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

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Series on the Safety of Manufactured Nanomaterials

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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

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FOREWORD

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

This document compiles information provided by delegations on the occasion of the 20th WPMN meeting (September 2020). It aims to summarise relevant information on activities related to manufactured nanomaterials, as well as other activities on nanotechnologies at the international level.

This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology of the OECD.

1 National development on human health and environmental safety

1.1. Austria

Highlight of developments

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

2. 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.

3. As a measure of implementation of the Austrian Nanotechnology Action plan the **national NANO Environment Health and Safety programme** (http://www.ffg.at/nano-ehs) has been established which has been prolonged. In the most recent call two projects (NanoAdd & NANA CYCLE) are funded dealing with the role of nanomaterials and "advanced materials" in the circular economy (project duration 2018 – 2019). This EHS programme is owned by the Austrian Federal Ministry of Climate Action, Environment, Energy, Mobility, Innovation and Technology (www.bmk.gv.at) and is handled by the FFG - Austrian Research Promotion Agency.

4. 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 9th, 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. The "4th **EU-Asia Dialogue on Nanosafety**", Oct 7th, 2020, Vienna, was organized by BioNanoNet (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. This workshop is focused towards more synergy between Asian and European countries with respect to safe nanomaterials including standardization and test guideline development. Two major themes will be addressed.

A. The Malta Initiative, activities to speed up the process of updated or developing OECD test guidelines and guidance documents by gathering and developing the essential information that is needed for this process1.

B. In addition, this workshop will be on developing a call-for-proposals in which collaboration between EU and Asian countries is enabled. The aim of the meeting is to publish a report (joint paper) about the needs & missing points & common interests EU-US / EU-Asia and which research needs shall be addressed.

6. This follows the three previous EU-Asia Dialogue Events and a successful meeting last year in Boston, USA: "EU-US PRIORITIES IN NANOSAFETY IDENTIFIED DURING THE BILAT US 4.0 EVENT "FOSTERING EU-US COOPERATION IN NANOSAFETY". The report will be sent to the EC and MS (e.g. via the EU-NSC and the program committee) as well as to the Asian countries (via ANF), OECD and to the EU-US BILAT colleagues. This shall enable the mentioned stakeholders to step forward towards joint funding of the areas of interest (e.g. joint calls, bilateral agreements on research collaboration, etc.). The format of the meeting is a mix of introduction, overview presentations and breakout sessions. The next dialogue forum will be held in March 2021 in Malaysia. More information and registration/reporting after the event can be found here: https://www.bnn.at/index.php?option=com_chronoforms5&chronoform=EUAsiaDialogue

National development on human health and environmental safety

7. As a measure of implementation of the Austrian Nanotechnology Action plan the Austrian **Nanoinformation Commission** was founded by the federal Ministry of Health to provide expertise regarding nanotechnology for consumers and decision makers. This commission comprises representatives from several ministries, agencies, NGOs, research institutions, industry and other experts. This work also includes the update of the **website on nanotechnology for the public** including opportunities and risks of nanomaterials: http://www.nanoinformation.at

8. 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), includes about 50 measures which will be implemented by Austrian stakeholders on national, EU and international level. The action plan was lead-managed by the Austrian Federal Ministry of Climate Action, Environment, Energy, Mobility, Innovation and Technology (www.bmk.gv.at) and elaborated based on a broad stakeholder involvement. The implementation report on the Austrian Nanotechnology Action plan including an English translation has been finalised after a public consultation see http://nanoinformation.at/oesterreichischer-aktionsplan/umsetzungsbericht-2012.html

1.2. Canada

9. The Government of Canada is developing a nanomaterial regulatory risk assessment framework, to outline approaches and key considerations (e.g., unique properties of nanomaterials). The framework will 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. It will provide guidance to regulators on the assessment of nanomaterials for their risk to the environment and human health, and will provide clarity to stakeholders on risk assessment lines of evidence for nanomaterials. A draft risk assessment framework will be shared with partners of the OECD WPMN for peer-review.

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

10. The New Substances program is responsible for administering the *New Substances Notification Regulations (Chemicals and Polymers)* [NSNR(C&P)] of CEPA. These regulations ensure that no new substances (chemicals or polymers) are introduced into the Canadian marketplace before undergoing ecological and human health assessments, and that any appropriate or required control measures have been taken. In total, Canada has assessed 15 nanomaterials and potential nanomaterials under the New Substances Program since WPMN19. In addition, six pre-notification consultation were initiated. Pre-notification consultations provide clarity on regulatory requirements prior to submission of a notification under the NSNR(C&P).

b. risk management approaches;

11. A significant new activity notice was published on one new substance to require re-notification and assessment should the substance be imported or manufactured in a form that meets Health Canada's working definition on manufactured nanomaterials (https://www.canada.ca/en/health-canada/services/science-research/reports-publications/nanomaterial/policy-statement-health-canada-working-definition.html), and to require submission of relevant information such as particle size distribution for the assessment. A ministerial condition was applied to another new substance, with potential to be produced at the nanoscale, to prevent it being used in a manner that could harm the environment or human health. Ministerial conditions and significant new activity notices are control measures used 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.

1.3. France

12. Within the framework of the Project "Serenade", **CEREGE** developed a mesocosm-based for exposure-driven risk assessments, in particular i): their use as (pre-normative) risk assessment and aging devices *(See Auffan et al. (2019) NanoImpact 13, 66; Masion et al. (2019), Materials, 12, 2447); ii) using statistical methods to single out determining parameters to monitor (cf. Nassar et al. (2020) Environ. Sci.: Nano, 7, 1661)*.

1.4. Germany

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

13. In 2019/2020 Germany carried out a Substance Evaluation according to the EU chemicals regulation REACH for non-rigid Multi-Walled Carbon Nanotubes (MWCNT). BfR was responsible for the evaluation of Human Health aspects. It was concluded that the submitted dossiers should be subject to a formal Compliance Check, considering the new nano-specific amendments of the REACH Annexes in force since 01.01.2020.

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

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

14. In 2019, the substance evaluation of the nanoforms of MWCNT (Multi-Walled Carbon Nanotubes (MWCNT), synthetic graphite in tubular shape) under the European Chemicals legislation REACH, evaluated by the Federal Institute for Occupational Safety and Health (BAuA), the Federal Institute for risk assessment (BfR) and the German Environment Agency (UBA) started and was continued in 2020(https://echa.europa.eu/de/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table).

The Federal Ministry of Education and Research (BMBF)

15. 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 September 2019 the latest results of the funded projects were presented as talks and posters. Further information on the funded projects is available on the web-based knowledge and data platform DANA (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.

1.5. Italy

16. In the framework of the development of the OECD Guidance Document on “Integrated in vitro approach for intestinal fate of orally ingested Nanomaterials” (led by Italy), the Italian Ministry of Health funded to the National Institute of Health (ISS) two projects to provide preliminary outputs useful for GD drafting. The first project (2019-2020) is preparatory for the development of in vitro intestinal models for the absorption of oral ingested nanomaterials (NMs) while the second is addressed to the definition of the best experimental conditions for simulated in vitro digestion (2019-2021). Second project is developed in cooperation with EcamRicert and the Italian Institute of Nanotechnology (IIT).

17. ISS coordinated a project on the development of a methodological approach for physico-chemical characterization and quali/quantitative determination of nanopesticides (2018-2019). The project was funded by the Italian Ministry of Health and developed in cooperation with EcamRicert. The output of the project are published in Food and Chemical Toxicology: Nanopesticides: physico-chemical characterization by a combination of advanced analytical techniques, in press.

18. In the framework of activities of the ISS Multidisciplinary Unit on Nanomaterials and Nanotechnologies (MUUN), a national meeting was organised on the 2nd of July 2019 in order to present its expertise and aims. During the meeting, a proposal for the establishment of a National Network on Nanotechnologies was discussed with the different attendees coming from regulators, industry, academy, public and private research institutes.

19. This initiative was also presented by ISS to the virtual SweNanoSafe workshop of national nanosafety initiatives in Europe, held on September 2020.

20. The Italian Workers' Compensation Authority (INAIL) founded 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). The project was developed by INAIL in cooperation with the Italian Institute of Technology (IIT). Main aims of the project are: *i)* improve risk analysis methodologies and tools in workplaces in which new NMs and KETs are introduced, *ii)* implement a Prevention-through-Design (PtD) approach in production processes, *iii)* expand the field of application of risk analysis methods also in R&D contexts, production, and use of nano- objects. Application of this approach in the contexts of research, production and handling of nano-objects may have a relevant impact in terms of responsible development and policy actions. Project outputs are reported in:

- L. Di Cristo, F. Boccuni, S. Iavicoli, S Sabella (2020). A Human-Relevant 3D In Vitro Platform for an Effective and Rapid Simulation of Workplace Exposure to Nanoparticles: Silica Nanoparticles as Case Study. Nanomaterials, 2020, 10, 1761
- 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, in press.

21. ISS, as part of the steering committee of the NANOINNOVATION 2020 Conference held in Rome, 15-18 September 2020, organized two sessions: "New approaches for safety evaluation of nanomaterials" and "Lipid-based nanocarriers as nanomedical devices". In particular, the first session was co-organized with the Italian Association for Industrial Research (AIRI) and the Italian Standardization Body (UNI).

1.6. Japan

22. 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 2019.

23. METI made a presentation on the study on Biodegradability of Carbon Nanotube in the meeting of the WPMN Discussion on the Programme of Work Including Advanced materials in December 2019. The result of its subsequent study carried out in the private sector is as follows. It should be noted that CNTs are effectively degraded into CO_2 with few drops of chlorine bleach. This finding is useful to formulate safer, effective and inexpensive voluntary management system over the life cycle from production, use and waste of CNTs. As is well-known, ClO^- is effectively mediated from H_2O_2 by myeloperoxidase in the presence of Cl^- during immunoreaction in human body. Considering this fact, the degradation of CNTs by chlorine bleach can be considered as an imitation of CNTs degradation in immune cells as leukocytes and macrophages. This hypothesis will be verified in further research for the development of better lifecycle management system of CNTs.

1.7. Netherlands

24. Maastricht University (Department of Toxicogenomics), in collaboration with the National Autonomous University of Mexico, are performing collaborative research into the effects of **titanium dioxide nanoparticles as component of food additives**. Based on inhalation studies, IARC classified titanium dioxide as a possible human carcinogen (Group 2B, IARC 2010). For the researchers this raised questions on potential effects after oral uptake, in particular of the food additive E171 on the development of colon cancer. E171 comprises titanium dioxide particles, including nanoparticles. In a mouse model, facilitation of colon tumour formation was noted and toxicogenomic approaches revealed different potentially underlying pathways, e.g. immune, inflammation, signal transduction pathways. A thesis on this

subject was published on November 2018 (H.A.A. Proquin: Beyond the white: effects of the titanium dioxide food additive E171 on the development of colorectal cancer). The next step is to investigate whether similar biomarkers (regulated genes or pathways) as those seen in the animal and *in vitro* studies can be found in humans after exposure to E171 or titanium dioxide nanoparticles. METC permission has been granted for performing an epidemiological intervention study.

25. In 2020, also two review papers relevant for risk assessment of titanium dioxide (TiO_2) were published. First, a review by RIVM on the 'Mechanism of action of TiO_2: recommendations to reduce uncertainties related to carcinogenic potential' (doi: 10.1146/annurev-pharmtox-101419-100049), in which adverse outcome pathways are considered and the available information on each of the key events is presented. A second review, by RIVM and WFSR, on 'Possible effects of TiO_2 particles on human liver, intestinal tissue, spleen and kidney after oral exposure' (doi: 10.1080/17435390.2020.1778809) aims to better understand the contradictions reported in adverse effects of TiO_2 and whether such effects can be expected at conditions relevant for humans. This review combines clinical and histopathological observations, adverse outcome pathways, and tissue concentrations from oral animal studies as well as concentrations in human post mortem organs that were recently published by RIVM and WFSR (doi: 10.1080/17435390.2020.1718232).

1.8. Sweden

26. 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.

27. 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 consisting of experts from several different universities in Sweden. The platform has also initiated a national network of nanosafety researchers and has hosted annual meetings of the network since 2018. Furthermore, the platform has now launched a corresponding network for education and several online meetings are planned to consolidate the network and promote nanosafety in education.

28. Another activity from SweNanoSafe, is to bring together other national nanosafety initiatives in Europe for first joint meeting in mid-September. The purpose is to discuss how to collaborate to better promote national and international initiatives for nanosafety.

29. 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 plans to follow up with a more detailed evaluation of nanomaterials in construction.*

30. SweNanoSafe recently compiled a report entitled "*Proposals for national measures for safe use, handling and development of nanomaterials. SweNanoSafe Report 2020:3*". The report has been submitted to the Ministry of the Environment as part of the assignment from the Ministry to the platform.

1.9. Switzerland

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

31. The Action Plan on Synthetic Nanomaterials was completed after eleven years at the end of 2019. A further extension was not necessary. The interagency agreements and concentrated actions resulted in a framework that allows facing upcoming tasks, like harmonizing regulations, scientific and technical exchanges and maintenance of tools, to ensure safe handling of nanomaterials in Switzerland.

1.10. Thailand

32. The Department of Industrial Works (DIW) under the Ministry of Industry have assigned its representative to be a member of the Nanosafety Network Working Group initiated by NANOTEC to promote initiative projects and awareness of nanosafety in industrial setting.

33. The Food and Drug Agency (FDA) is seriously look at product certification that have nanoparticles. They have seek the assistance of NANOTEC to implement awareness training for their staff on nanoparticles and labels. The Thai FDA have indicated that they would like to initiate a collaborative working agreement with NANOTEC to promote nanosafety awareness.

1.11. United States

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

34. The U.S. Environmental Protection Agency (EPA) completed review of low volume exemptions for two graphene oxide substances, a metal oxide substance, and a carbon nanotube. EPA allowed the exemptions under conditions that limited human and environmental exposures to prevent unreasonable risks. Additionally, the EPA reviewed and completed six pre-manufacture notices for nanoscale materials, including one carbon nanotube and six quantum dots. These new chemical substances were regulated with consent orders owing to limited available data on nanomaterials; these consent orders limited uses and human and environmental exposure to prevent unreasonable risks.

c. risk management approaches;

35. Between November 2018 and August 2020, EPA received notification of 10 nanoscale substances 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 77. 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.

36. Since January 2005, EPA has received and reviewed more than 230 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.

37. 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;

38. No, the approaches used given the level of available information are consistent with previous regulatory decisions.

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

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

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

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

1.12. European Union

42. The Changes to technical Annexes to REACH to (better) address nanomaterials are since 1 January 2020 in full application. By 1 January 2020, 86 unique submissions for 34 substances covering nanomaterials were received. A further 37 unique submissions[1] have been received so far in 2020 (i.e. by the deadline of the submission of this document), resulting in a total of 54 substances covering nanoforms for which registration dossiers have been submitted following the updated REACH requirements. Up to date information on the nanomaterials registered under the REACH regulation, as well as information on nanomaterials notified to different EU nanomaterials inventories can be found here: https://euon.echa.europa.eu/search-for-nanomaterials

43. European Chemicals Agency (ECHA) has already undertaken a number of awareness raising efforts such as bilateral discussions with companies, several Newsletter articles, two webinars and a letter campaign in November 2019 to over 3000 companies that may potentially market nanoforms within the EU. Although these efforts has been recognised, it is important to continue awareness activities and to extend this work to include Member States and in particular national helpdesks.

44. Through the two webinars organised by ECHA[2] to support potential registrants, several issues have been clarified and captured in extensive Question and Answer documents[3] available on ECHA's website.

[1] Status on 31 May 2020

[2] https://echa.europa.eu/webinars/2019, https://echa.europa.eu/webinars/2020

[3] https://echa.europa.eu/documents/10162/29019026/240420_reach_nano_practical_advice_webinar_qa_en.pdf/7282f0d3-602e-d01d-2fae-d8760b1bd9f2
https://echa.europa.eu/documents/10162/28526626/reach_nano_annexes_qa_en.pdf/b30fede8-0624-69f1-b86e-549c9d9c5f8b

2 Activities been initiated to implement the OECD Council Recommendation[4] (e.g. regulatory changes, guidance, voluntary, etc)

2.1. Canada

45. Canada's regulatory risk assessment framework for nanomaterials has adopted the Recommendation of the Council as one of its central pillars. The risk assessment framework builds on traditional chemicals frameworks, guidance documents and guidelines, and adapts existing knowledge to the unique characteristics of manufactured nanomaterials.

46. One request from the industry was received for a multi-country substance registration using the OECD Mutual Acceptance of Data (MAD) system. Guidance on required regulatory information was provided via a multilateral pre-notification consultation process involving Canada, USA and Australia on notification procedures, information requirements and a multilateral limited disclosure agreement.

2.2. France

47. **LNE** (Laboratoire national de métrologie et d'essais) participated in the inter-laboratory comparison organised in the frame of OECD to validate the draft test guideline on particle size distribution (contribution with 5 techniques: AFM, SEM, DLS, sp ICP-MS and ESI-DMA).

48. **LNE, INERIS, INRS, CEA** are registered to participate in the OECD inter-laboratory comparison to validate the draft OECD Test Guideline on dustiness measurement.

2.3. Germany

49. At WNT-32, the "OECD Guidance Document for the testing of dissolution and dispersion stability of nanomaterials, and the use of the data for further environmental testing and assessment strategies" was adopted. This GD was developed within the WNT project 3.9 led by Germany. It features an important building block for the testing and interpretation of data on dispersion stability and dissolution rate of nanomaterials. It supports interpretation and presentation of data coming from OECD TG 318 on dispersion stability of nanomaterials in environmental media. Furthermore, it informs how to determine

[4] Recommendation of the Council on the Safety Testing and Assessment of Manufactured Nanomaterials

heteroagglomeration of nanomaterials with natural occurring matter which isn`t addressed in the TG 318. It gives interim guidance on determination and interpretation of dissolution (rate) of nanomaterials in environmental media while the intended TG on this endpoint is still pending. It also presents a testing strategy to inform further environmental testing based on data on these endpoints. The GD is published at the website of the OECD Test Guideline Programme.

