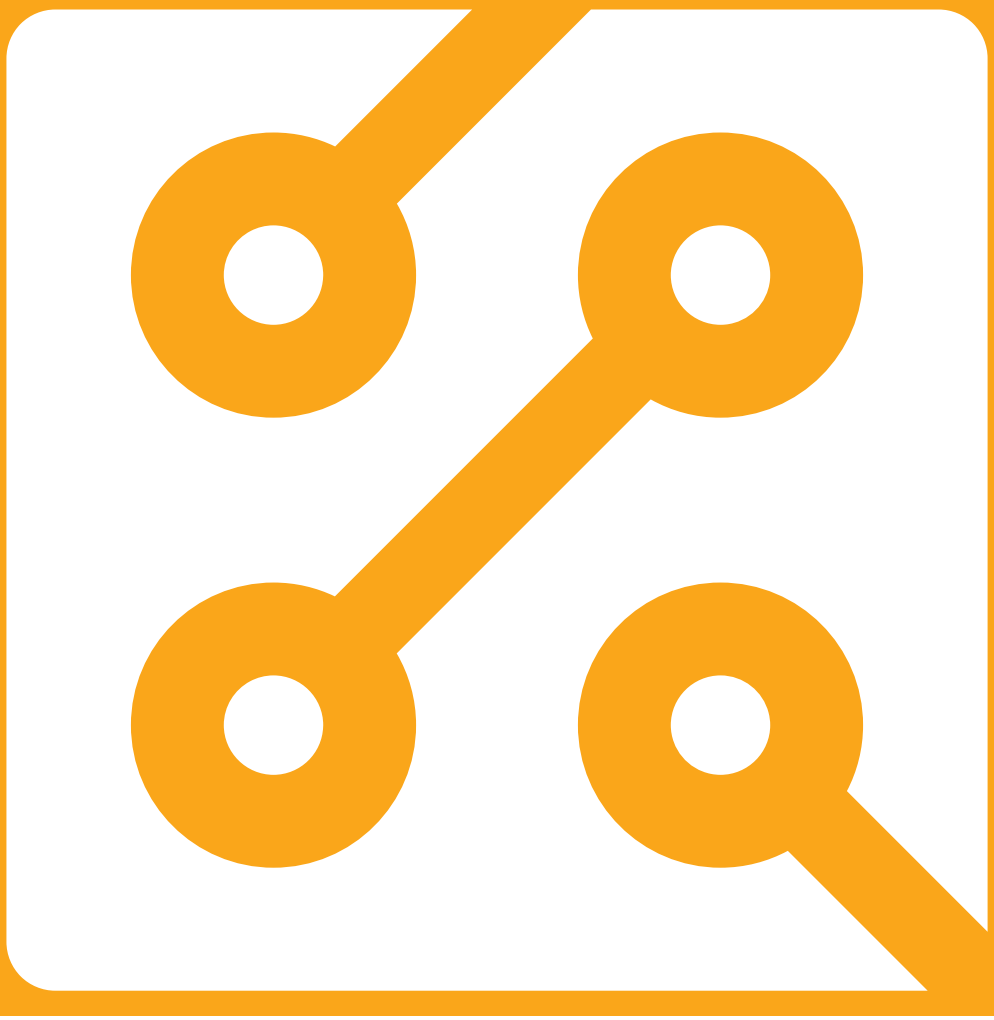
ECHA
EUROPEAN CHEMICALS AGENCY

TOPICAL SCIENTIFIC WORKSHOP
Regulatory Challenges in the Risk Assessment of Nanomaterials

Proceedings

23 – 24 October 2014, Helsinki, Finland



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Topical Scientific Workshop: Regulatory Challenges in the Risk Assessment of Nanomaterials

