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CATEGORISATION OF MANUFACTURED NANOMATERIALS

WORKSHOP REPORT

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CATEGORISATION OF MANUFACTURED NANOMATERIALS WORKSHOP REPORT

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Also published in the Series of Safety of Manufactured Nanomaterials:

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http://www.oecd.org/chemicalsafety/nanosafety/testing-programme-manufactured-nanomaterials.htm

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The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 34 industrialised countries in North and South America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

The Environment, Health and Safety Division publishes free-of-charge documents in 11 different series: **Testing and Assessment; Good Laboratory Practice and Compliance Monitoring; Pesticides; Biocides; Risk Management; Harmonisation of Regulatory Oversight in Biotechnology; Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents; and Safety of Manufactured Nanomaterials.** More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (www.oecd.org/chemicalsafety/).

This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organisations.

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

The OECD Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology (the Joint Meeting) held a Special Session on the Potential Implications of Manufactured Nanomaterials for Human Health and Environmental Safety (June 2005). This was the first opportunity for OECD member countries, together with observers and invited experts, to begin to identify human health and environmental safety related aspects of manufactured nanomaterials. The scope of this session was intended to address the chemicals sector.

As a follow-up, the Joint Meeting decided to hold a Workshop on the Safety of Manufactured Nanomaterials in December 2005, in Washington, D.C. The main objective was to determine the "state of the art" for the safety assessment of manufactured nanomaterials with a particular focus on identifying future needs for risk assessment within a regulatory context.

Based on the conclusions and recommendations of the Workshop [ENV/JM/MONO(2006)19] it was recognised as essential to ensure the efficient assessment of manufactured nanomaterials so as to avoid adverse effects from the use of these materials in the short, medium and longer term. With this in mind, the OECD Council established the OECD Working Party on Manufactured Nanomaterials (WPMN) as a subsidiary body of the OECD Chemicals Committee in September 2006. 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. This programme 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 is the report of the OECD Expert Meeting on Categorisation of Manufactured Nanomaterials, which was hosted by the US Environment Protection Agency (EPA). It took place on 17-19 September 2014, Washington D.C., US.

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

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Abbreviations

ATS	Alternative testing strategy
BALF	Bronchoalveolar lavage fluid
BIAC	Business and Industry Advisory Committee
CEA	Commissariat à l'Energie Atomique et aux énergies alternatives (France) / Energy and Alternative Energies Commission (France)
CEINT	Center for the Environmental Implications of NanoTechnology
CEPA	Canadian Environmental Protection Act (Canada)
CNT	Carbon nanotube
CVD	Chemical vapour deposition
DLS	Dynamic Light Scattering (Test Method)
EMPA	Swiss Federal Laboratories for Materials Science and Technology
ENMSG	Emerging Nanoscale Materials Specialty Group
EOP	Exposure outcome pathway
EPA	Environmental Protection Agency (USA)
ERDC	Engineer Research and Development Center (USA)
EU	European Union
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act (USA)
FOPH	Federal Office of Public Health (Switzerland)
FSP	Flame spray pyrolysis
GD	Guidance document
GERA-PC	Grouping, equivalence, and read-across based on physical-chemical properties
GHS	Globally harmonized system (for classification and labelling)
HTS	High-throughput screening
ID	Identifier
IH	Inhalation
ISO	International Organization for Standardization

IT	Intratracheal
METI	Ministry of Economy, Trade and Industry (Japan)
MNM	Manufactured nanomaterial
MOx	Metal Oxide with x oxygen atoms
MSDS	Material safety data sheet
MWCNT	Multi-walled carbon nanotube
nanoEHS	Nanomaterial environment, health, and safety
NIOSH	The National Institute for Occupational Safety and Health (USA)
NIST	National Institute for Standards and Technology (USA)
NM	Nanomaterial
NOAEC	No observed adverse effect concentration
NOAEL	No observed adverse effect level
NOM	Natural Organic Matter
NP	Nanoparticle
OEB	Occupational exposure bands
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OM	Organic matter
PBPK	Physiologically based pharmacokinetics
PCA	Principal component analysis
QSAR	Quantitative structure-activity relationship
RCC	Regulatory Cooperation Council (Canada-USA)
R&D	Research & Development
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals (EU legislation)
RPSP	Respirable, poorly soluble particulates
SAR	Structure-activity relationship

SEM	Scanning electron microscope (test method)
SG-AP	Steering Group on Risk Assessment and Regulatory Programs (OECD WPMN)
SNAc	Significant New Activity Notices
SRA	Society for Risk Analysis
STIS	Short-term inhalation study
SUN	Sustainable Nanotechnologies
TEM	Transmission electron microscopy (test method)
TG	Test guideline
TSCA	Toxic Substances Control Act (USA)
USA	Unites States of America
WOE	Weight of evidence
WPMN	Working Party on Manufactured Nanomaterials (OECD)

CATEGORISATION OF MANUFACTURED NANOMATERIALS

Background

1. The overarching goal of the OECD expert meeting was to develop and define categorisation of nanomaterials. Grouping schemes were proposed for purposes of testing, assessing endpoints, read across/Structure-Activity Relationships (SARs) for use in hazard assessment and exposure assessment, risk assessment, and how the schemes can be used to better target risk management. It is most likely not possible to categorise nanomaterials in the same way as chemicals because of their unique physical-chemical properties as well as differences among nanoforms of a chemical species, and between nano and non-nanoforms. Nanomaterials also differ from other chemicals because they often appear as agglomerates or aggregates. Due to nanomaterials' special physicochemical properties (e.g. size and shape) that have to be taken in consideration, they are exceptionally hard to categorise.

2. While this expert meeting largely focused on nanomaterials' specific properties, regulators typically distinguish substances based on a chemical/molecular identity (material) approach as opposed to only a properties approach. Since OECD WPMN's goal was to develop categorisation of nanomaterials to accurately assess them, any categories proposed at the meeting should also consider molecular identity. Specifically, the initially proposed framework of the suggested categorisation scheme started with the following molecular identities: inorganic carbon-based materials, metalloids, metalloid oxides and other metalloid compounds, metals, metal oxides and other metal compounds, quantum dots, and organic compounds. A refined categorisation scheme was developed for each focus area (e.g. fate, hazard) through discussions of physical-chemical characterization, fate, exposure, ecotoxicity, human health toxicity, and risk assessment, and may schemes incorporate multiple properties.

3. This summary is intended to capture the main ideas that were presented and discussed at the expert meeting.

Welcome Remarks and General Introduction

Jeff Morris, Environmental Protection Agency (EPA), US; Mar Gonzalez, OECD

4. Jeff Morris introduced the workshop and explained that the EPA has a New Chemicals programme for assessing new chemicals being introduced into the marketplace, and that they need to be able to distinguish between individual material types in order to focus testing requirements and other measures.

5. On behalf of the OECD, Mar Gonzalez explained that in the past year, the OECD conducted a review of test guidelines (TG) for nanomaterials and more than 150 OECD TGs are part of a legally binding agreement between all of the governments in the OECD today. Groups are aiming at assessing the applicability of the TGs and the guidelines and make sure that they can be applicable to regulatory

processes. The OECD expert meeting was designed to assist the discussions aiming to take a scientific approach for categorising for regulatory purposes.

Introduction to the Workshop

Maria Doa, Environmental Protection Agency (EPA), US

6. The goal of the meeting was to develop a categorisation approach for manufactured nanomaterials in order to improve the decision making process. The end goal was to agree on a set of recommendations on how to move forward so manufactured nanomaterials could be categorised for each focus area for testing, for read across/structure-activity relationships (SARs), for use in hazard assessment and exposure and risk assessment, and to better target risk management.

7. The categorisation scheme would take into consideration the chemical composition and shape and properties such as surface charge of the chemicals. A categorisation scheme needs to be able to be used within a regulatory scheme.

8. The following questions were proposed to be addressed during the expert meeting:

- Is the proposed categorisation scheme presented a reasonable starting point for general categorisation in a regulatory context? For further categorisation?
- Are the proposed categories a reasonable starting point for further sub-categorisation as is?
- What specific activities would be needed to provide sufficient evidence for the use of categorisation for risk assessment and risk management?
- What information is required for assessing the validity of each (sub) category?
- What categories are applicable across multiple endpoints?
- To what extent can SAR be used?
- Are there categories that are relevant for an occupational setting?
- How can the data from the Testing Programme (WPMN) be used to support categorisation efforts?[1]

9. The sessions addressed during the workshop are outlined in this report (cf. Agenda Annex 1).

[1] See Session 1, presentation by Mrs Groenewold.

SESSION 1: CONTEXT FOR THE NEED FOR THE USE OF CATEGORIES, AND PERSPECTIVES ON THEIR APPLICATION TO NANOMATERIALS

Importance of Categorisation for Risk Assessment and Risk Management

Maria Doa, Environmental Protection Agency (EPA), US

10. Categorisation of traditional chemicals has been an important tool for purposes of testing, read across/Structure-Activity Relationships (SARs), and hazard assessment. Not only has this aided in conducting assessments with limited data and reducing the amount of testing required, it has helped promote the design, development, and application of safer chemicals and processes. This latter consideration then has an impact upon the potential risk management tools that would be used to address the chemical. These same benefits are anticipated from a categorisation scheme for manufactured nanomaterials. Categorisation of manufactured nanomaterials will improve risk assessments because it will help reduce uncertainties in both hazard assessments and exposure assessments, and decrease the amount of data needed for individual manufactured nanomaterials.

11. For regulators, categorisation helps to focus the assessment and it will determine early what types of additional data are needed, and adjustments can be made based on this information.

12. Categorisation allows for a more refined assessment of worker and consumer risk. The decision making process can be improved by targeting risk management tools such as lowering uncertainties, identify where more protection is needed, and identify where the risk management action is overly conservative.

Approaches to Develop or Use Concepts of Grouping, Equivalence and Read-Across Based on Physical-Chemical Properties (GERA-PC) of Nanomaterials for their Hazard Assessment in Regulatory Regimes

Takuya Igarashi, National Institute of Advanced Industrial Science and Technology (AIST), Japan

13. Takuya Igarashi's lecture gave a snapshot of OECD member countries' approaches to develop or use GERA-PC (Grouping, Equivalence and Read-Across based on Physical-chemical properties) concepts of nanomaterials for their human health and ecosystem hazard assessments in regulatory regimes. He presented the results of a questionnaire-based survey[2] conducted under the OECD project on Risk Assessment and Regulatory Programmes and ran from October through December 2013. The survey examined the present use of GERA-PC concepts, R&D activities as well as other information on GERA-PC concepts. The preliminary analysis of the outcomes of the survey is presented below, and further analysis of the responses is on-going to identify common issues.

14. There were four specific GERA-PC concepts analysed in the survey:

1) The concept of grouping: This may be a category approach or an analogue approach, where nanomaterials are grouped based on their physical-chemical properties;
2) The concept of equivalence: The equivalence of new and known nanomaterials is assessed on the basis of physical-chemical property criteria;

[2] "Survey on approaches to develop or use concepts of grouping, equivalence and read-across based on physical-chemical properties of nanomaterials for their human health and ecosystem hazard assessment in regulatory regimes", which is expected to be publicly available in 2016.

3) The concept of read-across: This may be a technique of read-across, trend analysis, or QSAR, e.g., data from a nanoform (or a non-nanoform) is read across to another nanoform (or a non-nanoform) of the material; and
4) Any other concept of similar nature.

15. The survey was circulated to OECD delegations, and thirteen responses were received from: Australia, Canada, Denmark, Germany, Japan, Switzerland, United Kingdom (UK), United States (US), the European Union (EU), and the Business and Industry Advisory Committee (BIAC).

16. Some responses showed that GERA-PC concepts were either in use or being prepared for use in hazard assessments in their regulatory regimes. Also, it was noted that various R&D activities aimed at supporting the development of GERA-PC concepts for regulatory purposes.

17. In response to the survey, the EU, Germany, US, and Australia answered that there were some hazard assessments in their regulatory regimes, for which GERA-PC concepts of nanomaterials were employed. It was reported that a classification scheme for nanomaterials developed by the US-Canadian Regulatory Cooperation Council Nanotechnology Initiative (RCC) is considered for nanomaterials. Germany pointed out that there was an example of employing GERA-PC concepts of nanomaterials in the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) governed by the US EPA.

18. Australia, Canada, Japan, Germany, UK, US, and the EU reported that there were some on-going or planned R&D activities on a GERA-PC concept of nanomaterials for their hazard assessment. BIAC (US) reported that there was a project coordinated by a non-governmental research foundation regarding GERA-PC. There were many R&D activities reported and different types of approaches for the projects including (but not limited to) grouping and read-across, grouping and equivalence, biomolecular corona, uniqueness, ranking, definition of mechanistic categories, correlation of physical-chemical properties and biomolecular corona.

19. In addition to answering the questions, the respondents addressed needs and challenges in the development and regulatory implementation of GERA-PC concepts and expressed their views on the limitations of, and alternatives to, those concepts. These responses were mapped to a limited number of issues such as: (1) Scientific challenges; (1.1) Comprehensive and reliable data-sets with standardized testing methods; (1.2) Mechanistic understanding; (1.3) Dealing with surface modifications/properties; (2) Technical challenges, i.e., Sample preparation and material characterization; (3) Regulatory implementation; and (4) Other suggestions.

20. In their responses, Switzerland pointed out that grouping should not be based on a chemical composition approach alone since some nanomaterials show very different physico-chemical properties only depending on minor surface modifications, and Australia mentioned challenges in evaluating the properties of nanomaterials in realistic environmental matrices, and Germany called for efforts to translate research into guidance for assessment.

21. The UK recommended in the questionnaire that further fundamental research, possibly focused on the most commonly encountered/most hazardous nanomaterials, will be needed to accompany the development of approaches. The BIAC suggested that until nano-specific practices are developed, if needed, the OECD Guidance on Grouping of Chemicals, Second Edition [ENV/JM/MONO(2014)4] provides a set of useful approaches that are generally applicable to nanomaterials.

Use of Category Approach and Groupings of Nanomaterials Regionally and Nationally

Panel Discussion
Chair: Ken Moss, Environmental Protection Agency (EPA), US

1. Development of a Classification Scheme under the Canada-United States Regulatory Cooperation Council Nanotechnology Initiative

Brad Fisher, Environment Canada, Canada, and Jim Alwood, Environmental Protection Agency (EPA), US

20. The Canada-US Regulatory Cooperation Council (RCC) was established on February 2011, to increase regulatory transparency and coordination between both countries in a wide range of areas, including nanomaterials.

21. Twenty nine initiatives were launched at the RCC, including one on nanotechnology. The RCC Nanotechnology Work Plan[3] is now complete and both Canada and the US are implementing the new approaches and lessons learned in risk assessments of nanomaterials. The Nanotechnology Work Plan aimed to better align the regulatory environment between Canada and the US, increase regulatory transparency and coordination between the two countries, develop systemic solutions, and provide a strong foundation for ongoing cooperation. The RCC encouraged strong stakeholder engagement in each work plan and regulators were challenged to ensure that outcomes were tangible and relevant to the regulated community.

22. The overall outcome of the Nanotechnology Work Plan was to be able to share information and develop joint approaches on regulatory aspects of nanomaterials. The Work Plan was important because nanomaterials are considered to be new substances regulated in Canada and the US under the Canadian Environmental Protection Act (CEPA) and Toxic Substances Control Act (TSCA).

23. Five RCC nanotechnology work plan elements were issued:

1. **Principles**: The identification of common principles for the regulation of nanomaterials to help ensure consistency for industry and consumers in both countries

2. **Priority-Setting**: The identification of common criteria for determining characteristics of industrial nanomaterials of concern/no-concern (First Step: Classification)

3. **Risk Assessment/Management**: The sharing of best practices for assessing and managing the risks of industrial nanomaterials

4. **Commercial Information**: The characterization of existing commercial activities and identification of gaps and priorities for future knowledge gathering for industrial nanomaterials; and

5. **Regulatory Cooperation in Areas of Emerging Technologies**: The development of a model framework providing key elements and approaches to regulating products and

[3] Dodds, K., Geller, H., & Malanoski, M. (2012). Nanotechnology Work Plan. RCC Nanotechnology Working Group, (pp. 1-3). Retrieved from http://actionplan.gc.ca/grfx/BAP-RCC/Nanotechnology_ENG.pdf

applications of emerging technologies with respect to potential impacts on the environment, human health, food, or agriculture.

24. The Work Plan developed a classification scheme to inform stakeholders that not all substances that fall within the nano-range exhibit unique properties (e.g., organic dyes/pigments). The scheme could enable the programmes to communicate which nanomaterials require nano-specific information for risk assessment purposes. The classification scheme was also developed to progress from using substance-specific data to using analogue information, whenever appropriate, in order to reduce regulatory burden on stakeholders by leveraging existing datasets. The classification scheme that was developed is *not* a hazard prioritisation tool, and the Work Plan expects that the classification scheme will feed into discussions when developing hazard-driven lists of concern/no-concern.

25. To develop the scheme, the group looked at risk assessment and risk management, the commercial information available and different uses of nanomaterials. Prior to the RCC, the US EPA was sorting nanomaterials according to similarities in chemical composition. The RCC discussed the chemical composition approach and other types of approaches such as those based on types of exposure, SARs, use profiles, and physical-chemical properties. Stakeholders agreed that a classification scheme based on similarities in chemical composition was most appropriate since it provides consistency with current chemical-based regulatory frameworks; is consistent with international regulatory and scientific activities including the OECD Council Recommendation [C(2013)107]; and is sufficiently flexible/broad to be a good starting point. The US EPA preliminary classes were refined using up-to-date information from both Canada and US Regulatory notifications, expert opinions, and multiple stakeholders.

26. The RCC is not just about regulators sharing ideas but it is also sharing ideas with the regulators. There was transparency in the decision making process and the RCC looked at how better to inform stakeholders about substances in the nano range to figure out how to better target information needs.

27. The classification scheme for nanomaterials is illustrated in Figure 1:

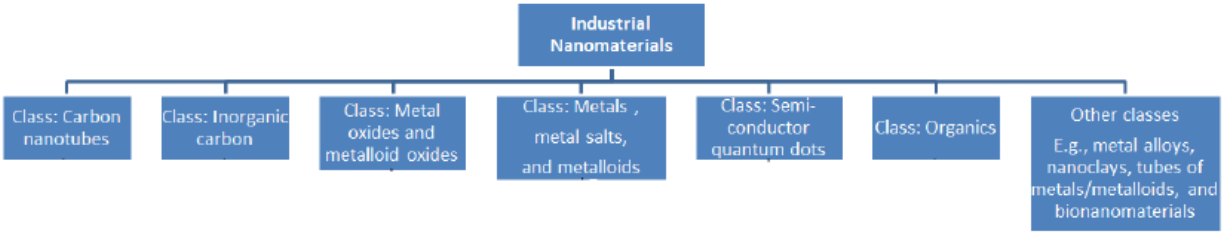


Figure 1. Proposed RCC Nanomaterial Classification Scheme.

28. Carbon nanotubes were separated from inorganic carbon to group nanomaterials with high aspect ratios, which may share similar properties/behaviour (e.g., tubes and fibers). The class for organics includes those that exhibit unique properties (e.g., nano-cellulosic materials). Hybrid materials were not captured in the classification scheme. The other classes included inorganic carbon, metal oxides and metalloid oxides, metals/metal salts/metalloids, semi-conductor quantum dots, organics, and other classes.

Conclusion

29. Stakeholder feedback from the RCC indicated that classification based on similarities in chemical composition is a good starting point to improve regulatory consistency between the two countries. Stakeholder feedback provides the beginnings of a framework to select analogues within classes to leverage relevant data.

30. The categories that were developed are flexible and the Programmes are participating in forums (e.g., the RCC workshop) and meeting with other countries to discuss the proposed approach. The categories will be refined or amended as the knowledge base increases and joint case studies are being proposed to explore the applicability of the classification scheme in a regulatory setting.

31. Brad Fisher reported that Canada is exploring the applicability of the classification scheme by collecting literature within a class (metal oxides) to learn about patterns in physical-chemical properties and environmental fate and releases. Canada is also comparing the classes with the use information, collected under the RCC, to determine if patterns arise that can inform release and exposure scenarios in risk assessments. Canada is informing the Canadian regulatory programme by preparing a guidance document (advisory note[4]) and clarifying when manufactured nanomaterials require notification and under which circumstances the Programmes will request additional nano-specific information. The classification scheme is an integral part of this guidance since it is used to identify which nanomaterials typically need nano-relevant considerations and which do not for the purposes of risk assessment.

32. Jim Alwood reported that the US EPA is developing the applicability of the classification scheme and increasing capability to use structural analogy/read-across evaluation of classes of nanomaterials by: requiring additional physical-chemical property data for nanomaterials such as carbon nanotubes and quantum dots, requiring toxicity studies for new chemical nanomaterials, and collecting published studies for nanomaterials to help fill data gaps.

2. EU REACH Perspective of Categorisation, Grouping and Read-Across

Jenny Holmqvist, European Chemicals Agency (ECHA), EU

33. REACH is an EU horizontal regulation which set out criteria for ensuring the safe use of chemicals (EC 1907/2006). It contains the following main elements; Registration, Evaluation, Authorization and Restriction of chemicals, and entered into force on 1 June 2007.

34. Currently (2014), based on concerns expressed by EU Member States, the European Parliament and the European Council, REACH is undergoing a review in the context of nanomaterials explicitly addressing the information requirements as laid out in the Annexes to REACH. This is to ensure that nanomaterials are adequately addressed by REACH and their safe use can be demonstrated. This work has in particular identified a need to find pragmatic and scientifically justified approaches to categorise and group nanomaterials, for example, to minimize unnecessary animal testing and cost for industry. However, any approach must not compromise on the safe use of these materials in the EU.

35. Within the implementation of REACH, ECHA has found it difficult to identify substances containing nanoform(s) as they are poorly indicated by the registrants, and each registration dossier will have to be carefully scrutinised to gain an understanding whether registration (also) addresses as a nanomaterials or not.

36. Categorisation, grouping, and read-across are recognized under REACH as adaptation to the information requirements where a test on one substance or form can be used to cover a data gap on another substance or form. Grouping is used when there is enough information to ensure that the data generated can be applicable to a set of substances. This approach is sometimes used for petrochemicals under well-defined conditions. The justification for both the use of read across and grouping as adaption to fulfil the information requirements in REACH is never solely based on chemical similarity but always combined with a proper understanding of sameness of the toxicokinetic behaviour.