50. Germany took over the leadership of the OECD project on dissolution rate of nanomaterials in aquatic environment, and will merge it with the OECD project on "Standard method for determination of dissolution rate of nanomaterials in environmental media (dynamic method)". The project will be continued with the scientific support of a national funded project (see projected presented under 6) and will include a further refinement of the work performed so far. For example, it will include the refinement of the batch method but also development of the dynamic method to determine solubility and dissolution (rate). Within the course of the project, both methods will be validated. An international expert group will be established to ensure transparency and consideration of current international scientific knowledge at an early stage. An exchange with other WNT projects with respect to synergies will take place (WNT projects 1.5 and 3.16). As follow up to the anticipated changes within project 3.10, the work plan had been updated and a revised SPSF will be submitted to WNT in November 2020.

51. The Recommendation notes the importance of the OECD Test Guidelines for the Safety Testing of Chemicals, concluding that many of the existing guidelines are also suitable for the safety assessment of nanomaterials. At the same time, it recognises that some guidelines may need to be adapted to take into account the specific properties of nanomaterials.

52. BAuA supports the adaptation and development of guidelines for nanomaterials by leading Work Package 2 in the Gov4Nano project supporting research activities for eight OECD TG/GD developments and a new EU Horizon 2020 project NanoHarmony (Towards harmonized test methods for nanomaterials). The NanoHarmony project 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. 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 started on April 1, 2020 and brings together 14 European partners and an increasing number of international associated partners. It will work alongside OECD in accelerating the development of priority Test guidelines and Guidance Documents for nanomaterials.

2.4. Italy

53. Italy is leading a project on development of a new Guidance Document regarding "Integrated in vitro approach for intestinal fate of orally ingested Nanomaterials". After a round of comments at WPMN the project was approved in June 2019 and included in the programme of work. The project is coordinated by the Italian National Institute of Health (ISS) with the participation of EcamRicert, EU-JRC, Italian Institute of Technology, Luxembourg Institute of Science and Technology, Universitat Autonoma de Barcelona.

54. ISS is participating to the development of the OECD Guidance Document on the Adaptation of *In Vitro* Mammalian Cell Based Genotoxicity TGs for Testing of Manufactured Nanomaterials led by JRC, and it will take part to the inter-laboratory comparison study.

2.5. Korea

55. 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 term of nanomaterials is

defined, and nano-risk assessment approaches will be provided. The Ministry of Environment (MOE) 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.

2.6. Switzerland

56. 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.

2.7. United Kingdom

NanoHarmony

57. NanoHarmony aims to ensure that nanomaterial safety and regulation keeps at pace with innovation and aims to strengthen European and International cooperation. This work aims to set priorities in OECD TG/GDs by developing and validating test methods for OECD protocols for nanomaterials by developing a structure to translate science into regulation. NanoHarmony acts as a scientific base to support development of OECD Test Guidelines and Guidance Documents associated with human and eco-toxicity as well as phys-chem characterization which includes UK scientific coordination, support and taking part in cross-cutting activities. The UK is involved in a number of tasks within NanoHarmony including Task 1.3 (providing the scientific basis for a new TG on toxicokinetics of nanoparticles) looking at data gap analysis on study design requirements for *in vivo* toxicokinetic studies; Task 1.2 (providing scientific basis to support a possible tiered approach for bioaccumulation potential of NMs, looking to develop recommendations of a tiered approach); Task 1.4 (providing scientific basis for a GD on the determination of concentrations of NMs in biological samples aiming to identify state-of-the-art gaps and utilize spICP-MS). More information on specific recent developments can be found below.

58. The UK is co-leading the WPMN project to develop or revise the current Toxicokinetic Test Guideline to address nanomaterials. The SPSF for the project was approved at WNT in April 2020.

59. The UK is also developing a Guidance Document on the determination of concentrations of nanomaterials in biological samples for eco-toxicity studies. An initial commenting round at WPMN on the draft SPSF has been completed and it is currently under revision for re-submission.

60. The UK has put forward a project proposal looking to develop a scoping review to consider how to trigger or waiver the TG 305 bioaccumulation test in fish for nanomaterials. Log Kow may not be applicable to predicting bioaccumulation potential of nanomaterials since this relies on steady-state-kinetics of soluble chemicals rather than nanomaterials which exist in suspension, resulting in nanomaterials to be evaluated using TG 305. This scoping review will explore the development of a tiered approach to bioaccumulation assessment to ensure that only appropriate nanomaterials are tested in fish to minimise animal testing and to deliver cost savings to industry whilst maintaining high level of environmental protection. This project will be presented at WPMN 2020 in an effort to be added onto the programme of work. Work will be developed contingent with task 1.2 within NanoHarmony as a UK partner.

61. Workshops for all NanoHarmony TG/GD associated tasks are planned for 3-5 November 2020 to obtain expert input to the process,

RiskGone

62. 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.

63. Considerable progress has been made on the development of an Adverse Outcome Pathway for chronic (reproduction) toxicity and multigenerational toxicity arising from exposure to nanomaterials. About 65 relevant publications have been identified and literature mined using agreed (annotated) templates. From these, a process based on the OECD working group NanoAOP project will be utilised to determine the plausibility, measurability, and regulatory relevance of the identified Key Events (KES). The KEs were also assessed for cross-AOP application. An additional challenge is to identify the most representative key biological events KEs that are sequential and essential for toxicity from the multitude of events triggered and processes that are altered following a (disease) stimulus – this is underway now.

64. RiskGONE are planning an AOP workshop at NanoSAFE 2020, as a follow-on to the previous two workshops organised with the NanoAOP project. Abstracts have been submitted by RiskGOne (x2), the NanoAOP project (x2), SmartNanoTox and PATROLs. Further updates to follow.

65. Within RiskGONE, University of Birmingham and Swansea University are becoming associated partners of the NanoHarmony project also to support ongoing test guideline harmonisation activities.

66. University of Birmingham are participating in the following NanoHarmony activities:

- Determination of solubility and dissolution rate of nanomaterials in water and relevant synthetic biologically mediums
- Identification and quantification of the surface chemistry and coatings on nano- and microscale materials
- Aquatic (Environmental) Transformation of Nanomaterials
- A tiered testing strategy for bioaccumulation assessment of engineered nanomaterials
- Standard method for determination of dissolution rate of nanomaterials in environmental media (dynamic method)
- Development of Guidance Document on the Adaptation of the OECD TG 474 Mammalian Erythrocyte Micronucleus Test for Nanomaterials
- Guidance document on the determination of concentrations of nanoparticles in biological samples for (eco) toxicity studies

67. Additionally, RiskGONE (University of Birmingham on Ecotoxicity and Swansea University on toxicity) have proposed a number of new tasks on eco toxicity as follows:

- New Comet assay to detect strand breaks and specific DNA lesions of Daphnia magna (or other species) exposed in vivo
- Daphnia magna reproduction test (with male induction)

2.8. United States

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

2.9. European Union

69. Implementing policy on nanomaterials, in particular in relation to the implementation of changes to REACH, the difficulties arising from the lack of methods for some endpoints has been acknowledged by EU Member States and industry. Work is ongoing but methods are not all already there. Together with the lack of laboratory capacity, which has been further compromised by Covid 19, it is evident that industry is facing challenges to generate the necessary data required. Under REACH, ECHA set a temporary approach to address this issue: for endpoints in REACH Annex VII and VIII (lower volume registrations), where there is currently no internationally agreed test method available, the registrants can document in their REACH registration dossier the efforts done to comply with the information requirements and their commitment to address them once suitable test methods become available. For Annex IX and X endpoints at higher registration volumes, registrants are expected to submit testing proposals before the study is initiated. Up to now, ECHA has not received any such proposals although it is understood from discussions with industry that testing proposals are being considered.

70. ECHA therefore would therefore like the stress the importance of the work done by OECD delegations in revising the relevant OECD Test Guidelines and Guidance documents to ensure these have a regulatory applicable for nanoforms of substances. ECHA also notes the timeframe needed to complete this work and the indirect impact it has on the necessary updates of existing REACH guidance for nanomaterials in relation to human health and environmental endpoints.

71. ECHA would also welcome a better understanding of the impact of potential lack of laboratory capacity in the EU.

3 Development related to good practice documents

3.1. Canada

72. The Government of Canada participated in a round robin comparison organized by Bundesanstalt für Materialforschung und -prüfung (BAM) and Federal Institute of Occupational Safety and Health to support development of an OECD test guideline on particle size distributions for nanomaterials. Data sets for TEM, AFM and DLS of 12 nanoparticle and fibre samples were submitted.

73. The Government of Canada organized an inter-laboratory comparison for measurement of particle size distributions for cellulose nanocrystals using AFM and TEM. Data sets were returned from 10 participants (from Asia, Australia, Europe, and North America) for each method. The data provide pre-normative data for an ISO TC229 –Nanotechnologies technical specification (TS 23151) on CNC particle size that is currently being balloted. Full results will be published, with one paper submitted and one in preparation.

Publications

- F. Kunc, O. Kodra, A. Brinkmann, G. P. Lopinski, L. J. Johnston, A Multi-method Approach for Quantification of Surface Coatings on Commercial Zinc Oxide Nanomaterials, Nanomaterials, 10, 678, 2020 (relevant to to NRC-HC project on characterization and nanotoxicology of metal oxides).
- L. J. Johnston, N. Gonzalez-Rojano, K. J. Wilkinson, B. Xing, Key challenges for evaluation of the safety of engineered nanomaterials, NanoImpact, 18, 100219, 2020. (Summary of IUPAC Workshop on Safety of Nanomaterials)

3.2. France

Protection measures for populations potentially exposed around industrial sites handling titanium dioxide (TiO_2)

74. The report “Elements Relating to Metrological Monitoring in the Environment and to the Feasibility Investigation” prepared by experts from **HCSP** (Haut Conseil de la santé)/ Commission spécialisée « Risques liés à l’environnement » has been published and is available at https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=868 (in French).

Review of analytical methods available for characterising nano-objects and their aggregates and agglomerates, in order to meet regulatory requirements

75. In the framework of European Commission public consultation on the revision of the definition of nanomaterials, **ANSES** (French Agency for Food, Environmental and Occupational Health & Safety) carried out a review of the analytical methods available for characterising nanomaterials with the support of its expert committees (experts from **LNE, INRS, INERIS, CNRS, CIRIMAT, CEA…)**. This review includes: a description of the techniques generally used to characterise the eight physicochemical parameters essential to the characterisation of nanomaterials and a summary of their respective advantages and limitations, including their accessibility. The document published in February this year is available at https://www.anses.fr/en/content/review-analytical-methods-available-characterising-nano-objects-and-their-aggregates-and (in French)

Nanomaterials in food

76. **ANSES** received a formal request to investigate the uses of engineered nanomaterials in the food industry from the Directorate General for Food (DGAL), Directorate General for Health (DGS), Directorate General for Labour (DGT), Directorate General for Risk Prevention (DGPR) and Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF). The collective expert report, identifying the main uses of engineered nanomaterials in the food industry, has been published recently (May 2020). It is available at: https://www.anses.fr/en/content/nanomaterials-food-ansess-recommendations-improving-their-identification-and-better (in French).

Classification of chemicals as nanomaterials

77. LNE has published a dossier on how to reliably classify chemicals as nanomaterial according to EC recommendation of definition (EC/2011): https://www.lne.fr/fr/focus-classification-substances-chimiques-nanomateriaux (in French)

Socio-economic analysis of industrial sectors

78. **INERIS** initiated last year a synthesis on the use of nanomaterials in the construction sector. A first literature review was carried out and it is continuing this year. This work aims to provide information on the economic realities of current and prospective uses, to study, if applicable, possible alternative solutions, and to analyze the results of the registered declarations in "R-nano"[5] for this sector.

Pre-normative and standardisation activities

79. **LNE** has been selected in 2019 to contribute to two projects carried out under the auspices 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

[5] Since 2013, manufacturers, importers and distributors of more than 100 grams of nanoparticle substances per year are required to declare the identity of the substances, the quantities handled and the intended uses.

- 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.

80. **LNE** (Georges Favre) has been elected as Chairman of the new CEN/TC 352 Nanotechnologies WG4 *Manufactured nano-objects in food additives*

81. **LNE**, SCL and member of the French standardization body AFNOR have engaged in 2018 an initiative aiming to develop a guidance document to determine the nanofraction of additive integrated in food product by using electron microscopy (EM) 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). Sciensano (Belgium), DTU (Denmark) & RIKILT (Netherlands) are also involved in the project

82. **LNE** is involved in the nPSize EMPIR project (coordinated by BAM) 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.

83. **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

84. **LNE** contributed to the AFNOR XP T16-402 standard entitled “Conduct of risk management by inhalation of nano-objects, their aggregates and agglomerates (NOAA) and nanoparticulate substances, for proximity guards”

Scientific publications

- Measurement good practice as an output of an inter-laboratory comparison carried out in the frame of the French network Club nanoMétrologie (www.club-nanometrologie.fr): *Gaie-Levrel, F., Bau, S., Bregonzio-Rozier, L. et al. An intercomparison exercise of good laboratory practices for nano-aerosol size measurements by mobility spectrometers, J. Nanopart Res (2020) 22:103, https://doi.org/10.1007/s11051-020-04820-y.*
- Sample preparation protocol: Bouzakher-Ghomrasni N., Chivas-Joly C., Devoille L., Hochepied J-F., Feltin N., Challenges in sample preparation for measuring nanoparticles size by scanning electron microscopy from suspensions, powder form and complex media, Powder Technology Volume 359, 1 January 2020, Pages 226-237, *https://doi.org/10.1016/j.powtec.2019.10.022*.
- Investigating the behavior and fate of nanosilicas from filled polydimethylsiloxane nanocomposites burnt under two different scenarios of incineration: *Ounoughene G., Longuet C., Chivas-Joly C., Le Bihan O., Debray B., Joubert A., Lopez Cuesta J., Le Coq L., Evaluation of Nanosilica Emission in Polydimethylsiloxane Composite During Incineration, Journal of Hazardous Materials 371 (2019) 415-422*

3.3. Germany

85. Colleagues from UBA published a scientific discussion paper on the possibilities and limits of current hazard grouping of nanomaterials for aquatic ecotoxicity endpoints for regulatory applicability. Schwirn, K. and D. Völker (2019). "Hazard grouping of nanomaterials for daphnia and algae toxicity: lessons learned from scientific projects for regulatory applicability." Environmental Sciences Europe **31**(1): 48.

86. Colleagues from RIVM and UBA published a scientific paper on the considerations of environmental risk assessment of nanomaterials from a regulatory perspective. The paper presents current challenges in regulatory hazard and exposure assessment under REACH as well as classification, and makes proposals to address them (Schwirn K, Voelker D, Galert W, Quik J, Tietjen L. Environmental Risk Assessment of Nanomaterials in the Light of New Obligations Under the REACH Regulation: Which Challenges Remain and How to Approach Them? Integr Environ Assess Manag. 00:1-12.).

3.4. Italy

87. As consequence of adoption Commission Regulation (EU) 2018/1881 of 3 December 2018 amending the Annexes of REACH regulation to address nanoforms of substances, ECHA has promoting a Partner Expert Group (PEG) in order to update the ECHA “Guidance on information requirements and chemical safety assessment" focusing on nanomaterials. ISS takes part of this PEG devoted to revision of specific sections of Appendix R7-1 to Chapter R.7a Appendix R7-2 to Chapter R7c in the framework of human health endpoints for nanomaterials.

88. Colleagues of the ISS Multidisciplinary Unit on Nanotechnologies and Nanomaterials published a chapter on “Regulatory perspectives on medical nanotechnologies” in “Nanomaterials for theranostics and tissue engineering” (edited by F. Rossi and A. Rainer, Elsevier-Amsterdam). The chapter presents an overview of the main regulatory drivers for EMNs for non-medical products, pharmaceutical products, and medical device.

3.5. Japan

89. 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 22 “Particle size and shape distribution measurement using transmission electron microscopy” (IS 21363), and now IS 21363 has been published. JISC also jointly (with ANSI) 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 this is under publication process. JISC leads “Measurement of film thickness of nanomaterials by using ellipsometry” (TS 23397), now this is under voting. JISC leads “Positron annihilation lifetime measurement for nanopore evaluation in materials″ (PWI TS 23397), now this will go for NWIP. In TC229/WG3 (Health, Safety and Environmental Aspects of Nanotechnologies), JISC leads a New Work Item Proposal “Method for quantification of cellular uptake of carbon nanomaterials by using optical absorption measurement” (TS 23034), and now this is under publication process.

90. As outcomes of the project "Development of Safety Assessment Methods for Cellulose Nanofibers (CNFs)" (JFY 2017-2019) commissioned by the New Energy and Industrial Technology Development Organization (NEDO) and led by METI, the National Institute of Advanced Industrial Science and Technology (AIST) and four CNF-manufacturing companies released the following three documents (only in Japanese) in March 2020:

- "Examples of Detection and Quantification of Cellulose Nanofibers"
- "Procedure for Toxicity Testing of Cellulose Nanofibers"
- "Examples of Emissions and Exposure Assessment of Cellulose Nanofibers and Their Applied Products"

91. These documents are available on the website: https://www.aist-riss.jp/assessment/45276/.

3.6. Korea

92. MOE has modified OECD TG 318 for dispersion stability of nanomaterials in simulated environmental media and suggested as a technical guideline at the pre-treatment step for *in vivo* and *in vitro* cytotoxicity test of nanomaterials.