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LIST OF ABBREVIATIONS

Ag	Silver
AOP	Adverse outcome pathways
ASTM	American Society for Testing and Materials
Au	Gold
BCF	Bioaccumulation or bio-concentration factor
BET	Brunauer–Emmett–Teller
BPR	Biocidal Products Regulation
BSI	British Standards Institution
C60	Fullerene
CEN	European Committee for Standardisation
CLP	Classification, Labelling and Packaging
CLS	Characteristic loss spectroscopy
CNT	Carbon nanotube
DG	Directorate-General
DIS	Draft international standard
DLS	Dynamic light scattering
DSL	Domestic Substances List
EC	European Commission
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
EM	Electron microscopy
ENM	Engineered nanomaterial
ENP	Engineered nanoparticle
EPA	Environmental Protection Agency
ERA	Environmental risk assessment
EU	European Union
FDIS	Final draft international standard
FMPS	Fast mobility particle sizer
FP	Framework Programme
GAARN	Group Assessing Already Registered Nanomaterials
HARN	High aspect ratio nanomaterials
ICP-MS	Inductively coupled plasma mass spectrometry
IOM	Institute of Occupational Medicine
ISO	International Organisation for Standardisation
ITS	Intelligent testing strategy
IUTA	Institut für Energie- und Umwelttechnik
JRC	Joint Research Centre
Kd	Partitioning coefficient
Kow	Octanol/water partition coefficient
Kr	Batch retention coefficients
LD	Laser diffraction
MPS	Mononuclear phagocytic system
MSC	Member State Committee

MSCA	Marie Skłodowska-Curie actions
MWCNT	Multi-walled carbon nanotubes
NGO	Non-governmental organisation
NM	Nanomaterial
NMWG	Nanomaterial Working Group
NOAEC	No observed adverse effect concentration
NRCWE	National Research Centre for the Working Environment
OECD	Organisation for Economic Cooperation and Development
PCA	Principle component analysis
PEC	Predicted environmental concentration
PEG	Polyethylene glycol
PNEC	Predicted no effect concentration
PSD	Particle size distribution
PVP	Polyvinylpyrrolidone
QSAR	Quantitative structure–activity relationship
R&D	Research and development
RAC	Regional advisory councils
RCC	Regulatory Cooperation Council
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RIP-oN	REACH Implementation Projects on Nanomaterials
RIVM	National Institute for Public Health and the Environment
ROS	Reactive oxygen species
SAXS	Small-angle X-ray scattering
SCCS	Scientific Committee on Consumer Safety
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SEM	Scanning electron microscopy
SOP	Standard operating procedure
STIS	Short-term inhalation studies
SWCNT	Single-walled carbon nanotubes
TEM	Transmission electron microscopy
TG	Test guideline
TiO2	Titanium dioxide
TR	Technical report
TS	Technical standard
TSCA	Toxic Substances Control Act
UK	United Kingdom
US	United States
UV	Ultraviolet
VSSA	Volume-specific surface area
WG	Working group
WPMN	Working Party on Manufactured Nanomaterials
XRD	X-ray diffraction
ZnO	Zinc oxide

1 PREFACE

The European Chemicals Agency's (ECHA) topical scientific workshops contribute to the Agency's third strategic objective to be a hub to promote good regulatory science.

The workshops provide a platform for academia and regulators to come together to address important long-term challenges in regulatory science. The idea is to discuss issues framed from the regulatory perspective with scientists who are experts in the field.

This bringing together of science and regulatory affairs professionals should help see the topic from different perspectives. The aspiration is that a better understanding of how to move forward in solving the regulatory challenges will arise. This may be through ideas on better approaches that can be adopted in the short term, when the science is 'ripe'.

Just as important, the discussions will help steer scientific research and development (R&D) by communicating important regulatory challenges. Although ECHA does not undertake research, it has a role in influencing R&D work by encouraging developments that could be relevant to the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), Classification, Labelling and Packaging (CLP) and the Biocidal Products Regulations (BPR).

The latest scientific developments in key topic areas are brought together with their potential use in existing regulatory schemes. This means that this workshop is not just an information sharing event, but an opportunity to contribute ideas for improved methodologies that may lead to better guidance, new tools for use by ECHA and its stakeholders and help with a more rapid integration of scientific development into regulatory decision making.

2 INTRODUCTION

The Topical Scientific Workshop on Nanomaterials, held on 23-24 October 2014 at ECHA in Helsinki, Finland, brought together close to 200 experts in the field of risk assessment of nanomaterials representing academia, policy makers, industry and non-governmental organisations (NGOs).