[4] Environment Canada. (2014). Assessment of nanomaterials under the New Substances Notification Regulations (Chemicals and Polymers). New Substances Program Advisory Note, 1-4. Retrieved from https://www.ec.gc.ca/subsnouvelles-newsubs/default.asp?lang=En&n=53527F9D-1

37. In the EU, read-across and grouping is done as a part of performing a hazard characterisation, where there is typically a data gap because a test is missing. Read-across should not be used to predict toxicity for an entire endpoint or hazard level. This means that it is not possible to conclude on mutagenicity of a substance based on a conclusion from other substance but instead the issue is whether data from e.g. a micronucleus test can be used to bridge a data gap for another substance.

38. Safety must be ensured and demonstrated for each nanoform. One question that arose is if data generated from the bulk form should be used for all nanoforms and if not, which nanoforms can be used to generate data applicable to other nanoforms. Such conclusion is decided on case by case where each read across has to be scientifically justified.

39. There are potential common denominators for read-across, including bio-elution, coatings, and toxicokinetics. Toxicokinetics is crucial to understand better how one nanoform might react differently from another nanoform. There is a need to reach a common agreement on criteria for judging this and ECHA has advanced significantly on how to perform the assessment and guide registrants on how this could be done for normal substances.

Conclusion

40. The final goal of REACH is to be able to demonstrate safe use of chemicals. Further discussions will take place together with EU Member States, stakeholders and industry to develop a pragmatic and acceptable framework that will not compromise on safe use whilst allowing for flexibility to minimise the use of animals and costs. The discussions at the workshop will help in bringing the international perspective on the issues and also highlight where potential differences of the scope and purposes of conducting the read-across and grouping.

Physiochemical Characterisation of Nanomaterials (for Grouping)

Monique Groenewold, National Institute for Public Health and the Environment, the Netherlands

41. In June 2014, the OECD expert meeting on "Nanomaterials Physical-Chemical Parameters: Measurements and Methods" was held in Washington DC, USA. About 40 experts from member countries and industry were present to assess the methods applied for testing the physical-chemical endpoints in the Testing programme. The objective of the June 2014 meeting was to identify the appropriate test methods for physical-chemical parameters for manufactured nanomaterials and to determine which test methods are appropriate for both a particular parameter and particular types of nanomaterials. The assessment of submitted physical-chemical data included available data from the 11 nanomaterials in the Testing programme and assessed for validity, where the OECD developed an online questionnaire for the assessment of this data. During the meeting the experts present were able to make very concrete recommendations to the WPMN for modifying existing test guidelines and developing new test guidelines for nanomaterials.[5]

42. Physical-chemical data from the Testing Programme was assessed by experts prior to the meeting. At the time of the meeting, it was noted that not all the data on physical-chemical properties was yet

[5] OECD 2015. Physical-chemical Parameters: Measurements and methods relevant for the Regulation of Nanomaterials: OECD Meeting. Declassification process.

available. 24 test methods were evaluated, none of which were OECD guidelines. ISO standards were used in physical identification of particle shape[6], aggregation[7], and porosity[8].

43. The complexity of grouping of nanomaterials is due to the physical-chemical parameters that may affect fate and exposure, kinetics, and/or hazard. The physical-chemical parameters may include size, aggregation/agglomeration, shape, coating/surface functionalization, surface chemistry, surface charge, dissolution rate, composition, reactivity, photoreactivity, etc. There is limited knowledge on the relation between physical-chemical parameters and endpoint test results. Variation in physical-chemical parameters can affect fate and exposure, kinetics, and hazard of a nanomaterial compared to normal chemicals.

44. The preliminary results applied on the test methods indicate that almost all were considered suitable and sufficient for only the specific parameter and nanomaterial tested (2/24), specific types of nanomaterials / specific conditions (14/24) and broad application (6/24). Three different test methods for size measurement (TEM, SEM, DLS) were assessed by the experts. TEM and SEM were given the maximal validity score of 10 by experts but it was noted that there were limitations because the methods are resource-intensive. DLS was given a maximal validity score of 6, noting that e.g. it is not able to discriminate between particles and aggregates and has shortcomings for polydisperse materials. A number of the standardised methods were adapted for testing nanomaterials within the OECD Testing Programme.

Physical-chemical parameters: measurements and methods relevant for the regulation of nanomaterials/ Highlights from the OECD workshop

45. Surface properties and parameters relevant for fate and exposure were discussed in the June 2014 OECD meeting. Particle dispersion protocols are essential to understanding size and size distribution data and there should be a selection of appropriate techniques by a decision tree analysis. The workgroup discussed aggregation and agglomeration and whether there is a need for a new test guideline on aggregation.

46. The workgroup also discussed chemical composition, crystallinity, and crystal structure. Guidance is needed on measuring chemical composition, crystallinity, surface property and their applicability for nanomaterials.

47. Regarding methods to measure surface charge there were no recommendations at this point in time. ISO has developed a standard for zeta potential, also known as electrokinetic potential, measurement by light.

48. It was recommended that OECD develops an outline for dustiness and also general guidance based on the chemical identification descriptors/behaviours that lead to the selection of techniques/methodologies for specific chemical characterization

49. Surface reactivity and photocatalysis were also discussed. Photocatalysis use screening methods for photoactive materials. There is a need to consider solubility, size, absorption, agglomeration, etc., in a decision tree, prior to making decisions. Parameters are relevant for fate and exposure.

50. OECD will continue the assessment of data of the Testing programme and looking for pragmatic approaches to deal with grouping. One proposal is to start grouping data based on endpoints and based on the limited variation in physical-chemical properties, the likelihood of trends between physical-chemical and exposure, kinetics and hazard, targeted testing, and read-across by interpolation. It was suggested to

[6] ISO 9276- 6:2008
[7] ISO TR 13097: 2013
[8] ISO 18757:2003

start the assessments should start from the study of the available data and the constraints they present, and then to consider tests that can help to fulfil the lacks and then the constraints.

Novel Properties as an Organizing Concept for Categorising Manufactured Nanomaterials for Regulatory Purposes

Mark Wiesner, Duke University, US

51. Some materials exhibit properties at the nanoscale that are different from the properties observed for bulk materials. Surface affinity is an example of a novel property and is a characterization parameter that can be easily evaluated as a functional assay related to: melting point, heat of fusion, strength, electrical conductivity, heat conduction, photocatalytic, dissolution, optical properties, interfacial reactivity, and magnetic properties. Such novel properties are responsible for both the purposeful interactions that drive performance of manufactured nanomaterials (MNMs) as well concern and investigation with regard to collateral nanomaterial environment, health, and safety (nanoEHS) concerns. These properties will drive interactions and transformations within environmental compartments and biota, and they will be the basis of decisions to develop and utilise, or abandon, individual MNMs.

52. Nanomaterial categorisation scheme should be based on the novel properties exhibited by, and often specifically exploited in, MNMs. MNMs made from toxic materials (metals in particular) can be predicted from redox pairs, which are system-dependent. To determine redox and toxicity, there are now heat maps that show when something is made from toxic materials and in the heat map, red shows areas of concern. The criteria utilised in determining which materials to develop, are performance based which will often be related to the effective harnessing of these novel properties.

53. It is important to determine a categorisation scheme so that nanomaterials can be grouped in a manner that will be meaningful in predicting risk. Both exposure and hazard need to be assessed to assess risk.

54. Proposals for categorisation fall into the three categories: physical-chemical characterisation, hazard potential, and exposure potential. Physical-chemical characterisation could be based on composition, shape, band gap, and may include high-throughput screening (HTS) and models. Hazard potential could include tests for biomolecular, cellular, organismal, population, or ecosystem responses (which may include HTS and models). Exposure potential could be based on release mechanisms, product/matrix, pathways, persistence, and transformations.

55. Arsenic absorbed by iron oxide particles is given as an example when normalising is made based on surface area opposed to the mass. In that case, particles behave in the same way as the bulk, and the smaller particles are able to absorb similar amounts of iron oxide particles. New reactions can occur during the reactions accompanied with unexpected risk.

56. Categorisation is complex. One of the areas of confusion is that physical-chemical properties can be mapped into risk, but half of the properties are a function of the system in which the nanomaterials are placed[9], and it is not a characteristic that can be broken apart from the nanomaterials themselves.

57. Functional assays are needed to assess nanomaterial risk (often done in toxicology) and largely absent by the fate and transport aspect of exposure. There is a hierarchy and notion of functional assay and

[9] For example, type of products, life cycles, product use, etc.; and system properties (pH, natural organic matter (NOM), ionic strength, etc.)

the question is: what measurements to use at the different levels? Mark Wiesner posed the question of using the idea of novel properties as the first level of evaluation or characterisation of nanomaterial instead of physical-chemical properties. A focus on novel properties may incorporate the critical issue of complexity into categorisation of materials, allowing for the development of categories of what can be expected in terms of important transformation reactions. Materials with specific antimicrobial activity may transform similarly in similar surrounding media. In this regard, traditional methods of categorising materials based on similar core composition, for example, may align and complement a categorisation scheme that focuses on novel properties.

58. A mechanistic understanding of these novel properties will likely be critical to predicting their behaviour not only in the engineered systems in which they are being designed to perform, but also within the natural systems that will be the ultimate sink/receptors for released nanomaterials and their transformation products.

59. Categorising materials according to novel property bridges the discussion of what the nanomaterials are being utilised for in the first place, with consideration of what collateral impacts may be expected. This consideration is relevant both mechanistically and practically.

60. Novel properties may be be associated with exposure pathways, the manner in which nanomaterials are applied (surface vs. embedded), structural reinforcement – related to the novel property to be extracted, and the value chain for MWCNTs (used as an example).

61. Mark Wiesner presented a characterisation scheme shown in Figure 2. Tier 0 would include assessing novel properties.

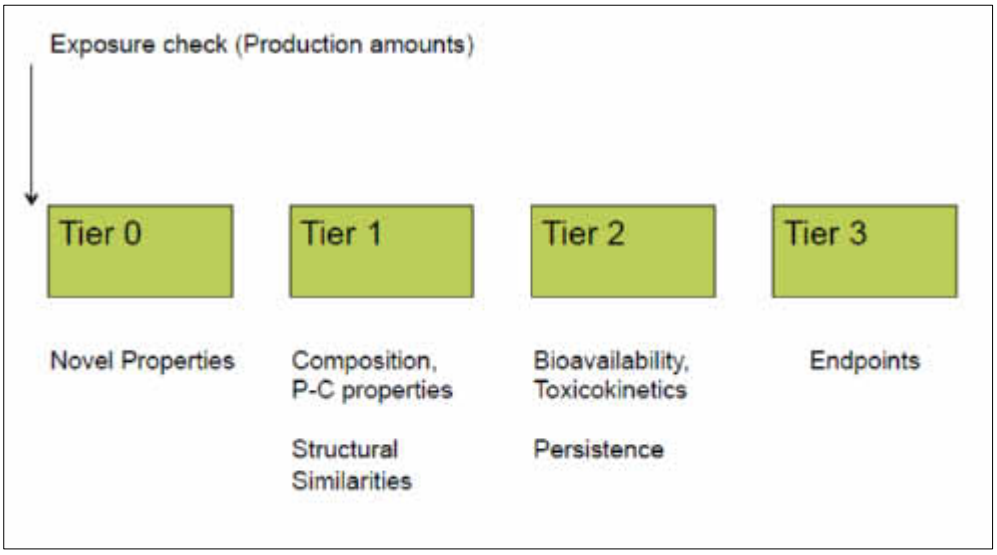


Figure 2. Proposed Tiers by Duke University and CEINT

62. He proposed the following list of novel properties of materials that could be used to categorise materials. Note that some nanomaterials may be represented in multiple categories.

- Catalysis
- Redox properties
- Photoactivity
- Mechanical strength
- Antimicrobial properties

- Adsorption
- Semiconductor and fluorescent properties (quantum confinement and band gap)
- Magnetic properties
- Shape (e.g., cavities for programmable drug delivery or hydrogen storage)
- Heat conductivity/insulation
- Optical properties (UV block, transparency)
- Superconduction.

Novel Techniques for Toxic Nanoparticle Categorisation

Suman Pokhrel, University of Bremen, Germany

63. The unique properties of nanoparticles can have adverse bio-impacts. The safe utilisation of nanotechnology governing environmental health and safety is a multidisciplinary task that goes beyond the traditional risk assessment procedures. One approach for countering the impacts is to probe the number of newly emerging nanoparticles and their wide range of properties by using a high-throughput screening (HTS) platform that utilises nanoparticle libraries exhibiting a range of compositions and combinatorial properties to study their relationship to a specific injury response as well as exploiting computational methods to assist in the establishment of quantitative safer-by-design approaches.

64. In the development of conceptual paradigms in environmental and health assessment, it has been recognised that the physical-chemical properties of MNMs play a key role in their fate and transport, human and environmental exposure, and hazard generation. As an attempt, 24 metal oxide nanoparticles (NPs) from different groups and periods from the periodic table were chosen and assessed based on their potential overlap of conduction band energy and cellular redox potential (-4.12 to -4.84 eV). The assessment of the cellular response was performed using mammalian cell line, sea organism (zebra-fish), and bacteria 1-3. The reasonable correlation observed within these wide test models provided clear evidence that these 24 NPs could be categorised as toxic or non-toxic according to their specific physical-chemical properties. Results acquired from these models showed (1) conduction band energy overlapping with the redox potential in the cellular interior are toxic, (2) metal oxide NPs ionising in the cells and chelating with the biological species are toxic, and (3) metal oxide NPs having hydration energy > -70eV are toxic. The acquired knowledge in this area (through extensive categorisation of the NPs) will offer new opportunities to remediate environmental toxins through multi-disciplinary scientific research. The group needs to have integrative and collective knowledge to better understand the chemicals. There needs to be characterisation of particles.

65. The compositional and combinatorial libraries are important and the meeting should have addressed them. For instance, silicon has many types of properties. There are many descriptors and there are many data gaps. One single aspect should be chosen and then the particles should be characterised according to the framework.

66. The flame spray pyrolysis (FSP) set up contains different types of spray, and very small particles ranging from a nanometer to a micrometer. The small particles do anything they want within the parameters of the flame. When utilising the double FSP for heterojunction design, temperature will be much lower at the heterojunction of the flames than at the bottom if the nozzles are brought together.

67. When testing was done with fish embryos, there was a more predictive effect in the embryo than other mechanistic toxicological pathways. There is documentation about the work at the University of Bremen.

Suman Pokhrel also presented discussion about the following:

- Energy range of biological active redox couples in cells
- Metal oxide selection for toxicity
- Conduction band vs. biological redox potential
- Heat map display of MOx HTS in raw cells
- Metal oxides dissolution assessment (the particles that are dissolving are ultra toxic)
- Metal dissolution – ZnO and CuO are toxic
- Hydration energy: The hydration energy range of -70 eV to 0 eV are where all toxic chemicals are found.

68. Dissolution and overlapping with redox potential are the two ways that chemicals were characterised for toxicity. Particles are also completely involved in the toxicity. The group may be able to categorise particles. Toxic particles should be categorised.

Conclusion

69. Categorisation should be based on hypothesis formulations, physiochemical characterisation, response assessments, mechanism of the injury response, and toxicity.

The Use of Alternative Testing Strategies to Advance Risk Analysis of Nanoscale Materials

Jo Anne Shatkin, Vireo Advisors, LLC, US

70. The Emerging Nanoscale Materials Specialty Group (ENMSG) of the Society for Risk Analysis (SRA) held a workshop (September 15-16, 2014) to investigate the use of alternative testing strategies (ATS) for exposure and risk analyses of nanoscale materials (www.srananoworkshop.org). The workshop convened a diverse group of international experts to discuss how current and evolving *in vitro* assays might be applied in a "multiple models" approach to inform risk assessments of nanoscale materials, including assessing hazard, potency, and exposure potential.

71. A Pilot Project entitled *Alternative Testing Strategies: State of Science for Read Across and Risk Assessment Guidance* was created. Three white papers were presented at the workshop addressed human health, ecological and exposure considerations for risk assessment of nanomaterials, and considered alternative strategies.

72. A case study of nanoscale Titanium Dioxide (n-TiO_2) was examined and there was an analysis of 1,820 results from 96 publications of *in vitro* and *in vivo* studies that were incorporated in a database. A variety of TiOx types were reported. The top five endpoints studied were: cytotoxicity, oxidative stress, immunology, genotoxicity, and viability (*in vivo*).

73. The participants were charged to evaluate how the findings from ATS could be used in combination with conventional testing methods to reduce uncertainty and better inform screening-level risk assessments (with respect to human health, ecosystem health, and exposure). Also they should think of the additional work needed in the near-term (3-5 years) so that ATS can better support risk assessments that inform screening-level risk management decisions (with respect to human health, ecosystem health, and exposure).

Recommendations

74. Five main recommendations were made at the workshop:

1. Data sharing, including negative findings.
2. Data mining, using protocols for assessing the quality of existing *in vitro*, human, and *in vivo* data, for screening information.
3. New standards of practice for environmentally relevant testing.
4. Tools adopted from the risk analysis toolbox to include tiered approaches, statistical, and mechanistic approaches. Start with the K (kinetics) in PBPK modeling.
5. Use of ATS taking into account their limitations.

75. The following are the recommendations for 3- to 5-year results:

1. Link Adverse Outcome Pathways into ATS protocols
2. Develop Exposure Outcome Pathways (EOPs) that capture transformations of particles in key scenarios with underrepresented endpoints
3. Incorporate assays with long-term relevance into ATS
4. Integrate concept of influence of standardized biological fluids and corona issues
5. Encourage risk-contextualized relevance in basic research.

76. ATS for human health risk assessment is a good place to start and it is an ongoing work in Europe. It provides a foundation to move toward more complex issues where there is less information.

77. The exposure characterization framework for assessment has the following four stages:

Stage 1: Exposure Assessment: Develop scenarios for exposure and understand the areas of concern across the lifecycle of a product. There needs to be a context to the physical-chemical characterization.

Stage 2: Context-specific nanomaterial (NM) characterization

Stage 3: Tailor an *in vitro* testing strategy to exposure conditions.

Stage 4: Evaluate the Strength of Evidence for Exposure.

78. Jo Anne Shatkin also presented strength of evidence matrix for categorisation. The matrix contained different tests and examined each test within the scope of exposure source, dose, transformations, and biological response. An Ecological Impact Strategy was also presented. The strategy is currently in progress but it examines global considerations and prioritises the major steps in the impact strategy. The strategy begins with the dynamic energy budget and works toward more complex testing.

Eco-ATS for weight of Evidence Risk Assessment

79. ATS can be used for population (e.g., bacteria) growth and select assays. The five-year needs to improve ATS include establishing conventions for controls (MNM and assay), articulating the screening, SAR, prediction and confirmation, prioritising compartments/services/receptors, and evaluating ATS potential more broadly. For ecosystems, there is a need to differentiate ATS from ATM. "Alternative" is a tiered ecosystem approach, and "Additional to" individual organism testing can be used to inform Read Across.

80. The next step is that the workgroup will produce a workshop report and present findings to the OECD, SRA, and co-sponsoring organisations. The workgroup will finalise the OECD/SRA Pilot Project on ATS in Risk Assessment for MNM. The final step will be to publish the white papers, case study, workshop report, and perspectives.

Grouping of Nanomaterials for Health Assessment – Genotoxicity

Maria Donner, Business and Industry Advisory Committee (BIAC)

81. One of the main focuses of the OECD expert meeting on Genotoxicity[10] was to discuss the current genotoxicity data as well as the adaptation of new chemical guidelines to the OECD test guidelines. The OECD guidelines should and can be adapted to accommodate nanomaterials. However, genotoxicity data are insufficient and inconsistent. For example, current data show largely positive results for the *in vitro* comet assay and a limited array of other genotoxicity tests. Additional data from genotoxicity are greatly needed to build up the training set and data that can be used for risk assessment. The ultimate goal is to use the data generated as well as new information on nanomaterials' unique physical/chemical properties to revise the OECD guidelines.

82. The creation of categories will help in determining exposure and testing conditions as well as building a training set for computational approaches. Donner noted that the categorisation is likely to be driven based on aspects other than genotoxicity (despite of its importance) such as physiochemical properties.

Health Effects of Nanomaterials and their Regulatory Implications

Tom Van Teunenbroek, National Institute for Public Health and the Environment, the Netherlands

83. Tom Van Teunenbroek spoke about the need for representative health data of high quality for nanomaterials. There are currently large data gaps and a lack of quality control in testing. There is a fairly large amount of nano-toxicity testing that focuses on *in vitro* testing. However, the quality of the *in vitro* testing is questionable as it often does not account for the nanomaterial's transformation throughout its lifecycle and there are inconsistencies in the testing methods. *In vivo* testing on nanomaterials is important in order to find the relationship between their *in vivo* behaviours and physical/chemical properties, but testing must be performed consistently and accurately. This will help assess nano-toxicity, which can in turn lead to predictive models for nano-toxicity assessment.

84. The OECD has begun to coordinate the testing on nanomaterials in order to determine the implications of nanomaterials on human health. These tests have largely focused on the inhalation exposure route, as that is perceived to be the most critical route of exposure. It has been found that respirable nano dust is of particular concern since it is known to be highly persistent in biological systems.

[10] OECD, 2014. Genotoxicity of Manufactured Nanomaterials: Report of the OECD expert meeting. OECD Series on the Safety of Manufactured Nanomaterials. No. 43 - ENV/JM/MONO(2014)34

Overall systemic toxicity evidence is generally low but evidence has indicated brain toxicity, similar to manganese toxicity, as well as long-term issues with lymph nodes. Lastly, Van Teunenbroek noted the importance of testing micromaterials alongside nanomaterials for data comparison.

