollution), specifically sites of nanomaterial manufacturing, formulation/development of NPEs, and also gain an understanding of the commercialisation extent of NEPs.

232. The achievements by these research centres within this HSE programme can therefore be summarised:

- The provision of a broad base for the nanotechnology HSE research to support evidence-based regulatory decision-making.
- the establishment of the required tests and the necessary infrastructure to assess the hazardous nature and determine exposure of NMs that are being synthesised and soon to be commercialised in South Africa.
- the establishment of the necessary human capital development to conduct such tests.

The formulation of the Industry Engagement Plan in order to serve as a roadmap that facilitates a mutually beneficial relationship with various industry role players.

#### 6.14. Spain

233. Spain is participating in a number of European and National projects related with the safety and risk assessment of manufactured nanomaterials (MNs).

234. H2020 project BIORIMA (GA No. 760928) “Risk Management of Nanobiomaterials (NBM)”. BIORIMA aims to develop an Integrated Risk Management (IRM) framework for NBM used in advanced therapy medicinal products (ATMP) and medical devices (MD). The BIORIMA IRM framework is a structure upon which the validated tools and methods for materials, exposure, hazard and risk identification/assessment and management are allocated plus a rationale for selecting and using them to manage and reduce the risk for specific NBM used in ATMP and MD. The Spanish National Institute for Agricultural and Food Research and Technology (INIA) from the Superior Council for Scientific Research (CSIC) is participating in the project studying the acute and chronic toxicity of NBM in vitro using different fish cell lines. Also, the acute and chronic toxicity and the bioaccumulation of these materials is being studied in vivo in invertebrates (*Daphnia magna*) and in fish (*Oncorhynchus mykiss*). The test methods have been adapted for the testing of these materials.

235. H2020 project Gov4Nano (GA No. 814401). The Gov4Nano project will develop the first implementation of a future-proof operational Nano Risk Governance Model (NRGM) that addresses the needs of the transdisciplinary field and innovative (and key enabling) character of nanotechnology. INIA is responsible of preparing an OECD guidance document (GD) to conduct the test on bioaccumulation in fish

described in the OECD test guideline (TG) No. 305 with MNs. In addition, INIA is participating in the development of templates for ecotoxicity studies which will allow the reusability of data and which will include a system to score the quality score of the data introduced.

236. H2020 project NanoHarmony (GA No. 885931) has the mission to support the development of OECD test guidelines and guidance documents for eight endpoints where nanomaterial-adapted test methods have been identified as a regulatory priority. INIA is responsible of developing annexes to the OECD GD No. 317 on Aquatic and Sediment Toxicological Testing of Nanomaterials to guide on the testing of nanomaterials following the OECD TGs No. 201 “Freshwater alga and cyanobacteria growth inhibition test”, No. 202 “Daphnia sp. acute immobilization test” and No. 203 “Fish, acute toxicity test”.

237. CSIC, is also participating in the European Graphene Flagship, specifically in WP4 on Health and Environmental implications of the use of Graphene Related Materials (GRMs) (GA No. 649953). The Graphene Flagship aims to secure a major role for Europe in the ongoing technological revolution, helping to bring graphene innovation out of the lab and into commercial applications by 2023. INIA is participating in the Graphene Flagship WP4 INIA with the main aim of studying the applicability of the mentioned TG 201, 202 and 203 to GRM.

238. In the framework of the EU HARMLESS project (Advanced High Aspect Ratio and Multicomponent materials: towards comprehensive intelligent Testing and Safe by design Strategies, Grant Agreement No 953183) Spain is studying the bioaccumulation of high aspect ratio and multicomponent materials in order to establish appropriate testing strategies allowing reducing resources and the use of animals.

239. In addition Spain participates at the Nanomaterials Expert Group (NMEG) of ECHA and at the SPINE strategy (the Safe-by-Design Policy International Network). SPINE is a follow-up initiative to the conference “A future proof approach to nanomaterials” (Rotterdam, 17-18 April 2018) with nine participating countries: Austria, Denmark, Estonia, Germany, the Netherlands, Spain, Sweden, the United Kingdom and Switzerland.