The workshop provided a unique platform for academia and regulators to discuss how to address current challenges from the regulatory perspective, which can be reflected and employed in the on-going and future research topics on nanomaterials. The discussions were reinforced by information of the recent developments and of risk assessment methodologies applied in chemicals management both within and outside the European Union (EU).

2.1 WORKSHOP ORGANISATION

2.1.1 Scientific Committee

The Chairman of the workshop, Prof. Wim De Coen from the European Chemicals Agency, was supported by an international Scientific Committee in the preparation of the workshop programme. The members of the Scientific Committee were:

- Prof. Wim De Coen (chairman), European Chemicals Agency, Finland

- Dr David Carlander, Nanotechnology Industries Association, Portugal
- Prof. Kenneth A. Dawson, Centre for BioNano Interactions, Ireland
- Dr Roger Doome, Industrial Minerals Association Europe, Belgium
- Jenny Holmqvist, European Chemicals Agency, Finland
  Chair of the OECD WPMN's Steering Group on Testing and Assessment of Manufactured nanomaterials
- Dr Derek Knight, European Chemicals Agency, Finland
- Prof. Frank Le Curieux, European Chemicals Agency, Finland
- Prof. Kai Savolainen, Finnish Institute of Occupational Health, Finland
- Dr Kathrin Schwirn, Federal Environment Agency, Germany
- Dr Nicolas Segebarth, European Commission, Directorate-General for Research and Innovation, Belgium
- Dr Hermann Stamm, European Commission, Joint Research Centre, Italy
- Dr Claus Svendsen, Centre of Ecology & Hydrology, United Kingdom
- Dr Tom Van Teunenbroek, Ministry of Infrastructure and Environment, The Netherlands
- Dr Violaine Verougstraete, Eurometaux, Belgium

2.1.2 Workshop themes

The workshop was structured into five sessions, each mirroring a prioritised area where further discussion is needed and where science and frontline research may offer solutions to be applied in a regulatory context.

1. Challenges in the regulatory risk assessment of nanomaterials.
2. Measurements and characterisation of nanomaterials.
3. Metrology and dose metrics for hazard and exposure assessment throughout the life cycle.
4. Environmental fate, persistence and bioaccumulation throughout the life cycle.
5. Read-across and categories of nanomaterials.

2.1.3 Scope and format of the workshop proceedings

This proceedings document provides an account of the workshop, in conjunction with the original presentations for additional detail, structured to reflect the themes and conduct of the workshop, and citing content from the Background Paper developed by ECHA for the purposes of this workshop.

It then provides an overview of the current state of practice or research in each of the themes, with the synopses contributed by many of the invited speakers, along with an unattributed discourse of the dialogue from the facilitated panel discussions.

While the content of this Proceedings document does not represent a consensus view of ECHA, the Scientific Committee or the workshop delegates, it serves as a record of on-going activities and highlights remaining needs and potential future directions.

2.1.4 Discussion questions

The following questions were identified by the Scientific Committee and intended to be used to initiate the session and panel discussions:

Characterisation

1. How should deliberated surface modifications such as coatings of the nanoparticle be characterised once released in the environment (absorption of air pollution or in the organism such as formation of protein corona)?
2. What existing methods (SOP) are currently available to ensure a proper characterisation of nanomaterials and nanoforms, such as dissolution protocols etc.?
3. Assuming that the nanomaterial changes its morphology in the supply chain and depending on the media it is exposed to, does this mean that the existing criteria for characterisation of a substance to aid the understanding of potential impact throughout the life cycle should be different for nanomaterials?
4. Currently, only imaging techniques such as electro and scanning force microscopies are potentially able to distinguish between aggregates, agglomerates and primary particles. How can these challenges be overcome? What are the needs currently in forms of validated methods and how far away are those from being utilised in a regulatory context?