Decision for adopting International Standards for measurement technology in nanosafety

93. In December 2019, the 'Testing of the photocatalytic activity of nanoparticles for NADH oxidation' jointly proposed by Korea Research Institute of Standards and Science (KRISS) and U.S. National Institute of Standards and Technology (NIST) has been adopted in the International Standard for Nanotechnology (ISO/TC 229). ISO 20814 documents approved as international standards provide a method for the measurement of the photocatalytic activity (PCA) of nanoparticles (NPs), suspended in an aqueous environment in physiologically relevant conditions, by measuring the ultraviolet (UV)-induced nicotine adenine dinucleotide hydrate (NADH) oxidation. This work was promoted under the agreement of the 'the 8th Joint Committee Meeting on Scientific and Technical Cooperation between Korea and U.S.' in 2014, and was supported by Nano Safety Metrology Centre funded by the Ministry of Science and ICT.

- ISO 20814: Nanotechnologies - Testing the photocatalytic activity of nanoparticles for NADH oxidation - https://www.iso.org/standard/69298.html

94. In May 2020, the 'Assessment of nanomaterial toxicity using dechlorinated zebrafish embryo' jointly proposed by Korea Institute of Toxicology (KIT) and American National Standards Institute (ANSI) has been adopted in the International Standard for Nanotechnology (ISO/TC 229). ISO 22082 documents approved as international standards provide a method for rapidly assessing nanomaterial toxicity (fish early life stage, 0 HPF to 120 HPF). It includes information on the importance of acellular chorion removal, detailed chorion removal procedures, and a complete protocol for the toxicity assessment of nanomaterials using dechlorinated zebrafish embryos. This work was supported by Nano Safety Metrology Centre funded by the Ministry of Science and ICT.

- ISO 22082: Nanotechnologies - Assessment of nanomaterial toxicity using dechlorinated zebrafish embryo - https://www.iso.org/standard/72516.html.

3.7. Netherlands

95. RIVM (Dutch Institute for Public Health & the Environment) coordinates the EU research project GOV4nano (www.gov4nano.eu). An important work package of the project contributes to the work of the

OECD via the Malta Initiative**.** The Malta Initiative is aligned with procedures as determined by OECD. The work in Gov4nano will focus on research and experimental work needed to adapt or create new specific test guidelines or guidance documents for nanomaterials. This is closely linked to the OECD Test Guidelines Programme (OECD TGP project numbers are indicated):

- Scientific basis for dissolution testing of nanomaterials (based on TG105) (OECD TGP Project 1.5)
- Identification and quantification of the surface chemistry (OECD TGP Project 1.6)
- Measuring the volume specific surface area (VSSA) of nanomaterials (OECD TGP Project 1.3)
- Evaluating the applicability of TG 442D in testing nanomaterials for skin sensitisation (OECD Project 4.133)
- Dustiness testing for exposure and industrial risks (OECD Project 1.8)
- Abiotic transformation of nanomaterials in environmental aquatic media (OECD Project 3.16)
- Evaluating the applicability of TG 305 in testing the bioaccumulation of nanomaterials in fish (OECD Project 3.12)

96. Apart from coordinating this work in Gov4Nano as co-lead of the work package (RIVM), the Netherlands actively contributes to the work on dustiness (TNO coordinates intra- and inter-laboratory testing) and bioaccumulation (RIVM ensures the relevance for risk assessment).

97. In April 2020 the OECD SPSF "Development of new Test Guideline on **toxicokinetics** to accommodate testing of nanoparticles" was approved by the WNT and included as project 4.146 in the WNP Programme of Work. This project 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, since the current OECD TG 417 on toxicokinetics is not applicable to nanomaterials. The new TG will more specifically address 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. This project will use the ISO Technical Report (ISO TR 22019) "Consideration of performing toxicokinetic studies of nanomaterials" which was published in May 2019.

98. RIVM is preparing a **report for the European Food Safety Authority (EFSA) on environmental risk assessment (ERA)** of nanomaterials, to be finalised in November 2020. This report aims to support EFSA in preparing future guidance on ERA of the application of nanoscience and nanotechnology in the food and feed chain. Existing ERA guidance documents by EFSA were analysed for their adequacy to cover issues that are specific for nanomaterials, e.g. related to nanospecific behaviour. Each nanospecific issue identified was addressed by briefly reviewing the existing methods to address the issue in each separate step of ERA: estimating release and emission, exposure assessment, hazard characterisation and risk characterisation. Although the project focusses on the food and feed chain, the final report is likely to be broader applicable as well.

99. RIVM and TNO were partners in the EU project "Performance testing, calibration & implementation of a next generation system-of-systems risk governance framework for nanomaterials" (**caLIBRAte**). The caLIBRAte project (www.nanocalibrate.eu), which has ended in November 2019, aimed to establish a state-of-the-art risk governance framework for assessment and management of human and environmental risks of manufactured nanomaterials and nano-enabled products. The developed framework is a web-portal linking different tested and calibrated models and methods for screening of apparent and perceived risks, for control banding, decision support tools, and risk surveillance, risk management and risk guidance documents. Available risk assessment modelling tools were tested and calibrated. By engaging stakeholders, caLIBRAte has developed a Nano Risk Governance Framework, which serves as a basis for the Nanosafety Governance Portal that will be established within the H2020-project Gov4Nano.

100. In March 2020 the **EC4SafeNano** project published a set of guidelines for the planning, development and networking of sustainable national centres dealing with the safety of nanomaterials and nanotechnologies toward public health and environment (doi: 10.1007/s11569-020-00364-6). By providing an overview of the organizational design of existing national nanosafety centres across EU and converging demands in the field of nanosafety, this EC4SafeNano publication principally aims to support EU member states without a national nanosafety centre that intend to develop at a national level an entity to manage the human health, environmental, ethical, and social concerns/risks toward the growing nationwide activities on engineered nanomaterials (e.g., their production, use or disposal).

3.8. Sweden

101. Sweden 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 presents a comprehensive overview of the current knowledge on principles and basic mechanisms of immunotoxicity caused by engineered nanomaterials, and how to test for such effects.

3.9. Thailand

102. NANOTEC have indicated to TISI that it has developed an Easy To Read version of the 7 Industrial Manuals (info graphic) related to nanotechnology as recommended by DIW. TISI has indicated to NANOTEC to go ahead and convert the 2 industrial manuals submitted to TISI in 2019 to Easy To Read version. TISI informed that for future submission that are considered industrial manuals guidelines to convert to Easy To Read version. However for manuals that relates to new products TISI would still like to have it submitted to TISI.

103. Discussion with TISI to re-initiate NANOTEC to be observer at ISO/TC229 meeting in November 2019 in China. At the request of Prof. Lee of KRISS, South Korea NANOTEC is looking to initiate a PWI in WG3 of ISO/TC 229 on the topic of using intestinal organoid or 3D-intestinal model for nanosafety evaluation.

104. Due to COVID 19 and restriction of traveling overseas, NANOTEC is working with Prof. Kearns to identify and produce a short video clip (6-10 mins duration) to promote awareness of nanosafety, regulatory measures and international co-operation from EU perspectives. The video clip can be used as a tool for on-line workshops, meeting, and seminars. For 2020, two video clip has been produced on "Nanosafety: Regulatory measures and the value of international co-operation" by Prof. Kearns and "Respirators and their effectiveness in reducing nanoparticle exposures" by Prof. John Cherrie. Six video clips is being considered for this project. The video clip will be use as inserts during in-house seminar programs.

3.10. United Kingdom

Occupational Health and Safety

105. The UK (HSE Safety Division) is leading the revision of ISO/TS 12901:2012 Nanotechnologies — Occupational Risk Management Applied to Engineered Nanomaterials - Part 1: Principles and approaches (2012). This provides guidance on occupational health and safety measures relating to engineered nanomaterials, including the use of engineering controls and appropriate personal protective equipment, guidance on dealing with spills and accidental releases, and guidance on appropriate handling of these materials during disposal.

106. The UK Nanosafety Group will start updating its national guidelines: Working Safely with Nanomaterials in Research and Development (2nd Edition, 2016).

Graphene Standardization

107. The UK delegations, including NPL, HSE SD, PHE, are involved in the development and review of technical report and technical specifications under ISO TC 229 (Nanotechnology), CEN TC 352 (Nanotechnology) with a focus on metrology and measurement (including Graphene) and Health and Safety.

NanoCommons

108. 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.

109. Extensive progress has been made this year including:

- Consensus building on *metadata needs* for nanosafety data, led by NanoCommons and involving EU and US collaboration. A paper has been submitted to NanoMaterials special issue on nanoinformatics and nanomaterials risk Governance.
- Development of a proposal for a nano-extension to the InChi chemical structural identifiers for chemicals to allow identification of a specific nanomaterial (core, size, shape, coating, functionalisaion, etc.) from with a “family” of nanomaterials, to support FAIR data, to support nanoinformatics and to support regulatory assessment of nanomaterials. Working with IUPAC InChi Trust and EUON to build support for the proposed extension, and NanoCommons is also building the tools to support implementation also. Final stages of drafting with the paper to be submitted to the same special issue of Nanomaterials.
- Extending the eNanoMapper ontology to include regulatory and Test guideline terms, and to align with IUCLID6.
- Extensive support to the OECD NanoAOP project in terms of data mining, data quality assessment, and database building to support the process of AOP development for nanomaterials risk assessment. First publication on a roadmap for onward development of nanomateirals AOP published recently (Ede et al., Nanomaterials, 2020, 10, 1229, with further publications, including on the database itself, and the quality analysis of the data, in advanced stages of development.
- NanoCommons KnowledgeBase available for public use and currently also being updated with the dataset mined from the literature and used for the OECD NanoAOP project, which consists of >300 individual studies.
- Extending the range of projects and initiatives that we are supporting with data management, and working directly with the Electronic Laboratory notebook companies (e.g., SciNote) to support direct import of protocols and direct output of data into the aligned data warehouses.
- Extensive series of training events (webinars and hakathons) on use of electronic lab notebooks, modelling tools, the NanoCommons KnowledgeBase (data upload / download / annotation etc.). All materials recorded and available online, and bespoke training can be provided to interested stakeholders.

3.11. United States

110. In 2019, the U. S. National Institute for Occupational Safety and Health (NIOSH) conducted a survey to gather information about companies' safety and health practices surrounding the use of engineered nanomaterials to assess the impact of the NIOSH guidance. Forty five respondents participated in the survey (https://www.cdc.gov/niosh/programs/ppops/ntrc.html).

111. U.S. NIOSH expanded field team efforts to evaluate occupational health and safety of 3D printers used in industrial and school settings. This resulted in an increase in the number of field assessments from 8 in 2018 to 20 in 2019.

112. U.S. NIOSH published 80 journal articles in the peer reviewed scientific literature (https://www2a.cdc.gov/nioshtic-2/) and a science blog with an overview of the Nanotechnology Research Program (https://blogs.cdc.gov/niosh-science-blog/2019/10/09/ntrc/) during 2019.

113. U.S. NIOSH published "Continuing to Protect the Nanotechnology Workforce: NIOSH Nanotechnology Research Plan for 2018-2025," in January 2019 (https://www.cdc.gov/niosh/docs/2019-116/pdfs/2019-116.pdf).

3.12. European Union

114. The Scientific Committee of the European Food and safety Authority (EFSA) has launched an *open consultation on its draft EFSA Guidance on Particle - TR* : Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles. Consultation is open until 9th September 2020. This document sets out information requirements for applications in the regulated food and feed product areas, and establishes criteria for assessing the presence of a fraction of small particles. These requirements apply to particles requiring specific assessment at the nanoscale in conventional materials that do not meet the definition of engineered nanomaterial as set out in the Novel Food Regulation (EU) 2015/2283.

115. This Guidance on Particle-TR complements the Guidance on Nanoscience and Nanotechnology adopted by the EFSA Scientific Committee in 2018[6], called *Guidance on nano-RA* (RA = risk assessment) as it is covering the scientific details for risk assessment considering the nano aspects.

Joint Research Centre of the European Commission (JRC) has published the following reports:

JRC GUIDANCE(s) on the EC Definition of Nanomaterial

116. The JRC published guidance on implementation of the European Commission's definition of nanomaterial in two Science for Policy Reports.

First part: H. Rauscher et al., An overview of concepts and terms used in the European Commission's definition of nanomaterial (2019), doi: 10.2760/459136 (online).

1. This report addresses the key concepts and terms of the European Commission's Recommendation on a definition of nanomaterial (2011/696/EU) and discusses them in a regulatory context. Corresponding to the broad scope of the definition the considerations in this report can be applied across all relevant legislative areas; they are not specific to any particular piece of legislation. The report provides recommendations for a harmonised and coherent

6 Now in final update phase.

implementation of the nanomaterial definition in any specific regulatory context at European Union and national level.

Second part: H. Rauscher et al., Identification of nanomaterials through measurements (2019), doi: 10.2760/053982.

2. The report discusses options and points to consider when assessing whether a particulate material is a nanomaterial or not. For a correct classification a thorough knowledge of the applied measurement method is needed to correctly interpret the outcome of a measurement and to understand whether a specific technique is fit for the purpose. This report provides examples and practical options for consideration, including a flowchart that can assist users with relevant technical knowledge in the identification of nanomaterials.
3. The JRC decision flowchart and the NanoDefine Decision Support Flow Scheme were published were published in the paper "Nano or Not Nano? A Structured Approach for Identifying Nanomaterials According to the European Commission's Definition" and comparatively discussed (see also NanoDefine below) (A. Mech et al., Small, 2020, Art. Nr. 2002228).

NanoDefine

• *Publication of the NanoDefine Methods Manual (A. Mech, H. Rauscher et al.; doi: 10.2760/79490 (online).*

1. The NanoDefine Methods Manual provides guidance throughout the nanomaterial characterization process on the use of the characterization methods as well as their application range and their limits to assist the user in choosing the most appropriate measurement method(s) to identify any substance according to the EC recommendation for a definition of nanomaterial (EC NM Definition). The NanoDefine Methods Manual consists of three parts.
2. Part 1 (doi:10.2760/55181) covers the NanoDefiner framework. It includes short introduction to the NanoDefine Framework and summarizes the results of a comprehensive study of the available Characterisation Methods (CMs) which were candidates for a reliable analysis of the number based size distribution of a particulate material, with the goal to identify nanomaterials according to the EC NM Definition. The report presents the Decision Support Flow Scheme, which guides the user logically through a sequence of tasks, decision nodes and options in order to decide whether a material is a nanomaterial according to the EC NM Definition. Finally the report introduce the NanoDefiner e–tool which implements all tools developed within the NanoDefine framework in a software and assists the user in the decision process whether a material is a nanomaterial according to the EC NM Definition.
3. Part 2 (doi:10.2760/071877) discusses the outcome of the evaluation of the nanomaterials characterisation methods. The document is based on the results of a comprehensive study performed within the NanoDefine project on the available Characterisation Methods (CMs) which are candidates for performing a reliable analysis of the number-based size distribution of a particulate material, with the goal to identify nanomaterials according to the EC NM Definition. This report discusses most available size characterisation methods for nanomaterials. Different types of methods that allow for the determination of size and size distributions are described and an overview of techniques and their capabilities is presented in the form of detailed, user-friendly tables.
4. Part 3 (doi:10.2760/02910) gathers all Standard Operating Procedures (SOPs) developed within the NanoDefine project (available at the editorial deadline of the Manual) for nanomaterial characterisation. The aim of this document is to present SOPs developed within NanoDefine project to facilitate and harmonise the particle size distribution measurements. The presented

SOPs are detailed, material/method specific protocols designed to produce liquid dispersions of the NanoDefine priority substances such that the resulting dispersions are stable and contain only or mainly primary constituent particles. All SOPs are presented in the document as standalone, self-explanatory documents which can be easily extracted from the report. Special attention is given to the sonication issue, as it seems to be one of the most challenging steps in the sample preparation.

117. The JRC published a Technical report on In vitro cytotoxicity and cellular uptake evaluation of gold, silica and silver nanoparticles in five different cell lines: Caco-2, A549, CHO, V79 and TK6. This is a second report of the OCED Test Guidelines project 4.95, which focuses on availability of vitro methods for the assessment of the genotoxic potential of nanomaterials. An international partnership including the JRC aims to adapt the in vitro micronucleus test (OECD Test Guideline 487) to specific testing requirements for nanomaterials in a stepwise approach. It is now focussing on the evaluation of in vitro cytotoxicity testing and the uptake of selected representative nanomaterials. 5 nm gold, 30 nm gold, 22 nm silica, 30 nm citrate and 30 nm PVP stabilised silver nanoparticles have been analysed in 5 different cell lines. All cell lines demonstrated their capability to internalise the tested NMs and their storage in endosomes. However, only silver NMs induced cytotoxicity to various degrees depending on the sensitivity of the used cell line.

- **Citation:** Bogni A., Ponti J., Drewes C., Kinsner-Ovaskainen A., Bremer-Hoffmann S., In vitro cytotoxicity and cellular uptake evaluation of gold, silica and silver nanoparticles in five different cell lines: Caco-2, A549, CHO, V79 and TK6, European Commission, Ispra, 2020, JRC120791.

118. The JRC published the report from the ***Global Summit on Regulatory Science 2019 Nanotechnology and Nanoplastics***, (GSRS19) that took place 24-26 September 2019 in Italy. This report reflects global science-for-policy perspectives on nanotechnology and nanoplastics and summarizes the discussions and conclusions drawn by the Summit's almost 200 scientists representing regulatory agencies, academia and industry from 36 countries around the world. Co-organised by the European Commission's Joint Research Centre (JRC) and the Global Coalition for Regulatory Science Research (GCRSR), the Summit provided a unique venue for regulators, policy makers, and scientists to exchange views on innovative technologies, methods and regulatory assessments, as well as harmonising strategies to address emerging challenges via global collaborations.

- **Citation:** Allan, J., Global Summit on Regulatory Science 2019 Nanotechnology and Nanoplastics, Sokull-Kluettgen, B. and Patri, A. (editors), EUR 30195 EN, Publications Office of the European Union, Luxembourg, 2020, ISBN 978-92-76-18435-5 (online), doi:10.2760/517689 (online), JRC120318.