## 6.15. Sweden

240. SweNanoSafe monitors national participation in international nanosafety projects, including the H2020 project Gov4Nano, with close collaborations with two other risk governance projects funded under the same call, i.e., RiskGONE and NanoRIGO, all focused on risk governance, and NanoSolveIT, a project that is focused on nano-informatics and the development of IATAs. The [Gov4Nano](#) project will develop the first implementation of a future-proof operational Nano Risk Governance Model (NRGM) addressing the needs of the transdisciplinary field and innovative (and key enabling) character of nanotechnology. Karolinska Institutet (Sweden) supports specifically developments for FAIR (findability, accessibility, interoperability, reusability) data, implementation of new approaches for risk assessment, policy, and decision-making. The partners recently published on this topic: [here](#).

241. SweNanoSafe, in partnership with the Institute of Environmental Medicine, also contributes to the planning of the Partnership for the Assessment of Risk from Chemicals (PARC) in Horizon Europe.

242. The Swedish Foundation for Strategic Environmental Research (MISTRA) funded the MISTRA Environmental Nanosafety program from 2014 until 2018. The consortium was then comprised of 5 Swedish universities (Chalmers Technical University, Gothenburg University, Lund University, Royal Institute of Technology, and Karolinska Institutet) and one industrial partner (AkzoNobel), and it was coordinated by Chalmers Technical University. MISTRA decided to fund a 4-year extension of the program and the second phase was launched in 2019. The current consortium is coordinated by Lund University, and the Technical University of Denmark (DTU) was added to the consortium (<https://www.mistraenvironmentalnanosafety.org>). The program represents the largest nanosafety project in Sweden with a combined budget of 90 MSEK. The aim is to develop research, knowledge and best

practices on risks associated with nanomaterials and their impact on the environment. The program currently is focused on the assessment of nano- and microplastics. There is a strong synergy between the MISTRA funded research program and the national nanosafety platform, SweNanoSafe.

243. SIO Grafen is a national strategic innovation programme supporting the industrial use of graphene in Sweden. The vision for 2030 is that Sweden is among the world's top ten countries in deploying graphene to ensure industrial leadership. Notably, Chalmers University of Technology in Gothenburg coordinates the Future Emerging Technologies (FET) Graphene Flagship, a 10-year (2013-2023) project with 150 academic and industrial partners across Europe. Karolinska Institutet participates in the work package on health & environment (human and ecotoxicology) since the Flagship project started. Furthermore, SIO Grafen is now (since 2020) a partnering project of the Graphene Flagship project, thus enabling connections between the Swedish and European "eco-systems" for graphene.

244. Within SIO Grafen, a strategic project entitled "Safe introduction and management of the graphene in Swedish industry" started in early 2021. The goal of the project is to make it easier for Swedish companies to introduce graphene into their operations and to be able to handle it routinely and safely in the long term. A supplementary report with an overview of regulations that apply to the production, import, or use of graphene, will be published in the fall of 2021. Furthermore, the MISTRA Environmental Nanosafety programme hosted an online workshop in May 2020 together with SIO Grafen. Fifty participants representing different stakeholders including academia and industry took part in the discussions on nanomaterials in the work environment and on regulations.

## 6.16. Thailand

245. Thailand joined OECD agreement on mutual acceptance of chemical safety data (MAD). On 7th September 2020, Thailand has joined the OECD system for the Mutual Acceptance of Data (MAD) in the Assessment of Chemicals, ensuring that its non-clinical safety data related to the protection of human health and the environment will be accepted by all 44 countries adhering to MAD.

246. Seminar on Protecting factory workers from potential risks of nanomaterials. On 23rd September 2020, The Nanosafety Network for Industry project initiated by NANOTEC organized a seminar on "Protecting factory workers from potential risks of nanomaterials exposure" to promote awareness of nanosafety and industrial standards.

247. New President of Nanotechnology Association of Thailand. On 26th September 2020, Dr. Wannee Chinsirikul, Executive Director of NANOTEC has been selected as the new president of the Nanotechnology Association of Thailand (NAT)

248. 4th EU-Asia Dialogue on NanoSafety Advanced Materials and Emerging Issues Forum Commercialization Workshop. Due to the COVID-19 pandemic, the virtual meeting on "4th EU-Asia Dialogue on NanoSafety Advanced Materials and Emerging Issues Forum Commercialization Workshop" was held on 7th October 2020.