Metrology and Metrics

1. Which metrics should be used for regulatory risk assessment mass, surface area, number of particles per cm^3/kg? If mass is not the preferred metric, how can the other metrics be bridged/extrapolated to allow for the use of them in a regulatory setting which is based on mass?
2. Comprehensive monitoring surveys required sophisticated equipment and can only be carried out by experts. In addition, there is a lack of harmonisation on the available data (collected by different instruments, in different metrics, representing different scenarios: release, area, personal), which hampers the use of this data for risk assessment. How can this be overcome?
3. There is a need to develop portable instruments that can be used for personal monitoring; most available instruments can only be used as stationary instruments. Where is the development on this?
4. When measuring the exposure to particles in the workplace, how can we discriminate between particles based on physico-chemical characteristics such as elemental composition to allow for subcomponents of measured particle population to be attributed to different sources?

Environmental fate, persistence

1. Which nanomaterials are likely to accumulate in humans and the environment?
2. What specific endpoints on nanomaterials physical/chemical alteration in the environment are deemed necessary to appropriately assess the nanomaterial (NM) fate and behavior?
3. How could the physical/chemical alteration of nanomaterials be taken into account for the determination of the effects in the environment?
4. How does the trophic mobility of different nanomaterials differ and what impact does this have on potential bioaccumulation in different (including higher) organisms?
5. Under which conditions can a nanomaterial be considered as completely dissolved to describe the environmental behavior and effects? And how should nanomaterials that are just partly dissolved be considered during the period of observation?
6. What is the current level of knowledge/understanding on the fate of nanomaterials in the different environmental compartments (air, water, soil, sediment) and what are the main knowledge gaps?
7. What are the synergies and differences in the current regulatory schemes regarding nanomaterials? Is there a need for harmonisation of the environmental risk assessment of nanomaterials?
8. How could the current scientific knowledge be best translated into the regulatory action?

Read across

1. How can different surface treatments/modifications be grouped based on their predictability for alternating biokinetics? Compared to size, will the surface chemistry be of more importance?
2. Which environmental fate/behavior and effect endpoints related to the different compartments may be needed to know to be able to decide on grouping/read-across, if that grouping is not possible based on physicochemical parameters alone?

3 TOPIC 1: INTRODUCTION TO INTERNATIONAL VIEWS ON SCIENTIFIC CHALLENGES IN REGULATORY RISK ASSESSMENT OF NANOMATERIALS

3.1 BACKGROUND

Although there are currently no provisions in REACH that refer explicitly to nanomaterials[1] , they are considered to be covered by the substance definition under REACH. The basic principle stated in Article 1(3) is: 'This Regulation is based on the principle that it is for manufacturers, importers and downstream users to ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment' applies to nanomaterials. Moreover, the Commission's second regulatory review on nanomaterials emphasised that 'REACH applies equally to substances for which all or some forms are nanomaterials'.

Safe use claims under REACH should be based on explicit and transparent documentation supporting the hazard, exposure and risk assessment of nanomaterials and the existing risk assessment paradigm developed for traditional chemicals should, in principle, also be applied to nanomaterials. However, in line with scientific developments, there are specific considerations that registrants should report in specific endpoint sections, as this information will aid the evaluation of the adequacy of the tests performed and data obtained with regard to the safety assessment of nanomaterials (e.g. sample preparation, solubility/ dispersion, use of stabilisers etc.)[2]

Together with industry, stakeholder groups, Member States and the Commission, ECHA has given more clarity to registrants on how to demonstrate the safe use of their substances in all forms under REACH. This work has generated best practice, clarified policy lines and improved the existing guidance for nanomaterials[3 4 5 6]

ECHA was actively involved in the REACH Implementation Projects on Nanomaterials (RIP-oN) projects addressing substance identity, information requirements and exposure assessment (RIP-oNs 1-3)[7] and in the NANOSUPPORT2 project with Directorate-General (DG) Joint Research Centre (JRC).

ECHA also began a Nanomaterial Working Group (NMWG) as an advisory group consisting of experts from Member States, the European Commission, ECHA and accredited stakeholder organisations and coordinated the GAARN project (Group Assessing Already Registered Nanomaterials) to assess current registrations for representative nanomaterials with their respective registrants to give information on best practice[3-6].