Grouping of Nanomaterials for Health Assessment in a National or International Regulatory Context

Jun Kanno, National Institute of Health Sciences, Japan

85. Dr. Jun Kanno addressed the need for grouping nanomaterials for health assessment. The toxicity for engineered nanomaterials is largely unknown; however, it is very likely that they show low acute toxicity especially when they are biopersistent and insoluble. The proposed study direction covers both those for which mechanism of toxicity is known and unknown. One known mechanism is the fiber carcinogenesis well applicable to biopersistent fibers with size and shape similar to mesotheliomagenic asbestos. The other known phenomenon is shown by thorotrast that such biopersistent nano-sized particle ends up in the body, especially in the reticuloendothelial system and is not released. The unknown mechanism still has to follow the basic toxicology approach by using animal experiments with human relevant routes of exposure. These experiments consist of inhalation studies, which use the Taquann method and Taquann Direct Injection Whole Body Inhalation system. The Taquann method is based on liquid phase dispersion and filtration and critical point drying to avoid surface tension. This method is able to generate well-dispersed nanomaterial without aggregates/agglomerates. Inhalation tests were conducted on C57Bl/6 mice at the concentration of 1 or 2 mg/m3 of the nanomaterial (Mitsui MWNT-7) aerosol for 2 hours/day per week for 5 weeks, resulting in lung burden of 4μg/lung in the group of 2 mg/m3 at the end of exposure and then followed up for up to 52 weeks. The length distribution of the single fibers in the lung did not change throughout the experiment. Histology showed that single fibers reached the alveolar spaces without proximal lesions such as epithelioid cell granulomas. Fibers are also found in the parietal pleura near/above the stoma where submicroscopic lentiform lesions made of fiber-laden phagocytic cells and lymphocytes are formed, covered by a layer of activated mesothelial cells. In conclusion, the Taquann method is an effective method for testing the health effects from the inhalation of nanomaterials and is applicable to a variety of different nanomaterial samples. Lastly, it is affordable, easy to operate, and no sample is lost after filtration.

Grouping of Nanomaterials by Release Type

Thomas Kuhlbusch, Institute of Energy and Environmental Technology, Germany

86. The current assessment of exposure to nanomaterials is mainly based on direct measurements of nanomaterials in their corresponding exposure media. However, taking direct measurements for each nanomaterial is tedious, costly, and nearly impossible. As an alternative, models need to be applied to assess the exposures of nanomaterials. In order to accomplish this there is a need for more basic data on the release of nanomaterials and a more accurate way to predict the likelihood of exposure without knowledge on possible release rates.

87. Thomas Khulbusch recommended grouping nanomaterials by release type, as it is easily linked to exposure through modeling. Modeling by release type will capture the nanomaterial's exposure through its entire lifecycle (production, processing, use, and end of life).

88. Grouping by release needs testing of the release processes. These can include mechanical processes (e.g., cutting, drilling), thermal processes (e.g., incineration), chemical processes (e.g.,

dissolution), and mixed processes (e.g., sanding, which is a mechanical and thermal process). He performed a series of tests to determine the exposures from sanding. Numerous variables influence the release process of sanding, such as sanding speed, grit size, heat production, the matrix material, and the properties of the nano objects, etc. For the test the sanding parameters were set and multiple labs duplicated the tests. The results from the testing varied greatly in a single lab as well as between the other labs. Possible reasons may be the design of the setup, the flow regimes, and/or the position and design of the sampling points.

Conclusion

89. It is nearly impossible to test all nanomaterials and the products in which they are used for all possible release scenarios. Therefore, a grouping or categorisation of nanomaterials is needed. However, the following questions still need to be addressed to allow for grouping:

1. Which release mechanisms/processes can be differentiated and possibly used for grouping in view of release probabilities and rates?
2. How can the link from release (testing) to exposure be established and used for grouping of exposure scenarios?
3. Which metric/particle parameter has to be used in view of sensitivity and possible impacts?

Can a Grouping Approach Help Solve Some Key Nanomaterial Exposure Assessment Challenges?

Charles Geraci, Nanotechnology Research Center, US

90. Charles Geraci discussed grouping nanomaterials for exposure assessments when the nanomaterials are contained in different mediums (air, water, or soil). Exposure assessments are important for accurate risk characterization and the development of risk management strategies. The exposure of nanomaterials throughout their entire lifecycle affects many populations, such as consumers, and professional (researchers, manufacturers), etc.

91. There are two types of exposure assessment strategies: receptor-based and contaminant-based. Receptor-based assessment relies on identifying the exposed population, exposure scenarios, and the medium containing the nanomaterial. Contaminant-based groupings rely on physical/chemical properties, the transformation of the nanomaterial, and the dose rate and relevance. Both approaches require gathering data on past and current nanomaterials. It is important that data be collected on the most commonly used nanomaterials which still need to be determined. These data will help connect key exposure assessment elements for single or similar nanomaterials as depicted in Figure 3.

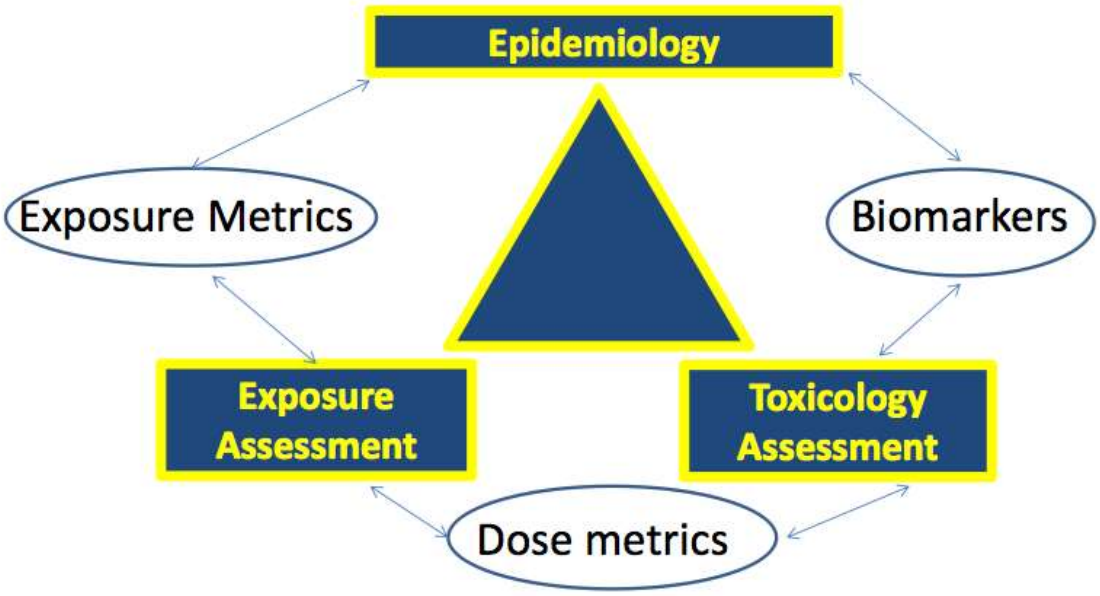


Figure 3. Relationship between epidemiology, toxicology assessment and exposure assessment.

92. Ultimately, the goal is to create a matrix consisting on populations matching with groupings of nanomaterials and in the meantime weighted by the nanomaterial's parameters, such as production volume and the nature of the product using the nanomaterial. It should also be noted that additional factors such as agglomeration/deagglomeration, transformation, matrix degradation, and bioavailability will impact exposure assessment in both the human and environmental sectors, but will likely need to be addressed differently. Future work includes determining mixed-nanomaterial exposure scenarios, meaning exposure to consumers and workers, as well as identifying high-priority manufactured nanomaterials and connecting health assessment with exposure assessment.

SESSION 2: RISK ASSESSMENT AND RISK MANAGEMENT

Risk Assessment: Utilization of Categories in Risk Assessment

Panel
Co-chairs: Yasir Sultan, Environment Canada, Canada, and Maila Puolamaa, European Commission, EU

The Use of Categories in Risk Assessment: A perspective of the WPMN's work on Risk Assessment and Regulatory Programmes

Yasir Sultan, Environment Canada, Canada/ Chair of the OECD WPMN Steering Group on Risk Assessment and Regulatory Programmes

93. Yasir Sultan said that the objective of the OECD project on *Risk Assessment and Regulatory Programmes* (SG-AP) is to support the *OECD Recommendation of the Council on the Safety Testing and Assessment of Manufactured Nanomaterials*[11]. The Recommendation states that nanomaterials be regulated using the existing regulatory chemical framework, but regulations might need to be adapted to account for nanomaterials' unique properties. The regulatory frame defines the (un)acceptable risk level and takes into consideration the following factors: identification, physical-chemical properties, fate in the environment, human health effects, environmental effects, exposure pathways to humans and the environment, as well as others.

94. Chemical-based frameworks must encompass nanomaterials' unique properties and behaviours and utilise information from multiple data-sets. While categorisation is a helpful tool, it should not be applied to all nanomaterials or endpoints and will not replace e.g. substance-specific risk assessments or parts thereof. There will not be one overarching categorisation scheme to regulate nanomaterials; instead there will be a series of categorisation schemes, which will be picked based on the needs of each nanomaterial. Currently the OECD is exploring how physical/chemical data are being used in ecotoxicity and human health categories. There is also work on using alternative testing strategies for categorisation and determining, as an example, if dissolution/solubility data on nano-silver can be used to generate rules for risk assessors. Lastly, additional work needs to be done to adapt existing regulations to better regulate nanomaterials. The next steps will include identifying regulatory needs specific to the risk assessment, determining the applicability of the current methodology, adapting existing regulations, and applying them to nanomaterials.

The ITS-NANO Approach to Risk Assessment, including Grouping and Ranking

Vicki Stone, Heriot-Watt University, UK

95. Vicki Stone, from the ITS-NANO Project, stated that their goal was to develop an intelligent testing strategy for engineering nanomaterials, meaning it will accurately, effectively, and efficiently assess

[11] http://www.oecd.org/newsroom/oecd-countries-address-the-safety-of-manufactured-nanomaterials.htm

nanomaterials. The strategy includes the risk evaluation paradigm based on physical/chemical characterization, exposure, and hazard.

96. The short-term goal in developing this strategy is to understand the connection between physical/chemical characterization, exposure, and hazard to enable grouping and ranking. The long-term goal is to develop a modelling approach for risk assessment in order to reduce the amount of testing. ITS-NANO's first steps were to define each ID, prioritize research needed to deliver each ID, identify aspects relevant to grouping/ranking and modelling, and relate it to the regulatory frameworks. These goals are outlined more specifically in **Figure 4**.

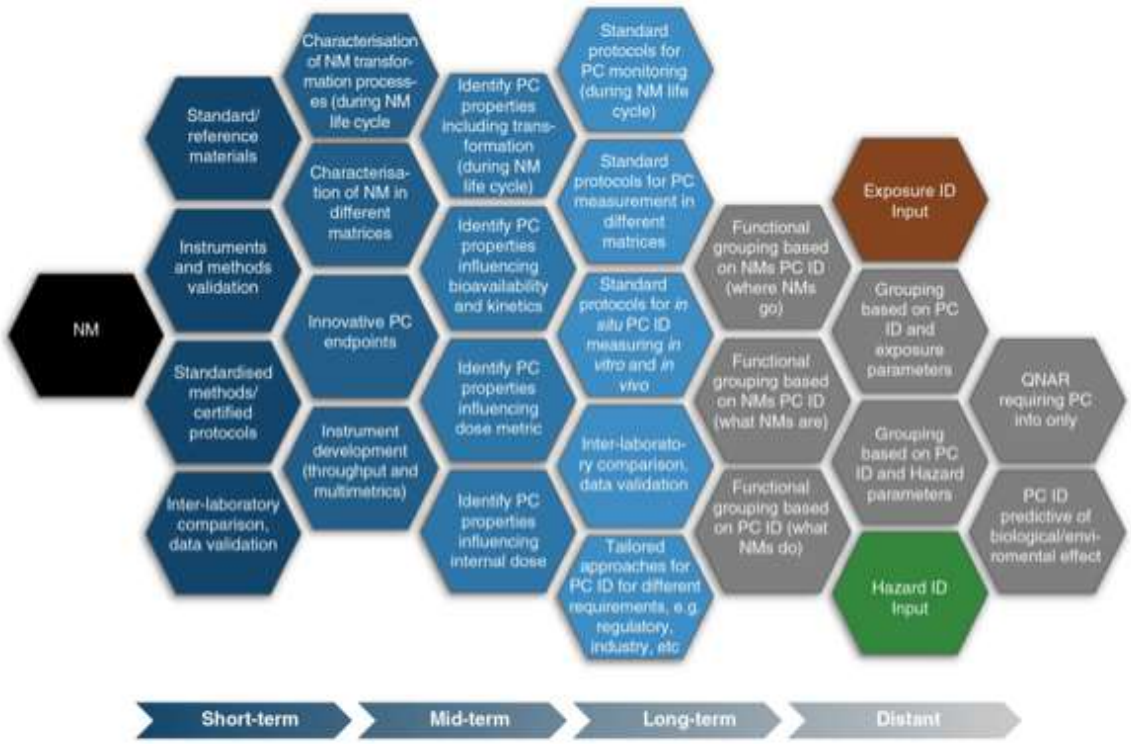


Figure 4. ITS-NANO's Future Goals.

97. ITS-NANO objective was to group nanomaterials by common attributes that are relevant to risk (possibly physical/chemical properties or exposure potential). They also aimed to rank nanomaterials on a risk-based scale such as their potential for exposure or potential to cause harm due to intrinsic toxicity. Grouping and ranking will streamline risk assessment and testing as well as contribute to strategies for risk decision making. Grouping and ranking by physical/chemical characteristic (i.e., composition, shape, charge, or band gap) has already been used but is not yet based on a realistic relationship to risk as the relationship between all the characteristics is very complex. For grouping and ranking by physical/chemical characteristics to be effective, a relatively small number of characteristics need to dominate the risk. An additional way to group and rank nanomaterials is by their use and exposures. This approach is very similar to the regulatory models used for food, medicine, and cosmetics.

98. The grouping and ranking of nanomaterials requires the interaction of physical/chemical characteristics, hazard identification, and exposure assessment as well as integration within the existing regulatory frameworks. New research is needed to determine the mode of action and its relationship to exposure and physical/chemical characteristics in addition to the identification of the base sets of physical-chemical characteristics.

Evaluating the Evidence to Develop Occupational Exposure Bands for Nanomaterials

Eileen Kuempel, National Institute for Occupational Safety and Health (NIOSH), US

99. Eileen Kuempel's presentation addressed worker exposures to nanomaterials, which is a concern as they are the first people exposed in the nanomaterial's lifecycle. Currently NIOSH is trying to develop methodologies to limit worker exposure; however, the number of chemicals itself prevent regulating them individually. One current methodology is control band matrix, which is a performance-based exposure control system. Several control-banding schemes have been developed for nanomaterials, which include: CB Nanotool, ANSES 2010, Stoffenmanager Nano, and International Organization for Standardization (ISO) 2013.

100. Hazard banding is another methodology where chemicals are grouped by the type and severity of their adverse health effects. It has not been specifically evaluated for nanomaterials. However, the following questions have been developed to more effectively assign hazard bands to nanomaterials:

1. Has the nanomaterial **already been classified** and labelled according to national or regional legislation or GHS?
2. Is the nanomaterial **soluble** in water (<0.1 g/l)?
3. Does the nanomaterial contain **biopersistent fibers** or fiber-like structures (defined as rigid fiber with length >5 µm, diameter <3 µm, and length/diameter ratio >3)?
4. Are there hazardous indications for the nanomaterial?
    i. 4a: Do screening tests indicate carcinogenicity, mutagenicity, reproductive toxicity, or sensitisation by inhalation (CMRS) properties?
    –If yes, assign to hazard band E.

    –If no, go to next question.

    ii. 4b: Are comprehensive hazard data available for the ENM?
    –If yes, assign to most protective hazard band (starting with E), according to toxicological data.

    –If no, go to next question.
5. Is there a hazard band for the bulk material or an analogous material?
    –If yes, and the bulk hazard band is A, then assign the nanomaterial to hazard band A; if yes, and the bulk hazard band is B, C, or D, then add one band and assign the nanomaterial to hazard band C, D, or E.

    –If no, assign to hazard band E.

101. In general when assessing the hazard and exposure bands for inhalation hazards ISO recommends assigning nanomaterials one occupational exposure limit (OEL) category more protective. OELs vary by the methods and assumptions applied to the animal data (subchronic/chronic inhalation), there is a considerable amount of uncertainty about safe levels, endpoints associated with OELs vary in severity, and occupational exposure bands (OEBs) are generally more protective but do not distinguish relative hazards.

102. The next steps for developing OEBs include evaluating hazard band criteria for nanomaterials, improving the utility of nanotoxicology data, developing predictive models, and examining the uncertainty seen at key steps in risk assessment process.

Risk Assessment and Factors to Consider for Differing Regulatory Programs

Tala Henry, Environmental Protection Agency (EPA), US

103. Tala Henry described the EPA's Office of Pollution Prevention and Toxics "fit for purpose" approach to the risk assessment of nanomaterials. Risk assessments are useful for their intended purpose, they will vary with the problem, they are designed to maximise their utility for their intended purpose, and the level of acceptable uncertainty will depend on the context of the decision.

104. Although nanomaterials were not specifically considered in the development of the OECD Categories Guidance, some, if not all the principles for Grouping of Chemicals or Category Development and Use, apply to what this expert meeting strived to achieve. If grouping is applied, this means that not every nanomaterial would require testing for every endpoint. Grouping will also benefit nanomaterials that have limited data available or are difficult to test.

105. Both analogue and category approaches are useful. The analogue approach is where the analogue(s) or source chemical can be used to predict the same endpoint for the target chemical. In the category approach chemicals whose properties are likely to be similar (or follow a regular pattern as a result of structural similarity) may be considered as a group or category. The rationale underpinning the analogue and the category approach may be based on a variety of factors:

- Common functional group(s) (e.g., aldehyde, epoxide, ester, specific metal ion)
- Common mode or mechanism of action or adverse outcome pathway
- Common constituents or chemical classes, similar carbon range numbers
- Likelihood of common precursors and/or breakdown products via physical or biological processes that result in structurally similar chemicals
- An incremental and constant change across the category, often observed in physical-chemical properties.

106. Any of these approaches may be applicable for a particular risk assessment. The idea of subcategories has also been introduced in order to improve the practicality of the category approach.

107. The risk assessment of chemicals as a category can be more efficient and accurate than the assessment of single compounds for a number of reasons. For example, the identification of compounds as members of a category provides an insight into the potential effects of the compounds. This is especially useful when there is a lack of data for some nanomaterials. It may also provide significant advantages in the evaluation of compounds for which it is too difficult to carry out standard test protocols.

Risk Management

Panel
Co-chairs: Maria Doa, Environmental Protection Agency (EPA), US; Henrik Laursen, European Commission, EU
Rapporteur: Shaun Clancy, BIAC

Canada's Approach to Risk Management of Nanomaterials under the New Substances Notification Regulations (Chemicals and Polymers)

Brad Fisher, Environment Canada, Canada

108. Brad Fisher spoke on how Canada manages nanomaterials under their *Substances Hazard Communication Act*. Nanomaterials are not on Canada's Domestic Substances List so they are classified as a new substance and producers have to include information on physical/chemical properties, toxicology, exposure, and releases. In addition to this information a notification must be submitted if the nanomaterial exceeds the trigger quantity. The assessment period ranges from 5 to 75 days and is conducted in conjunction with Health Canada.

109. Their approach to risk assessment for nanomaterials is the same as all other chemicals assessed. The assessment includes determining the human/environmental exposures and hazards to establish the degree of risk. Often it is necessary to request additional information to determine the nano-specific properties (e.g., particle size/distribution). The main focus in this assessment is to accurately protect against consumer exposure.

110. Canada's options for control measures for nanomaterials include prohibitions, ministerial requests for additional information, ministerial conditions regarding the use of the substance and Significant New Activity Notices (SNAcs). So far Canada has only used SNAcs to regulate nanomaterials and has issued 16 SNAcs to nanomaterials. Recently, Canada has reconsidered the use of SNACs in regulating nanomaterials. This is due to stakeholder concerns associated with the regulatory burden of SNAcs as there are significant data requirements being requested for all nanomaterials but also because of low reporting triggers.

111. Changes in the SNAc regulation from 2008 to present include:

1. Increased SNAc reporting trigger from 10 kg/year to 100 kg/year
2. Transition from highest level of regulatory testing by default to targeted testing requirements based on exposure
3. Improving the design of SNAc by better defining new activities that would trigger a notification
4. Publication of a guidance document (Advisory Note) outlining notification requirements for nanomaterials.

112. Future work will include identifying new activities of concern in order to control exposure and developing categories to further refine uses, which could significantly improve the SNAc design. SNACs will need to evolve along with the growing knowledge base on nanomaterials.

Categorisation: Risk Management—EU perspective

Henrik Laursen, European Commission (EC), EU

113. Henrik Laursen reviewed the development of risk management, from the perspective of the EU, along with how it can be adapted to address nanomaterials. In order to address the potential risks of nanomaterials, the EC can request characterisation and exposure information, use "hierarchy of control" such as engineering controls, modify safety data sheets, impose restrictions/authorisations, and introduce product-specific restriction of categories (which can be based purely on intrinsic hazards).

114. Currently, there are no specific risk management tools for assessing nanomaterials, so instead it is important to do a case-by-case assessment. This is becoming increasingly difficult as new nanomaterials are constantly being created. In addition to the sheer quantity of nanomaterials they are also difficult to regulate due to a lack of information, their complexity, and a regulatory framework tailored for chemicals rather than manufactured materials. The ultimate goal is to develop categorisation that will allow for a more precise assessment of nanomaterials resulting in less risk of being too conservative or not conservative enough. In his closing remarks, Lauren emphasised that no risk management is better than the underlying data.

Risk Management of New Manufactured Nanomaterials Under the Toxic Substances Control Act

Maria Doa, Environmental Protection Agency (EPA), US

115. The US regulates submitted nanomaterials before they are commercialised, by utilising a 90-day review period of the material where it is determined if the manufacturing, processing, distribution in commerce, use, or disposal of the substance presents, or may present, an unreasonable risk to human health or the environment. Under the EPA's Toxic Substances Control Act (TSCA), manufacturers are required to submit all data they have on the materials but they are not required to perform testing prior to the EPA's review of the material. During the assessment of the chemical, it is determined if the information available to the EPA is sufficient for a reasoned evaluation of the health/environmental effects of the nanomaterial. If the information is insufficient, the focus is on whether the substance might present an unreasonable risk of injury to human health or the environment. Last, it is determined if the substance will be produced in substantial quantities and therefore possibly enter the environment in substantial quantities and present an increased risk of human exposure.

116. Due to the limited data on nanomaterials the EPA is not able to group nanomaterials. However, they do use the category "respirable, poorly soluble particulates" (RPSP), which is based on crystalline silica, talc, carbon black, lithium magnesium oxide, and titanium dioxide. This category requires appropriate respiratory personal protective equipment and no releases to the environment. If there is a high production volume, then a 90-day inhalation test is required. The nanomaterial cannot be manufactured unless these criteria are met or they provide testing that indicates that the material does not cause adverse effects.