249. Completed an easy to read version of the approved 7 industrial standards manuals related to nanotechnology and will use for workers' training program.

250. On June 16, 2020 NANOTEC was invited to participate in a panel discussion session under the topic of "Directions for the use of plastic in packaging". Panelists included Dr. Wannee Chinsirikul, Executive Director NANOTEC, Mr. Veera Kwanloetchit, President of Plastic Institute of Thailand, Dr. Waluree Thongkam, Senior Technical Officer, NANOTEC with Dr. Sanchai Kuboon, Researcher NANOTEC acting as moderator. The panel discussion covered topics such as Bio Circular and Green Economy (BCG), trends and status of plastic use in Thailand, standards and safety, and use of nanotechnology in packaging. Over 300 online registration viewed this panel discussion session.

251. On 24 March 2021, the Nanofety Working Group initiated a forum as a joint collaboration between the National Nanotechnology Centre Malaysia (NNC) and National Nanotechnology Center Thailand (NANOTEC) with support from ANF. The forum was divided into 3 sessions: Technical/Research, Awareness, and Panel Discussion and aims to encourage the discussion of nanosafety in various capacities from research to public awareness activities to standardization. It also provides a venue for sharing of experiences and networking. Participants discussed specific research collaboration opportunities as well as challenges. Speakers from Australia, France, Japan, Malaysia, Philippines, Iran, Thailand, and USA, including representative from WPMN/OECD participated in the forum and over 200 participants registered to attend the forum.

252. NANOTEC participated in the drafting of the “International Network Initiative on Safe & Sustainable Nanotechnology” INISS-nano concept paper, which shall prepare the ecosystem for global collaboration in selected fields of action enabling “collaboration without borders” within joint projects, joint funding initiatives, and any further way of cooperation. The goal of this initiative would be to establish a collaboration between the European NanoSafety Cluster/ Community and interested countries from other continents in order to expand the common knowledge base for (nano)materials of regulatory significance and to support the needs of various stakeholders including regulatory bodies and industry. A concept paper shall be prepared, that is then delivered to the European Commission and to each of the participating countries’ government. Alexander Pogány of the Republic of Austria Federal Ministry for Climate Action, Environment, Energy, Mobility, Innovation and Technology is leading this initiative.

253. A webinar Forum on Nanosafety: Countries Experiences and Predictive Model Developments for Safety Guidelines and Standardization is scheduled for 5 August 2021 as part of the Asia Nano Forum Summit 2021 (ANFoS 2021).

254. The Nanotechnology Association of Thailand will also organize an international webinar NanoThailand 2021 scheduled for December 2021. Nanosafety will be one of the topic of discussion at this event.

## 6.17. United Kingdom

### a. *PATROLS*

255. The H2020 project PATROLS started in January 2018 and is led by Swansea University (Prof Shareen Doak). This aims to establish and standardize 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 has achieved significant innovative developments that has 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. Thus, PATROLS has already created advances in state-of-the-art ENM hazard testing. The PATROLS partners have been pro-active in developing relationships and engaging with a range of stakeholders to raise awareness of the project and facilitate its impact. This has involved active interactions with stakeholders through dedicated workshops, webinars, distribution of e-newsletters, public engagement activities and transfer of knowledge generated within the project to on-going OECD WPMN initiatives and standardisation activities.

**b. ACENano**

256. The ACENano project led by the University of Birmingham (Prof Eva Valsami-Jones) is a H2020 project which aims to introduce confidence, adaptability and clarity into nanomaterial risk assessment by developing a widely implementable and robust tiered approach to physiochemical characterization that will facilitate contextual (hazard or exposure) description and its transcription into nanomaterial grouping framework. The ACENano project led by the University of Birmingham (Prof Eva Valsami-Jones) is a H2020 project which aims to introduce confidence, adaptability and clarity into nanomaterial risk assessment by developing a widely implementable and robust tiered approach to physiochemical characterization that will facilitate contextual (hazard or exposure) description and its transcription into nanomaterial grouping framework. The project is currently wrapping up activities and will be finishing in June 2021. Open access outputs are available on the project website ([www.acenano-project.eu](http://www.acenano-project.eu)). Two final stakeholder-focused virtual events are highlighted:

- A **training event** on the 'ACENano Toolbox', held on the **28th May** (<http://www.acenano-project.eu/images/ACENano-final-training-event-02.pdf>). This event provided interested stakeholders with the opportunity to find out about the capabilities of the ACENano Toolbox, to try out the Toolbox with the help of experienced users, and to provide feedback to ACENano on the usefulness of the Toolbox.
- The **ACENano final stakeholder event**, to be held on the 21st June. This 2½ hour virtual event provides an overview and specific examples of the outputs of the project, and an opportunity for stakeholders to feed back their views on the usefulness of the project outputs for their needs.

**c. Environmental Exposures and Health (EEH)**

257. 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 Public Health England, 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.

# 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

258. The SAFERA partnership has funded the project **SafeLiBatt** (start: Nov. 2020, end: Oct. 2023, <https://projects.safera.eu/project/27>), coordinated by **BOKU Vienna** (contact: Florian Part) in cooperation with BAM (Germany), INERIS (France), ITA-OeAW (Austria), and Brimatech Services GmbH (Austria). The project aims to provide a scientific basis for the safe and sustainable development and use of 1<sup>st</sup> and 2<sup>nd</sup> life lithium-ion batteries (used for e-vehicles and energy storage systems, resp.). Thermal runaway tests at laboratory-scale as well as social-economic assessment and life cycle analysis (LCA) are conducted to gain data on possible risks and environmental impacts. Finally, the project will give recommendations for the safe use of 2<sup>nd</sup> life applications (i.e., safety criteria for UN, OECD, ISO standards, etc.).

259. 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 “collaboration without borders” [following the European Commission slogan “open to the world”].

260. The “4<sup>th</sup> **EU-Asia Dialogue on Nanosafety**”, Oct 7<sup>th</sup>, 2020, was successfully held as an on-line meeting and was organized by BioNanoNet Forschungsgesellschaft mbH (short: **BNN**) (contact: Andreas Falk) together with the Ministry for Climate Action, Environment, Energy, Mobility, Innovation and Technology (contact: Alexander Pogany), the EU NanoSafety Cluster, and the Asia Nano Forum in the context of the national project NanoSyn. As an outcome a concept paper for an “International network initiative on safe and sustainable Nanotechnology” (INISS-nano) had been elaborated by international experts on Nanosafety under the lead of the BNN and the Austrian Federal Ministry of Climate Action, Environment, Energy, Mobility, Innovation and Technology.

261. In April 2021, Andreas Falk(**BNN**) was nominated by the Austrian delegation for specific contributions as expert to be involved in the WPMN e.g. for the adhoc study group related to Safe(r) Innovation Approaches, etc.

## 7.2. European Union

262. As indicated under the general heading, the Commission services has started preparing criteria for Safe and Sustainable by design chemicals as part of the strategic vision for innovation under the adopted Chemicals Strategy for Sustainability. The work importantly builds on the Safe by design and Safe Innovation Approach as developed for nanomaterials, applying it to all chemical innovation.

## 7.3. France

263. **LNE** is taking part in the EU **NanoFabNet** project aiming at building an international Hub to support sustainable nanofabrication (<https://nanofabnet.net>). **LNE** is responsible of activities dealing with validation, harmonisation and standardization issues. Discussions have taken place to create in the next months an **European Metrology Network** (EMN) within EURAMET to support Advanced Manufacturing. **A section of this EMN will be directly dedicated to Advanced Materials** (with an official link to VAMAS).

264. **LNE** took over the co-charimanship of the WG-B *Materials and Standards* within the NanoSafety Cluster (<https://www.nanosafetycluster.eu/nsc-overview/nsc-structure/working-groups/wgb/>).

265. **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 risk):

- 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, and
- to share information (*regulation, standardisation, call for proposal, inter-laboratories comparisons...*).