1 http://ec.europa.eu/enterprise/sectors/chemicals/files/reach/nanomaterials_en.pdf Follow-up to the sixth meeting of the REACH competent authorities for the implementation of Regulation (EC) 1907/2006 (REACH) on 15-16 December 2008
2 http://echa.europa.eu/documents/10162/13643/appendix_r14_05-2012_en.pdf ECHA Guidance, Appendix to Chapter R.14, 2012
3 http://echa.europa.eu/regulations/nanomaterials ECHA nanomaterials web page
4 http://echa.europa.eu/documents/10162/5399565/best_practices_physiochem_subst_id_nano_en.pdf Best practice on physicochemical and substance identity information for nanomaterials - Report from first GAARN meeting
5 http://echa.europa.eu/documents/10162/5399565/best_practices_human_health_environment_nano_en.pdf Assessing human health and environmental hazards of nanomaterials - Best practice for REACH Registrants - Report from second GAARN meeting
6 http://echa.europa.eu/documents/10162/5399565/best_practices_human_health_environment_nano_3rd_en.pdf
7 http://ec.europa.eu/environment/chemicals/nanotech/reach-clp/ripon_en.htm

3.1.1 Issues to be addressed

It is recognised that there are issues that still need to be further clarified when the conventional risk assessment paradigm is applied to nanomaterials. Currently, a key issue in regulatory risk assessment of nanomaterials is to identify, if and when, revisions and amendments in guidance and procedure are needed to make sure that the risk of nanomaterials can be appropriately assessed and documented. Moreover, the approach to the regulatory assessment of nanomaterials is subject to the legal frameworks in place in each jurisdiction, which can differ markedly.

This session sought to give an overview, based on approaches in Europe, the United States and Canada, of the current challenges in the regulatory risk assessment of nanomaterials, including how uncertainties on the applicability of the conventional risk assessment paradigm should be identified and, more importantly, how these knowledge gaps can be filled. Furthermore, an aim of the session was to identify how current methodologies for assessing the potential risks of nanomaterials can be improved.

The following are key issues in regulatory risk assessment:

- identification and characterisation of the relevant key characteristics or properties affecting the release, exposure behaviour (fate and kinetics), effects (hazards) and the subsequent risks of nanomaterials (including their different nanoforms);
- lack of available and validated data on the hazard properties of nanomaterials (including their different nanoforms);
- lack of common understanding on how to distinguish between different nanoforms and what criteria should be used to make such assessments;
- lack of scientific justification for extrapolations between nanomaterials and 'standard' ("bulk") chemicals, including the grouping and read-across between different nanoforms;
- selection of appropriate risk assessment approaches and methodologies for the most relevant hazard endpoints related to the risks of nanomaterials;
- uncertainty associated with reaching conclusions about the fate and distribution of the nanomaterials in the environment.

The following are key issues in risk management:

- knowledge of use profiles of nanomaterials;
- methods to mitigate exposure;
- validation of exposure models (e.g. computational modelling tools) for nanomaterials.

3.2 PRESENTATIONS

For Topic 1 of the workshop, the following presentations were made:

- "Nano challenges in the EU" – Ms Jenny Holmqvist, European Chemicals Agency
- "Assessment and management of nanomaterials under the Toxic Substances Control Act" – Mr Jim Alwood, US Environmental Protection Agency
- "Canada's experience with chemicals assessment and management and its application to nanomaterials" – Dr Brad Fisher, Environment Canada

3.2.1 "Nano Challenges in the EU"

Jenny Holmqvist (European Chemicals Agency), in her presentation entitled "Nano challenges in the EU", stated:

> Although there are no explicit requirements for nanomaterials under REACH or CLP, they meet the regulations' substance definition and therefore the provisions apply. In 2011, the European Commission

released a specific recommendation on the definition of a nanomaterial. The recommendation should be used in different European regulations, including REACH and CLP.

While there are clear practical and commercial prospects in the use of nanomaterials, the rapid increase in their use raises questions about their potential effects on health and the environment. There is a need to adequately assess and manage the potential risks of these new forms of materials. Even though manufacturers, importers and downstream users must ensure the safe use of each substance (whatever its form) under REACH, this introduces new challenges for regulators, such as the Commission and ECHA, as well as all other stakeholders.