119. Within the H2020 project Gov4Nano, JRC initiated the arrangements for the inter-laboratory comparison (ring trial) for a new protocol for testing the Volume Specific Surface Area of Manufactured Nanomaterials (WNT Project 1.3). 7 laboratories, including JRC, confirmed participation in the exercise. 7 subsamples materials including some CRM were randomly coded and were distributed to participant laboratories in May 2020 with an agreed SOP. The Covid-19 crisis is delaying the laboratory work, however testing and evaluation of results should be available in September.

120. Successful implementation of grouping and read-across of nanomaterials relies on the availability of detailed characterisation of their physicochemical properties, which allows the definition of groups based on read-across similarity. Within the H2020 project GRACIOUS the JRC has assessed the availability and completeness of existing (meta) data on 11 experimentally determined physicochemical properties and 18 NMs. A completeness score (CS) between 0 and 1 was calculated for each (meta) data unit, property, technique and NM. The results show a heterogeneous distribution of available (meta) data across materials and properties, with none of the selected NMs fully characterised. Low CS were largely caused by missing information regarding sample preparation and standard operating procedures, and was attributed to a lack of harmonised data reporting and entry procedures. This study therefore suggests that a persistent use of

well-defined and harmonised reporting schemes for experimental results is a useful tool to increase (meta) data completeness and ensure their integration and reuse.

- Publication: Quality of physicochemical data on nanomaterials: an assessment of data completeness and variability (D. Comandella, S. Gottardo, I. Rio, H. Rauscher, Nanoscale, 2020,12, 4695-4708).

121. The JRC participates in the H2020 project GRACIOUS and has led the development of 6 new Excel® templates and updated 3 existing NANoREG templates for harmonised reporting of nanomaterial properties. The templates are free to use and can be modified under Creative Commons – Share Alike license. Harmonised recording of experimental data on nanomaterial properties generated in different research projects is a key issue in nanosafety. Each template is based on ISA-TAB-Nano and relates the result of an experiment to the conditions, protocols, method and instrument that have been used to generate it, thus ensuring reproducibility, comparability and re-use of the data by other scientists.

- **Publication of data reporting templates**: S. Gottardo et al., GRACIOUS data logging templates for the environmental, health and safety assessment of nanomaterials, 2019, doi: 10.2760/142959 (online).

122. The European Commission recently mandated the Scientific Committee on Consumer Safety (SCCS) to issue a scientific advice on the safety of nanomaterials in cosmetics. The mandate, to be implemented in 2020, is available here: https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs2016_q_044.pdf

123. Draft opinion is now available on https://ec.europa.eu/health/scientific_committees/consumer_safety/opinions_en and open for commenting until 2 November 2020.

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

4.1. Canada

124. 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. This database has been shared with NanoSolveIT, a project introducing IATA for the environmental health and safety of nanomaterials. Further collaboration on this project is ongoing.

4.2. Germany

125. Within the EU H2020 project GRACIOUS a grouping framework for nanomaterials is being developed, which includes the establishment of corresponding IATAs to substantiate grouping decisions. BfR is leading the work package on “Human and Environmental Toxicity”. Several IATAs covering different routes of exposure (inhalation, ingestion, dermal) have been developed and are currently being published.

4.3. Korea

126. 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 TC 229 WG4 (material specifications), Nano-object-assembled layers for electrochemical bio-sensing applications-specification of characteristics and measurement methods.

127. The standards under development by KATS;

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

4.4. Netherlands

128. The main goal of the EU project **GRACIOUS** (www.h2020gracious.eu) is to generate a science-based framework to enable practical application of grouping and read-across of nanomaterials. The project has developed a draft framework that has been 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 the framework (which has recently been published in NanoToday, doi: 10.1016/j.nantod.2020.100941) and target further research. The project will continue to seek input from stakeholders to ensure that the framework effectively meets the needs of both regulators and industry. The GRACIOUS Framework will be 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 will allow movement 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. 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.

129. The EU project **REFINE** (refine-nanomed.com) 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 SUN project. The Decision Support System will be used to identify the most efficient way to deliver the data required by regulation by the best fitting methods for registration of nanomedicinal products. In 2019 the project produced a white paper on regulatory aspects and needs, and safety testing of nanomedicinal products. A start was made on addressing methodological gaps in the assessment of physicochemical parameters, ADME, and immunotoxic effects of nanomedicines. This includes an animal toxicokinetic study, as well as preliminary work on kinetic modelling at cellular and organ level to potentially replace or limit animal testing. In addition, the applicability of a “starter set” of assays for nanomedicine characterisation and determination of potential immunotoxicity was tested for two nanomedicines.

4.5. Sweden

130. Sweden participates in the Horizon2020 project, BIORIMA (‘biomaterial risk management’) 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. Both projects are coordinated by UK partners. BIORIMA recently submitted a paper describing the risk management framework for NBMs.

4.6. United Kingdom

GRACIOUS

131. The H2020 funded GRACIOUS project led by Heriot-Watt University aims to develop a Framework that facilitates the grouping and read-across of nanoforms in order to support safe by design approaches to innovation, risk assessment and risk decision making. The overall Framework design is now accepted for publication in Nano Today, and a link can be provided when available.

132. In accordance with ECHA requirements, the Framework supports the user to generate a hypothesis that identifies the scientific reasoning for grouping different nanoforms. In total approximately 35 pre-defined hypotheses, that cover human and environmental hazards, have been generated. Each hypothesis is accompanied by a tailored Integrated Approach to Testing and Assessment (IATA), that formulates the most relevant information to be gathered from existing sources (e.g. via databases such as

eNanoMapper), and the testing required to fill information gaps. As well as streamlining data gathering, the IATAs also provide a tiered testing strategy in order to promote alternative models, and to reduce both time and costs. These IATAs are being written up for publication.

133. In order to make decisions about grouping, the similarity of NFs needs to be assessed. The consortium have identified several methods for assessing similarity which are currently under discussion development. It seems that different types of parameters might require different methods to assess similarity. Methods will be generated and guidance provided.

134. The Framework is supported by a wiki that ensures consistent use of terminology throughout the project. The GRACIOUS steering board have been asked to share this wiki with OECD so that it can be used in other international projects.

135. The Framework and its IATAs have been combined to make a software blueprint that will open access and can be incorporated into any risk assessment software tools (e.g. GUIDEnano and SUNDS). The software blueprint is currently being tested by partners with case studies.

136. The project is currently working with stakeholders (regulatory, industrial and academic) to ensure implementation of the Framework meets their needs. This involves an online consultation, but in the near future will involve use of case studies to test the Framework.

137. Finally, the project is supporting a number of dissemination events, NanoTox 2021 (20-22 April, Edinburgh) and the NanoSafety Training School (22-27 March 2021.)

138. In order to ensure the IATAs are robust standardised protocols are incorporated where possible. Some protocols are widely published but not standardised. The project has therefore included some method development and standardisation. Some of these activities have already fed into the OECD (e.g. dissolution), and others are proposed (e.g. surface reactivity measurements).

NanoSolveIT

139. 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. NanoSolveIT will undertake 4 case studies, 3 building on existing OECD case studies and one overarching one utilizing data.

140. A limited amount of work has been done on the case studies so far, as this task starts at Month 19 (July 2020). Detailed updates will be given at the next Tour de Table.

141. Considerable work has been made on the development of individual components of the IATA, including the first deep learning models for daphnia ecotoxicity based on phenotypical changes, such as loss of tail, lipid deposits and other changes including loss of eyes (developmental issues). This model has recently been published in Small, based on UoB's experimental data generated within a NERC-funded project (Karatzas et al., Small, 2020, 2001080. Interestingly, a strong link to accelerated ageing has been identified and is being explored further via genome mapping (further papers in draft).

142. Extensive work underway developing user friendly interfaces for existing models, including human inhalation (indoor air) and the NanoFASE soil-water-organism model, both to enhance their individual utility and regulatory readiness, but also as a key step in the integration of the overall IATA whereby the outputs of one model are aligned to the inputs needs of the next step in the IATA. Beta versions currently in place.

143. An overview paper of the NanoSIveIT approach was published earlier this year: Afantitis et al, Computational and Structural Biotechnology Journal, 2020, 18, 583-602.

RiskGone

144. RiskGone will develop regulatory-relevant guidance, addressing both human and environmental health prioritizing in vitro methods, based on an IATA framework. The first decision trees are now being implemented which were initially based on the ethical review, to tease out what the decision support tools will look like. The first version is already available, but the full platform beta version is planned for end 2020. A strong focus on revising the test guideline 211 for chronic reproductive toxicity, including a strong recommendation to include at least two additional exposed and recovery generations as UoB have found epigenetic changes in the recovery generations following parental (F0) exposure to EC5 concentrations of TiO_2 NMs (Ellis et al, Small, 2020, 2000301; Ellis et al, Environ Sci: Nano, 2020, 7, 1136-1149). IATA framework is strongly aligned with NanoSolveIT approach, aligning the outputs of one model / approach as the inputs of the next step in the IATA.

4.7. European Union

145. Within GRACIOUS the JRC, among others, contributes to the development of a framework to facilitate the application of grouping of nanomaterials or nanoforms (NFs), in a regulatory context and to support innovation. The Framework provides an initial set of hypotheses for the grouping of NFs, which take into account the identity and use(s) of the NFs, as well as the purpose of grouping. Initial collection of basic information allows selection of an appropriate pre-defined grouping hypothesis and a tailored Integrated Approach to Testing and Assessment (IATA), designed to generate new evidence to support acceptance or rejection of the hypothesis. Users needing to develop their own user-defined hypothesis (and IATA) are also supported by the Framework. In addition, the IATA guides acquisition of the information needed to support read-across.

- **Publication:** V. Stone et al, A Framework for Grouping and Read-Across of Nanomaterials-Supporting Innovation and Risk Assessment, Nano Today, in press

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

146. Funding from the PETA International Science Consortium Ltd. [member of the International Council for Animal Protection in OECD Programmes (ICAPO)] has contributed to the development of an advanced, three-dimensional *in vitro* system that can be used to predict the potential of manufactured nanomaterials to cause lung fibrosis in humans. The project started in 2015 with an expert workshop, the goal of which was to review the state-of-the-science and determine the technical needs to develop an *in vitro* system that is predictive of pulmonary fibrosis. As one of the outputs of the project MatTek Life Sciences developed EpiAlveolar™, a model of the lower respiratory tract which is now commercially available, and the report including characterisation of the model was published (Barosova et al. 2020). The model is being further tested under the European Union's Horizon 2020 project (PATROLS).

147. In collaboration with the US Environmental Protection Agency and the Physicians Committee for Responsible Medicine, the PETA International Science Consortium is co-hosting an ongoing webinar series on the use of new approach methodologies (NAMs) in risk assessment. So far, six webinars have been held, presented by experts from industry, academia, and government on *in vitro* and *in silico* approaches that may be applicable to nanomaterials.

148. A 2016 workshop co-organised by the PETA International Science Consortium and the US NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) resulted in four specific recommendations. One of the recommendations was to conduct proof of concept testing to show the utility of *in vitro* approaches to assess respiratory toxicity. The initial phase of the project funded by the PETA International Science Consortium used BEAS-2B cells (a human bronchial epithelial cell line) as a model to assess the ability of silanes to cause portal-of-entry effects on the human respiratory tract. Additional testing is ongoing.

149. The approaches developed are intended to be generally applicable to the testing of nanomaterials and other substances. More information on this project is available at: https://www.piscltd.org.uk/acute_inhalation_toxicity/.

5 Developments and/or considerations related to "advanced" materials (multicomponent / complex)

5.1. France

150. France (**INERIS**), The Netherlands (RIVM) and BIAC co-lead the project "Moving towards a 'Safer Innovation Approach' for More Sustainable Nanomaterials and Nano-enabled Products", which was included in the work plan of the WPMN in 2018. Lead countries with the inputs of the SIA Ad hoc expert group produced a three-part report that will be discussed at the next meeting of WPMN (Part 1: Working Descriptions on Safe(r) Innovation Approach; Part 2: Safe(r) Innovation Approach: Risk Assessment Tools, Frameworks and Initiatives related Safer-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).

151. **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.

5.2. Germany

152. Within a new research project called "Advanced materials - Thematic conferences: Assessment of needs to act on chemical safety" (see project presented under 6), UBA organises a series of three thematic conference on advanced materials. The first conference focused on gaining an overview of the heterogeneous field of advanced materials and took place last December at the headquarter of UBA in Dessau, Germany. Results of that conference were presented at the WPMN PoW Special Meeting in December 2019 in Paris. Due to the Covid-19 pandemic, the 2nd thematic conference was divided into two online sessions which are executed as joint events with OECD WPMN. The first online session took place in June 2020 and focused on approaches to cluster the field advanced materials and approaches to prioritise those to assess their relevance for chemical safety.

153. The 2nd online session will take place on 15 September 2020 and will discuss challenges of (types of) advanced materials with regard to chemical safety, including hazard and exposure assessment as well

as examples of advanced materials already identified of potential concern for chemical safety and/or circular economy. In preparation of the first and second thematic conference comprehensive research had been performed to (1) propose a structuring of the field of advanced materials by screening existing definitions and proposed classes as well scientific activities related to advanced materials and to (2) present potential clusters of advanced materials by brief characterisation of identified clusters in the format of factsheets. Furthermore, (3) a set of proposed criteria to assess the relevance of advanced materials regarding chemical safety was developed. The results of this research are intended as discussion input to the thematic conferences and are summarised in a report which is available for download at: https://www.umweltbundesamt.de/publikationen/advanced-materials-overview-of-the-field-screening. The findings of the report and first two conferences will also build the basis for discussion on options for action at the final, 3rd thematic conference in May 2021 in Berlin.

154. Currently a German interagency working group on advanced materials is being established, which will be coordinated by BfR. The kick-off meeting is scheduled for November 2020.

5.3. Italy

155. ISS is planning to organise a thematic conference on advanced materials in 2021 to introduce and discuss this relevant theme at national level.

5.4. Netherlands

156. Advanced materials are increasingly being recognized as drivers for innovations for the European market and are thought to play an important role in the societal transitions towards a circular economy and the energy transition. The topic of **advanced materials** is being explored in the Netherlands, aiming at ways for timely anticipation on developments within such material science. With the aim of facilitating the safe and sustainable design, production, use and end-of-life treatment of advanced materials, RIVM has initiated activities towards a systematic identification of emerging issues of advanced nano-based materials. The exploration consists of working on a signalling approach to systematically gather information relevant for decision making, and gain experience by working on case advanced materials. RIVM developed a stepwise approach towards identifying the specific characteristics that potentially may develop into future risks or into sustainability issues of advanced materials. The step-wise approach is currently being applied to the specific case of nano-carbon-metal hybrids for application in the energy sector. The case study and the proposal for the overarching systematic approach will be presented in autumn 2020. Results from the exploration are presented at international meetings.

157. Driven by the concept of the “four generations of nanomaterials”, TNO has explored the current state of the knowledge on **risk assessment of future generation for active nanomaterials** in a position paper which is under review for its peer-reviewed publication. Through case studies, certain challenges have been identified and preparedness of existing characterization methods, risk assessment modelling tools and analytical instrumentation for such future generation active nanomaterials with dynamic hybrid structures of biotic-abiotic and organic-inorganic combinations have been evaluated. This work can provide the basis for potential future developments in risk assessment modelling tools and analytical techniques for a more future proof approach to secure the safety of the next generations of nanomaterials.

5.5. Sweden

158. The 10th International Conference on Nanotoxicology, organized jointly by the EU projects BIORIMA, GRACIOUS and PATROLS, will address not only nanomaterials but also advanced materials,

reflecting the increased interest in multi-component/multi-functional materials. The conference is scheduled for April 20-22, 2021 in Edinburgh, UK. Sweden participates in the BIORIMA project and in the scientific advisory panel of NanoTox2021.

159. Scientists engaged in the national MISTRA Environmental Nanosafety consortium have recently published an evaluation of the risks of so-called nano-robots, 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. Aug 27 [Epub ahead of print]).

5.6. United Kingdom

Workshops related to Advanced Materials

160. The UK (BSI NTI/1, HSE, DEFRA and other government departments) are exploring the possibility of organising a workshop on Advanced Materials to discuss the proposed German approach on categorisation and prioritisation of advanced materials.

Health and Safety Executive (UK) Advanced Materials project

161. 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.

5.7. United States

162. U.S. NIOSH Nanotechnology program expanded its focus to include advanced materials and manufacturing (https://www.cdc.gov/niosh/topics/advancedmnf/default.html).

5.8. European Union

Workshop on Smart and Sustainable Smart Nanomaterials

163. The European Commission's Joint Research Centre (JRC) and the Directorate-General for Research and Innovation (RTD) will jointly organise a Workshop on Safe and Sustainable Smart Nanomaterials, which will take place on 9-10 September 2020 as a virtual event due to the current Covid-19 situation. It is focused on smart (responsive, multi-functional) nanomaterials, as such or embedded in products, which are developed for application in industrial sectors such as agriculture, food, packaging and cosmetics.

164. In general, the workshop aims at facilitating the exchange of information on functionality, safety, sustainability and legislative aspects of smart nanomaterials among developers, scientists and regulators.

165. The workshop is structured in four sessions of presentations, each followed by a dedicated breakout session:

166. Session 1 "Designing smart nanomaterials" will be entirely dedicated to developers.

167. Session 2 "From Safe-by-Design to Safe-and-Sustainable-by-Design" will give the floor to experts on assessing safety and sustainability of nanotechnology, to illustrate and discuss challenges with smart nanomaterials.

168. In Session 3 “Regulatory preparedness”, regulators will present the legislative context and some initiatives concerning smart nanomaterials.

169. Session 4 "How to shift towards a more sustainable path? Implications of the Chemical Strategy for Sustainability" is dedicated to consulting the priority areas of Sustainable-by-Design in view of Horizon Europe, EU's next framework programme for research and innovation.

- More information: https://ec.europa.eu/jrc/en/event/workshop/ec-workshop-safe-and-sustainable-smart-nanomaterials
- Contact: JRC-SMART-NANOMATERIALS-WORKSHOP@ec.europa.eu.