## 7.4. Germany

### a. **Max Rubner-Institut (MRI)**

266. As data on particle size distributions of (nano-)particulate food additives are increasingly required for regulatory purposes (e.g. labelling, evaluation and re-evaluation of food additives), for toxicity assessment and for estimating consumer exposure to nanoparticles, the German Max Rubner-Institut (MRI) characterised pearlescent pigments in food, including the particle size distribution of the nano-scaled TiO<sub>2</sub> fraction. For all constituent metal oxide nanoparticles in the coating layer a median minimum Feret diameter below 100 nm was obtained by quantitative SEM image analysis (<https://doi.org/10.1080/19440049.2021.1901998>).

### b. **Federal Ministry of Education and Research (BMBF)**

267. BMBF is partner in M-ERA.NET, a strong European network of 50 public funding organisations from 36 countries for reserach and innovtion on materials and battery technologies, supporting the

European Green Deal. In the preparation for the next transnational joint call 2022, BMBF is launching the discussion to include the aspect of (advanced) materials safety in the topics as one issue which can be addressed.

**c. Federal Institute for Risk Assessment (BfR)**

268. The HARMLESS project, EU H2020, aims to provide guidance and decision support to enable safe-by-design strategies. Within the HARMLESS project, developed IATAs and safe-by-design strategies are tested in several industrial case studies.

**d. Federal Institute for Occupational Safety and Health (BAuA)**

269. High aspect ratio materials (HARM) like carbon nanotubes (CNT) show material properties that enable innovative applications but also raise concerns about harmful effects to humans due to their asbestos-like morphology. A risk banding approach for HARM with hazard- and exposure-related parameters has been developed as a promising way to enable risk assessment and risk mitigation for an important family of advanced materials. It also provides guidance for a safer design of HARM and corresponding products.

- Dirk Broßell, Asmus Meyer-Plath, Kerstin Kämpf, Sabine Plitzko, Wendel Wohlleben, Burkhard Stahlmecke, Martin Wiemann, Andrea Haase in: R. Martijn Wagterveld, Jan C.M. Marijnissen, Leon Gradoń and Arkadiusz Moskal (Ed.): Synthetic Nano- and Microfibers, WETSUS (NL), 2020, Chapter 7 <https://osf.io/preprints/487wv/>

270. In 2020 BAuA has finalized a research project on dustiness and particle morphology of nano carbon materials. Different methods for the activity-related investigation of dustiness behaviour were used to examine different CNTs for their dustiness. The comparability of the different methods was demonstrated, which is an important building block for the evaluation of materials with regard to their dustiness. These results were compared with a selection of morphological properties (e.g. length, diameter and curvature). The materials with the highest dustiness are all in a diameter range between 20 and 50 nm and in the lower middle range in terms of their curvature. This is an interesting indication, as in this diameter range a transition between a critical and a less critical rigidity (fibre stiffness) in terms of damaging effect is expected. Initial findings from the analysis of fibre curvature point to a further connection between dusting tendency, morphology and rigidity of a material. This is further investigated in an ongoing research project F 2365 "Development of an enforceable test method for determination of the rigidity of respirable biopersistent fibres".

- <https://www.baua.de/EN/Tasks/Research/Research-projects/f2380.html>  
see also (in German)  
D. Bäger et al.: Anwendungssichere, nanokohlenstoffbasierte Fasermaterialien, Gefahrstoffe 80(2020), Nr. 7-8, 257 - 265

## 7.5. Netherlands

271. The **OECD project** 'Moving Towards a Safer Innovation Approach' for More Sustainable Nanomaterials and Nano-enabled Products: Overview of existing risk assessment tools and frameworks, and their applicability in industrial innovations is led by France, the Netherlands and BIAC. The [final report](#) was published in December 2020. The report consists of 3 parts: Part 1 – Working Descriptions on Safe(r) Innovation Approach, Part 2 – Safe(r) Innovation Approach: Risk Assessment Tools, Frameworks and Initiatives related Safe(r)-by-Design, and Part 3 – Anticipatory Governance/Regulatory Preparedness: Inventory of Strategies for Awareness and Decision- Safe(r) Innovation Approach Making on Safe(r)

Innovation Approach. The SIA Ad Hoc group have identified areas of SIA that could be further explored. These will be discussed in WPMN 21 (June 2021).

272. 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. In June 2021, an EIONET platform will be opened for SPINE members to exchange information, materials and other documents on Safe-by-Design, such as educational material. SPINE will also conduct research on Safe-by-Design best practices on a national level, develop a communication plan, and work on other products, such as a roadmap and a stakeholder involvement plan.