117. If the nanomaterial is in a solution, and therefore does not fit into the RPSP category, the focus is on appropriate dermal protection as well as no releases to the environment. After the regulation is determined, the manufacturer must notify the EPA if there are any new uses for the nanomaterial so the

risk can be reassessed. In the future the EPA would like to work toward creating sub categorisations for nanomaterials, especially pertaining to consumer uses.

SESSION 3: PHYSICAL-CHEMICAL CHARACTERISATION

Co-chairs: Vicki L. Colvin, Rice University, US, and Angela Hight Walker, National Institute of Standards and Technology (NIST), US

Rapporteur: Scott Brown, BIAC

Introduction to Physical-Chemical Characterisation

Heidi Grecsek, Perkin Elmer, US

118. Heidi Grecsek spoke about a new approach to physical-chemical characterisation. The overarching goal is to assess to what degree physical-chemical properties can or should be used to guide the categorisation of manufactured nano-objects as well as to ensure direct communication between the characterisation and toxicology communities. In the past there has been an effort to draw a line from physical/chemical properties to effects, but this relation has been too hard to define. The new approach consists of correlating behaviours (functional assays) to effects. The first step in this will be to define what functional assays are the priorities.

Industrial Perspective on Physical/Chemistry Properties and Correlating Effect

Scott Brown, BIAC

119. Scott Brown spoke about utilising physical/chemical characterisation as an essential tool for nanomaterial regulation. Proper characterisation enables the identification of a material, the differences between materials, new or unusual properties, and insights into the behaviours of materials. In order to accomplish accurate characterisation, progress is still needed on relating the nanomaterial's structure to its function, dealing with a nanomaterial's transformations, and determining how to reduce testing without compromising the content. Categorising by physical/chemical properties of nanomaterials is especially difficult due to the heterogeneity of each particle system. Heterogeneity can skew measurements of the physical/chemical properties because the measures are an average of the entire nanomaterial.

120. The benefits of physical/chemical categorisation is that it can safeguard against unperceived contributions to risk, can more efficiently identify contributing material properties, and will likely reduce the cost and time used for analytical testing. There are still many challenges to be overcome such as implementing and defining testing methods that are adequate for different environments/media, interpreting the results from said tests, and identifying/harmonising functional assay strategies to determine what properties are important.

A Metrological Perspective

Angela Hight Walker, National Institute of Standards and Technology (NIST), US

121. Angela Hight Walker talked about the problems regarding data quality for nanomaterials. Currently the lack of quality in the data inhibits the ability to understand, predict, and manage potential risks of MNMs.

122. Frequently, the exact type and size of the nanomaterial used in the study is not clearly identified so comparability of research is not possible. This may be partly due to the fact that measurement science for nanomaterials is not well understood and consequently documentary standards and measurement standards cannot be addressed. These standards will include defining appropriate reference materials, which can aid in comparability of data. Current measures to ensure data consistency for physical/chemical measurements or functional assays include calibrating instruments, having consistent sample prep methodology, validating protocols on how to perform measurements, having a statistically valid analysis of the data (including error analysis), and reporting all data. NIST is currently working on transmission electron microscopy measurements, validation methods, and performing a round robin of experiments on the nanomaterials to collect data.

123. She concluded with questions:

1. Is there sufficient evidence to suggest that physical-chemical parameters can be used to predict or categorise MNMs based on the potential for biological or environmental impact? To what extent can physical-chemical characterisation be used to inform risk assessment or risk management?
2. To what extent should physical-chemical parameters like composition be used to guide other "necessary" physical-chemical parameters and should fate and exposure or biological endpoints be integrated to assist in guiding physical-chemical analysis?
3. What physical-chemical functional tests are most applicable for assessing potential human health or environmental impact? How do we ensure that the test regimens remain relevant despite the increasing complexity of materials and enhanced capabilities in terms of material design and synthesis?
4. What are the barriers to implementing detailed physical-chemical characterisation into toxicology assessments?
5. Is the proposed straw man categorisation scheme a reasonable strategy for MNMs? Should physical-chemical parameters like composition lead categorisation or should it support other schemes?
    i. Composition-based categorisation schemes, such as the proposed straw man categorisation, provide a framework that lends itself to the development of specific physical-chemical test guidance based on a material's assigned category.
6. To what extent is there a need for standardised test protocols, media, and reference materials? How does one introduce a suitable amount of flexibility to ensure that the recommended procedures are valid within a given test substance? How do we ensure compliance with the recommendations?
7. How should physical-chemical functional assays be implemented? Is there a need for a tiered approach integrating parallel biological and environmental endpoints?

Summary

124. Functional assays provide higher level information regarding the behaviour of nano-objects. These tests may simplify characterisation and provide broader insights to the correlation between behaviours and principal physical-chemical properties, but they are not devoid of complications. There is a need to draw a balance between functional testing and more traditional testing strategies. Brown showed

interest in learning how people from different communities select and utilise tests. Certain tests will require more work, as far as normalising the different variations of protocols. The goal is to eventually validate testing strategies and standardise protocols for the tests that are fit-for-purpose.

125. The goals proposed for this session were to determine how physical-chemical characteristics and functional assays can support categorisation. Key behaviours needed to be selected and ranked. The data gaps needed to be identified and the existing functionalised assays that are meaningful needed to be listed. When functional assays were addressed, he asked that the attendees think about reference systems that could be developed in order to enable thorough and proper physical-chemical characterisation of manufactured nano-objects.

Physical-Chemical Characteriation

126. Physical-chemical parameters collectively define how a nanomaterial will behave within a given system and therefore likely influence the environmental and human health impact of nanomaterials. Physical-chemical properties can be further broken down into two categories; functional assays and physical-chemical characterisations. Some functional assays are more of a behavioural probe, rather than testing a property of the material in its regular environment. These assays can still be important depending on the endpoint. The ultimate driver of selecting a testing strategy is purpose.

127. Scott Brown states that the physical-chemical properties are considered to be the parameters that can be measured. Functional assays address the transient physical-chemical effects. But how do we measure such properties as agglomeration?

128. A function test describes behaviour under a given set of conditions, the particular system of interest. The material may exhibit abnormal properties. The processes and the results of functional assays are usually quite varied. When standardisation was considered, relevance of types of assays was called into question.

129. Behaviours were selected from the background document, and meeting participants were asked to prioritise them in order to be explored further and determine how functional assays can support categorisation. The behaviours listed were: dissolution/precipitation, dispersibility/agglomeration, dispersibility/dustiness, surface charge, hydration, surface reactivity, photocatalytic activity, biodegradation, and adsorption from environment.

130. The types of measurements are on a continuum from physics through biology. The goal was to have solidified key behaviours of interest, then to have identified the existing functional assays for them, and finally, to have developed reference systems to close the data gaps between the different studies.

SESSION 4: ENVIRONMENTAL FATE

Co-chairs: Willie Peijnenburg, National Institute for Public Health and the Environment, The Netherlands, and Elijah Petersen, National Institute of Standards and Technology (NIST), US

Rapporteur: Steffi Friedrichs, Nanotechnology Industries Association, BIAC

131. The Session 4 breakout group discussed the possibilities of grouping of nanomaterials with regard to their environmental fate. The discussion centred on the characteristics of groups of nanomaterials that determine the main processes that jointly determine the fate of a nanomaterial in water/soil/sediment.

Relevant endpoints

132. The environmental fate of nanomaterials is affected by the physical-chemical composition of the environmental compartments, and the chemical and physical-chemical composition of the nanomaterial. In modelling and assessing the fate of nanomaterials, it is common to use a bottom-up approach in which the basic processes/mechanisms are integrated in an overall fate model that is typically applicable to a specified class of chemicals. A schematic overview of the important fate processes for nanomaterials in the aquatic environment is given in Figure 5.

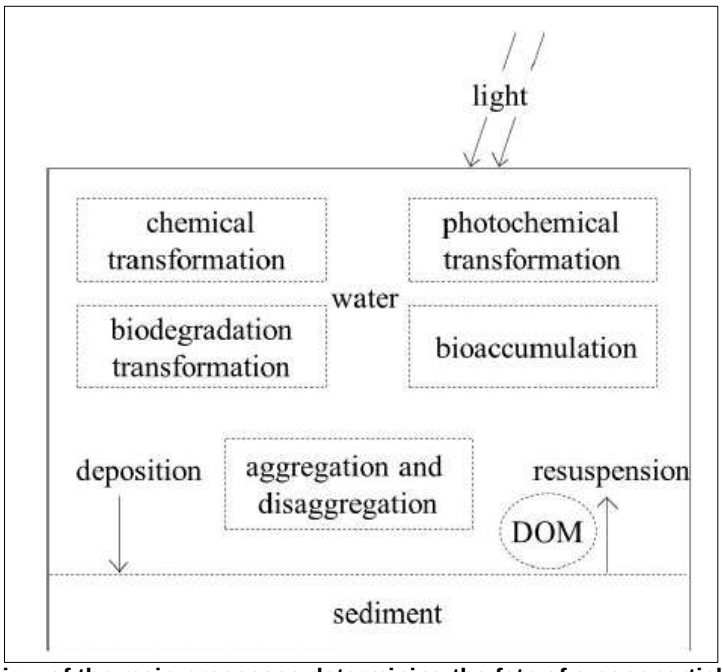


Figure 5. General overview of the main processes determining the fate of a nanoparticle in a stagnant aquatic environment.

133. As discussed by Baalousha et al. (2014)[12] the main processes determining environmental fate include:

- Aggregation/disaggregation
- Dissolution/precipitation
- (Bio)degradation
- Diffusion/sedimentation
- Nanoparticle coating, ageing/weathering.

134. The main goal of grouping of nanomaterials is to identify groups of nanomaterials that allow filling in data gaps by using information from other, related nanomaterials, subsequently providing guidance on what information is needed for actual read-across and for data interpolation. As mechanism-based insight in the relationships between physical-chemical parameters and fate-determining processes is currently in its infancy, the members of the breakout group are expected to discuss the best strategy for grouping of nanomaterials for this purpose. As such, a distinction may be made between what is achievable in the near future and the way forward in the long run. An important consideration in this respect will be on the properties of nanomaterials that affect the various processes, such as the following:

- Charge
- Size
- Morphology

[12] M. Baalousha, G. Cornelis, T. Kuhlbusch, I. Lynch, K. Nickel, W. Peijnenburg. Validation of model formulations for fate and behaviour assessment of engineered nanomaterials. Environmental Science and Technology, in preparation, 2014.

- Coating/natural corona
- Chemical composition.

135. When combining the most important fate determining processes and general knowledge on particle composition, some potential categories of nanomaterials may be distinguished beforehand.

Nanomaterial Classification Considerations for Environmental Fate

Iseult Lynch, University of Birmingham, UK, and Claus Svendsen, Centre for Ecology and Hydrology, UK

136. Iseult Lynch and Claus Svendsen began the session by posing the question "Are the proposed categories a reasonable starting point for general categorisation for environmental fate?" To respond, participants discussed the environmental transformations which nanomaterials can undergo (physical, chemical, biological, adsorption) and the theoretical impacts of environmental ageing and transformation. The EU FP7 NanoMILE Project Deliverable "Report on environmental transformation reactions" by Denise Mitrano (Birmingham University) and Bernd Nowack (EMPA), Sylvie Motellier and Simon Clavaguera (CEA), was cited to explain the theoretical impacts of environmental ageing and transformation. Nanomaterials can increase in similarity or diversity as a result of environmental transformation. For example, binding of biomolecules (e.g. humic acid) may increase similarity by masking the underlying nanomaterial, chemical transformation (e.g. sulfidation) increases similarity and different nanomaterials released from similar composite materials coated in the same matrix may have increased similarity. However, there is still significant potential for nanomaterials to differentiate in the environment by binding different components, dissolving and reprecipitating etc.

137. Another EU project, NanoFATE, addressed nanomaterial transformation in practice looking at the transformation of ZnO > ZnS in sewage sludge. Each earthworm produced offspring per week but there was a dramatic decrease in earthworm reproduction when there was the presence of nanomaterials. The aged soil sludge mixture results showed that sludge organic matter is good for earthworm reproduction. However, there was no Zn speciation difference and no ZnO left, yet the NP toxicity was greater than the Zn ionic control toxicity. Same effect was observed within TINE project by Unrine et al. for plants.

Does coating/size matter for impacts?

138. In the ModNanoTox FP7 project, Eawag (Swiss Federal Institute of Aquatic Science and Technology) assessed species effects of AgNPs and LC_{50} and EC_{50} were grouped for the same species and the same material. Data varied by up to four orders of magnitude in several species. In ten studies of Ag NPs impacts on daphnia, the materials assessed had eight different coatings, and no studies had the same particle sizes. Between studies there was no similarity. Thus, only talking about silver or quantum dots may not be sufficient, and there is a need to specify the coating type also and whether it is physically or chemically associated with the nanoparticles.

139. Another EU FP7 project, QualityNano, assessed how sensitive organisms or assays are to median nanoparticle size or size distribution. QualityNano attempted to examine if and how cells/assays can discriminate between a 25nm median versus a 30nm median versus a 40nm median etc. Due to different particle sizes used in different studies, there is a need to understand how to compare datasets. Could grouping be based on biologically sorted physical-chemical categories?

140. Iseult Lynch and Claus Svendsen proposed the following classifications for the functional role of coatings:

- Protective: Slow dissolution/increase stabilisation
- Passivation: Capping reactive surface/reducing reactivity
- Modulatory: e.g., Changing miscibility/solubility – changing surface chemistry to facilitate further functionalisation, or reduce biomolecule binding/biofouling
- Other?

141. Another proposed classification scheme could be by environmental "behaviour" or "effect" of nanomaterial coating. Coating behaviour in the environment may be permanent or easily exchangeable and it may be inert versus toxic (including degradation components). Coating behaviour should be assessed in the context of the nanomaterial's local environment. Human health and human toxicity studies have embraced the idea of understanding the nanomaterial in a local environmental context via protein corona and there is emerging evidence of differences in coronas from healthy versus disease state plasma. Some "functional effects" won't occur in the environment. The group should use the environmental context to guide what testing is needed, and it may be relevant to the specific case.

Effects of Local Water Chemistry on NP Sedimentation

142. Another study performed within the NanoFATE project analysed all of the EU waters and mapped them into 7 classes covering all of Europe. The study used Debye length calculations (the amount of electrostatic screening, which is related to the ionic strength of the water) to assess the stability of nanoparticles in the different waters. In waters that had low ionic strength (low Debye length) and low organic content, the nanomaterials persist in the water. A functional sedimentation assay measures the MNMs behaviour in the different types of water. Several parameters could be linked together e.g. ionic strength, pH, Cation Exchange Capacity, Dissolved Organic Carbon etc.).

143. Classification based on multiple physical-chemical contributors via Principal Components Analysis (PCA) could include ageing, environmental fate, quantum effects, etc. Extrinsic and intrinsic factors could be adapted further to include ageing and environmental behaviour. Some research says that there is no relation between corona and uptake, and some research says that there is a relationship.

Current Conclusions

144. QSARs currently in literature do not match current measured physical-chemical properties, as they often calculate quantum effects or derived parameters. It is more important to measure functional assays. Research began to take TEM images of size and started to develop those into prediction models. Categorisation has to relate to when nanospecific effects or functions occur rather than just when they theoretically might occur. The group needs to know how nanomaterials look at the exposure site, which can be assessed by fingerprinting, speciation, bioavailability, biopersistence, etc.

Nanotechnology Categorisation by Environmental Fate and the Implications on Exposure and Hazard

Al Kennedy, US Army Corps of Engineers, US

145. Categorisation is done to simplify analysis, decisions, and to guide relevant testing. Scientists can predict the implications of nanomaterials that are in the same category. The group needs to scale down the process of categorisation. Fate categories could possibly be used to dictate the need for hazard tests. The group needs to examine why and when in the lifecycle of a nanomaterial do we categorise. Categorisations could be determined by final transformations that are system-specific, properties inherent to the parent particles (from a vial), by nanotechnology product categories, or by particle (1 to 100nm) release potential.

146. NanoGrid is a current research program that has created an adaptive guidance framework. The programme proposed a five-tier categorisation scheme by category use in each tier. The following is the **Tiered Categorisation Scheme**:

> **Tier 1**: Screening criteria: Based on material amount, size, properties, technology categories, and use
>
> **Tier 2**: Release potential: Conservatively assume 100% release; determine actual amount released
>
> **Tier 3**: Environmental persistence: Determine free particle persistence and dissolved fraction
>
> **Tier 4**: Sustainability testing: Biological testing for acute and chronic toxicity
>
> **Tier 5:** In-depth product investigation: Material-specific and site-specific.

147. The research programme has a focus on fate (and exposure) for categorisation. In the first tier (screening), categorisation of nanotechnologies and products should be based on physical structure, and intended use and fate categorisation of nanoparticles should be by composition and size. In the second tier (release), fate categorisation of nanoparticles should be by release potential. In the third tier (fate), fate categorisation of nanoparticles should be by dispersibility and stability (coating, charge, and media) and by dissolution kinetics (and completeness). The fourth and fifth tiers are linked by hazard categorisation. Hazard categorisation in the fourth and fifth tiers should be categorised by hazard ranks and by interactions (ligands, transformations). Guidance documents are necessary to get quality repeatable data.

148. Current efforts to develop OECD testing guidelines and guidance documents include work on dispersion and stability, dissolution, and hazard as documented below:

- Dispersion/stability – Germany/Universität Wien (Austria)
  - Standardise dispersion protocol: 1, 10, 100 mg/L
  - Dispersible? > Stable under relevant conditions?
  - Low/high energy sonication > settle > dispersible fraction
- Dissolution (particle-ion separation) – US (ERDC)/Denmark
  - Harmonise methods; select most consistent, accurate
  - Different particles, ring test, discussed later
- Hazard (eco) – US (ERDC, NIST)/CAN/UK
  - Harmonise current ecotoxicity methods for consistent hazard (bioassay) results
  - Fate categorisation and the 80-120% guideline
    1. Generation stock – harmonise with dispersion TG

2. Exposure media production and dosing
3. Bioassay conduct, measurement, and monitoring
4. Data analysis, dosimetry, interpretation

149. Discussion focused on the suggested tiers for characterisation. It was proposed that Tier 1 could be categorised by technology type with candidate technologies. Nanos could be tested categorically to find trends. It was proposed that Tier 2 could be categorised by unique properties and release potential. Intended use (whether the use is indoor or outdoor), proximity to surface, and release/no release could be a way to categorise Tier 2.

150. Tier 3 could be categorised by kinetics or half-life and parent nanoparticle properties could possibly be used. Proposed parent nanoparticle properties were dispersible/not dispersible, stable/not stable, coated/uncoated, steric/electrostatic, agglomeration kinetics, and dissolution potential. Tier 3 categorisation should consider toxicity, surface area, equilibrium, and rate/kinetics when considering dissolution and OECD TG. Complete dissolution would have implications on the persistence particles. OECD TG harmonises methods in the dispersibility protocol. Running different dissolution tests over different time points will assist in selecting a method. There should also be guidance on how to calculate dissolution rate and kinetics.

151. Tier 4, which was proposed to be categorised by hazard, should examine half-life of stability. Fate stability of half-life categories should inform the bioassay duration. Categorisation should be relevant by hazard rankings and unique properties.

152. Tier 5, which was proposed to be categorised by interactions and transformations, should look at system-specific and case-specific investigations. It was also proposed that ageing and ligand equilibration should be considered rather than size and that mechanisms of toxicity should be considered. As examples, environmental ligands or photolysis could increase the persistence of the particles and decrease toxicological implications of the particles. The seemingly larger particle and smaller particle in relative conditions may have the same impact.

Conclusion

153. Other technologies that use TiO_2 may have a lower dissolution potential. There are various technologies that can be used including technologies related to structure, proximity to surface, intended use, release potential, and particle size distribution.

OECD Tests for assessing Fate in Soil and Water

Thomas Kuhlbusch, Institute of Energy and Environmental Technology, Germany

154. Thomas Kuhlbusch reported on the OECD Expert Meeting in Berlin held on January 29-31, 2013[13]. The meeting agreed that dispersion and dissolution are key factors when assessing the properties of particles. The Berlin meeting looked at testing guidelines that were already in place for environmental fate

[13] OECD, 2014. Ecotoxicology and Environmental Fate of Manufactured Nanomaterials: Test Guidelines. OECD Series on the Safety of Manufactured Nanomaterials No. 40 - ENV/JM/MONO(2014)1 - ENV/JM/MONO(2014)1/ADD.

to determine how they can be applied to NMs. The meeting assessed the applicability, addition, extension, updates, and development of new environmental fate and ecotoxicology OECD test guidelines for the testing of MNMs. The TGs that were discussed were TG 105 (Water Solubility) and TG 305 (Biodegradation: Flow through Fish Test). TG 105 was found to be not applicable to nanomaterials and TG 305 is generally applicable to nanomaterials but there is no steady state/equilibrium for the ENM-K_{ow} value. In TG 305, only the dietary approach is applicable for ENM. There should be a review of ecotoxicology when looking at fate and behaviour.

155. Testing at different environmental representative conditions in water (pH, ionic strength, NOM) could assist in the grouping of natural conditions and pristine/altered materials demonstrate that the transformation processes are important. A new testing strategy based on a decision tree and tiered approach was developed at the Berlin meeting as shown in Figure 6 and Figure 7. The tiered approaches and decision trees provide guidance on stock suspension preparation, preparation of exposure suspensions, and test conditions.