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

6.1. Austria

Projects funded by the national NANO Environment Health and Safety programme (http://www.ffg.at/nano-ehs)

170. The project **SolarCircle** (duaration 2020 – 2021) aims to qualitatively assess the potential environmental risks and the recyclability of advanced materials, such as perovskite semiconductors, quantum dots, CIGS or organic dyes, which 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 an der JKU.

171. 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).

172. The transnational **Nano EHS ERANET-SIINN project NanoFarm** is a collaborative project between the University of Vienna (Department of Environmental Geosciences, contact Frank von der Kammer), the Carnegie Mellon University (US), the University of Kentucky (US) and the University of Aveiro (PT). It aims to understand the benefits and impacts of inorganic nanopesticides like CuO. The project covers characterisation in environmental media, transformation and transport, plant uptake and trophic transfer as well as ecotoxicological effects. The project NanoFarm has been finished in December 2019.

173. In the **FWF funded Elise Richter project Nanopesticides** Dr. Melanie Kah from the University of Vienna (Department of Environmental Geosciences, contact Melanie Kah) investigates the advantages and problems arising from the use of organic, nano-enhanced pesticides (nanopesticides). Focus is on improvements in pesticide application and differences in transport, degradation and efficiency caused by the nano-specific formulations. This project was finished in 2019. Melanie Kah moved to the University of Auckland (NZ)

174. In the **FWF funded project CNT-NOM** Prof. Thilo Hofmann and Dr. Melanie Kah (Department of Environmental Geosciences, contact Thilo Hofmann, Melanie Kah) investigate the processes of natural organic matter adsorption to carbon nanotubes.

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

176. The project **NanoTrust,** funded by the Austrian Federal Ministry of Climate Action, Environment, Energy, Mobility, Innovation and Technology (www.bmk.gv.at) is a research project 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.oeaw.ac.at/ita/nanotrust-dossiers, last publication May 2020 regarding nano-TiO_2 as food additive.

177. The project **NanoSyn** (contact: Andreas Falk), funded by the Ministry for Climate Action, Environment, Energy, Mobility, Innovation and Technology (BMK), aims to address nanosciences and nanotechnologies in Austria comprehensively. The relevant community in scientific and applied research as well as the industrial value chain shall be further developed. The aim of the project is the initiation of specific cooperation with special attention to the promotion of young scientists through conferences and trade fair presentations. The collaboration of "BioNanoNet Forschungsgesellschaft mbH" (coordinator), and the project partners "nanoNET-Austria e.V." and "Erwin Schrödinger Gesellschaft für Nanowissenschaften e.V." will strengthen the national community, support science and research activities as well as industrial collaboration from basic to applied sciences. Multidisciplinary collaboration on national and international level from research and development towards sustainable innovation will be facilitated, e.g. by supporting the EU-Asia dialogue on NanoSafety, that shall contribute to the Malta Initiative and thus to OECD work. https://www.bnn.at/projects/nanosyn

178. 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

179. 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. **BioNanoNet** was 3rd party from the project beginning, and now joined in July 2020 as full partner (contact: **Andreas Falk**) 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 will end in June 2021.

180. In the H2020 project **PANDORA**, **Albert Duschl (University of Salzburg)** is partner and work package leader. The project is an ITN in which doctoral students work on effects of nanomaterials on the innate immune response. Since innate immunity is evolutionary old, it is highly conserved in the animal kingdom. This allows a direct comparison of human and environmental species (e.g. mussels, wood lice

and earthworms). The project thus provides strong links between human nanotoxicology and environmental nanotoxicology, using the options available to both of these fields. http://www.pandora-h2020.eu/

181. The **Sparkling Science Project Nan-O-Style** run by **University of Salzburg** (Martin Himly and Mark Geppert) investigated the combinatorial effects of nanoparticles and ingredients of modern lifestyle products, such as henna tattoos, cosmetics, *etc.* towards human skin cells. In addition, a survey on public perception and knowledge on nanotechnology among the Austrian population was launched and more than 1000 questionnaires were evaluated. The project resulted in more than a dozen peer-reviewed publications by students from different high schools in Austria (Open Schools Journal @ OpenAire) and developed teaching materials for high school teachers. In Feb 2019 the Open NanoScience Congress with >500 attendees was organized (www.uni-salzburg.at/Nan-O-Style).

182. **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.

183. 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).

184. In the **H2020 project NanoCommons** (start: January 2018) **BioNanoNet** (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/) .

185. The **H2020 project NanoFase** will develop a comprehensive modelling framework for nanomaterials in the environment, including release, transformation in waste streams, and behaviour in fresh waters, estuarine and marine waters, soil and sediments. Uptake routes are addressed as well. The project is coordinated by the UK NERC. The Department for Environmental Geosciences, University of Vienna (contact: Frank von der Kammer) is involved in several work packages. The central work package on surface water and sediments is led by University of Vienna.

186. The **European Center for Nanotoxicology** (EURO-NanoTOX) is a topic-oriented platform which is co-ordinated by the BioNanoNet Forschungsgesellschaft mbH. EURO-NanoTOX develops nanosafety strategies and serves as an international node for nanotoxicology. The 5th revised edition of the ENT-expertise-catalogue named "compilation of resources and tools to support nanotoxicology, risk & safety testing" was published in September 2018. See: https://www.bionanonet.at/index.php/about-nanotoxicology/ (contact: Andreas Falk)

187. In the **H2020 pilot-project Smart-4-Fabry** (http://smart4fabry.eu/), Austrian partner BioNanoNet is responsible for the nano-related safety-tasks. BioNanoNet is developing an integrated safety strategy together with international project partners, to reduce the potential risk upon worker's exposure to MNMs during production and manipulation processes, and to ensure the responsible implementation of

nanomaterials (NMs) along the entire value chain of industrial innovation processes (contact: Andreas Falk).

188. The H2020 project “NextGenMicrofluidics - Next generation test bed for upscaling of microfluidic devices based on nano-enabled surfaces and membranes” (grant agreement n°862092) has started in April 2020, coordinated by JOANNEUM RESEARCH Forschungsgesellschaft mbH (Austria). Nano enabled components are essential key parts for microfluidic applications - mostly in form of nano-enabled surfaces (NES) and nano-enabled membranes (NEMs). However, crucial challenges hinder the transfer of NES and NEMs into commercial microfluidic devices. Current production technologies (e.g. injection moulding) don’t allow large volume upscaling of complex nano-patterned surfaces and the produced microfluidic components need to be handled in single pieces in all subsequent processes. Therefore, subsequent backend processing (nano-coatings, printing of nano-based inks, lamination of NEMs) demands for complex single peace handling operations. This restricts upscaling potential and process throughput.The proposed project NextGenMicrofluidics addresses this challenge with a platform for production of NES and NEMs based microfluidics on large area polymer foils. This approach enables upscaling to high throughput of 1 million devices per year and more. The polymer foil technology is complemented with classic technologies of injection moulding and wafer based glass and silicon processing. These core facilities are combined with essential backend processing steps like high resolution biomolecule printing with the worldwide first roll-to-roll microarray spotter, printing of nano-enabled inks, as well as coating and lamination processes. These unique facilities will be combined and upgraded to a platform for testing of upscaling of microfluidic use cases from TRL4 to TRL7. The services comprise device simulation, mastering of nanostructures, nanomaterial development, material testing, rapid prototyping, device testing, nano-safety assessment and support in regulatory and standardization issues. The platform will be opened for additional use cases from outside of the consortium, and is therefore called Open Innovation Test Bed (OITB). The operation of such use cases will form the basis for self-sufficient operation of the platform after the project duration of 4 years. BioNanoNet Forschungsgesellschaft mbH (BNN) (contact: Andreas Falk) is responsible for the evaluation of potential hazards and safety issues in all Demo Cases as well as regulatory issues, and is closely working together with all partners. 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.

189. The H2020 project “**SIXTHSENSE - Smart integrated extreme environment health monitor with sensory feedback for enhanced situation awareness**” (grant agreement n°883315) hast started in May 2020. As task leader for 'safety', BioNanoNet Forschungsgesellschaft mbH (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.).

190. In the H2020 project **SABYDOMA** (SAfety BY Design Of nanoMAterials – Project coordinated by Andrew Nelson (University of Leeds) and started in April 2020) (RIA), grant agreement n°862296), the Austrian partner BioNanoNet (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.

191. In the EU funded H2020 Research and Innovation action **NanoPAT** (Process Analytical Technologies for Industrial Nanoparticle Production – project coordinated by Simona Neri (IRIS Technologies) and started in June 2020, grant agreement n°862583), BioNanoNet (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 Gerhard Prossliner) is 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).

192. 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. BioNanoNet (contact: Andreas Falk) and Joanneum Research Department HEALTH (Thomas Birngruber) are part of the BIORIMA consortium.

193. 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 activites on the currently ongoing development of a nanorisk governance framework. Training activities include further stakeholder engagement (researchers, industry, regulators, insurances, NGOs, policy makers, open public) for the establishment of a pan-european NanoRisk Governance Council.

194. In Sep 2019 the **12th International Particle Toxicology Conference** was organized by the **University of Salzburg** (chair of organizing committee Albert Duschl) in collaboration with DECHEMA. This included the **1st International Young Scientists Meeting** which was dedicated to communication, education, training and orientation for early-stage researchers.

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

6.2. Canada

196. Environmental transformation and fate of metal-based nanomaterials were evaluated in natural waters by Government of Canada researchers. The fate of nanomaterials such as silver nanoparticles released from municipal wastewaters and their toxicity to exposed fish and bivalves were assessed. Silver nanoparticles and their transformation products were analysed in Canadian municipal wastewater effluents as potential additional silver sources in natural waters. The bioavailability and toxicity of Ag nanoparticles (NPs) and transformed products to aquatic organisms were documented and environmental exposure was characterized as influenced by the nature and size of particles.

Publications

- Gagnon C. 2019. Fate, transformation and bioaccumulation of silver nanoparticles (nAg) and metal oxide nanoparticles (nCeO2, nCuO, nZnO) in the aquatic environment. Final report for the Chemical Management Plan. 22 p.
- Auclair J, Turcotte P, Gagnon C, Peyrot C, Wilkinson KJ, Gagné F. 2019. The influence of surface coatings of silver nanoparticles on the bioavailability and toxicity of freshwater mussels. J. Nanomaterials, ID 7843025, 10 p. doi.org/10.1155/2019/7843025

197. A new specific method for the detection of Ag NPs by single particle (SP) - ICP-MS in natural waters was developed within the Government of Canada. For accurate detection of Ag NPs (i.e., avoiding isobaric interferences in mass spectrometry), it is necessary to take into account the abundance of particulate Zr and to consider the likelihood of a false positive. The results showed that for a given Zr particle, the interference on the 107Ag is greater than that on 109 isotope. For greater reliability of the analysis, the isotope 109 Ag was thus selected for the analysis of Ag NPs in natural water samples. Though these Zr interferences do not have potential impacts on the determination of total Ag concentrations in natural waters, false positive detection using SP-ICP-MS technique must be considered in the measurement of Ag NPs.

Publication

- Turcotte P, Gagnon C. 2020. Zirconium Interferences on the detection of silver nanoparticles by single particle ICP-MS: implications on natural water analysis. Nanomed. Nanotech. J. (in press)

198. As part of Canada's Chemicals Management Plan (CMP) Phase 3, the Government of Canada has developed strategies to address NMs that are listed on the Domestic Substances List (DSL). For this purpose, regulators have identified a number of priority DSL NMs for which data on physico-chemical characterization and toxicity are required for risk assessment. To fill these data needs, the Government of Canada initiated projects to characterise the physico-chemical properties in laboratory and to investigate the toxicological potential of several DSL NM substances, including cerium oxide, iron oxide, and nickel oxide. Characteristics of the nanoforms of these NMs, such as size, shape, surface area, surface charge, type and quantity of surface coating or surface modification, were studied along with their toxic effects on cell viability, membrane integrity, and cellular stress. In 2019-2020, powder X-ray diffraction (XRD) was used to identify the mineral phases (crystalline and amorphous) of several nanoforms of the priority metal oxides (Cu, Zn, Ti, Al), and to estimate crystallite size based on XRD spectral features. These analyses complemented toxicological studies conducted on the same nanomaterials. Data obtained from the projects will allow regulators from the Government of Canada to evaluate the relationships between NM properties and their biological outcomes and to fill the data needs to inform regulatory decisions on the priority DSL NMs.

199. The Government of Canada is conducting research to tackle the challenge of determining the degree to which observed toxicity is caused by metal oxide NPs, aggregates/agglomerates of the NPs, or by the release of metal ions. This work contributes to the current debate as to whether toxic effects are due to NPs themselves or the released ions.

Publications

- 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, accepted July 2 2020.
- Avramescu, M-L, Chénier, M, Gardner, HD, and Rasmussen, P.E. (2019) Solubility of metal oxide nanomaterials: observations on method development. Journal of Physics, 1323:1 https://iopscience.iop.org/article/10.1088/1742-6596/1323/1/012001

200. Research projects are currently underway within the Government of Canada to obtain toxicity information on amorphous silica, titanium dioxide, and zinc oxide nanomaterials and to explore the impact of physico-chemical properties on toxicity. These research projects are also relevant to IATA due to the integrated nature of toxicity testing and can also be applicable to the developments and consideration related to multicomponent/complex advanced materials, in the context of understanding the toxicology of these nanoforms and relationship between physical and chemical properties and associated toxicity. These projects are conducted in collaboration with other government departments and academic partners.

Amorphous Silica nanoforms

201. In this project, a set of newly synthesized amorphous silica nanoparticles including pristine and surface-modified NPs are screened for in vitro toxicity. This work includes, some physicochemical characterization (e.g. ICP analyses, DLS, TEM of cells after exposure, etc.), development of an acellular oxidative potential testing (e.g. oxidative stress) for tier 1 toxicity screening of these materials, also, exposure experiments with mitochondrial fractions from monocyte/macrophage cells for toxicity screening at the molecular level, and in vitro cell culture exposure experiments using multiple cell lines (human lung

epithelial cells-A549; mouse monocyte/macrophage cells-J774, and in cells from biopsy samples from healthy and pulmonary diseases (e.g. cystic fibrosis). Toxicity of nanoparticles after atmospheric transformation under simulated experimental atmospheres is examined as well. Integrated toxicity testing approach is applied with multiple cytotoxicity endpoints testing (e.g. viability, cell metabolism, and membrane integrity), molecular level changes (proteins/metabolite changes), and functional assays as well as testing of association with physicochemical properties using statistical and bioinformatic approaches. In addition, exploration of toxicity mechanisms in support of adverse outcome pathway construction is another aspect of this project.

Titanium dioxide nanoforms

202. In this project, a set of pristine and surface-modified TiO2 NPs 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). Toxicity of nanoparticles after atmospheric transformation under simulated experimental atmospheres is examined as well. Integrated toxicity testing approach is applied with multiple cytotoxicity endpoints testing (e.g. viability, cell metabolism, membrane integrity) and molecular level changes (e.g inflammatory proteins, ROS), as well as testing of association with physicochemical properties using statistical and bioinformatic approaches. In addition, exploration of toxicity mechanisms in support of adverse outcome pathway construction is also an aim of this project.

Zinc oxide nanoforms

203. Here, a set of pristine and surface-modified zinc oxide NPs are screened for in vitro toxicity. This work included some physicochemical characterization (e.g. ICP) and in vitro cell culture exposure experiments using multiple cell lines (human lung epithelial cells-A549; mouse monocyte/macrophage cells-J774). Integrated toxicity testing approach is applied with multiple cytotoxicity endpoints testing (e.g. viability, cell metabolism, membrane integrity) and molecular level changes (e.g inflammatory proteins, ROS), as well as testing of association with physicochemical properties using statistical and bioinformatic approaches. In addition, exploration of toxicity mechanisms in support of adverse outcome pathway construction is another goal of this project.

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

Publications

- Dalibor Breznan, Dharani D. Das, Christine MacKinnon-Roy, Stéphane Bernatchez, Abdelhamid Sayari, Myriam Hill, Renaud Vincent and Prem Kumarathasan. Physicochemical Properties can be Key Determinants of Mesoporous Silica Nanoparticle Potency In Vitro. ACS Nano. 2018. Nov 26. 12(12):12062-12079. doi: 10.1021/acsnano.8b04910.
- Qifan Liu, John Liggio, Dalibor Breznan, Errol M. Thomson, Premkumari Kumarathasan, Renaud Vincent, Kun Li, and Shao-Meng Li. Oxidative and Toxicological Evolution of Engineered Nanoparticles with Atmospherically Relevant Coatings. Environ Sci Technol. 2019 Mar 19;53(6):3058-3066. doi: 10.1021/acs.est.8b06879.
- Breznan D , Nazemof N , Kunc F , Hill M , Vladisavljevic D , Gomes J , Johnston LJ , Vincent R , Kumarathasan P. Acellular oxidative potential assay for screening of amorphous silica nanoparticles. Analyst. 2020 Jul 21;145(14):4867-4879. doi: 10.1039/d0an00380h.

Presentations at Scientific meetings

- Prem Kumarathasan (oral presentation). Exposure to nanosilica particles and mitochondrial protein changes. Canadian National Proteomics Network 2019 Annual Meeting. Quebec City, QC, Canada. May 6-8.
- Prem Kumarathasan (oral presentation). Mitochondrial protein changes after exposure to amorphous SiO2 nanoparticles. 2019. 20th Technological Advances in Science, Medicine and Engineering Conference and Workshop, Hospital for Sick Kids, Toronto, Canada. July 6.
- Dalibor Breznan, Nazila Nazemof, James Gomes and Prem Kumarathasan. Cytotoxicity screening and ultrastructural study of nonporous silica nanoparticles uptake by mammalian cells. 2019. Society of Toxicology of Canada, 51st Annual Symposium, Shaw Centre, Ottawa, ON. December 2-4.
- Prem Kumarathasan, Nazila Nazemof, Dalibor Breznan, Erica Blais, James Gomes, Mohan Babu and Renaud Vincent. Nano silica exposure and protein changes in mitochondria from J774 macrophage cells. 2019. Society of Toxicology of Canada, 51st Annual Symposium, Shaw Centre, Ottawa, ON. December 2-4.