273. Within the EU project **SABYNA** ([www.sabyrna.eu](http://www.sabyrna.eu)), a guidance platform for the development of safer nanomaterials and nano-enabled products is being developed. SABYNA builds further upon existing resources, such as existing databases, test methods, models, frameworks and tools. From these existing resources, the ones that are suitable for safe-by-design have been extracted based on SbD criteria. These criteria have been developed within SABYNA and include applicability in different stages of the innovation or design process, assessment of the NF life cycle, inclusion of relevant hazard endpoints, accessibility, user-friendliness, costs and suitability for the SABYNA case studies. Currently, tools, models and methods are being optimized for their use in a SbD platform. This platform will be web-based, interactive and user-friendly to provide the user SbD options based on limited data. To test the SABYNA platform, case studies are being conducted based on two sectors: paints and 3D printing.

274. The Dutch Ministry of Infrastructure and Water Management and RIVM are developing frameworks and materials to facilitate the implementation of **Safe-by-Design (SbD)** in higher vocational education and academic education. In collaboration with several Dutch universities different types of materials have been developed, e.g. a SbD serious game with a nanotechnology case and a workshop aimed at nanotechnology PhD students. In addition, an educational framework is being considered which describes Safe-by-Design in terms of learning goals, both as a general mindset and as domain specific skill sets. This serves as exploratory for future development of SbD learning activities and to support its integration within existing educational programs. Moreover, a [SbD website](#) has been developed aiming to inform several stakeholders on SbD implementation.

## 7.6. Sweden

275. 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. Through in-depth interviews (approx. 20 stakeholders) followed by two feedback workshops, information was gathered on how companies and other stakeholders work with nano-innovation and nanosafety. The project, conducted by Action Research (Sweden) will be finalized and reported in the spring 2021.

276. The Mistra Environmental Nanosafety programme hosted a webinar in April 2021 on "Nanomaterial Regulation – a Driver or Barrier for Nanotechnology Innovation" with Andrej Kobe from the European Commission as the keynote speaker. The seminar included a discussion on key challenges connected to responsible innovation, and a discussion on the definition of nanomaterials. The concept "Responsible research and innovation" has gained prominence as an approach to governing emerging technologies, and it is worth investigating what it means in the context of nanotechnology innovations.

277. The H2020 project [HARMLESS](#) develops a novel, multifaceted safe innovation approach to complex multi-component, hybrid nanomaterials and high aspect ratio nanoparticles (MCNM & HARNs) by integrating a toolbox of new approach methodologies, which can test key data according to latest scientific insights into MCNM & HARNs. Implementation of FAIR high-throughput and omics data, as well as non-animal new approach methodologies into safe and sustainable by design-approaches, are specifically supported by Karolinska Institutet (Sweden). The project is coordinated from Germany.

## 7.7. United Kingdom

### a. *SUNSHINE*

278. 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. So far SUNSHINE have confirmed a list of multicomponent nanomaterials provided by industry partners, and the project is about to meet with the sister projects DIAGONAL and HARMLESS which are funded under the same call, to discuss opportunities to interact. This H2020 project looks at the safe-by-design of Advanced Materials with Shareen Doak (Swansea University) and Vicki Stone (Heriot-Watt University) both leading work packages in the UK. One of these work packages focuses on identifying, adapting and improving relevant experimental methods to generate knowledge and data on the EHS implications and functionality of multi-component nanomaterials (MCNMs). This data will inform the development of IATA and support the development and testing of the S&SbD strategies.