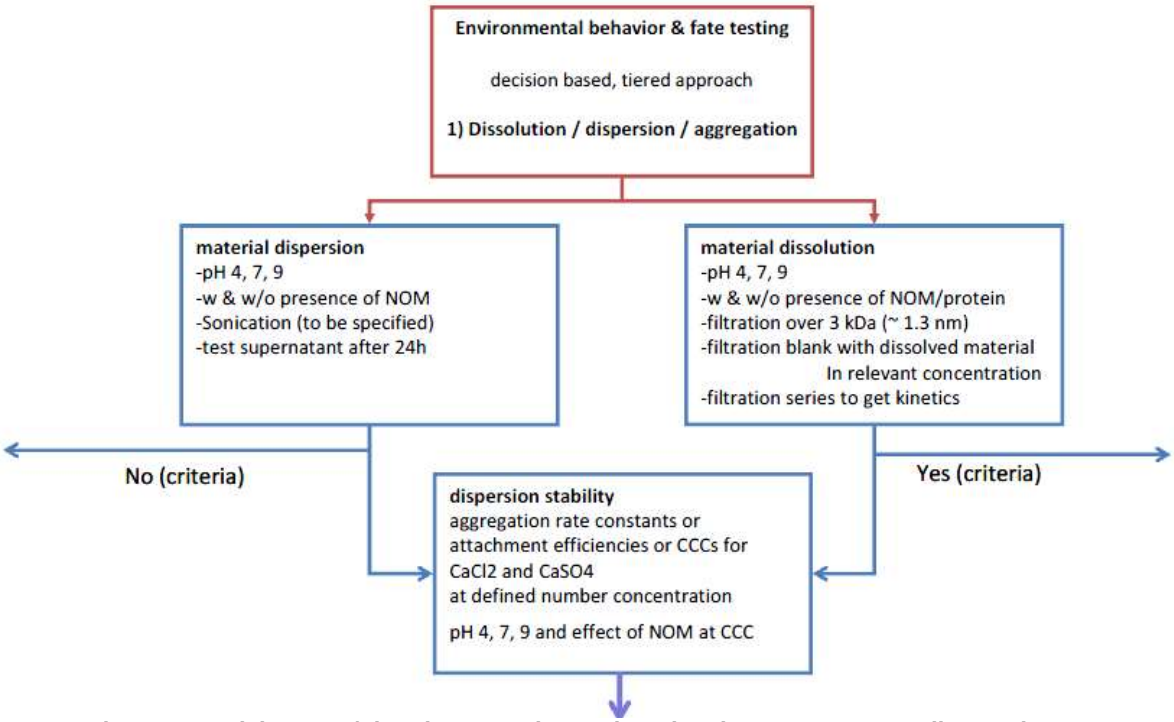


Figure 6. Decision Tree/Tiered Approach Developed at the 2013 OECD Berlin Meeting.

156. Other TGs discussed at the Berlin meeting were:

- TG 106 (Adsorption/Desorption): As currently worded this TG is not applicable to MNMs since the TG cannot separate solid dispersed NMs from the solid soil matter. A new TG should be developed.
- TG 312 (Leaching in Soil): This TG is generally applicable but nanospecific guidance is needed (application of ENM – wet spiking preferred, soil types, NOM).
- TG 315 and 317: These TGs are generally applicable but homogeneous exposure for longer time periods is a major issue.

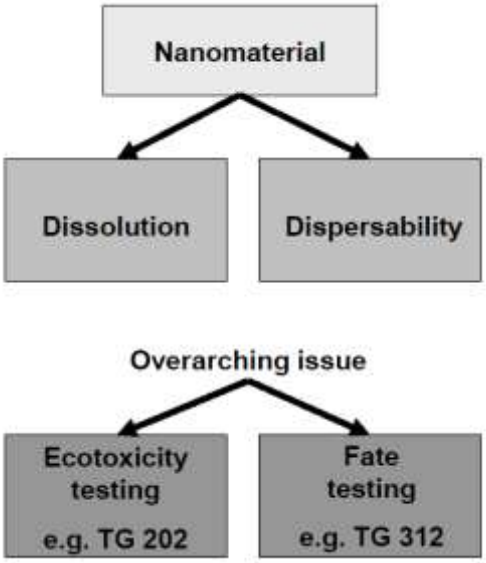


Figure 7. Decision Tree developed at the 2013 OECD Berlin Meeting.

157. Harmonisation between ecotoxicology and fate studies showed that both studies were often using similar test conditions such as application of MNMs, stem suspensions, and physical-chemical parameters of the suspension and test media. Testing of transformed and aged MNMs instead or as an addition of pristine materials is recommended since the behaviour and toxicity potential may be altered by ageing.

158. A loss of the applied MNM in the experimental set-ups is expected. The decision tree must be able to be used to figure out the right tests and target the correct organisms. It is also important to identify which metrics can be used and are sensitive enough for detection as well as how this metric can be related to the original material so that a linkage can be made. The decision tree leads to "categorisation" of MNM to improve selection of applicable or new test protocols. The decision tree is a kind of categorisation that can be used in a way to group nanomaterials and reduce case-by-case approaches, as well as assist in read-across.

159. Other categorisation should include the preparation of MNM suspensions and application of MNM to the test system. Different starting points for grouping were identified, based on material properties and characteristics, mode of application, etc.

Summary

Willie Peijnenburg, National Institute of Public Health and the Environment, the Netherlands, and Elijah Peterson, National Institute of Standards and Technology (NIST), US, and Steffi Friedrichs, Nanotechnology Industries Association, BIAC

160. The group questioned whether categories can be used as prescriptions to tests (e.g., AgNPs should undergo dissolution testing) or whether it should be the other way around (e.g., low dispersion stability nanomaterials are grouped as a class). One set of arguments favouring the use of categories as a prescription for which tests to conduct is that regulators already use categorisation for this purpose for other classes of chemicals (e.g., organic chemicals could be tested for biodegradability but dissolved metals would not). The other argument was that there may not be sufficient evidence to distinguish categories prior to behaviour tests to determine which tests to conduct; for example, it may not be possible to categorise complex nanomaterials with regard to whether a dissolution rate test should be conducted. Tests need to be assessed before determining categories. For example, it may be possible to categorise nanoparticles based on their dispersion stability or dissolution rate; tests for both of these nanomaterial properties are currently being developed by the OECD. Standardised tests for other key characteristics (surface affinity, sorption, photo (Fenton) degradation rate, etc.) related to environmental fate of nanomaterials may need to be developed for proper fate assessment.

161. The group continually questioned whether the categorisation approach based on the nanomaterial chemical formula (i.e., metal or metal oxide nanomaterial, carbon nanomaterial, etc.) is the starting point to work with. The group agreed that categorisation approaches based on chemical composition and/or structure, as commonly used for the regulation and risk assessment of chemicals, can play a central role in nanomaterial categorisation. However, more knowledge (i.e. measurement and testing) is necessary both before and after such chemical categorisation (see Figure 8): nanomaterials would need to be released into the environment before environmental fate modelling and assessment are to be considered, and hence methods to quantify release are needed. Tests need to be done first that are similar and depending on the outcome, categorisation can be done such as for quickly dissolving or nanomaterials unstable in the aqueous phase. As standardised tests are promulgated and various nanomaterials are tested with these assays, it may become possible to conduct *a priori* categorisation based on the nanomaterial properties (elemental composition, surface coating, size, etc.).

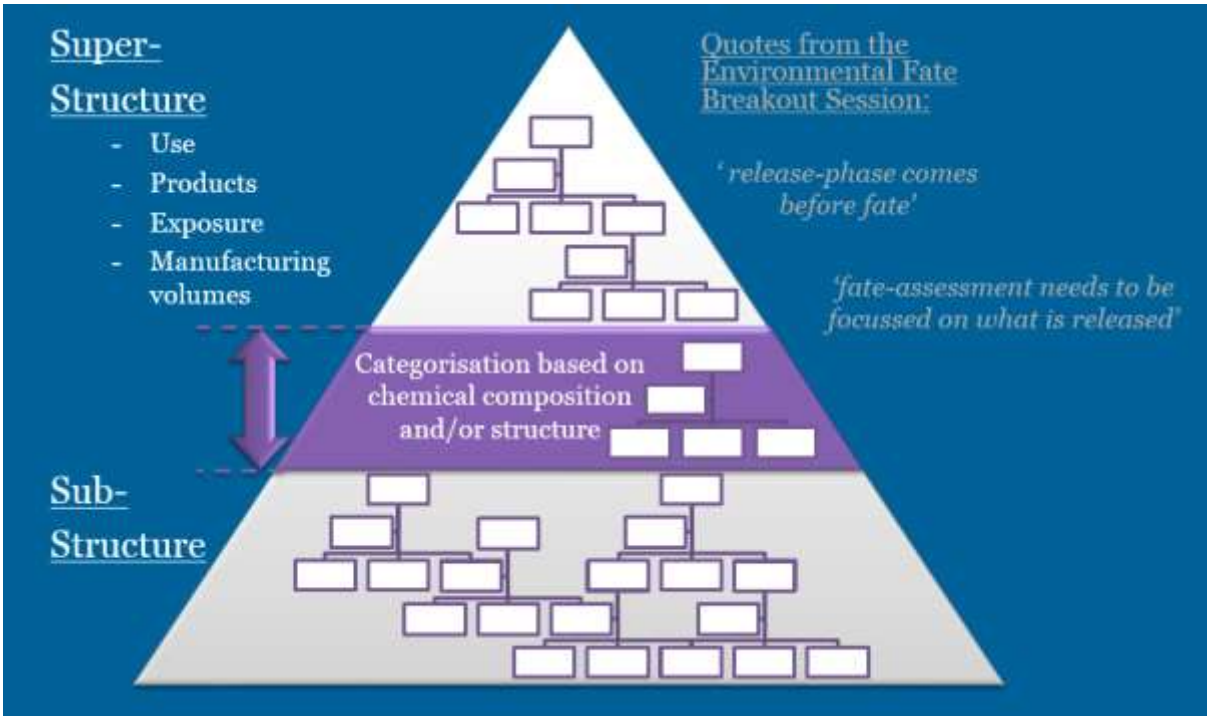


Figure 8: Illustration of the role of a categorisation approach based on chemical composition and/or structure in the environmental fate assessment of nanomaterials: classic chemical composition/structure based approaches should follow considerations of exposure (i.e. Super-Structure), and should preceed nanospecific fate- and behaviour considerations (i.e. Sub-Structure).

162. The following were the Q&A from Session 4:

- Should key nanomaterial properties or behaviours be part of the super-structure or the sub-structure?
  Key nanomaterial properties should be part of the sub-structure of the fate assessment decision pyramid, while economic, release and exposure parameters should be the parameters considered in the super-structure.

- Are the proposed categories presented in the thought starter a reasonable starting point for general categorisation? Yes, categorising nanomaterials based on potential key environmental behaviours (e.g., dissolution) is reasonable.
- Are the proposed categories a reasonable starting point for further sub-categorisation as is? Yes.
- What specific activities would be needed to provide sufficient evidence for the use of categorisation in these questions for risk assessment and risk management? Sufficient time was not available to decide upon the specific activities. One activity that was proposed was meta-analysis of the existing data to identify trends.
- What information is required for assessing the validity of each sub-category? Sufficient time was not available to decide upon this question.

163. The experts discussed an approach based on chemical composition, similar to that currently applied in many jurisdictions' chemicals regulation. The experts thought there should be a middle tier of

molecular identity. The next steps are to take the list of key points and decide where they exist in the final plan. The group discussed where chemical composition belonged in the pyramid (see Figure 8).

164. The group moved on to discuss risk assessment. The group recommends risk assessment to be linked from the release all the way to the effects. The group chose the tests prescribing categories and asked how categories could be chosen before we have tests to define categories: Real scheme Tests→ categories → prescription of tests.

SESSION 5: HUMAN HEALTH (GROUP 1)

Panel
Co-chairs: Jenny Holmqvist, ECHA, EU, and Jürgen Schnekenburger, Biomedical Technology Center of the Medical Faculty Münster, Germany
Rapporteur: Myriam Hill, Health Canada, Canada

165. The scope of the discussion from this breakout session focused on regulatory categorisation of nanomaterials.

BASF Approach of Grouping of Nanomaterials

Karin Wiench, Badische Anilin und Soda Fabrik (BASF), BIAC

166. It is unrealistic to assume that the safety profile of each nanomaterial can be adequately tested or verified for all relevant hazard endpoints in a timely manner, which is why it is necessary to implement a framework in order to focus testing by means of nanogrouping.

167. No single parameter or property is sufficient to group all nanomaterials. There is a need for a multi-perspective categorisation method for purposes of testing. The EU had done work on this task. The development of functional categories for manufactured nanomaterials for the purposes of read-across evaluations will require a trial and error approach. There are many places to start the nanogrouping process: by identity, function or motility. Wiench chose to start with the material properties of the substance in order to learn more about the nanomaterials and progress from source to outcome.

168. First start with the nanomaterial → The type of release or dispersion → The route of uptake in the body → Modification in the body → Distribution in the body → Primary Effect → Finally, the toxic effect.

169. The nanomaterial of concern must be identified, and then the concerns must be refined in order to develop targeted testing. Characterisation of the nanomaterial and the properties is first considered, the basic testing of interactions and finally specific testing of exposure and biological endpoints based on the outcome of the basic testing. Wiench presented this decision making framework as a tiered approach (Figure 9).

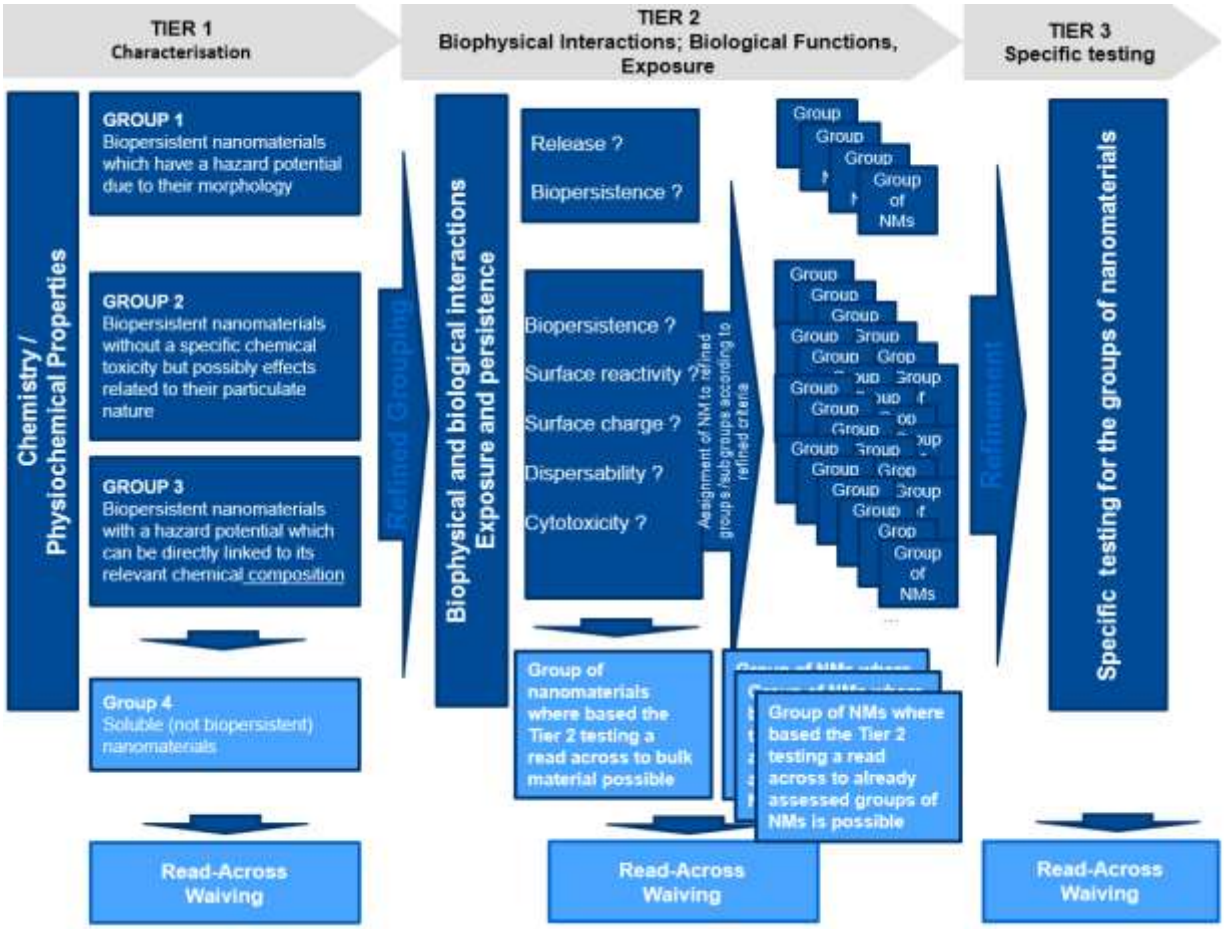


Figure 9. BASF Tiered Decision Making Approach.

170. The characteristics in Tier 1 for this specific study were the chemical composition, the impurities, and the coatings of the nanomaterial. These physical-chemical characterisations assign nanomaterials to one of four groups based on their biopersistence. If a chemical was deemed soluble or non-biopersistent, it was designated to "Group 4." Group 4 was design to have no need for nano-specific grouping or assessment because the chemical composition supersedes the nanostructure in terms of risk. Groups that were determined to be biopersistent and hazardous, either due to the morphology, chemical composition, or particulate nature, advanced to Tier 2 to be further divided by nano-forms of the same substance.

171. The Tier 2 subgroupings were developed to test dispersibility in relevant media, surface charge and reactivity, *in vitro* macrophage assay, and biopersistence. If there was a low toxicological potency of the nanoparticle, supplementary exposure-derived endpoints are needed to support read-across waiving from Tier 2.

172. Finally, Tier 3 was specific testing for a refinement of the concerns with specific groups of nanomaterials in their application. This tier requires screening for toxic, genotoxic, and ecotoxic effects.

173. There are many routes of exposure to a nanomaterial: inhalation, dermal, and digestion. Wiench focused on the toxicity of the nanomaterial to the body. In this study, Wiench used aerosol suspension as the type of dispersion to focus the testing.

174. Barium sulfate and cerium oxide were tested using a macrophage assay and were compared against a macrophage assay of orange and red pigments in their bulk and nano-forms. The tests were

evaluated for the endpoints of cytotoxicity/tissue damage, oxidative stress, macrophage activation, and inflammation. The barium sulfate and cerium oxide both showed low cytotoxicity while CeO2 showed moderate inflammation.

In vitro and *in vivo* Approaches to Assessing the Pulmonary Toxicity of Nanomaterials, and How They Can Inform Categorisation

Vicki Stone, Heriot-Watt University, UK

175. Given the relevant paucity of *in vivo* hazard information on specific manufactured nanomaterials and given that some regulatory authorities continue to request *in vivo* testing given the limited alternatives, Stone seeks to answer how we can utilize alternative testing strategies (ATS) and logically link *in vitro* models to *in vivo* systems.

176. There are many different tools for toxicity testing. Toxicity studies are dominated by *in vitro* single cell types. Less commonly used are co-cultures, and *in vitro* cultures using multiple tissues are even less common. Unfortunately, the current risk assessment approaches are heavily dependent on long-term *in vivo* models. The longer-term inhalation studies are useful because they provide some flexibility in evaluating endpoints. Recently there has been an increased use in the short-term inhalation, *in vivo* protocol, which dictates a 5-day animal exposure then 28 days of observation. A gross necropsy, histological examination, and bronchoalveolar lavage are performed on different groups at the beginning and end of the 28-day observation period. The results of this protocol demonstrate organ burdens and the body's ability to recover from the exposure. Sustainable Nanotechnologies (SUN) sought to adapt this protocol to a short-term oral study.

177. Instillation may be a suitable alternative to inhalation in terms of categorisation and benchmarking data. Instillation is more accessible, cheaper, and more ethical. For a full risk assessment, it would probably not be a viable alternative, but categorisation is not a conventional risk assessment. Therefore it would prove useful to look for alternative testing strategies.

178. A majority of the biological response is explained by the surface area of a nanoparticle rather than the surface reactivity. The area of the lung in which nanoparticles deposit are typically in the alveoli. They are not evenly distributed across the lung's epithelial tissue. In a published study in *Inhalation Toxicology* by Donaldson et al., Stone draws an example of where an *in vitro* model was able to obtain similar results to an *in vivo* study. Both obtained a threshold value for onset of inflammation at 1 cm^2 particle surface area to 1 cm^2 of the surface area of the medium in which it was tested; proximal alveolar region for the *in vivo* study and the dish for the *in vitro* model. The important message of this experiment was that it is possible to compare *in vitro* and *in vivo* data if the test is performed logically.

179. Again, Stone suggests that the when choosing a testing strategy, the first considerations should be the physical-chemical characteristics of the nanomaterial. Characteristics to be tested include:

- **Size**: Effect on the translocation and entry route of the nanoparticle
- **Electrical conductance**: Effect on electrochemical gradients and membrane potential
- **Strength**: Effect on durability, biopersistence, and clearance
- **Solubility**: Effect on biopersistence, release of toxic components, and clearance
- **Crystal Structure**. Effect of crystalline silica versus amorphous silica
- **Charge**: Effect on molecular interactions
- **Composition**: Effect on inherent toxicity

- **Shape**: Effect of fiber shape on clearance.

180. Shape was the physical-chemical characterisation chosen for this study. Stone chose different length carbon nanotubes that had different shapes when aggregated. Long straight nanotubes (NT1) ~50 µm length, nanotubes 10+ µm length (NT2) that crossed, and entangled nanotubes (NT3) were chosen to be exposed to macrophages and were measured against asbestos exposed to macrophages (Figure 10). A frustrated phagocytosis was observed with the nanotubes.

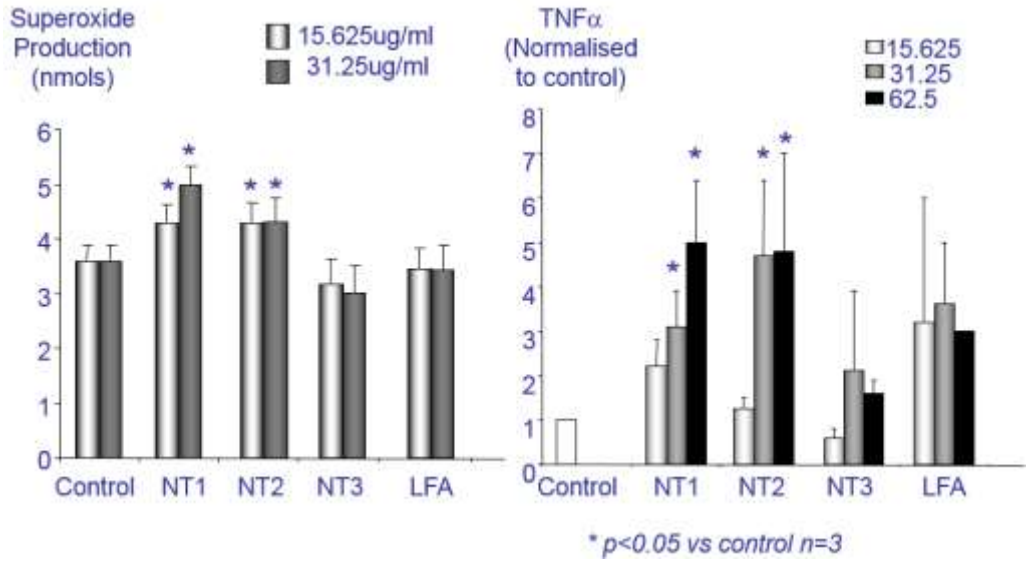


Figure 10. Superoxide Production.