205. In keeping with the ongoing efforts to advance alternative testing strategies for chemicals by the OECD Working Party on Manufactured Nanomaterials (WPMN), a project proposal that was initiated in 2016 on advancing the development of Adverse Outcome Pathways for human health risk assessment of nanomaterials, led by the Canadian delegation was completed. A new manuscript describing the outcomes of the project is finalised for submission for the scientific peer review.

- Sabina Halappanavar, James D. Ede, Harald F. Krug, Indrani Mahapatra, Eileen D. Kuempel, Rob J. Vandebriel, Iseult Lynch, Jo Anne Shatkin. A methodology for developing key events to advance nanomaterial relevant adverse outcome pathways for informing the process of risk assessment.

206. 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. In one project, transcriptomics tools are being used to investigate if genome-wide gene expression profiles can be used 1) 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. The preliminary results from one of the metal oxides is summarised in a scientific article that is at present under peer review.

- Andrey Boyadzhiev, Mary-Luyza Avramescu, Dongmei Wu, Andrew Williams, Pat Rasmussen, Sabina Halappanavar. Impact of copper oxide particle solubility on lung epithelial cell toxicity: Response characterization using global transcriptional analysis.

207. A group of researchers from the Government of Canada are also validating an ex vivo precision lung slice technique and a gene panel for predicting lung fibrosis induced by nanomaterials, results of which were published recently.

- Rahman L, Williams A, Gelda K, et al. 21st Century Tools for Nanotoxicology: Transcriptomic Biomarker Panel and Precision-Cut Lung Slice Organ Mimic System for the Assessment of Nanomaterial-Induced Lung Fibrosis. Small. 2020;e2000272. doi:10.1002/smll.202000272.

208. An Adverse Outcome Pathway for lung fibrosis (AOP173) which is led by Government of Canada scientists, has completed the external review facilitated by the OECD WNT and EAGMST committee. A manuscript related to the topic has been recently published.

- Halappanavar S, van den Brule S, Nymark P, et al. Adverse outcome pathways as a tool for the design of testing strategies to support the safety assessment of emerging advanced materials at the nanoscale. Part Fibre Toxicol. 2020;17(1):16.

209. Government of Canada scientists completed a study investigating the utility of the Enhanced Darkfield Hyperspectral Imaging technique for the detection of nanomaterials in consumer products and for investigating dermal penetration of nanomaterials from consumer products application. The results were recently published.

- Boyadzhiev A, Trevithick-Sutton C, Wu D, et al. Enhanced Dark-Field Hyperspectral Imaging and Spectral Angle Mapping for Nanomaterial Detection in Consumer Care Products and in Skin Following Dermal Exposure. Chem Res Toxicol. 2020;33(5):1266-1278.

6.3. France

210. In France, the Ministries of Health and of Labour entrusted the French Public Health Institute (**Santé publique France**) to implement an ongoing surveillance system of labourers in the industry potentially exposed to engineered nanomaterials (ENMs) released during their synthesis or incorporation in solid/liquid matrices or packaging. This system, denominated EpiNano, was launched in 2014. Exposed labourers will be included and followed up by **Santé publique France** using auto-questionnaires and will be paired to information available through national databases (health insurance; national causes of death registry). Unexposed workers recruited in similar cohorts will serve as controls for comparisons of diseases rates. The surveillance incorporates a methodology for the traceability of occupational exposures to nanomaterials, based on control-banding methods (notably the Stoffenmanager nano tool). Currently, four families of nanomaterials (titanium/silicium dioxyde, carbon nanotubes, carbon black) were selected among those listed by the OECD. This list could be extended to other families depending on the scientific and industrial context.

211. **INERIS** has been working on the bio-nano interactions, specifically the interaction between metallic oxide NMs (12 nanoparticles with different physicochemical properties) and the surface of freshwater microalgae (3 species of Chlorophyceae: *Raphidocelis subcapitata*, *Desmodesmus subspicatus*, *Chlorella vulgaris*); additionally, the study has been focused on the relationship between this interaction and the physicochemical properties of NMs e.g. Zeta potential, and hydrophobicity (in collaboration with JRC-Ispra).

212. See Rivero-Arze A., Manier N., Chatel A., Mouneyrac C., Characterization of the nano-bio interaction between metallic oxide nanomaterials and freshwater microalgae using flow cytometry, accepted for publication in Nanotoxicology, https://doi.org/10.1080/17435390.2020.1808106

213. Moreover, the ongoing research of **INERIS** in ecotoxicity of nanomaterials 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.

214. **INERIS** studied the emissivity of wood stains (whether or not containing cerium dioxide nanoparticles) after artificial ageing. Optimized long-term ageing conditions (2.5 months) according to ISO 11341 have been applied, alternating rain periods and UV exposure in an air-conditioned enclosure. After exposure, the treated planks with a coating containing or not containing nano-CeO_2 have been sanded down. The electron microscopy analysis of the collected fragments revealed particles, more or less spherical, containing CeO_2, wood debris (fibrous) with or without copper particles metal (sometimes nanometric). However, no free CeO_2 particles were detected. Nanometric copper metal has also been found on the surface of the wood fibres of the control plank.

215. **LNE** has conducted studies on the impact of fire degradation on phys-chem properties and toxicity of released nanoobjects used in EVA matrix (boehmite, silica, alumina with different coatings and shapes)

within the NANOTOX'IN project (French national funding / ADEME) and 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 continuing its study on the impact of ageing on nanoobjects' release by thermal degradation of nanocomposites (containing nanomaterials as flame retardants) and contributed also to the study of the potential impact on brain functions of released (nano)particles from nanocomposite materials (paint with TiO_2) under use (ageing, wear, UV) under the Release_Nanotox project (French national funding / ANSES). Finally, **LNE** is 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_2) by the inhalation route.

216. **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).

217. **LNE** has initiated an inter-laboratory comparison at the French national level in the frame of the Club nanoMétrologie (network which gathers almost 400 members coming from academics and industry to share issues on nanomaterials characterization/metrology and launch different initiatives to help its members to progress on this topic / www.club-nanometrologie.fr). Around 30 participants using 10 different techniques are involved in this ILC on nanoparticles size characterization (ERM-FD304, E171, SiO_2 with two populations and different ratios). **LNE** is also participating to the ILC organized by RIKILT for the characterization of Au nanoparticles by SEM and AFM in the frame of the Horizon 2020 ACEnano project. Finally, **LNE** launched a new topic on nanoaerosol characterization and metrology issues within the Club nanoMétrologie with INRS, IRSN and CEA.

218. **CEREGE** is involved in a bilateral program CEREGE (CNRS-UMR 7330, France) - Dpt. Plant & Soil Sci., U. Kentucky (USA) funded by CNRS -PICS 08322 SODA Light to investigate characterization opportunities focusing on nanomaterial based on light (i.e. Z<20) elements.

219. Two French research teams **INRS** (Laurent Gaté) and **UMR 7198 CNRS-UL** (Olivier Joubert) are participating in the European project SmartNanoTox, (Smart Tools for Gauging Nano Hazards).

220. This project addresses the main respiratory toxicity pathways for representative set of nanomaterials, identifies the mechanistic key events of the pathways, and relates them to interactions at bionano interface via careful post-uptake nanoparticle characterisation and molecular modelling. This approach will allow to formulate novel set of toxicological mechanism-aware end-points that can be assessed in by means of economic and straightforward tests. The use of the exhaustive list of end-points and pathways for the selected nanomaterials and exposure routes will enable clear discrimination between different pathways and to relate the toxicity pathway to the properties of the material via intelligent QSARs. This approach will allow grouping of materials based on their ability to produce the pathway-relevant key events, identification of properties of concern for new materials, and will help to reduce the need for blanket toxicity testing and animal testing in the future.

6.4. Germany

221. The research project supporting the development of the OECD "Guidance Document for the testing of dissolution and dispersion stability of nanomaterials, and the use of the data for further environmental testing and assessment strategies" was finalised. The scientific rationale, the course of GD development as well as its relevance for risk assessment and regulation was summarised in a project report. This report will be available for download at: https://www.umweltbundesamt.de/en/topics/chemicals/nanotechnology/research-development-projects.

222. In autumn 2019, UBA launched a new research project which will serve as scientific support of the WNT project 3.10 "New TG on dissolution rate of nanomaterials in aquatic environment". The project is

entitled “Standardisation of methods regarding fate and behaviour of nanomaterials in environmental media – solubility and dissolution rate” and will run until autumn 2022. The objective is to develop working protocols to determine solubility and dissolution rate under environmental conditions and will include measurement development under static and dynamic conditions. It builds upon the experimental work of WNT project 3.10 performed so far and will extend the protocol by addition of dynamic testing. The project will also include the organisation and coordination of the validation testing of protocols developed for both methods (static, dynamic) (https://www.umweltbundesamt.de/en/topics/chemicals/nanotechnology/research-development-projects).

223. In 2019, UBA and the Federal Ministry of Environment, Nature Conservation and Nuclear Safety (BMU) launched a new research project called **“Advanced materials - Thematic conferences: Assessment of needs to act on chemical safety” (see activity on thematic conferences for advanced materials under 5). The project consists of two parts: The first part aims at gathering, evaluating and preparing information on advanced materials and their (potential) applications to provide discussion input to the thematic conference. For this objective, comprehensive research on** structuring of the field of advanced materials by screening existing definitions and classes as well scientific activities related to advanced materials had been performed and potential clusters of advanced materials were identified and suggested. Furthermore, possible criteria to assess the relevance of advanced materials regarding chemical safety were developed as support for the discussion on the challenges for risk assessment and regulation of advanced materials.

224. The 2nd part of the project consists of three thematic conferences which will allow stakeholder discussions of different relevant topics, i.e. overview on the field of advanced materials, their functionalities and potential applications (Thematic conference 1, Dec 2019, Dessau, Germany), challenges for risk assessment and regulation (Thematic conference 2 as joint event with OECD, executed as 2 online sessions in June and September 2020), evaluation of project results and recommendations for action (Thematic conference 3, May 2021, Berlin, Germany) (https://www.umweltbundesamt.de/en/topics/chemicals/nanotechnology/research-development-projects).

225. UBA acts as associated member to the EU NMBP 34 CSA “NanoHarmony”. Main focus of its associated membership is to promote cooperation and harmonised development of NanoHarmony activities and WNT activities led by UBA related to OECD TG and GD for environmental assessment of nanomaterials. BMU is member of the board. This project is part of the Malta Initiative which was founded by BMU in 2017(https://nanoharmony.eu/ and https://www.bmu.de/en/topics/health-chemical-safety-nanotechnology/nanotechnology/the-malta-initiative/).

226. UBA is member of the project support group of a project dealing with carbon fibres in circular economy. The project “CarbonFibreCycle - Carbon fibres in circular economy – release behaviour and toxicity due to thermal and mechanical treatment” started in January 2019 and will be finalised end of 2021 (https://www.nanopartikel.info/en/projects/current-projects/carbonfibrecycle).

Current national BMBF-NanoCare4.0 Projects with a funding period of 3 years at maximum are listed here:

CarboBreak

- Prerequisites and mechanisms for the release of alveolar fibrous carbon fibre fragments

CarbonFibreCycle

- Carbon fibres in circular economy – release behaviour and toxicity due to thermal and mechanical treatment

MetalSafety

- Development of evaluation concepts for fibrous and granular metal compounds - bioavailability, toxicological efficacy profiles and comparative in vitro, ex vivo and in vivo studies. The aim of the scientific project MetalSafety is to design comparatively easy-to-use in vitro models for the toxicological evaluation and grouping of different metal-based compounds, which differ in their solubility and bioavailability.

NanoBioQuant

- Quantification of nanomaterials in tissue for regulatory analysis and development of in vitro methods. In this project, the analytical detection methods (LA-ICP-MS, ToF-SIMS) will be further developed and refined. The reliable detection and quantification of NP in tissue sections shall be carried out for histopathological sections as used for regulatory toxicology. By means of a standard operation procedure, the method shall add to existing OECD approved guidelines for risk analysis of inhaled particles and, eventually, may become part of the routine procedure.

NanoCELL

- Comprehensive characterization and human toxicological assessment of nanocellulose along its life cycle for reliable risk assessment and safe use in environmentally friendly packaging materials

InnoMat.Life

- Innovative Materials and new production processes: Safety along the Life Cycle and in industrial value chains. The overarching aim of the InnoMat.Life project is the establishment of criteria and similarity concepts that allow for a grouping based on hazard or risk profiles of those innovative and/or more complex material types. InnoMat.Life focuses on three material classes: (1) polydisperse materials for industrial applications such as metals or polymer powders for additive manufacturing or 3D printing, (2) materials with other and potentially critical morphologies such as rods, plates or fibres and (3) hybrid materials such as mixed organic and inorganic structures.

NanoINHAL

- In-vitro test methods for airborne nanomaterials to investigate toxic potential and uptake after inhalation exposure using innovative organ-on-a-chip technology. NanoINHALs' aim is to develop an on-site test system for airborne nanomaterials, which is able to carry out long-term studies with daily repeated real exposure. In addition to the direct effects on the human airway models, the system simultaneously generates data for absorption and effects on secondary organs.
- BfR is a partner in the new the EU H2020 Project HARMLESS (Advanced High Aspect Ratio and Multicomponent materials: towards comprehensive intelLigent tEsting and Safe by design Strategies) that will start in autumn 2020. HARMLESS will elucidate the role of next generation nanostructures, focusing on high aspect ratio (HARN) and multicomponent nanomaterials, their transformation, and their initiation of adverse outcome pathways. It also aims to provide guidance and decision support for balancing functionality versus risk to enable Safe-by-Design strategies.

6.5. Italy

227. Gov4nano project, "Implementation of Risk Governance: meeting the needs of nanotechnology" (2019-2022), is aimed to develop a proof of concept of an efficient and effective risk governance process for nanotechnologies, dealing with the legacy as well as future technological developments. Italy is involved in WP1, Establishing a sustainable and FAIR nano-EHS infrastructure (ISS, AIRI), WP2 Research and Development towards guidance and guidelines for testing of nanomaterials (EcamRicert), WP3 Risk perception, acceptance and education for civil society and (re-)insurance industry (AIRI), WP4 Support tools for risk governance within the NRGC (AIRI, EcamRicert), WP5 Establish Nano Risk Governance

Council (ISS, AIRI, EcamRicert), WP6 Building a stakeholder framework for the NRGC (ISS AIRI, EcamRicert).

228. For its institutional role at national level and as partner of the Gov4Nano project, ISS attended the Regulatory Risk Analysis Summit 2019 - Meeting nanosafety needs across disciplines and domains, Dec 4-5, 2019, the Netherlands, organized to discuss risk assessment needs and expectations of stakeholders and together find solutions to address the complexity of risk analysis for nanomaterials.

229. University Ca'Foscari Venice is partner of the RiskGONE project "Science-based Risk Governance of Nano-Technology" (2019-2023). RiskGONE is part of a cluster of EU H2020 projects, together with Gov4nano and NANORIGO, addressing specific tools to better predict human health and environmental impacts of nanomaterials, as well as the more general safety governance of nanomaterials.

230. CNR-ISTEC Faenza and University of Pisa are actively involved in PATROLS project- "Physiologically Anchored Tools for Realistic Nanomaterial Hazard Assessment (2018-2021) aimed to deliver advanced and realistic tools and methods for NMs safety assessment.

231. Italian Institute of Technology (IIT) takes part in GRACIOUS project (2018-2021) whose main goal is to generate a highly innovative science-based framework to enable practical application of grouping, leading to read-across and nanomaterials classification.

232. Italy (CNR, University of Turin, University Tor Vergata Rome, University CàFoscari Venice, Warrant Group srl, Nanovector srl, Colorobbia Consulting srl, Fin-Ceramica Faenza spa, GreenDecision) is actively participating to the BIORIMA project "Risk Assessment and Risk Management of Nano-Biomaterials in Medical Applications" (2017-2021).

233. NanoHarmony project, towards harmonised test methods for nanomaterials (2020-2023), supports the development of Test Guidelines and Guidance Documents for eight endpoints where nanomaterial-adapted test methods have been identified as a regulatory priority. It will work alongside OECD and ECHA in accelerating the development of priority Test guidelines and Guidance Documents for nanomaterials. ISS is leader of task 1.8 "Scientific basis for a new GD on integrated in vitro approach for intestinal fate of orally ingested nanomaterials" aimed to product a consensus document supporting OECD activities on development of a new GD to determine ingested NMs behaviour in intestinal environment.

6.6. Japan

234. METI launched a new five-year project "Development of Hazard Assessment Methods and Safety Assessment for Various Product Applications of Cellulose Nanofibers" (JFY 2020-2024). The project is being implemented by AIST and the University of Fukui commissioned by NEDO. The themes of this project include development of in vitro inhalation toxicity testing, evaluation of mesothelioma induction, ecotoxicological 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.

235. 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 2020, five research projects, including a basic research on development of methods for evaluating hazard and disposition of nanomaterials on human health, are progressing.

236. 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 2019 MOE continued collecting and reviewing existing literature on ecotoxicity of manufactured nanomaterials including TiO2, silver and CNTs to identify any harmful effects attributed to their particle sizes.

6.7. Korea

237. The Ministry of Trade, Industry and Energy (MOTIE) launched a research program titled "Development of hazard test evaluation of carbon based nanomaterial (graphene) to respond to international regulation".

238. The Ministry of Food and Drug Safety (MFDS) has developed skin sensitization test methods of nanomaterials since 2018. Through this, MFDS has researched the physicochemical properties considered in skin sensitization test using metal-based nanomaterials, and the applicability of nanomaterials to the in vitro skin sensitization test methods (OECD TG 442D, 442E). Also, from 2020, it has been participating in international joint research to support development of new OECD TG on toxicokinetics to accommodate testing of nanomaterials.