ECHA works in close collaboration with Member State competent authorities, the European Commission, stakeholders and international organisations such as the Organisation for Economic Cooperation and Development (OECD).

ECHA's activities on nanomaterials under REACH

Since REACH and CLP cover nanomaterials, ECHA needs to be able to carry out its tasks within the various REACH processes (e.g. registration, evaluation, authorisation and restriction) and CLP processes (e.g. classification and labelling) for nanoforms as it would for any other form of a substance and needs to have sufficient scientific and technical capacity to do so.

With this aim, ECHA has gradually increased its activities in this area since 2011 focusing on:

- Internal and external capacity building;
- Sharing experience with and generating consensus among Member State competent authorities (MSCAs), Member State Committee (MSC) and Risk Assessment Committee (RAC) members on safety information for nanomaterials in REACH registration dossiers;
- Providing feedback and advice to registrants who wish to register nanomaterials;
- Participating and contributing to on-going international regulatory activities (such as the OECD Working Party on Manufactured Nanomaterials);
- Nanomaterials webinars to inform and discuss about the latest developments regarding REACH and CLP processes related to nanomaterials, and also to help registrants prepare and submit dossiers that involve nanomaterials.

In October 2012, ECHA established a Nanomaterials Working Group (ECHA-NMWG) to discuss scientific and technical questions relevant to REACH and CLP processes and to give recommendations on strategic issues. It is an informal advisory group consisting of experts from Member States, the European Commission, ECHA and accredited stakeholders organisations, with the mandate to "provide informal advice on any scientific and technical issues regarding the implementation of REACH and CLP legislation in relation to nanomaterials." ECHA-NMWG also aims to discuss with industry regarding the experience it gained in documenting the intrinsic properties of nanoforms using recent methods and its obligations towards fulfilling REACH requirements.

This last objective is closely related to the work carried out by ECHA through the Group Assessing Already Registered Nanomaterials (GAARN). Established in January 2012 by DG Environment from the European Commission and chaired by ECHA, the purpose of GAARN was to build a consensus in an informal setting on best practice for assessing and managing the safety of nanomaterials under the REACH Regulation and thereby increase confidence and mutual understanding among stakeholders so that nanomaterials can be sustainably developed. Conclusions and best practice from GAARN are reported to ECHA-NMWG and shared with stakeholders.

ECHA believes that the regulatory frameworks cover nanomaterials and while there might need to be some adaption to guidance and procedure, discussion is on-going to address the uncertainties and challenges.

ECHA is also involved in several of the European Commission's Framework Programme of research to facilitate knowledge transfer. There are challenges on both scientific and policy levels as well as issues that still need to be properly discussed and addressed; a commitment to which is evident from the aforementioned activities and on-going dialogues, including this workshop.

Regulators are addressing the challenges and uncertainties posed by nanomaterials, as they are with other substances, through the legal instruments and dialogue not only at the EU level but also at the international level as increasing knowledge exchange is crucial to bringing the issues forward.

3.2.2 "Assessment and management of nanomaterials under the Toxic Substances Control Act"

Mr Jim Alwood (US Environmental Protection Agency), in his presentation entitled "Assessment and management of nanomaterials under the Toxic Substances Control Act", outlined:

There has been considerable progress on standards, material characterisation, test guidelines and human health risk assessment of nanomaterials. Under the Toxic Substances Control Act (TSCA), the US Environmental Protection Agency (EPA) have assessed 160 nanomaterials (meaning there is evidence that the material contains particles <100 nm in a single dimension).

Where information is available that a product contains nanomaterials, the EPA check to see if these present new properties or old properties (e.g. established chemicals which turn out to contain materials on the nanoscale with no new properties) that may present an unreasonable risk to human health or the environment.

Categories are used for chemicals and in relation to nanomaterials, these tend to come under the poorly soluble low toxicity category and they use such categories to inform on things like hazard (e.g. primarily pulmonary toxicity). However, it is questionable whether there are sufficient categories to comprehensively consider exposure routes, types of materials etc.

In relation to characterisation, the EPA lists a range of properties that could be considered for substance characterisation, but the question is what degree of change in a property of a substance makes a big enough difference to the material to distinguish it as a nanomaterial?