181. Superoxide production was measured *in vitro* across all variables and returned a significantly higher production rate for NT1 and NT2 than the macrophages exposed to asbestos. *In vivo* results yielded similar findings by measuring the amount of TNFα.

182. Further investigation showed that long straight carbon nanotubes interact with the mesothelium to cause inflammation. Controls are essential in calculating the meaning. The results of this analysis were benchmarked to asbestos and carbon black. When designing the experiment the macrophage sizes and ability to uptake were considered *in vitro*. There are cell signalling mechanisms involved in the hazard response. There is a variation in responsiveness to different particle types based on their surface reactivity. Identifying endpoints or biomarkers comes from understanding the mechanism.

183. Stone stressed the importance of being able to communicate meaningful studies when using alternative testing strategies. There has been criticism of the inconsistencies between testing results. But nanomaterials have been shown to induce markers of inflammation and oxidative stress across a variety of testing strategies. Stone urged for prioritising the endpoints that are useful to have testing strategies developed and standardised.

184. However, a protocol cannot be usefully standardised until it is shown to generate meaningful information. The relevance to human response and the limitations of the model must be understood, and the concentration and dose metrics used must be justified.

185. The *in vitro* system was described as poor at predicting liver responses that were not injected directly into the liver. When nanoparticles are ingested, the particles are incorporated into the gut contents, microflora, and mucus. If inhaled, the particles are coated in lung lining fluid. However, in an *in vitro* model, the particles become coated in the medium content. Stone encouraged investigators to manipulate

the nanomaterial to reflect the route of entry into the body in order to make the *in vitro* experiments more relevant.

186. Nanomaterial coated in lung lining fluid was shown to increase toxicity in hepatocytes, but not macrophages. Different cytokines represent a different concentration of particles. Enhanced particle concentration showed an enhanced response of MCP-1 and IL1β responses in hepatocytes. Reduced particles induced IL6 production by macrophages.

187. The responses of macrophages, hepatocytes, and liver tissue are nanomaterial-specific, corona composition-specific, and route of exposure-specific. But these specificities can be determined by well-designed systematic *in vitro* studies. *In vitro* cultures can be improved by designing the exposure protocol to better reflect the exposure scenario.

SESSION 6: ENVIRONMENTAL TOXICITY

Chair: Greg Goss, University of Alberta, Canada
Rapporteur: Eric Bleeker, National Institute for Public Health and the Environment, the Netherlands

188. Session 6 focused on the grouping of nanomaterials with regard to their ecotoxicological effects. The discussion centered on the characteristics of groups of nanomaterials that jointly determine the environmental toxicity of a nanomaterial toward aquatic, terrestrial, and sediment species. Similar to non-nanomaterials, for risk assessment the main focus will be on aquatic ecotoxicology. The discussion also considered environmental fate and grouping of nanomaterials, as the environmental toxicity of materials will in part be determined by their fate, both in the environment and in the test system.

189. The chair posed a question whether regulators can be informed on the most important physical-chemical parameters for:

- Aquatic toxicology: physical parameters can be used to define toxicology in a large sense
- Sediment toxicology
- Soil toxicology.

190. Toxicology can be used to inform categorisation. There have been recent advancement in nanotoxicology and hazard identification and there have been huge advances in the quality of data. Tests are now conducted in a more reproducible manner. The functional differences that exist in ENMs have also been developed. There are some high throughput techniques that are used to create more robust data. Scientists have improved environmental relevance (NOM, dosage), and there has recently been well designed, mesocosm data to evaluate ecosystem-level effects. There have also been relevant exposure scenarios. The number of environmental toxicity publications has skyrocketed in the past couple of years as well.

191. The following challenges were presented as talking points in the session:

- Can we inform regulators?
- Who will be arbitrator of the types of data?
- Which are the appropriately performed "trusted" studies?
- Should we be gathering these diverse data sets together to figure out if potential hazard exists?
- Can we link new assays to ecosystem-level effects?
- Should there be measurement of nanoparticles to assign dose?
- Is there publication bias? Often non-significant results go unpublished because journals are looking for specific data to publish. A risk assessor may find relevant information in nonpublished data, but because it is unpublished, it cannot be cited.

- Super acute toxicity is not often demonstrated in materials that have been published.
- How do we determine underlying effects and physical-chemical parameters?
- How can we determine the applicability of current testing guidelines?

192. Moreover, regarding ecotoxicity data while there have been a lot of reviews, many are not adequate because methods were not identified. Data are usually collected in a scientifically acceptable way, but the data cannot be trusted because the data cannot be evaluated without an explanation of method.

193. A number of different articles have been published that have increased confidence in testing and results. However, companies will need to be trained in testing so that the data are collected correctly.

Decision Trees and Aquatic Toxicity Testing for Nanomaterials

Greg Goss, University of Alberta, Canada

194. There was an Aquatic Toxicity Decision Tree Workshop on July 1-2, 2014 hosted by OECD. The key goals were to decide if there is uniform and consistent bioassay data to inform future testing guidelines and risk decisions and to figure out what needs to be done. The group aimed to develop a guidance document using a decision tree (step-wise) approach. The guidance document, "Aquatic Toxicity Testing of Sparingly Soluble, Volatile and Unstable Substances," was discussed. The group looked extensively for guidance in the Difficult Substances document (OECD GD 26). The workshop created better weight of evidence (WOE) for decision making on hazard assessments.

195. The workshop determined that it is important that categorisation feeds into the decision tree and vice versa. If the group is to create a decision tree (or multiple ones) to allow for proper categorisation, what are the key points for those decisions and will the decision points need to be validated? The presenter asked if QSARs can be used, but the presenter believes that mistakes are going to be made if SAR is used, and he did not think that read-across can be used in this particular function. The group will eventually be deciding on making multiple decision trees. The pyramid that was set up is three-dimensional.

196. Greg Goss offered the following definitions:

> **Immuno-suppression:** Mast cell line (ATS for immunomodulation potential) shows a demonstrated reduction in degranulation in a dose- and time-dependent manner for only the TiO_2 core particles, less for CeO, and no response for other materials including shell alone. It is mediated through interaction with an FcE receptor.
>
> **Immuno-activation:** Macrophage cells line and primary macrophages show a demonstrated increase in phagocytosis in only the TiO_2 core particles, and there is no response for other materials including shell alone.

Considerations on Categorisation of NM regarding Ecotoxicity

Kerstin Hund-Rinke, Fraunhofer Institute for Molecular Biology and Applied Ecology, Germany

197. Many criteria for categorisation regarding ecotoxicity are discussed. These include parameters such as material type, crystalline structure, size, solubility, ion release, surface functionalization, reactivity, and coating. Examples were presented to demonstrate potential relationships of ecotoxicity and selected physico-chemical parameters. Based on the identified relationships a decision tree for categorisation regarding ecotoxicity was presented.

198. Hund-Rinke addressed the parameter solubility of nanomaterials by the effect of various nanomaterials (Ag, ZnO, CeO_2, CNT) in the reproduction test with earthworms. Soluble (ion-releasing) nanomaterials such as Ag and ZnO show concentration-effect-relationships. Rather stable nanomaterials such as CeO_2 and CNT can show a plateau with a maximum effect significantly below 100 %. Currently it is unknown why ecotoxicity can stop at a certain level. This is also observed in further terrestrial test systems and in aquatic tests.

199. The crystalline structure was addressed using the earthworm avoidance test as an example. In contrast to the reproduction test with earthworms which lasts over a period of 56 days, the incubation time in the avoidance test is 2 days. Earthworms avoided soil contaminated with nano-CeO_2 (NM-212) if the test was performed after an incubation period of 28 days. Freshly spiked soil showed no toxicity. In contrast, a second nano-CeO_2 (NM-211) showed no toxicity with and without an ageing period. There are indications that the crystalline structure of NM-212 changed during the ageing period resulting in ecotoxicity and that the crystalline structure can be a relevant parameter to differentiate nanomaterials.

200. The parameter reactivity was addressed by a test design using microorganisms. A well-known example for reactivity is the photocatalytic activity, where the effect of illumination on antibacterial activity is not limited to nanomaterials designed with photocatalytical properties.

201. Tests with aquatic organisms show that the toxicity of nanomaterials (in the example Ag) can be modified by coatings. Various coatings affected ecotoxicity of the same Ag core differently indicating a high priority of the parameter coating in categorisation.

202. In a publication on Ag-nanomaterials, shape was identified as relevant indicator for ecotoxicity.

203. From the results Hund-Rinke identified solubility, crystalline structure and coating as criteria of high priority for categorisation. She assumed that size and shape are covered by these parameters.

204. As starting point for further discussions, Hund-Rinke provided a decision tree ranking the identified parameter with respect to categorisation. In this decision tree, intentionally applied coating has the highest priority. A further criterion is stability of the coating followed by its hydrophilicity and hydrophobicity. If the coating is known to affect ecotoxicity, several categories depending on the resulting ecotoxicity / ecotoxic profile have to be agreed on. If the coating is unstable or the coating does not affect ecotoxicity the nanomaterial can be treated as an uncoated nanomaterial. For these nanomaterials solubility and reactivity are of high importance. By solubility also the size of nanomaterials should be covered. In this context also the effect of ageing has to be considered. Solubility and reactivity range from low to high and have to be treated pragmatically. Several categories have to be defined with a minimum of two categories (low / high) per parameter.

205. Ag and TiO_2 in the crystalline form of anatase and rutile were used to demonstrate the proposed decision tree. It is obvious that the compartment (e.g. soil, water) affects the outcome. It has to be

discussed whether a categorisation for every compartment is necessary or whether a concern driven approach is preferred.

206. In the discussion reactivity and charge of the coating were additionally addressed. Following the meeting the decision tree was slightly modified (Fig. 11a)

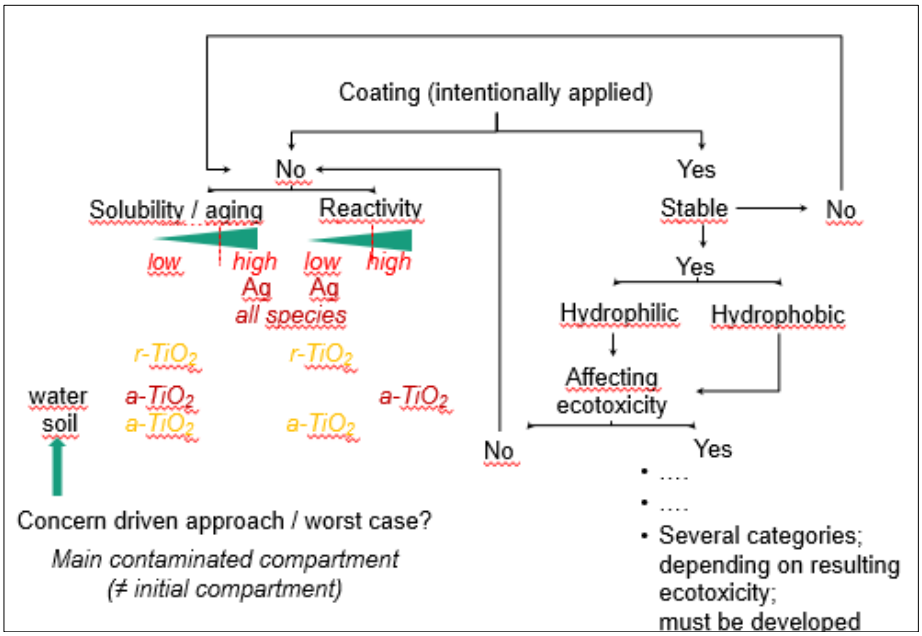


Figure 11. Decision Tree for Categorisation Regarding Ecotoxicity

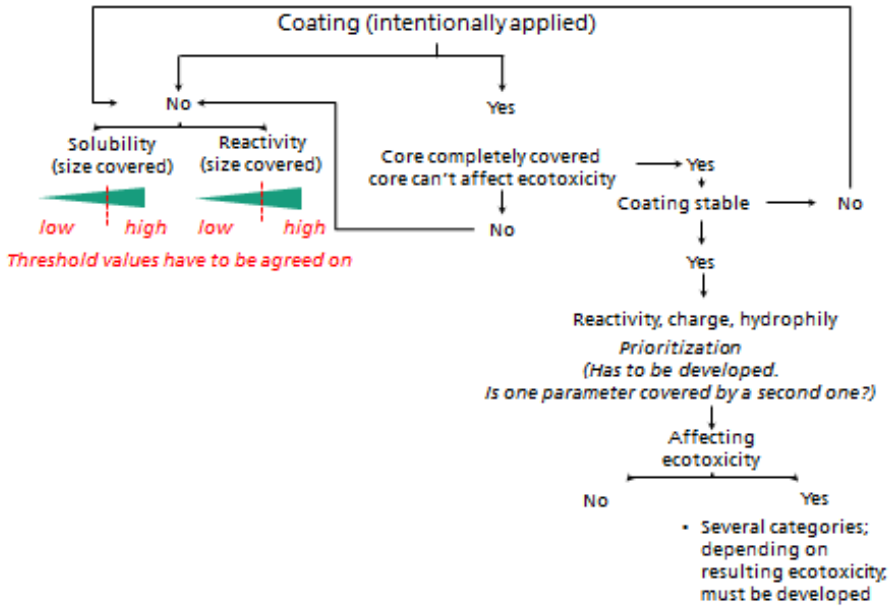


Figure 11a. Decision Tree for Categorisation Regarding Ecotoxicity Based on the Discussions in the break out group.

Summary

207. The Session 6 discussion focused on Kerstin Hund-Rinke's presentation: "Categorisation of NM Regarding Ecotoxicity." The group examined what information is available and what the properties of materials are. They looked at how that feeds into a testing scheme and how it affects ecotoxicity. The group mostly agreed on the ecotoxicity schemes on the bottom of the triangle that was presented and focused on their current knowledge of categories.

208. The group began by assessing decision trees, and then the discussion centered on tests. The outcome of tests will feed back into the decision trees, and the decision trees will feed back into grouping (which will reiterate a lot of the grouping).

209. The group proposed a three-dimensional scheme that may become more complicated. The scheme will not be a two-dimensional scheme.

210. The group agreed that Hund-Rinke's flow diagram is a good start with the end goal in mind. The flow diagram will help identify which toxicology studies to run. If a chemical is reactive, then appropriate studies with light should be used. It is not complete, but the diagram brought up key parameters or properties.

211. Development of characterisation scheme of physical-chemical properties: If characteristics were defined including the material makeup of the object or the nanomaterial in question, what would we do to apply the decision analysis or decision tree to figure out which test would be appropriate as part of the regulatory process to facilitate moving toward which specific guidelines? Regulators could work with industry to figure out the appropriate testing to move forward. The process should be iterative, where the tests that are being conducted are enough to be able to adjust and give confidence to regulators moving forward to protect human health. At the same time, the tests would not overwhelm the system because you have additional academic interest in how chemicals behave.

212. Moving forward, there needs to be a way to instil confidence in regulators and the public. Scientists are now in a better position to know how to conduct better toxicity testing.

213. In conclusion, the group would like to use a decision tree to figure out what tests are appropriate.

SESSION 7: HUMAN HEALTH (GROUP 2)

Co-chairs: David Warheit, BIAC, and Phil Sayre, Environmental Protection Agency (EPA), US.
Rapporteur: Agnes Oomen, National Institute of Public Health and the Environment, the Netherlands

214. The charge given was refinement of categories for use in tiered testing/read-across and identification of gaps in knowledge. Targeted areas for initial consideration include to what extent can categories be formed for pulmonary toxicity based on *in vitro* and shorter-term *in vivo* data, physical-chemical traits, and other approaches (e.g., mode-of-action grouping). The focus is on pulmonary toxicity and how categories can be used in reduced testing and/or read-across contexts and how similar approaches to reduce testing needs can be used for other health endpoints beyond pulmonary toxicity.

215. Physical-chemical groupings, in context of inhalation toxicity, are a good place to start, but it is hard to do a grouping scheme for all nanomaterials. Further approaches include consideration of mode of action (e.g., long-term lung inflammation, fibrosis, other MOAs and/or biokinetics anchors), targeted testing within a category (e.g., short-term study results anchored by longer-term *in vivo* studies to estimate toxicity of new MN within the category), and focus on individual "data rich" subcategories (e.g., toxicity outcomes based on varied metal oxide crystallinities and varied carbon allotrope forms).

216. In a study looking at titanium dioxide forms (ultrafine forms), samples have different crystalline and surface phases; chemical reactivity and pH are different, high and low, respectively, for one sample (with an 80/20 anatase/rutile crystalline phase). Pulmonary inflammation was observed for this sample even at 3 months post-exposure. Of note are the differences in toxicity for various carbon allotropes, for both subchronic inhalation data and a 5-day inhalation screen.

217. One suggestion is to begin categorisation with low/medium/high toxicity as a measure of effect, not just physical chemistry.

Development of Equivalence Criteria for Nanomaterials by Intratracheal Administration

Masashi Gamo, National Institute of Advanced Industrial Science and Technology (AIST), Japan

218. Japan's Ministry of Economy, Trade and Industry (METI) research project is focused on the development of innovative methodology for safety assessment of industrial nanomaterials (NMs) in FY2011–2015. Key areas include developing assessment methodologies for determining equivalence of nanomaterials (Tier 0), establishing intratracheal (IT) administration testing for screening of hazards of nanomaterials (Tier 1), and developing basic technologies supporting equivalence and IT administration for inhalation toxicity. Inhalation exposure testing (IH) is regarded as Tier 2 for new or extended category of NMs.

219. There are an infinite number of nanomaterial variations; equivalence criteria as Tier 0 is necessary to apply (explicitly or implicitly) to NMs but there is a need for strategic comparative studies to develop equivalence criteria; IT testing is beneficial for screening hazard of NMs but there have been discussions on the usefulness and limitations of IT in comparison with IH exposure testing.

220. Masashi Gamo's project is investigating the contribution of NMs' physical-chemical properties to toxicity using a set of IT studies of NMs with the same chemical composition but different size, shape, and surface treatment. The study was initiated with TiO_2 materials, NiO and SiO_2.

221. There have been discussions on the usefulness and limitations of IT in comparison with IH; based on literature and current research, the study team indicates the following components allow IT results to be interpretable as IH toxicity for screening:

- Well dispersed NM (up to 2–3 μm)
- Low dose level (up to 1 mg/rat)
- Low concentration of dispersant
- Observation period up to 3 or 6 months
- Standardised procedure of IT (development of standardised procedure).

222. Unpublished data from Oyabu and Morimoto (2014) examine IH and IT in a comparative study of NiO 15–35 mn in terms of lung burden and clearance, and also inflammatory response (total cell in BALF was shown). When the lung burden is similar between IH and IT, it is found that IH and IT are comparable in lung clearance and inflammatory response.

223. A total of 20 oxides (7 TiO_2, 4 NiO, and 9 SiO_2) were chosen as part of the study for variations in size, shape, surface, and ease of ability to detect in biological samples. Acute, sub-acute, and sub-chronic time points were chosen, and three doses were used. The inflammatory response was focused for a trial exploration of the equivalence concept. Evaluations of TiO_2 are complete and experiments for NiO and SiO_2 are underway.

224. Results (unpublished) obtained for the TiO_2 comparative study are drawn from a histopathological examination and BALF analysis of lung inflammation at 3 days, 28 days, 13 weeks as well as lung clearance.

225. In a comparison of the crystalline structure, there was no clear difference in inflammatory response and lung clearance. In a comparison by shape (represented by an aspect ratio), there was again no clear trend in the inflammatory response or clearance from lung. In comparison by primary particle size, a smaller primary size was expected to have a stronger effect with one exception, though no clear trend was found for lung clearance. In comparison by secondary particle size, the inflammatory response was weaker for materials with a larger secondary particle size at day 3, but again there was no clear trend in lung clearance. One compound with a surface coating of aluminium hydroxide was unique and showed persistent inflammatory response and retardation of clearance at all dose levels, indicating that surface treatment changes the biological response (toxicity).

226. In summary, the equivalence concept is necessary to apply both explicitly and implicitly, and strategic comparative studies are needed to develop equivalence criteria/categories. Intratracheal administration testing is considered beneficial for screening. For TiO_2 nanomaterials, a surface treatment was found to be a predominant factor affecting response in the lung; particle size may also affect the inflammatory response, but other factors showed no clear effect.

5-Day Inhalation Protocol and Results for Grouping of Nanomaterials

Karin Wiench, BIAC

227. Karin Wiench summarised a short-term inhalation study (STIS) that tested carbon nanotubes (MWCNT), graphene, graphite nanoplatelets, and carbon black. The study design was to **e**xpose rats and look at organ burden, distribution and translocation, particle size distribution within lung, histology of

selected organs, and cytological and biochemical parameters in broncho alveolar lavage fluid (BALF). Researchers developed a list of targeted biological parameters for inhalation exposure.

228. Results showed that graphite nanoplatelets and carbon black had an NOAEC of 10 mg/m^3. No adverse effect was seen in the BALF or pathology/histology findings for carbon black.

229. A total of 9 pigments (materials) were tested along with 14 metal and metaloid-oxide nano and micro-scale materials. No adverse effects were observed up to highest concentration tested for several pigments and roughly half of the metal and metaloid-oxide materials. Adverse effects were observed at 10 mg/m^3 for some materials and again at approximately 0.5 mg/m^3 for others. In particular, MWCNT and quartz showed NOAEC levels <0.5 mg/m^3 with progressive effects. Together, these data can be used to determine toxic potency and to examine translocation, pathology, and BALF (clinical pathology).

230. In a sub-acute and sub-chronic STIS case study of CeO_2, $BaSO_4$, lung burden (IH) was measured for CeO_2 NM-212 and for $BaSO_4$ NM-220 at 5 days, 4 weeks, and 13 weeks. Lavage was examined at these time intervals and it was concluded that deposition and clearance tendencies are comparable. The inflammatory effects were comparable in the 5-day and 28-day studies while reversibility was shown to decrease with an increase of exposure time. Within the STIS, the sub-acute NOAEC could be determined, indicating predictive value. Compared against long-term studies, STIS uses less animals and resources than traditional inhalation studies and examines effects in the lung, persistence, progression or regression of effects, effects outside lung, lung burden, and potential translocation to other tissues.