239. Occupational Safety and Health Research Institute (OSHRI) conducted the study which investigated characteristics of airborne particles generated during dry sanding of composite materials containing zinc oxide nanoparticles. Polypropylene (PP) materials containing zinc oxide (ZnO) nanomaterials at 4 levels (0 %, 1 %, 3%, 5%, and 10%) were sanded using 2 grit-sized zirconium aluminum oxide sandpapers (P80 and P180 grits) in an automated sanding chamber system. Concentrations and size of particles released into the air during sanding activity were measured by direct reading instruments. Morphology and chemical composition were analyzed using transmission electron microscopy and energy dispersive spectrometer mapping. Regardless grit sizes and contents of ZnO, size distributions of airborne particles did not show noticeable change. Increase of nano-sized particles less than 40 nm and micro-sized particles more than 1 um explained increase of number concentrations and mass concentrations respectively. Number concentrations were higher and respirable mass concentrations were lower with coarse sandpaper for all materials. All ZnO-PP composites with all grit sizes showed higher number and respirable mass concentrations. Number and respirable mass concentrations were positively correlated with contents of ZnO in composites. Free standing ZnO particles with various sizes from nano-sized monomers to micro-sized aggregates were observed and accounted 50% of number of nanoparticles. Composite particles embedded with ZnO particles were observed in lager particles. The results clearly show that more nanoparticles containing free standing ZnO particles are generated during sanding of the nanocomposites and the concentrations are positively related with the addition of ZnO nanomaterials into polypropylene. Further field evaluations and toxicological studies are required to elicit unknown risks imposed from processing ZnO composites mechanically.

6.8. Netherlands

240. **Gov4Nano** (www.gov4nano.eu; start date January 1st, 2019; see also TdT 2019) is a European research project that builds on more than 10 years of research funded by Framework Programmes into health and safety aspects of nanomaterials and nanotechnology by EC RTD. Gov4Nano 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 (Dutch Institute for Public Health & the Environment). Partners from Europe (28 partners) and other regions (Republic of Korea, South Africa) are participating. Concepts such as Safe by Design and Safe Innovation Approach have progressed from theoretical concepts to increasingly practical steps in the design, manufacture and use of nano-enabled products, including disposal and end of life.

241. The work in Gov4Nano follows a strategic concept leading to the establishment of the NRGC comprises three main elements, namely "Scientific Excellence" focusing on FAIR data and development of (OECD) test guidelines and guidance documents, "Co-creational Excellence" to ensure the NRGC will

fulfil expectations of stakeholders and "Proving the Outcomes" by designing the mandates and using case studies to provide a proof of principle of how the NRGC could function.

242. 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 Gov4Nano, RiskGONE and NANORIGO. There is no precursor to the NGRC, so this is the new State of the Art. Risk Governance of Nano materials will be entering new territory.

243. The EU-project **NanoFASE** (www.nanofase.eu) aimed to deliver an integrated Exposure Assessment Framework (protocols, models, parameter values, guidance ...) with the ambition to reach a level of fate and exposure assessment for nanomaterials that is at least comparable with that for conventional chemicals. The project was finalized in September 2019. Within the project Wageningen University and Research (WUR) was leading the work package on biota uptake of nanomaterials where exposure and uptake studies have been performed in earthworms (WUR) and in *in vitro* models for the human gastrointestinal tract (WFSR, formerly RIKILT). As a work package group effort (led by both WUR and WFSR), two critical review papers were published supporting modelling strategies on the uptake and/or bioaccumulation of NPs across species, one focusing on invertebrates (doi: 10.1039/C8EN01122B) and the other on the gut barrier (doi: 10.1039/D0EN00174K). RIVM contributed to development of algorithms for quantifying the fate of nanomaterials in the aquatic environment, and has worked on an update of the SimpleBox4nano model using the output from the project. This update is aimed at direct application in regulatory frameworks. TNO focused on unravelling the PMC-box (Production-Manufacturing and Consumption) in the environmental release model and on the quantification of production, manufacturing and consumption of nanomaterials. This resulted in a detailed study design to perform the laboratory release tests and wet/dry deposition experiments.

244. The project results will also be input to the current efforts in nanospecific modification of the OECD guidance documents on testing of chemicals.

245. The aim of the EU project **PATROLS** (www.patrols-h2020.eu, January 2018 until June 2021) is to establish and standardise methods for the next generation of advanced, physiologically anchored, hazard assessment tools. The ambition is to accurately predict adverse effects caused by long-term (chronic), low dose engineered nanomaterial exposure in humans and environmental systems to support regulatory risk decision making. Several Standard Operating Procedures that have incorporated aspects to be compatible with future OECD guidance have already been delivered. The procedures describe: 1) more realistic and predictive *in vitro* three dimensional lung, gastrointestinal tract and liver models for mechanism-based hazard assessment; 2) cross-species models linking human and environmental systems; 3) innovative methods for sub-lethal hazard endpoints in ecologically relevant test systems and organisms, selected according to their position in the food chain. Furthermore, a concept for *in vitro* to *in vivo* extrapolation by computer modelling has been developed. The rationale has been presented to the international community at the 12th International Particle and Fibre conference in September 2019.

246. RIVM has established a lung cell model that can be exposed repeatedly over time to engineered nanomaterials via air. The model comprises bronchial epithelial cells that line the lung. The protocol on how to culture the cells at the air-liquid interface and expose them via air is published in peer-reviewed video journal JOVE: https://www.jove.com/video/61210/an-air-liquid-interface-bronchial-epithelial-model-for-realistic.

247. Within the **EC4SafeNano** project (ec4safenano.eu) 15 well-known European institutes built a blueprint for a virtual institute/centre to assist governments and industries with their nanosafety issues through distributed networks of laboratories and research organizations supporting safe innovation in nanotechnologies. This self-sustainable entity is a one-stop shop for a wide variety of contract based nanosafety related services, and provides a central contact point for questions about nanosafety in Europe. The centre aims to meet the needs of industry and other parties concerned with the safe and responsible innovation of nanotechnology, and act as a crucial player between the Nano Risk Governance Council

(once established) and those parties using or providing nanosafety services. TNO leads WP1, in which the needs related to nanosafety experienced by governments, industries and other stakeholders are mapped. Simultaneously, the resources to answer to these needs are mapped and collected. Within the mapping and collection of resources, TNO is responsible for coordinating the inventory of tools or methods, trainings, standards, SOPs and Guidance or Best Practice documents. Through the participation of TNO, also the Dutch Nanocentre (www.nanocentre.nl) is connected to this European initiative, as an example of a national nanosafety platform. In addition, TNO leads the technological innovation (related to nanomaterials) network. Legal mechanisms have been set up during the course of the project to operate the centre after the end of the project, addressing the contractual relations, IPR issues, and governance.

248. TNO will assess the potential human health risks and provide a life cycle assessment to balance the risks and benefits of the application of nano-perovskites in lighting and energy harvesting applications within the framework of the European **PeroCUBE** project. A tiered approach will be applied over the full life cycle (manufacturing, use and end-of-life) by starting from a qualitative tool LICARA nanoSCAN (with relatively low input needs and higher uncertainty) to a full quantitative assessment (with more input needs, but lower uncertainty) towards the end of the project when the applications are better known. For selected nano-perovskites applications, the approach will include a hotspot quick scan, quantitative human health risk assessment and risk-benefit analysis to assess the release, potential risks of nano-perovskites into indoor and environmental compartments over the entire life cycle, and relevant economic impacts of the use of nano-perovskites in lighting and energy harvesting applications.

249. Research institute Wageningen Food Safety and Research (WFSR, the new name of RIKILT) is partner in the EU project **ACEnano** (www.acenano-project.eu). Based on the results from other EU projects progress has been made in the development of new methods and SOPs to test for e.g. particle solubility, particle reactivity and the identification of particle coatings. For decision making a method decision tool was developed (based on the NanoDefiner e-tool) that can support method decision making for regulation purposes, risk assessment and labelling of nanomaterials. In addition, and within this project, interlaboratory exercises have been organized to test the performance of laboratories (also outside the ACEnano project) to determine nanoparticles.

250. The EU **NanoSafety Cluster** (NSC, www.nanosafetycluster.eu) maximises the synergies between European research projects addressing the safety of materials and technologies enabled by the use of nanoparticles. The studied aspects include (eco)toxicology, exposure and risk. The NSC also functions as an open platform for dialogue and exchange of information among researchers, regulators, administrators, industry, civil society representatives, etc. The cluster has been reorganised in 2017 with more emphasis on establishing task forces that allow creating a rapid answer to emerging issues, for example responding to classification proposals of nanomaterials. The NSC has developed activities to offer the extensive knowledge available for the Malta Initiative, in this way contributing to the OECD developments/adaptations of technical guidelines and guidance documents to accommodate testing of nanomaterials.

251. TNO leads the Working Group on Exposure and Hazard assessment and coordinates a Task Force on a publicly accessible exposure database.

252. 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. RIVM, already participating in a substantial number of these project is also supporting the coordination via Flemming Cassee, being 1 of the 3 members of the coordination team (next to Eva Valsami-Jones from University Birmingham, UK, and Andreas Falk from BioNanoNet, AT). This team also has a strong connection with the EU DG R&I in Brussels (e.g. providing input for Horizon Europe) and initiates and maintains collaborations beyond the EU member states, e.g. with South-Africa, Mexico, USA, Korea and AsiaNanoForum.

253. The **NanoHarmony** project (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.

254. The three year project started on April 1, 2020 and brings together expert partners from European Countries and will work alongside OECD and ECHA.

a. Establish integration of other public and private resources (funding or labour) to adapt current and develop new OECD test guidelines and OECD guidance documents;

b. Establish maximum synergy of actions across industrial sectors and international cooperation;

c. Support the completion of the elaborated documents by the relevant international organisations involving the OECD Member States and relevant EU agencies;

d. Establish very close cooperation with Member States, OECD, OECD business network, Joint Research Centre, ECHA, EU and Member State agencies to act as leads and co-leads for the test guidelines and guidance documents to be developed.

255. 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'.

6.9. Sweden

256. 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. 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. In addition to these projects belonging to the nanosafety cluster, Sweden participates in the nanomedicine-focused project, BIORIMA ('biomaterial risk management') and coordinates the hazard assessment of nanobiomaterials (NBMs) in the latter project. The project aims to develop an integrated risk management framework for NBMs used in advanced therapy medicinal products (ATMP) and medical devices (MD). BIORIMA partners are currently planning the next international nanotoxicology conference with GRACIOUS and PATROLS (see above).

257. The Swedish Foundation for Strategic Environmental Research (MISTRA) funded the MISTRA Environmental Nanosafety program from 2014 until 2018. The consortium was 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 has now decided to fund a 4-year extension of the Environmental Nanosafety program. The second phase of the program was launched in 2019 and the consortium is coordinated by Lund University. In addition to the aforementioned partners, the Technical University of Denmark (DTU) also participates in the consortium. Furthermore, four industry partners are now involved in the program: Höganäs AB, Nouryon, SYSAV, and Tetra Pak. The program represents the largest nanosafety/nanotoxicology project in Sweden with a total 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. There is a strong synergy with the nanosafety platform, SweNanoSafe, through the expert panel of the platform.

258. The MISTRA Environmental Nanosafety project hosted an online workshop in May 2020 together with the national strategic innovation platform, SIO Grafen. Fifty participants representing different stakeholders including academia and industry took part in the discussions on nanomaterials in the work environment, nanomaterial regulations, etc. The vision, according to SIO Grafen, is that Sweden is among

the world's top ten countries in deploying graphene on an industrial scale by 2030. 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 (Stockholm) has participated in the work package on health and environment (human and ecotoxicology) since the Flagship project started.

259. SweNanoSafe submitted a report entitled "*Proposals for national measures for safe use, handling and development of nanomaterials. SweNanoSafe Report 2020:3*" to the Swedish Ministry of the Environment in December 2019. The report is based on the results of consultations with various stakeholders along with discussions among members of the expert panel and the steering group of the platform to identify hindrances and propose actionable solutions for the safe use and handling of engineered nanomaterials.

260. SweNanoSafe is currently coordinating a project on nanomaterials in the environment: "Identification of knowledge gaps and proposals for research initiatives", with a focus on Swedish conditions. The project will be finalized and reported in the autumn 2020.

6.10. Thailand

- Completed an easy to read version of the approved 7 industrial standards manuals related to nanotechnology and will use for workers' training program.
- Collaborating with Asia Nano Forum (ANF) and Nanotechnology Association of Thailand to organize the 3rd EU-Asia Dialogue on Nanosafety: Occupational Exposures to Manufactured Nanomaterials (MNMs) and Waste Disposal during ASEAN Next 2019 in Bangkok on 18 March 2019
- Organized the Seminar on NanoQ Label on 24 May 2019 at Centara Grand Hotel
- Participated as a speaker at the INCP2019 in the Philippines on 28 May 2019 on the topic of "Thailand Nanosafety and Standards Initiatives".
- Working with DIW to promote nanosafety awareness in industries during their annual conference on 6 June 2019
- Organized the Seminar to promote Nanosafety Network for Industries on 12 June 2019 at BITEC BangNa.
- On April 9, NANOTEC organized a nanosafety workshop for students and teachers from the College of Nanotechnology, King Mongkut's Institute of Technology Ladkrabang.
- 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.

6.11. United Kingdom

HISENTS

261. The H2020 project HISENTs led by the University of Leeds (Prof Andrew Nelson) has been running since April 2016 and is in the peak of activity. This project aims to revolutionize the toxicity testing of nanomaterials by developing a third generation platform composed of flow modules containing individual organelle and tissue sensor elements. This device mirrors the human physiology and is underwritten by a custom designed physiologically based pharmacokinetic in sillico model. HISENTS succeeded in every respect in achieving its technological vision. In fact three screening platforms were developed at three separate sites respectively and validated against each other to TRL4. The platforms were: biomembrane, cell-line (several) and placenta. The planned modules containing the different membrane/organ sensor elements in modules connected by microfluidic system were fully realised. The HISENTS system was also successfully simulated using, and correlated with the PBPK model.

EC4SafeNano

262. The H2020 project EC4SafeNano aims to build an open and collaborative network gathering expertise in risk management of nanotechnologies. The University of Birmingham is participating to support integration of science and research developments as well as developing approaches to overcome the barriers of data sharing.

263. This project ended in November 2019, but some final work is still underway. A publication summarising the key advances and support for SbD has been submitted to NanoImapact (for a special issue on SbD).

264. NanoCommons is working with partners D emokritos, BAM, PLUS and UoB to integrate the data from the case study on TiO_2 NMs transformations into the NanoCommons database, to accompany the publication detailing the protocols for ageing the NMs, the protocols for characterisation and the characterisation datasets.

NanoGenTools

265. The H2020 project NanoGenTools aims to develop fast in vitro high throughput assays with molecular based computational models for better understanding of the molecular fundamentals of nanotoxicity and will initiate the development of nanosafety assays for the use by SMEs during product development. The University of Birmingham is participating and working mainly on aspects of biophysical techniques and mathematical models for accurate nanotoxicity prediction linked to safety-by-design concepts.

266. This project ended in the past year in December 2019.

267. The outputs of this project were the development of predictive models for safe by design of nanomaterials, resulting in a publication (Varsou et al., Nanoscale Adv., 2019, 1, 706-718) and a tool for extraction of descriptors from TEM images of nanomaterials and direct implementation of these descriptors into predictive QSAR models for nanomaterials physico-chemical descriptors and if data is available for nanomaterials toxicity (Varsou et al., Small, 2020, 1906588)

PATROLS

268. 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. To date the project has generated advanced culture models of the human lung, GI tract and liver; these models have been applied to evaluate a range of hazard endpoints with engineered nanomaterials. Additionally, PATROLS has been working with Health Canada and the SmartNanoTox project on the NanoAOP project; we have co-hosted a workshop at the OECD that has resulted in a publication and an OECD workshop report (ENV/CHEM/NANO(2020)11).

ACENano

269. 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. ACEnano is now in its final year and a number of new technologies for the reliable characterisation of nanomaterials have been developed and demonstrated. The project has also produced a number of SOPs and other educational materials, including training videos that will be made available on the project web site over the coming months. ACEnano has also developed an e-tool for assisting in the selection of analytical pathways for the optimal characterisation of nanomaterials with emphasis on supporting industry; the tool is currently being tested and optimised.

Environmental Exposures and Health (EEH)

270. 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 and Imperial College and King's College, includes projects on exposures from nano consumer spray products (initial study published, Laycock et al, Atmos. Env 2020), particulate effects on asthma/allergic airway disease and the use of aerosol exposure air liquid interface (AE-ALI) systems for nanomaterial toxicity assessment

6.12. United States

271. The National Nanotechnology Initiative (NNI) 2011 EHS Research Strategy provides guidance to the Federal agencies that produce the scientific information for risk management, regulatory decision-making, product use, research planning, and public outreach. Participating agencies adaptively manage the strategy under the auspices of the interagency Nanotechnology Environmental and Health Implications working group of the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee. URL: http://nano.gov/about-nni/working-groups/nehi

272. The *OECD Guidance Document on Aquatic and Sediment Toxicological Testing of Nanomaterials* was published in July 2020. This project was co-led by the United States (U.S. Army Corps of Engineers and National Institute of Standards and Technology) and Canada.

6.13. European Union

273. There are a number of projects ongoing with significant relevance to the work of WPMN. For comprehensive information on ongoing and launched projects, calls and meetings, including the **Malta initiative**, go to Nanosafety Cluster website.