3.2.3 "Canada's experience with chemicals assessment and management and its application to nanomaterials"

Dr Brad Fisher (Environment Canada), in his presentation entitled "Canada's experience with chemicals assessment and management and its application to nanomaterials", stated:

In Canada, as well as internationally, there is general consensus that existing legislative and regulatory frameworks for chemicals are considered appropriate to assess and manage the potential risks to the environment and human health from manufactured nanomaterials. Adaptations may be necessary in some cases to account for the specific properties of nanomaterials. As such, any substance, including a nanomaterial, that is not listed on Canada's public inventory, the Domestic Substances List (DSL), is considered to be new and is subject to the notification requirements under the New Substances Notification Regulations (Chemicals and Polymers). Canada has assessed 18 nanomaterials under its new substances programme.

Information gathering and stakeholder engagement is a very important part of the regulatory process in Canada, including voluntary and regulatory approaches (e.g. mandatory information gathering).

Canada has also worked bilaterally with the United States Environmental Protection Agency under the nanotechnology initiative of the Regulatory Cooperation Council (RCC). This work aims to increase alignment in regulatory approaches for nanomaterials between Canada and the United States to reduce risk to human health and the environment, promote the sharing of scientific and regulatory expertise, and foster innovation.

In 2012, the lead departments for this initiative - Health Canada, Environment Canada, and the US Environmental Protection Agency (EPA) - developed the nanotechnology work plan, which included five work elements:

1. Principles: identification of common principles for the regulation of nanomaterials to help ensure consistency for industry and consumers in both countries.
2. Priority setting: identification of common criteria for determining characteristics of industrial nanomaterials of concern/no concern.
3. Risk assessment/management: sharing of best practice for assessing and managing the risks of industrial nanomaterials.
4. Commercial information: characterisation of existing commercial activities and identifying gaps and priorities for future knowledge gathering for industrial nanomaterials.
5. Regulatory cooperation in areas of emerging technologies: development of a model framework outlining key elements and approaches to regulating products and applications of emerging technologies with respect to potential impacts on the environment, human health, food and/or agriculture.

Changes to regulatory approaches as a result of the RCC:

Stakeholders can expect pragmatic changes in regulatory approaches within Canada based on the outcomes of the five work elements. These include a consistent policy approach for nanomaterials based on shared policy principles and consistent use of the nanomaterial classification scheme to:

- identify data needs (short-term);
- support the use of analogue/read-across information for risk assessment (medium to long-term);
- consistently use data submitted to support risk assessments based on the framework for human health information and common assumptions for ecological fate and effects; and
- use information to characterise exposures in risk assessments and focus information requests for new activities.

3.3 SUMMARY OF PRESENTATIONS FROM THE SPEAKERS

A collated summary of the main aspects from the presentations is provided below.

In general, the regulatory community believes that the regulatory frameworks cover nanomaterials and while there might need to be some adaption to guidance and procedure; discussion is on-going to address the uncertainties and challenges.

Canada is currently exploring an approach to address certain nanomaterials under the Canadian Environmental Protection Act (1999) that are not subject to the New Substances Notification Regulations (Chemicals and Polymers). Specifically, the approach will aim to address nanomaterials that are currently on Canada's public inventory – the Domestic Substances List (DSL). Canada is in the early stages of discussions with stakeholders on the proposed approach and plans to continue the dialogue in early 2015.

A need exists for agreed-upon technical standards that can be used by regulators - other than some test guidelines that include consideration of material characterisation, there are still very few technical standards that are widely accepted and understood to apply to nanomaterials that can be used by regulators.

A need exists to identify the key properties to assess risk and to differentiate between different forms of those nanomaterials that may have different environmental health and safety properties.

When identifying key properties for nanomaterials, including the consideration that for some nanomaterials some properties are no different than properties already well understood. For example, with multi-walled carbon nanotubes (MWCNT) existing data suggests that they demonstrate fibre toxicity that is already understood for inhalation. Only the relevant properties to assess and control risk need to be characterised. Conversely, for quantum dots, there is no understanding yet of the properties relevant to use in health and safety risk assessment and risk management.