Summary

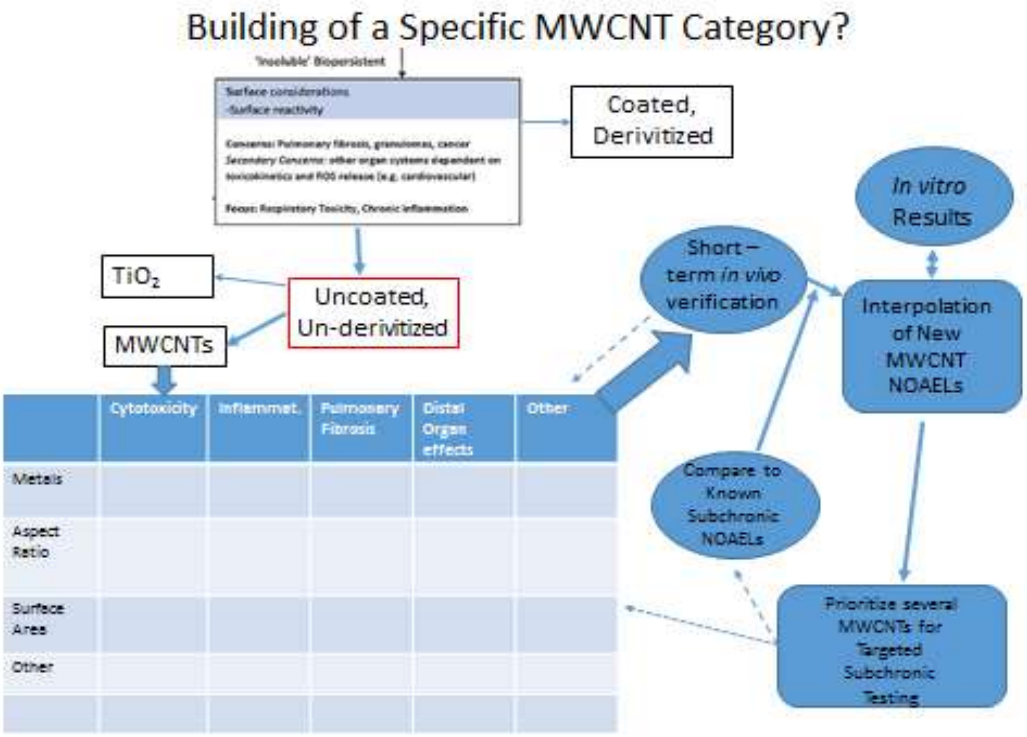
231. The suggested categorisation schemes included the following:

- The NOAEL is related to different endpoints; maybe consider an indication of how clinically significant the response is in humans. This might be a way to categorise but do not necessarily look at acute response because inflammation is almost always present.
- A construct for testing a targeted category: may shift short-term *in vivo* verification earlier in process (read-across context).
- MWCNTS: Maybe a high/medium/low categorisation scheme.

232. The general discussion points were as follows:

- Sustained inflammation and cytotoxicity are good predictors of 90-day IH studies; as a conceptual idea, listing low/medium/high for both categories could be used as a basic grouping. This might be a start for pulmonary toxicity *in vivo*.
- There are variations in how you aerosolise nanomaterials, which can cause different characteristics of the aerosols themselves; need data comparing aerosolisation techniques and then need to look at endpoints.
- There are some IH studies on nanotubes and inflammatory response; use these studies to potentially determine how an unknown (carbon nanotube) compares.
- It is not known to what extent we can link short-term IH studies to sub-chronic or chronic effects or if we have an understanding of why these effects formulate or not or if they correlate. Carbon nanotubes are very specific. Have done 28-day studies with pigment-grade titanium dioxide; response was consistent with 28 days and 2 years except in overload situations (then you get development of tumours).

- Looking at the following diagram, that was presented for discussion, you would think we could use read-across from other materials considering surface construct and surface reactivity:



- In a broad sense, the structure of comparative potency within a framework is where you compare shorter-term assays that you know something about to generate longer-term predictions, but you need validation of that using evidence (verifying, reproducible, reliable) of how predictive the short-term assays are. For inflammation (for carbon nanotubes) studies show inflammation decreases but fibrosis continues to develop. Maybe inflammation is not predictive of long-term effects such as those seen with metal oxides. Look if endpoints are indicative of chronic effects. Assays for genotoxicity may not carry over.
- A low/medium/high categorisation scheme is useful if we have enough data to quantify what we mean (using animal to human data).
- General question if short-term IH is a good approach; that is, is 5-day good or is longer-term needed?
- Concern is that inflammation/oxidative stress/etc. is a process. Are they all converging to same endpoint (e.g., fibrosis) or any other effects? Are they predictive enough for long-term effects? If it isn't focused on the lung, do you look at lungs, kidneys, brain for final pathological effects?
- Using high/medium/low categorisation seems to be a way to start but would hope within those categories there is some way to quantify the definitions, for consistency.
- Not a lot of long-term data for chemical effects; use expert judgment based on sub-chronic studies. Looking for indicators that might give an alert to triggering long-term effects. Look to short-term studies that are highly predictive and have sensitive parameters. This is

what we try to find out, not just perform long-term studies (uses a lot of resources such as animals and materials).

- Look at differences between chemicals and particles.
- Construct designed around data we have now, not to ignore other effects (other sections of respiratory tract).
- Any epidemiology among workers? There are studies with titanium dioxide and carbon black, but exposure metrics are not well established. There is data in workers; epidemiological data.
- With carbon nanotubes, there is not a lot of data. NIOSH put out for medical surveillance data.
- Three cohorts have been followed for carbon black: US, UK, Germany. About 8000 cohort in total. Updated US mortality study is hoped to be published at the end of the year.
- Not clear from diagram that we have articulated categories to divide particles into. We have persistent, respirable, etc. It is desirable to define categories and then corresponding pathway would be more obvious. sequence of steps (project management concept) are needed as well deciding which (on the slide) needs to precede another step (build a sequence of choices) and the data needed to make choices will be better defined.
- Slide is almost intentionally circular because it allows for learning at each step of the way; dotted lines are feedback loops to let you better fine-tune interpolations and extrapolation, which should lead to less testing over a longer term. Process designed to become less burdensome as more data become available.
- Not clear what happens when you go into coated/derivitized versus uncoated/underivitized (on slide); need further description on terms.
- Intent of such a process is to learn at each step. Long-term outcome is to reduce testing; then there should be a first step looking at available data before deciding on next step.

Recommendations

233. The focus of the session was on hazard endpoints (pulmonary toxicity) and categories for relative toxicity evaluation. The working hypothesis is that physical-chemical properties alone will not be sufficient to build scientifically justified categorisation of nanomaterials. However, it is not known to what extent categories can be formed. Physical-chemical properties are a good way to start for toxicological considerations but not sufficient for categorisation (different level of effects within groups with similar elemental composition; can think of commercial application and surface reactivity). Discussions were narrowed to targeted design for inhalation toxicity and what short-term inhalation studies/testing (STIS) can be used.

234. The following points were further discussed:

- A conservative approach may be needed for a subcategory to put information together; include physical-chemical factors, relate to STIS, put into context of known sub-chronic NOAELs.
- In principle, *in vitro* assays can be used for categorisation: standardise and validate, link to behaviour effects; generally not applicable for read-across at this time; possibly in future.
- Physical-chemical traits guide but they are not currently sufficient for categorisation.

- Short-term *in vivo* studies: preferred over *in vitro* studies for categorisation but not clear if they are sufficient for read-across.
- Need guidance on how to aerosolise.
- Discussion on instillation vs inhalation.
- Template is preliminary but represents a good start; very similar to scheme by Wiench et al. but focused to narrow application (carbon nanotubes; subcategorisation).
- Basing categorisation of effects (possible effect seen with short-term inhalation or instillation ranked as low/medium/high, but categories have to be validated).

SESSION 8: EXPOSURE ASSESSMENT

Chair: Vladimir Murashov, National Institute for Occupational Safety and Health (NIOSH), US
Rapporteur: Kim Rogers, EPA, US

Exposure Assessment Session 1

Facilitator: Chuck Geraci , Nanotechnology Research Center, US

235. The scope of this discussion was directed toward exposure assessment, not risk or toxicological assessments. The first presentation and discussion were specifically exposure to the worker and the second considered the exposure to the consumer. While exposure through the inhalation pathway is more significant and provides a larger hazard to the worker, a wider range of potential exposures should be considered for the consumer.

The 'Source Domain' Concept: Different Release Processes and Associated Exposure

Derk Brouwer, TNO, Risk Analysis for Products in Development, the Netherlands

236. The source domain concept is defined as the classification of different release processes and the associated potential for occupational exposure.

237. The life cycle of nanomaterials, as defined in the presentation and portrayed in Figure 12, begins at the raw material and continues through production to processing or manufacturing to use of the product until it reaches the end of life.

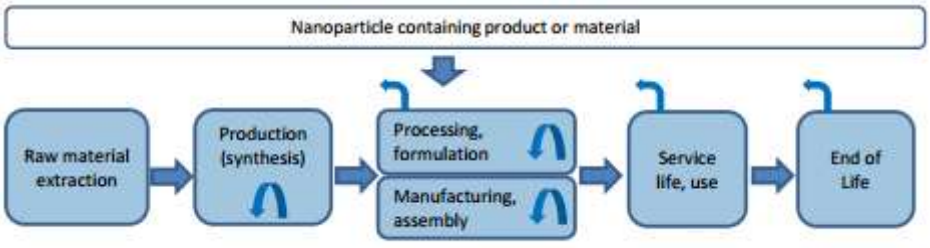


Figure 12. Life Cycle of Nanomaterials.

238. More specifically when considering lifecycle release, the assumption is that any release is from the nanoparticle-containing product. Depending on what stage in the lifecycle the nanoparticle is released, the nanomaterial can take different forms. The release can take the form of unused debris, unused liquid suspensions, aggregated aerosols, or even multi-composed heterogeneous aerosols. Effectively, the emission of the nanomaterial can be introduced to indoor air, outdoor air, groundwater or surface water, and soil.

239. The nanomaterial properties and the energy level in which it is released should affect the refinement of the exposure model that is chosen. The Local Control Influence Region (LCIR) may affect the amount and form of the nanomaterial from release to emission. The local control will affect dispersion/ventilation, segregation, and surface contamination during the transition of source to receptor. The parameters for consideration for exposure modelling are mass generation rate (g/min) and mass concentration (mg/m^3).

240. There is a need for additional features to satisfy nano-specific properties of this exposure model, such as particle size distribution and active surface area concentration. The idea of using source domains to categorise nanomaterials is to reflect that the mechanism of release has the possibility of changing the form of the nanoparticle.

241. The form is also clearly affected by what stage in the lifecycle the material is released, which is why the source domain approach is closely associated to the lifecycle. Brouwer suggests the use of timing of release during the lifecycle to determine who will be exposed. Workers can be affected at both ends of the lifecycle. The professional end users and consumers can be exposed after the finished product is assembled. The general public is ultimately exposed at all stages during the lifecycle.

242. There are four notable source domains. The first is point source or fugitive release can be described as the release during the synthesis of the nanoparticle-containing material. This source domain is including releases prior to the harvest of the bulk material. The rapid coagulation of nanoparticles during this phase of the lifecycle will alter the size distribution. An example of this source domain is emissions from leaks or other incidental releases.

243. Source domain 2 is called powder handling and refers to the handling and transfer of the bulk manufactured nanomaterial powders with low release energy. Examples that would be categorised under this source domain would be bagging, dumping, scooping and harvesting, that results in compounding composites.

244. Source domain 3 is considered to be dispersion of intermediates or application of nano-embedded products, such as coatings. This is normally a dispersion that will have a higher energy. For instance, the release could be dispersed by spraying, pouring, or injection moulding. This source domain normally reflects release of an intermediate that contains highly concentrated nanoparticles. The application of coatings or any form of spray that will form nano-sized aerosols after condensation should be considered source domain 3.

245. Source domain 4 includes low- or high-energy stresses to the material during the use phase of the lifecycle, such as any activity that results in fracturing of manufactured nanoparticle-enabled products. Low-energy examples of releases include abrasion or manual sanding. Mechanical sanding, grinding, or drilling are all considered high-energy. High-temperature processes, like burning, would be categorised as source domain 4 also.

246. After categorising the source domains, Brouwer introduces the next step. Data were extracted from the results of real workplace studies that had been published in open literature in order to normalise for local controls. The results were also corrected for background levels. For example, pseudo air suspended was used as emission.

Source domain 1	Upon testing, ‘pseudo air suspended emission’ gas-phase synthesis had a significantly higher particle concentration than CVD synthesis of nanoparticles. Additional categorisation could have been used for the type of process.

Source domain 2 — The assumption is that the release is a result of a nanomaterial property. Dustiness would be a physical-chemical property of a powder. Within each dustiness test result (Figure 13), there was some variation due to the materials. Overall the carbon-based nanomaterials had a relatively higher dustiness result than other forms of synthesised nanomaterials.

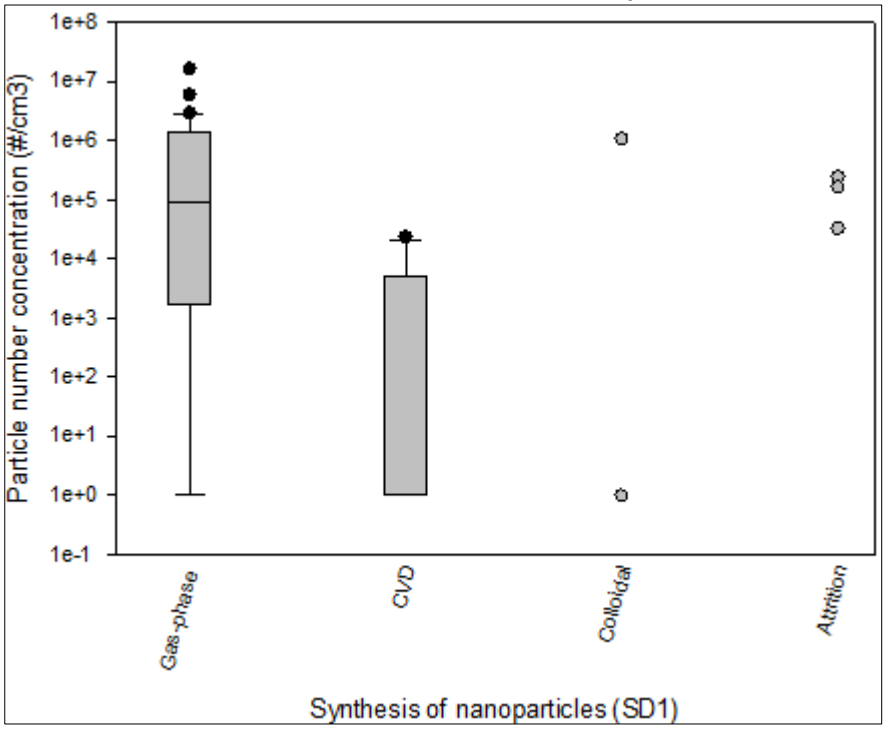


Figure 13. Particle Concentration of Dustiness by Different Syntheses of Nanoparticles

247. Source Domains 3 and 4 were both excluded from this presentation because currently there is limited workplace data available.

248. In order to consider dustiness testing as a functional assay, there is a need to link the characteristics of an exposure scenario to a specific dustiness test. There is a clear difference in force drag between each test, i.e. venturi aerosolisation, vortex shaker, and the rotating drum. This is due to properties of the test that will affect the results, such as friction caused by the device, particle interaction and impact.

249. The second determinant of release is the activity that causes the release. The activity of release and amount of bulk nanomaterial can affect particle concentration on release and energy levels. If you were to combine combinations of the type of nanomaterial, activity of release, and amount of bulk, there are many combinations with very different results (Figure 14).

250. Ultimately, understanding exposure will be the driving tool in classification.

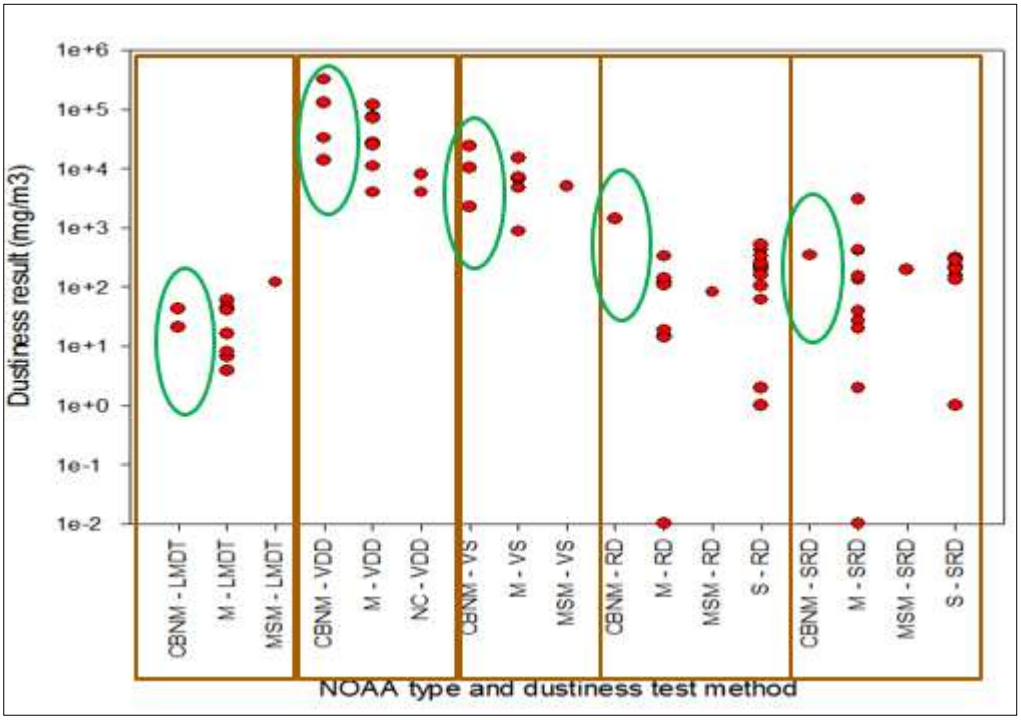


Figure 14. Diversity of Release Between Test Methods and Nanomaterial Type

Exposure Assessment Session 2

Facilitator: Treye Thomas, Consumer Product Safety Commission, US

251. Treye Thomas described potential categorisation techniques:

1. Grouping driven by exposed populations
2. Grouping driven by effects
3. Grouping driven by exposure scenarios
4. Grouping driven by availability of measurement techniques

252. Treye Thomas admitted that both stimulus presentations had lifecycle consideration. The breakout room for discussion has been opened based on questioning if proposing subgrouping based on likelihood of exposure in the lifecycle would be sufficient.

Case Studies in Consumer Exposure to ENPs; A Life Cycle Perspective

Robert Reed, Arizona State University, US

253. The most commonly used nanomaterials in products are silver, titanium dioxide, and zinc oxide, all of which have potential direct contact with consumers.

254. Silver nano-products include bandages, creams, and mineral supplements. The mineral supplement, "Mesosilver," is used as an example in this presentation. "Mesosilver" advertises that it has

the highest particle surface area to volume ratio to guarantee "maximum effectiveness" as its way of demonstrating the use of nanoparticles.

255. The environmental exposure modeling of the realistic concentrations of Ag nanoparticles in the air, water, and soil are 1.7 x 10^{-3} µg/m^{-3}, 0.03 µg/L^{-1}, and 0.02 µg/kg^{-1}, respectively. The percent of dissolution is an important environmental factor. The solution and coating are important to analyse when considering dissolution of the nanoparticle. Three different coatings on silver nanoparticles were tested. The particle coated in TA did dissolve, while Citrate and PVP coatings did not show dissolution of the nanoparticle.

256. Zinc oxide nano-products include sunscreen and supplement drinks as well. ZnO dissolves quickly, which should be a consideration of consumer exposure. There was no dissolution of the nanoparticle in the hard water. Nano-ZnO shows the same properties as dissolved Zn^{2+}.

257. Titanium is found in food and sunscreen. The graph in Figure 15 shows the amount of titanium found in common foods.

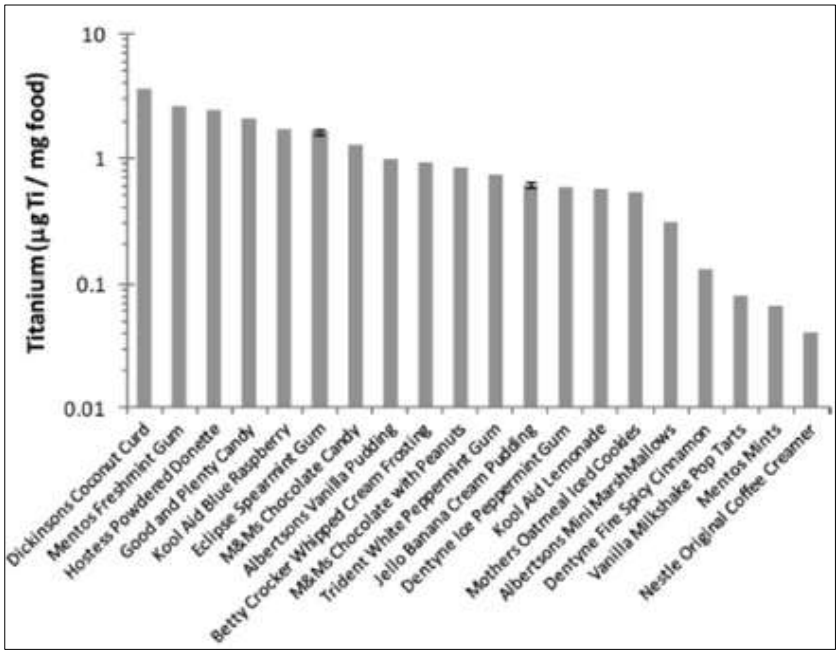


Figure15. Common foods that contain titanium

258. It is not known, but the likelihood that the trace amounts of Ti are actually nano-titanium dioxide is high.

259. Titanium dioxide is found in sunscreens on the market and is generally insoluble. However, it can be coated in Al_2O_3. It is important to consider whether the consumer is really being exposed to the titanium or its coating. What is really washing off into the water?