### b. *SABYDOMA*

279. SABYDOMA led by Prof. Andrew Nelson, University of Leeds, is a direct outcome of the HISENTS programme. SABYDOMA is a technical solution to the Safety by Design (SbD) paradigm and sees SbD essentially as a control system. In SABYDOMA, the production of nanomaterials is monitored at the point of production using the HISENTS screen and the screening signal is fed back to the production-line to moderate the nanomaterial manufacture. SABYDOMA is a direct outcome of the HISENTS programme whereby a third generation multimodule testing platform within flow systems was developed to replace the second generation well-plate screening strategy. SABYDOMA is a technical solution to the Safety by Design (SbD) paradigm and sees SbD essentially as a control system. In SABYDOMA, the manufacture of nanomaterials is monitored at the point of production using the HISENTS screen and the screening signal is fed back to the production-line to moderate the nanomaterial manufacture. The project's four case studies, representing different applications in nanomaterial production lines namely two bespoke particle synthesis lines, an electroplating and a biomaterial production line, are all currently being adapted to these SbD principles. At the same time work to identify losses in production (release studies) and to model material flows is underwriting and substantiating this aforementioned innovative technology

## 7.8. Business at OECD (BIAC)

280. As summarized by the European Commission at the **first Stakeholders workshop on Safe and Sustainable-by-Design criteria** (19/03/2021), the following projects are important activities in Europe related to safety aspects of nanomaterials:

- Regulations and standards ;
- The Nanomaterials Expert Group of ECHA Provide information and advice on scientific and technical issues regarding the implementation of REACH, CLP and BPR legislations;
- The Malta Initiative Towards safer nanomaterials Adapting/developing Test Guidelines and Guidance Documents for testing nanomaterials;
- The NanoSafetyCluster Platform for the coordination of nanosafety research in Europe;
- H2020 projects: Nanomet, ASINA, SAbyNA, SABYDOMA, HARMLESS, SUNSHINE, SbD4Nano, DIAGONAL, and many more.

# 8 Nanopesticides

## 8.1. Germany

281. The BfR participated in an IUPAC workshop aiming to develop risk assessment of nanopesticides. The results of the workshop will be communicated by a publication of Melanie Kah et al., Comprehensive Framework for Human Health Risk Assessment of Nanopesticides, Nature Nanotechnology.

## 8.2. Korea

282. (Ministry of Environment, ME) The following regulation is about nano biocidal products stipulated in 'Consumer Chemical Products and Biocides Safety Control Act':

- Article 21(Application for product approval, etc)

Where a biocidal product contains nanomaterials intentionally, it shall apply for product approval to the Minister of Environment with data on the name, purpose of use, and purpose of the specific nanomaterials.

- Article 27(Indication, etc. of biocidal products), Article 28(Standards for safety and indication of treated articles)

Where a biocidal product contains nanomaterials intentionally, the fact that nanomaterials are contained shall be indicated, and the names, purposes and uses of nanomaterials contained in biocidal products shall be included.

# 9 Additional Information

## 9.1. Canada

283. A data gap analysis has been conducted for nanoforms of 53 substances already in commerce in Canada in order to identify and prioritize data needs for human health regulatory risk assessment. The results of this analysis indicate that many nanoforms of substances already in commerce in Canada lack some or all of the information that is required for risk assessment, including physicochemical characterization, exposure information, and toxicological profiles. A document generated from this exercise has been shared with partners and industry, including WPMN/SGAP members and science advisory committee (SAC)/ ICG members (industry associations) and will be published in summer 2021.

284. Meanwhile, Canada is starting the development of assessment on ZnO and TiO<sub>2</sub> at the nanoscale in commerce in Canada, to evaluate their environmental and human health risks under CEPA.

285. The OECD has consulted with the WPEA regarding the finalization of the Evaluation of Tools and Models Used for Assessing Environmental Exposure to Manufactured Nanomaterials and Evaluation of Tools and, Assessing the Global Readiness of Regulatory and Non-regulatory Models for Assessing Occupational Exposure to Manufactured Nanomaterials. Canada is applying the results of modeling as a weight of evidence approach to the ecological assessment of ZnO.

## 9.2. Costa Rica

286. Some actions related to nanotechnology in Costa Rica:

- Creation of the National Nanotechnology Laboratory (LANOTEC) at the National High Technology Center (CeNAT), a program of the National Council of Rectors (CONARE) in 2004, and under the protection of the Ministry of Science, Innovation and Technology (MICITT), the Council for Science and Technology (CONICIT), CRUSA Foundation.
- Decree No. 36567-MICITT, 2011. "Declaration of public interest of research in nanotechnology and its applications"
- Creation of a National Work Committee (CTN060) in INTECO on Nanotechnology.
- Creation of the Costa Rican Cluster of Biotechnology, Medical Devices and Life Sciences and incorporation of themes in the area of nanobiotechnology
- Incorporation of nanotechnology topics in ILSI Mesoamerica.
- Creation of the National Bioeconomy Strategy 2020-2030.
- Membership of international networks related to nanotechnology such as Nanoandes, RELANS, NANODYF, BIORRECER, ENVABIO, NANOCELIA.