274. Based on the call NMBP-34-2019 in support of documentary standards (CSA), four project were recently launched:

1. SUSNANOFAB INTEGRATED EU STRATEGY, SERVICES AND INTERNATIONAL COORDINATION ACTIVITIES FOR THE PROMOTION OF COMPETITIVE AND SUSTAINABLE NANOFABRICATION INDUSTRY from: 1 March 2020 to: 28 February 2023
2. NanoFabNet - International Hub for sustainable industrial-scale Nanofabrication, from: 1 March 2020 to: 28 February 2022
3. NanoHarmony Towards harmonised test methods for nanomaterials, from: 1 April 2020 to: 31 March 2023, with the mission to support the development of Test Guidelines and Guidance Documents for eight endpoints where nanomaterial-adapted test methods have been identified as a regulatory priority. It 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. It will work alongside OECD in accelerating the development of priority Test guidelines and Guidance Documents for nanomaterials.
4. NANOMET Development and standardisation of methods for the safety testing of manufactured nanomaterials at OECD, from 1 May 2020 to: 30 April 2023

275. The European Union Observatory on Nanomaterials (EUON) has published two new studies related to the health and safety of nanomaterials. These are:

- A critical review of the factors determining dermal absorption of nanomaterials and available tools for the assessment of dermal absorption: Link to full study report
- A critical review of studies on the reproductive and developmental toxicity of nanomaterials: Link to full study report

276. In addition, the EUON has completed a study assessing the public perception of nanomaterials, which will be published in September 2020. The study, as well as previous studies run by the EUON will be found at https://euon.echa.europa.eu/reports following their publication

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. Canada

277. The Government of Canada has also established the Federal Sustainable Development Strategy (FSDS) 2019-2022 for responsible innovation and sustainable development (The strategy is described at https://www.fsds-sfdd.ca/index.html#/en/goals/)

278. The Clean Growth Hub is a Government of Canada focal point for clean technology focused on supporting companies and projects, coordinating programs and tracking results. It supports the use of SIA/SbD approaches to prevent, reduce, or eliminate pollution or any other degradation of the environment (https://www.ic.gc.ca/eic/site/099.nsf/eng/home).

7.2. France

279. **LNE** is taking part in the NanoFabNet project aiming at building an international Hub to support sustainable nanofabrication (https://nanofabnet.net) and is responsible of activities dealing with validation, harmonisation and standardization issues.

280. The Serenade project has funded the development of a new Safe-by-Design approach not focussing on the nanomaterial itself like the widely used stage-gate and three-pillar SbD strategies.

7.3. Italy

281. Italy (CNR-ISTEC) is coordinating ASINA project "Anticipating Safety Issues at the Design Stage of NAno Product Development" (2020-2023) to promote consistent, applicable and scientifically sound Safe-by-Design nano-practices, considering all the of nano-enabled products design dimensions:

functionality, production technologies, safety, environmental sustainability, cost effectiveness and regulatory requirements, in line with research responsible innovation policy.

7.4. Netherlands

282. The **NanoReg2** project (www.nanoreg2.eu), which ended in February 2019, was built around the challenge of coupling Safe by Design to the regulatory process. New principles and ideas were developed based on data from value chain implementation studies to establish Safe by Design as a fundamental pillar in the validation of a novel manufactured nanomaterial. The project contributed to further implementation of the Safe by Design and Regulatory Preparedness concept, with awareness raising activities among innovators and regulators. Furthermore, tools, methodologies and industrial case studies have been developed which support Safe by Design implementation.

283. 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.

284. The goals and tasks of SPINE are:

- Align European policy initiatives related to Safe-by-Design, especially policy initiatives regarding research and education programs
- Promote, develop and put into practice the concept of Safe-by-Design, together with innovators and industries.
- Primarily cover products and processes with
- chemicals (especially substitution for Substances of Very High Concern)
- advanced materials (incl. nanomaterials and nano-biomaterials)
- new technologies (e.g. synbiotechnology)
- Connect, share information, develop and align national policies on Safe-by-Design

285. Currently participating countries are Austria, Denmark, Estonia, Germany, Netherlands, Spain, Sweden and UK. SPINE aims to expand to other countries, and is therefore looking for policy makers interested in Safe-by-Design, and affiliated with new and emerging technologies, such as nanotechnology, biotechnology, the (petro) chemical industry and advanced materials.

286. 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 work started its implementation with the establishment of the SIA Ad Hoc Expert Group in 2017 comprising 33 participants from 14 delegations, which provided expertise and inputs in implementing the project. The objectives of this project are:

1) to develop working descriptions for a safer innovation approach concept, including the Safer-by-Design concept; and
2) to develop inventories of risk assessment tools and frameworks to
    a) help industry implement a 'Safer Innovation Approach' for NMs and nano-enabled products and

b) to help regulators anticipate regulatory challenges posed by innovations such as NMs and nano-enabled products.

287. The final report is now in its final review process and it will be finalised in 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.

288. The aim of the new EU project **SAbyNA** (www.sabyna.eu) is to develop a guidance platform for the development of safer nanomaterials and nano-enabled products. SAbyNA started in March 2020 and has a duration of 4 years.

289. Current safe-by-design (SbD) and safe innovation (SIA) approaches are quite complex and difficult to implement. Within SAbyNA, a user-friendly guidance platform will be developed that will advise the user on how to implement SbD options that fit their product or process. To do so, SAbyNA uses available resources – such as risk assessment tools, experimental methods and data – from previous projects. These resources are first selected based on their potential suitability for use in a SbD approach and next optimized to increase their usability and user-friendliness.

290. RIVM is actively participating in the development of the overall SAbyNA platform and is coordinating a work package on the selection and optimization of resources to facilitate hazard assessment of nanomaterials and nano-enabled products for SbD purposes.

291. 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 skillsets. This serves as exploratory for future development of SbD learning activities and to support its integration within existing educational programs.

292. TNO, Maastricht University and Thinkworks BV are involved in the EU **SbD4Nano** project (www.sbd4nano.eu) which aims to create a comprehensive new e-infrastructure to foster dialogue and collaboration between all actors in the supply chain for a knowledge-driven definition of SbD setups that optimize hazard, technical performance and economic costs. TNO takes the lead in developing a new exposure-driven modelling framework and coupling it with a rapid hazard profiling module into the NanoRiskQuantifier (NRQ) tool, which will be developed and validated (in collaboration with other partners) during the course of the project to ultimately reduce risk. To develop this new exposure framework, an up-to-date inventory/overview of available databases, modelling approaches (hazard/exposure) and knowledge is important. TNO is involved with other partners to develop such an inventory and identify current gaps and limitations. This also serves to establish a knowledge infrastructure with curated data and knowledge on nanomaterial properties, risks and functions. The project also forecasts for safe-born material to undergo a cost-benefit analysis algorithm to find the best compromise between safety and industrially convenient technical performance to suit all relevant stakeholders.

293. In line with continued efforts to further improve a **Safe Innovation Approach** (SIA) in its implementation, TNO and several international partners have developed a risk-aware integrated roadmap to be integrated in the SIA operational framework to make SIA implementation more sustainable. In addition to the conventional approach of embedding risk assessment and management in the early stage of innovation process, the proposed roadmap brings external actors together during the risk assessment, addresses the product value propositions, and includes the reporting and communication of the risks. Recommendations to further improve certain aspects of SIA innovation process are also provided in this

context, and the roadmap itself is based on these recommendations. A manuscript with all relevant details and proposed work flow has been submitted for its publication which is currently under revision.

7.5. Sweden

294. SweNanoSafe is currently exploring to what extent 'responsible research and innovation' (RRI) is implemented in Sweden with respect to nanomaterials and how RRI is managed in practice, for example, in terms of concepts such as the precautionary principle and safe-by-design. The goal is to mobilize a number of participants from different stakeholder groups in a joint learning process to promote improved RRI. The project will be finalized and reported in the autumn 2020.

7.6. Switzerland

295. Ongoing update of the Swiss Precautionary Matrix: Adaptations of the human exposure potentials and exposure models, as well as assess the implementation of uncertainty on results and the use of databases for information gathering.

7.7. United Kingdom

SABYDOMA

296. 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. This is the basis of the SABYDOMA Lead Demonstrator, which will be transferred and validated by two companies. SABYDOMA will work with two other companies on coating manufacture and the stability of and release from the coatings. Release from the coatings will be screened and the output signal fed back to moderate coating manufacture. Accordingly the core focus of SABYDOMA is its four case studies working through the four companies respectively taking the technology from TRL4 to TRL6. One of the novel themes of this study is the use of system control and optimization theory including the Model Predictive Control (MPC) philosophy to bind the whole subject of SbD from laboratory innovation to the industrial production line and from decision making processes to project governance. An equally important innovative step is the building of high throughput online platforms where nanomaterials are manufactured and screened at the point of production. The screening signal controls the NM redesign and production in a feedback loop. The University of Birmingham (Prof. Eva Valsami-Jones) are work package leads in monitoring particle and soluble species release under conditions relevant to each demonstrator.

7.8. European Union

297. EU in 2020 launched a call NMBP-16-2020: Safe by design, from science to regulation: multi-component nanomaterials (RIA). As a result two projects will be funded:

- Sunshine - to develop and validate Safe- and Sustainable by Design strategies for products enabled by MCNMs(including HARNs) and facilitate their implementation at industrial scale.
- Harmless – to develop a novel, multifaceted Safe Innovation Approach (SIA) to Nanomaterials and High Aspect Ratio Nanoparticles

8 Additional Information

8.1. Canada

298. 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. This data gap analysis took into consideration multiple sources of information, including results from a mandatory survey under CEPA, peer-reviewed scientific literature, publically available databases on nanomaterial use and toxicity, as well as outcomes of activities undertaken by international organisations (e.g. Regulatory Cooperation Council, OECD WPMN, European Union Joint Research Centre, and other international consortia). 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. The results of the data gap analysis have been shared with partners and industry, including WPMN/SGAP members and science advisory committee (SAC)/ ICG members (industry associations).

8.2. France

299. **LNE** organised a technical workshop on nanomaterials applications in food (regulations, insights regarding on-going R&D activities on toxicity assessment for food additives, characterization methodologies to verify labelling requirements …): Paris 3rd December 2019 which gathered around 50 participants mainly coming from the food industry.

300. **LNE** organized also the second 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.

301. **LNE** is participating in the NanoResp forum, a French initiative which aims to get all the different parties (industry, civil society, NGO, public institutions) around the table and discuss about the nanomaterials topic (performances, risk, metrology…). Three open meetings were organized on 2019 and a dedicated initiative on nano in food has been conducted in order to find conditions for mutual trust. Additives producers and users, NGO, toxicologist, national metrology institute… were involved in this NanoAlim working group.

8.3. Germany

302. 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). In 2022 this unique dialogue will end with an international congress in Berlin in cooperation with the OECD.

8.4. Netherlands

303. Commissioned by ECHA, RIVM and Triskelion B.V. conducted a literature study aimed to identify experimental and material related factors determining the **dermal penetration and absorption of nanomaterials** used in consumer products and occupational settings. In general, it was concluded that dermal absorption is at most very low for the nanomaterials investigated in the studies. Rodent skin studies were considered not very relevant, due to substantial differences in skin between rodents and human and lack of knowledge on how this affects skin penetration. The authors recommend to use *ex vivo* studies with human or porcine skin to evaluate dermal absorption of nanomaterials. Standardised study protocols, including full characterisation of nanomaterials, are needed to conclude on nanomaterials related factors that determine dermal absorption. The report is available at the European Union Observatory for Nanomaterials.

304. The EU project **nTRACK** (www.n-track.eu), which started in October 2017, aims to develop a safe and highly sensitive nano-imaging agent for stem cell tracking and whole body biodistribution. RIVM is leading the work package on regulatory issues of nTRACK with the aim to achieve regulatory preparedness and safe innovation approaches for these types of innovative products.

305. Regulatory classification of the product as either a medicinal product or a medical device is not straightforward, even after a meeting with the Innovative Task Force of the European Medicines Agency. The consortium decided to aim for a classification of the product as a medical device.

306. Initially the nanomaterial intended to serve as the imaging agent was a gold nanoparticle with an iron core to allow for both MRI and CT SCAN imaging. However, the project consortium experienced too many difficulties trying to upscale the production of the prototype under GMP conditions. The product that is now being moved forward into the regulatory process is a glucose-coated gold nanoparticle without the iron core, which only enables CT SCAN imaging. Preliminary safety data is now being generated for the product, which can be produced according to GMP. Advice on the required preclinical data for a first in human trial will be obtained from the National Competent Authority (BFARM and PEI) in Germany. Toward the end of the project, RIVM will host a workshop with regulators, innovators and other stakeholders where regulatory issues encountered throughout the project will be discussed.

8.5. Sweden

307. A working group of the Nordic Council of Ministers initiated 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.

308. The project was coordinated by Norway, Sweden, Finland and Denmark through the N-Nano project group of the Nordic Chemical Working Group (NKG). DHI was engaged to develop the website - eREACHNano - which is developed in close cooperation with the N-Nano project group

309. The tool focuses on – but is not limited to - helping Small and Medium-sized Enterprises (SMEs) who may not have sufficient in-house expertise in the regulation covering nanomaterials.

310. A case study for the nanoform of zinc oxide is also included as an example on how to make a proper identification registration of a nanoform in the registration process is included. This includes guidance on which data to select for the registration and how to enter the information into the IUCLID. Zinc oxide is here used as an example. The web tool is prepared in English. The web-tool can be freely accessed on http://ereachnano.dk/ or http://ereachnano.com/.

8.6. Thailand

311. Nanosafety awareness initiative by NANOTEC will put more emphasis on occupational safety as we see the workers as the frontline group to be exposed to nanoparticles. We will need to work more with the ministry of industry to conduct trainings and seminars, etc. We foresee additional collaboration with experts from EU with regards to awareness program for occupational safety of nanomaterials.

312. Participated in round robin for OECD test guideline on particle and fiber size distribution of manufactured nanomaterials which was headed by Bundesanstalt für Materialforschung und -prüfung (BAM). Results for the 2 inter lab comparison was submitted in June 2019.

313. Research Program;

- Development of zebrafish model methodology for safety assessment of nanoparticles
- Investigation of food matrix and nanoplastic interaction and determination of toxicity
- Efficacy and safety testing of nanoencapsulation of Fenugreek extract

8.7. United Kingdom

Additional Information

314. RiskGONE has strong component on ethics – initial decision tree is based on a 'Threshold analysis' approach to screening potential ethical impacts (of new technologies / applications of nanomaterials) and their severity.

315. PEROSH: NECID database - Nanoparticle Exposure Contextual Information Database (lead by IFA DGUV Germany). PEROSH institutes are looking at the option to open the central database to the public. IFA will check out options of cooperation with the aims of linking data to other databases (toxicity, chem-phys., material, etc) and providing a better visibility of NECID in the scientific community.

316. The UK Health and Safety Executive – Safety Division, is participating in the NANORIG EU project User Committee as a stakeholder.

8.8. United States

317. The U.S. National Nanotechnology Coordination Office (NNCO) holds webinars periodically to share information with the public and the nanotechnology research and development community. Examples of 2019 webinars include: "Evaluating Worker and Consumer Exposure to Engineered Nanomaterials," "Potential Respiratory Effects of Engineered Nanomaterials in Relation to Physiochemical Properties," and "Nanotechnology-Related Standards: Availability and Applications." Webinars from previous years include: "Technology Pathways Toward Commercializing Nanotechnology," "NanoEHS and Nanomedicine: Similarities and Synergisms," "The National Nanotechnology Coordinated Infrastructure (NNCI) Nodes and Environmental Research: Examples from the Field," "The Utility of Alternative Testing Strategies in Nanotechnology, Health, and Safety Evaluations"; "An Introduction to Voluntary Standards"; and "Water Sustainability through Nanotechnology."

318. The webinars are archived at URL: https://www.nano.gov/PublicWebinars

8.9. European Union

319. In 16-17 September 2020, U.S.-EU NanoEHS Communities of Research (CORs) Workshop is organized in virtual setting. It will address Risk Assessment, Risk Management & Control, Databases & Computational Modeling for NanoEHS as well as Characterization, Ecotoxicity, Human Toxicity, Exposure through Product Life.

320. The European Union Observatory on Nanomaterials (EUON) has completed a study assessing the public perception of nanomaterials, which will be published in September 2020. The study, as well as previous studies run by the EUON will be found at https://euon.echa.europa.eu/reports following their publication.

8.10. The United Nations Institute for Training and Research (UNITAR)

321. UNITAR's last major activities were a series of workshops in 2018, in the Latin American and Caribbean and Central and Eastern European regions, and a shorter workshop for the African and Asia-Pacific regions that we organized in Geneva. These were opportunities to highlight activities from the regions, as well as work by the OECD. Furthermore, we benefitted from experts to introduce the WHO guidelines on worker health and safety, and also underline the work that is ongoing under the Basel Convention of transboundary hazardous waste.

322. The Basel Convention, at its Conference of the Parties in 2019, invited Parties and others to make available information related to activities aimed at addressing issues related to waste containing nanomaterials, including case studies about and best practices. UNITAR helped to coordinate responses, with Switzerland, Thailand and UNITAR, as well as the EU and its Member States, submitting information. For best practices, the University of Fribourg also contributed information.

323. In its Open-ended working group meeting of today and Thursday of this week, there is a proposal to make a further invitation for information by the end of November 2020, and then the secretariat will submit a compilation to the Conference of the Parties of July 2021 for a decision. Hopefully that will be approved, and any other stakeholders would then be encouraged to submit such information.

324. To support these various initiatives, UNITAR has initiated work with senior experts (including Vladimir Murashov) to revise the nano e-Learning course, to update it and make it shorter. This will probably be available around the end of 2020, ready to launch for a first session in early 2021, initially with free participation. In addition, we are about to start development of case studies on best practice in managing waste containing nanomaterials. We hope to contribute this to the Basel convention for their decision making.

325. And finally, we continue to collaborate closely with the OECD to share the latest updates with our stakeholders, and to develop joint activities. Similarly, we plan to continue our collaboration with the WHO, to help disseminate the guidance for workers, and we take a particular interest in the work that was initiated in that document to relate certain nanomaterials to hazard classifications.