260. Information was cited from the *Journal of the American Academy of Dermatology*[14] in order to show that there is a significantly large difference in relative photoreactivity due to the coating of the

[14]Mitchnick et al., *Journal of the American Academy of Dermatology*. Volume 40, Issue 1, January 1999, Pages 85–90.

nanoparticles. The rate of isopropanol oxidation decreases from the pure nanoparticle to the coated nanoparticle.

261. Reed described his research in Old Danube Lake in Austria. Titanium concentrations in the water due to sunscreen use were analysed during different seasons. The results were normalised to aluminium concentrations. The results showed a slight increase of concentration in the summer. The conclusion of these results is that it is important, when considering modelling, to also be able to measure the nanomaterials in the environment. Assessing exposure depends on ability to detect low concentrations of release.

SESSION 9: RISK ASSESSMENT

Panel
Chair: Yasir Sultan, Environment Canada, Canada
Rapporteur: Kirsten Rasmussen, Institute for Health and Consumer Protection, EU

262. The purpose of this breakout session was to discuss the merits and purpose of the different types of categorisation schemes listed above and those available in literature. The purpose also extended to identify commonalities and differences between these schemes and determine which are appropriate for the purposes of risk assessment.

The Swiss Precautionary Matrix – a Supporting Tool for Industry and Regulators

Tobias Walser, Federal Office of Public Health (FOPH), Switzerland

263. The Precautionary Matrix is a pragmatic tool that has been in place in Switzerland for three to four years. The manufacturers have to prove the safety of their product, and the Swiss Authorities provide them with the tools to do so. The nanomaterials assessed in the Precautionary Matrix must be intentionally produced in order to be defined as an MNM. An action plan was approved in 2008 in order to promote dialogue between stakeholders and regulators, promote safety in the industry, and fund research projects that are dedicated to adapting the regulatory framework for nanomaterials.

Regulatory Situation

264. The guidance provided for the industry on the safe use of nanomaterials from the Swiss Authorities consists of the Precautionary Matrix, guidance on writing MSDS, guidance for the disposal of industrial waste containing synthetic nanomaterials, and guidance on self-supervision. The Swiss Authorities provide the "Method for Screening the Nano-Specific Health and Environmental Risks of Nanoproducts." It is not a tool for doing the risk assessment but rather an indication of where actions are needed to ensure the safety of nanomaterials.

265. The Precautionary Matrix is available in four languages and comes equipped with guidance materials. An interesting feature of this tool is that it is not legally binding, which means that the nanomaterial industry, researchers, consumers, and environmental stakeholders closely cooperate with the Swiss Authorities to ensure that the matrix is up to date. The Swiss Authorities assure the voluntary users

that the data are not saved on any federal web browsers. This tool is always employed in parallel to the existing assessment methods, not as an alternative.

266. When beginning to use the Precautionary Matrix, the user must define if the material under assessment is nano-relevant. The user must identify the state of knowledge, better described as the level of uncertainty. Next they have to familiarise themselves with emission and exposure guidance and the effect of the MNM, in terms of stability and reactivity. The very basic scale is quantitative and then further categorised into qualitative data of "low, medium, and high." The outcome of this system is that it detects the risk potential and knowledge gaps and points users toward acquiring additional information, which will be ultimately needed for the risk assessment.

267. Each stage of the MNM must be clearly defined by the manufacturer as part of the obligation to self-supervise. If the industry is using the tool correctly, then it helps them to provide the regulatory agency with necessary information. Emissions of nanomaterials by abrasion or combustion processes are exempt from this tool. The precautionary matrix is not influenced by non-nanospecific risks to health or the environment.

Concept

268. An equation was developed to determine a numeric value for the precautionary need (P). If the number is higher there is a higher need for precautionary measures. The equation is defined by the nano-status (N), the uncertainty of the state of knowledge (I), the potential effects (W) and the potential human exposure (E) or emission to the environment.

$$\mathbf{P = N\ (W \times E + I)}$$

269. The nano-relevancy of the material depends on the particle size and agglomeration properties. The level of uncertainty or state of knowledge is determined by whether or not the origins, nanoscales, next users, and material systems are known. The potential effect considers redox activity, oxygen radical formation, catalytic activity, and stability of the nanomaterial under physiological and environmental conditions. The potential human exposure or emission to the environment is affected by the biopersistence and amount of the nanoparticle and frequency of the particle exposure. If the final score is equal to or under 20 then the particle receives a classification of "A," which could be interpreted as a low need for nano-specific action. Anything above 20 requires nano-specific action and is labeled with a classification of "B." The precautionary need will vary for the same product during different stages of the lifecycle.

270. After the score is determined, a diagram is available to determine recommendations for further testing. For instance, if a material is found to have high persistency and high reactivity, then lung exposure is a critical aspect. Now the owner has to ask an expert to determine the risk of exposure.

271. A new version of the Precautionary Matrix was released during the summer of 2014 and has been downloaded more than 1,000 times. There has been ongoing dialogue between the different stakeholders. The feedback about the matrix has been positive. The users have applied the Precautionary Matrix primarily for a better understanding of potentially critical aspects during handling of nanomaterials. The fact that the matrix is not legally binding facilitated the discussion between regulators and industry for a further improvement of the tool and increased the self-motivation of the industry to actively learn and participate in the safety discussion on nanomaterials.

Outlook

272. Further amendments to the specific data requirements for nanomaterials are needed. There is a continuous need to support research for the identification of nanomaterials and dangerous applications. The

Swiss Authorities acknowledge the need to support the development of test guidelines and rules for read-across by categorisation.

A Theoretical Example of Using Concepts of Grouping in a Regulatory Submission

Shaun Clancy, BIAC

273. Shaun Clancy stated that this was an entirely theoretical presentation and none of examples provided were from a dossier. All of the concepts were presented with imaginary examples. The concepts were the important part of this presentation; whose intent was to stimulate discussion on grouping concepts.

274. One benefit of grouping from a risk assessment perspective is to have a single regulatory submission address more than one molecular identity, which leads to a quicker regulatory review and commercialisation process. Grouping will reduce the need for testing taking advantage of read-across using data for the materials in a group. The ultimate purpose is to present information that allows reviewers to conclude that the materials have enough similarities to be considered as a single group using information provided for individual members of the group and applying them to all to all of the grouped materials for the purposes of a risk assessment. Grouping may be possible for molecular identity, physical properties, hazards, and exposures.

Grouping by Molecular Identity of Substance(s)

275. If there is only a minor variation in the molecular composition between two or more substances, then they can be considered effectively identical. If there is a significant but inconsequential difference in the composition, such as multiple core-shell materials with different cores but the same shell, these nanomaterials could be considered identical from a regulatory perspective since, in the example provided, the shell is the part that is exposed to the external environment and there is no exposure to the core.

Physical Properties

276. There are many examples of physical properties that could be used to group nanoparticles. For instance, ZnO treated with NH_2-Si-EtO_3 versus ZnO treated with NH_2-Si-BuO_3 would be comparable since the significant common property that these materials share is that they both generate zinc ions. Materials that are surface treated with a chemical that does not provide additional reactivity can be considered a mixture. Another example of considering physical properties is assessing particle size. Al_2O_3 particles that have all been treated with the same coating but exhibit a different particle size can all be effectively the same particle. Aluminium oxide is relatively inert, and that should not change with size, same for ZnO particles ranging from 30-70 nm with the same coating. Essentially, the main impact of any zinc oxide particle size would be the release of zinc ions and might be treated as the same.

Eco/toxicological Properties

277. Cadmium sulfide and cadmium selenide in certain quantum dots would be categorised together because there are no releases of Cd ions in biological media.

Hazard Exposure

278. From a hazard perspective, if the levels of Zn^{2+} ions released from soluble Zn-based nanomaterials are comparable, then the materials may be considered comparable.

Conclusions

279. Grouping concepts may be useful in considering materials together in risk assessment or similar regulatory evaluations. Supporting information is needed to support these types of theories.

FINAL RECOMMENDATIONS

280. The expert meeting **concluded** that discussion and conclusions can be used to develop fit-for-purpose decision frameworks for categorisation that can be utilised under different regulatory systems for manufactured nanomaterials.

281. To support this, the expert meeting **recommends**:

1. Identifying and developing, where needed, methods for characterization of relevant physical-chemical properties for toxicokinetics, fate, hazard, and exposure assessments.

2. Use of methods that enable comparability, are reliable, and use the OECD Guidance on Sample Preparation and Dosimetry [ENV/JM/MONO(2012)40].

3. Agreeing on or developing experimental models (e.g., *in-vitro* and *in-vivo* assays) that are predictive of human health and environment effects and that support categorisation.

282. **Acknowledges** that tools and methodologies for categorisation might be different depending on the criteria to be analysed for the assessment of nanomaterials.

283. **Acknowledges** that definitions and terminologies need to be clarified and consistently applied.

284. **Supports** adapting existing approaches for conventional substances to fit specificities of categorisation frameworks for manufactured nanomaterials.

285. **Supports** case studies that inform categorisation schemes as they are developed and refined.

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ANNEX I: AGENDA

17th September 2014		**1ST DAY**
8h00	**Registration**	
8h20 - 8h30	**Welcome Remarks**	Jeff Morris (United States)
8h30 - 8h40	**Background**	Mar Gonzalez (OECD Secretariat)
8h40 - 8h55	**General Introduction to the Agenda**	Maria Doa (United States)
SESSION 1	**CONTEXT FOR NEED FOR THE USE OF CATEGORIES, AND PERSPECTIVES ON THEIR APPLICATION TO NANOMATERIALS**	
8h55 - 9h10	**Introduction to Session 1: Importance of Categorization for Risk Assessment and Risk Management**	Maria Doa (United States)
9h10 - 9h30	**Keynote lecture: "OECD Member Countries' Approaches to Develop or Use Concepts of Grouping, Equivalence and Read-Across Based on Physical-Chemical Properties (GERA-PC) of Nanomaterials for their Hazard Assessment in Regulatory Regimes"**	Takuya Igarashi (Japan)
9h30 – 10h30	**Panel: Use of Category Approach and Groupings of Nanomaterials Regionally and Nationally:** 1)**"Development of a Classification Scheme under the Canada-United States Regulatory Cooperation Council Nanotechnology Initiative"** 2) "**EU REACH Perspective of Categorization, Grouping and Read-Across"** *Q&A*	Chair of the Panel: Kenneth Moss (United States) 1) Brad Fisher (Canada) and Jim Alwood (United States) 2) Jenny Holmqvist (European Union)

10h30 - 10h50	**COFFEE BREAK**	
10h50 –11h10	**Keynote lecture on Physical-chemical Characterization**	Monique Groenewold (The Netherlands)
11h10 -- 11h30	**Keynote lecture on Fate Assesment: "Novel properties as an organizing concept for categorizing engineered nanomaterials for regulatory purposes"**	Mark Wiesner (United States)
11h30 -- 11h50	**Keynote lecture on Ecotoxicity Assessment: "Novel techniques for toxic nanoparticle categorization"**	Suman Pokhrel (Germany)
11h50 – 12h10	**Keynote lecture: "The use of Alternative Testing Strategies to Advance Risk Analysis of Nanoscale Materials"**	Jo Anne Shatkin (Society for Risk Analysis - SRA)
12h10 – 12h30	Discussion	
12h30 – 13h20	**LUNCH**	
13h20 – 13h45	**Keynote lecture on Health Assesment :** **"Grouping of Nanomaterials for Health Assessment-Genotoxicity"**	Maria Donner (BIAC)
13h45 – 14h10	**Keynote lecture on Health Assesment : "The State-of -the Art Health Effects of Nanomaterials and their Regulatory Implications"**	Tom Van Teunenbroek (The Netherlands)
	"Example of the Grouping of Nanomaterials for Health Assessment in a National or International Regulatory Context: *How to extend/verify the Concept: "Taquann" whole body inhalation system for speeding up the toxicity studies for categorization of manufactured nanomaterials"*	Jun Kanno (Japan)
14h10 – 14h30	**Keynote lecture: "Grouping of Nanomaterials by Release Type? "**	Thomas Kuhlbusch (Germany)
14h30 – 14h50	**Keynote lecture : "Can a Grouping Approach Help Solve Some Key Nanomaterial Exposure Assessment Challenges?"**	Charles Geraci (United States)
14h50 – 15h10	**COFFEE BREAK**	

SESSION 2	**RISK ASSESSMENT AND RISK MANAGEMENT**	
15h10 -16h30	**Risk Assessment: Utilization of Categories in Risk Assessment** **<u>Stimulus presentations:</u>** **"The Use of Categories in Risk Assessment: A perspective of the WPMN's work on Risk Assessment and Regulatory Programmes "** Yasir Sultan (Canada) **"The ITS-NANO Approach to Risk Assessment, including Grouping and Ranking"** Vicki Stone (Uunited Kingdom) **"Evaluating the Evidence to Develop Occupational Exposure Bands for Nanomaterials"** Eileen Kuempel (United States) **"Overview of Risk Assessment and Factors to Consider for Differing Regulatory Programmes"** Tala Henry (United States)	Co-chairs: Yasir Sultan (Canada) and Maila Poulamaa (European Union)
16h30 – 17h00	**Panel on Risk Management** Speakers: Maria Doa (United States) Henrik Laursen (European Union) Brad Fisher (Canada)	Co-chairs: Maria Doa (United States) and Henrik Laursen (European Union) Rapporteur: Shaun Clancy (BIAC)
17h00 – 17h20	**COFFEE BREAK**	
SESSION 3	**PHYSICAL-CHEMICAL CHARACTERIZATION** *Participants will be invbited to review the proposed **categorisation scheme** (see Background Document) and discuss the following issues:* • *Are the proposed categories presented in the Background Document a reasonable starting point for general categorization? For further categorization?* • *Are the proposed categories a reasonable starting point for further sub-categorization as is?* • *What physical-chemical endpoints are most applicable for assessing environmental toxicity? For human health endpoints?* • *What specific activities would be needed to provide sufficient evidence for the use of categorization in these questions for risk assessment and risk management?*	

	• *What information is required for assessing the validity of each (sub)category?* • What categories are applicable across multiple endpoints?	
17h20-18h20	**Physical-chemical Characterization** **<u>Stimulus presentations:</u>** **" An industrial perspective"** Scott Brown (BIAC) **"A metrological perspective"** Angela Hight Walker (United States)	Co-chairs: Vicki L. Colvin and Angela Hight Walker (United States) Rapporteur: Scott Brown (BIAC)
18h20 –18h30	Day 1 Summary of the Discussion	Maria Doa (United States)
18h30	**END OF DAY 1**	

18th September 2014		**2ND DAY**
8h30 — 8h40	**Welcome and Overview of Day 2 Agenda**	Maria Doa (United States)
SESSION 3	**PHYSICAL-CHEMICAL CHARACTERIZATION (Cont.)**	
8h40 – 9h30	**Physical-chemical Characterization**	Co-chairs: Vicki L. Colvin and Angela Hight Walker (United States) Rapporteur: Scott Brown (BIAC)
9h30 – 10h00	**Report of the Session 3 on Physical-chemical Characterization and Recommendations**	Scott Brown (BIAC)
10h00 – 10h20	**COFFEE BREAK**	

	SESSION 4 ENVIRONMENTAL FATE	**SESSION 5 HUMAN HEALTH (PART 1)**
	Each session will define which physical-chemical properties are most important for the assessment respectively. *Each session will address the following questions:* • *Are the proposed categories presented in the* ***Background Document*** *a reasonable starting point for general categorization? For further categorization?* • *Are the proposed categories a reasonable starting point for further sub-categorization as is?* • *What specific activities would be needed to provide sufficient evidence for the use of categorization in these questions for risk assessment and risk management?* • *What information is required for assessing the validity of each (sub)category?* • *What categories are applicable across multiple endpoints?* • *To what extent can Structure-Activity Relationships (SAR) be used?*	
10h20 – 12h20	**SESSION 4 ENVIRONMENTAL FATE** Co-chairs: Willie Peijnenburg (The Netherlands) and Elijah Petersen (United States) Rapporteur: Steffi Friedrichs (BIAC) **Stimulus presentations:** "Title of the presentation (TBC)" Jamie Lead (United Kingdom) **"Nanotechnology Categorization by Environmental Fate and the Implications on Exposure and Hazard"** Al Kennedy (United States) **"Environmental Fate Break out Group"** Thomas Kuhlbusch (Germany)	**SESSION 5 HUMAN HEALTH (PART 1)** Co-chairs: Jenny Holmqvist (European Union) and Juergen Schnekenburger (Germany) Rapporteur: Myriam Hill (Canada) **Stimulus presentation:** **"BASF approach of grouping of nanomaterials"** *Karin Weinch (BIAC)* **" *In vitro* and *in vivo* Approaches to Assessing the Pulmonary Toxicity of Nanomaterials, and How They Can Inform Categorisation"(P)** Vicki Stone (United Kingdom)
12h20 - 13h30	**LUNCH**	
	PLENARY REPORTS AND CONCLUSIONS FROM SESSIONS 4 AND 5	
13h30 - 14h00	Reports of the Breakout Session 4 – Recommendations	Steffi Friedrichs (BIAC)
14h00 – 14h30	Reports of the Breakout Session 5 – Recommendations	Myriam Hill (Canada)

	SESSION 6 ENVIRONMENTAL TOXICITY	SESSION 7 HUMAN HEALTH (PART 2)	SESSION 8 EXPOSURE ASSESSMENT
	Each session will review the proposed categorisation scheme (see Background Document) and address the following questions: • *Are the proposed categories presented in the **Background Document** a reasonable starting point for general categorization? For further categorization?* • *Are the proposed categories a reasonable starting point for further sub-categorization as is?* • *What specific activities would be needed to provide sufficient evidence for the use of categorization in these questions for risk assessment and risk management?* • *What information is required for assessing the validity of each (sub)category?* • *What categories are applicable across multiple endpoints?* • *To what extent can Structure-Activity Relationships (SAR) be used?*		
14h30 – 15h30	**SESSION 6** **ENVIRONMENTAL TOXICITY** Chair: Greg Goss (Canada) Rapporteur: Eric Bleeker (The Netherlands) **Stimulus presentations:** **"Categorization of NM regarding ecotoxicity"** Kerstin Hund-Rinke (Germany) **"Decision Trees and Aquatic Toxicity Testing for Nanomaterials"** Greg Goss (Canada)	**SESSION 7** **HUMAN HEALTH (PART 2)** Co-chairs: David Warheit (BIAC) and Phil Sayre (United States) Rapporteur: Agnes Oomen (The Netherlands) **Stimulus presentations:** **"Development of Equivalence Criteria for Nanomaterials by Intratracheal Administration Study"** Masashi Gamo (Japan) **"5-day Inhalation Protocol and Results for Grouping of Nanomaterials"** Karin Weinch (BIAC)	**SESSION 8** **EXPOSURE ASSESSMENT** Chair: Vladimir Murashov (United States) Rapporteur: Kim Rogers (United States) Session 1: Facilitator : Chuck Geraci (United States) **Stimulus presentation:** **"The 'Source Domain' Concept: Different Release Processes and Associated Exposure"** Derk Brouwer (The Netherlands) Session 2: Facilitator : Treye Thomas (United States) **Stimulus presentation:** **"Case Studies in Consumer Exposure to**

			ENPs; A Life Cycle Perspective" Rob Reed (United States)
15h30 – 15h50	**COFFEE BREAK**		
	SESSION 6 ENVIRONMENTAL TOXICITY (CONT.)	**SESSION 7 HUMAN HEALTH: Part2 (CONT.)**	**SESSION 8 EXPOSURE ASSESSMENT (CONT.)**
15h50 – 16h50	Chair: Greg Goss (Canada) Rapporteur: Eric Bleeker (The Netherlands)	Co-chairs: David Warheit (BIAC) and Phil Sayre (United States) Rapporteur: Agnes Oomen (The Netherlands)	Chair: Vladimir Murashov (United States) Rapporteur: Kim Rogers (United States)
	PLENARY REPORTS AND CONCLUSIONS FROM SESSIONS 6 AND 7		
16h50 – 17h20	Reports of the Breakout Session 6 – Recommendations		Eric Bleeker (The Netherlands)
17h20 – 17h50	Reports of the Breakout Session 7 – Recommendations		Agnes Oomen (The Netherlands)
17h50 – 18h00	Summary of day 2		Maria Doa (United States)
18h00	**END OF DAY 2**		

19 September 2014		**3RD DAY**
8h30 – 8h40	**WELCOME AND OVERVIEW OF DAY 3 AGENDA**	
8h40 – 9h10	Reports of the Breakout Session 8 – Recommendations	Kim Rogers (United States)
9h10 – 10h10	Synthesis of Results – What can be deduced across endpoints disucssed in the Breakout Sessions 2-7	Panel: Chairs of Breakout Sessions 2-7
10h10 – 10h30	**COFFEE BREAK**	
SESSION 9	**SESSION 9 RISK ASSESSMENT**	
10h30 - 12h00	**Session 9 Risk Assessment: Utilization of Categories in Risk Assessment**	Chair: Yasir Sultan (Canada)

	<u>Stimulus presentations:</u> ***"The Swiss Precautionary Matrix – a supporting tool for industry and regulators"*** Tobias Walser (Switzerland) **"A Theoretical Example of Using Concepts of Grouping in a Regulatory Submission"** Shaun Clancy (BIAC)	Rapporteur: Kirsten Rasmussen (JRC European Union)
12h00 – 13h10	**LUNCH**	
SESSION 9	**SESSION 9 RISK ASSESSMENT (Cont.)**	
13h10 – 14h10	**Session 9 Risk Assessment (Cont.)**	Chair: Yasir Sultan (Canada) Rapporteur: Kirsten Rasmussen (JRC European Union)
14h10 – 14h40	**Risk Assessment** Reports of the Session 9 – Recommendations	Kirsten Rasmussen (JRC European Union)
14h40 – 15h00	**COFFEE BREAK**	
15h00 – 16h00	**Risk Management** –Recommendations for better risk management tools	Maria Doa (United States) and Henrik Laursen (European Union)
16h00 – 16h30	Summary of the Meeting	
16h30	**END OF DAY 3 – ADJOURN**	

ANNEX II. LIST OF PARTICIPANTS

Participants list for Workshop : OECD Expert Meeting on Categorisation of Manufactured Nanomaterials/Liste des participants pour Atelier : Groupe de travail OCDE sur les nanomatériaux manufacturés

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17/9/2014 - 19/9/2014

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