### 9.3. European Union

287. EU would like to inform on the continuous evolution of the [European Observatory for Nanomaterials](#), providing links to information related to nanomaterials, publishing further reports of commissioned studies in 2020/21 (e.g. [Study on Understanding public perception of nanomaterials and their safety in the EU](#)). As part of EUON activities, ECHA has recently also launched a [market research survey regarding nanomaterials in the EU market](#).

### 9.4. France

288. LNE organized the third 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.

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

### 9.5. Germany

#### a. German Environment Agency (UBA)

290. The background paper on “Nanomaterials in the environment – current state of knowledge and regulations on chemical safety” developed by UBA in 2016 was updated to take into account new scientific knowledge and activities as well as adaption of some substance legislations by nano-specific provision. The document published in November 2020 can be found at the webpage of UBA: <https://www.umweltbundesamt.de/publikationen/nanomaterials-in-the-environment>

#### b. Federal Ministry for the Environment, Nature Conservation and Nuclear Safety

291. 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, Nature Conservation and Nuclear Safety (BMU). Since the Covid19-pandemic made NanoDialogue's characteristic and essential face-to-face meetings impossible, it was forced to pause in 2020 and 2021. The NanoDialogue will be continued in 2022 an end in June 2023 with an international congress in Berlin.

### 9.6. Sweden

292. The Mistra Environmental Nanosafety programme published an overview on nanomaterials and the availability and suitability of methods needed to fulfil the new nano-specific requirements in Europe:

- Maria Bille Nielsen, et al. Nanomaterials in the European chemicals legislation – methodological challenges for registration and environmental safety assessment. *Environ. Sci. Nano.* 2021;8:731–747.

293. 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 for methods to determine nanomaterial adsorption/desorption, degradation, exposure scenarios and ability to cross biological membranes.

294. Furthermore, a working group of the Nordic Council of Ministers have launched a web page on REACH-relevant regulation for nanoforms with the aim of developing a simple and easily usable online tool to explain EU chemical legislation requirements for nanoforms. The tool focuses helping SMEs who may not have sufficient expertise in regulations of nanomaterials ([www.ereachnano.dk](http://www.ereachnano.dk)).

### **Testbed Nano**

295. RISE (Research Institutes of Sweden) is in the process of setting up an AI-supported test platform that enables risk assessment of new nanomaterials, with broad support from both academia and industry in Sweden. Today, there is a lack of clear regulations and validated methods, i.e., new standards and test methods are needed to fulfil regulatory information requirements for nanomaterials in REACH as of 1 January 2020. Work includes identification of test methods that will be included in a first “minimum viable product”, based on authorities' requirements and industry's needs. A market analysis that gives a picture of the potential market for such a test platform is included. The test platform is seen as a unique opportunity for Swedish collaboration, between RISE, the academy and industry and thereafter advancing into international partnerships.

## **9.7. Thailand**

296. On-going research projects in Thailand :

- Phototoxicity study of marigold (*Tagetes erecta*) flower extraction by solvent extraction
- The design methods for testing anti-aging efficacy in active ingredients and herbal extracts using human ex-vivo skin model
- Development of zebrafish model methodology for safety assessment of nanoparticles
- Pre-validation and applications of a 3D-intestinal model for nanosafety research in phase I
- Establishment of biomimetic intestinal models for applications in food and agricultural industries, drug development and herb industries
- Silver Nanoprisms by Prime Nanotechnology by (Prime Nanotechnology Co., Ltd., Thailand)
- Application of zinc oxide in cosmetics, agriculture, printing, anti-bacteria by IRPC, Thailand
- Silica-based Solar Coat for Solar Thermal and Solar Photovoltaic application, NANOTEC, Thailand
- Nanosensors for healthcare sector, King Mongkut's University of Technology Thonburi (KMUTT), Thailand