In summary, for the topic of international views on scientific challenges in regulatory risk assessment of nanomaterials:

- It is considered that much more information is needed on the key properties of nanomaterials;
- Identification and nomenclature is of particular interest to regulators – i.e. how to distinguish different forms of nanomaterials;
- Better material characterisation of materials is needed for substances subject to toxicity studies, enabling more tailored regulatory decisions;
- A need still exists for testing, nomenclature, and characterisation standards applicable to both individual nanomaterials and groups of nanomaterials;
- The lack of data makes it more difficult for regulators to assess and manage potential risks, resulting in a more conservative approach in the absence of data;
- Opportunities exist for further collaboration, cooperation and sharing lessons learnt between jurisdictions, regionally and internationally.

4 TOPIC 2: MEASUREMENT AND CHARACTERISATION OF NANOMATERIALS

4.1 BACKGROUND

The measurement and characterisation of nanomaterials is one of the key pre-requisites for a proper hazard and risk characterisation of substances and even more so for nanomaterials. Far from being straightforward, this is a multi-faceted challenge that requires knowledge on a number of key elements, including at a minimum the following:

1. An enforceable definition for nanomaterials;
2. Agreed data set of physico-chemical properties of nanomaterials necessary to be characterised (e.g. size, surface area, etc.);
3. Standardised methods for the quantification of these parameters.

The EC has proposed a recommendation for a regulatory definition of "nanomaterial" to be implemented in all EU regulations in Oct 2011[8]. Although there are other definitions available[9] and although this definition may undergo changes[10], the EU recommended definition is the one currently being implemented for regulatory purposes across the EU legal frameworks. The Biocidal Products Regulation[11] and the Regulation of Medical Devices[12] are the first EU regulations to include reference to the recommendation in the legal text followed by the Cosmetics Regulation[13] and the new EU food labelling rules[14]. It is foreseen that modifications of the REACH annexes for nanomaterials will explicitly include the recommendation[15].

ECHA is already referring to the recommendation where nanomaterials are seen as substances in their own right or as forms of a substance[16]. This was discussed in detail at the first GAARN (Group Assessing Already Registered Nanomaterials) project meeting where it was stressed that the use of several analytical techniques for characterising nanoforms (multi-method approach) was favoured as no single currently available method can provide sufficient information on all the physicochemical parameters necessary to characterise nanoforms; a reasoning that, to some extent, holds true for any substance.

8 Commission Recommendation of 18th October 2011 on the definition of nanomaterial available at http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF
9 reports EUR 24403 and EUR 26567, ISO/TS 80004-1:2010; Nanotechnologies -- Vocabulary -- Part 1: Core terms
10 Commission Recommendation of 18th October 2011 on the definition of nanomaterial available at http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF
11 http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02012R0528-20140425&from=EN
12 REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on medical devices COM(2012)542
13 EU Regulation 1223/2009 available at http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2009R1223:20130711:en:PDF
14 http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R1169&from=EN
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16 GAARN meeting best practices report available at https://echa.europa.eu/documents/10162/5399565/best_practices_physiochem_subst_id_nano_en.pdf

4.1.1 Issues to be addressed

The term "measurement and characterisation" itself can refer to a wide variety of regulatory and scientific problems that need to be addressed to ensure the safe use of nanomaterials. There is a need to address the characterisation of nanomaterials in different stages of the life cycle and for different (regulatory) purposes, namely characterisation of nanomaterials:

1. for the purpose of identification;
2. during (hazard) testing; and
3. for the purpose of exposure assessment.

For the purpose of identifying nanomaterials, the EC recommendation for the definition of nanomaterials serves as the reference point. However, implementation of the recommendation is not trivial due to a variety of challenges. These include the absence of standard methods, the absence of reference materials, and the diversity in what is covered by the EU recommendation for nanomaterials.

The JRC report[17] has highlighted the need for standard methods and the complexities of applying existing non-standard methods to determine particle size on a number basis (as required by the EU recommendation) and the challenges with agglomerates and aggregates.

Many on-going Framework Programme (FP) 7 projects are addressing this challenge (NANOREG, NanoDefine etc.)[18] with regards to measurement of nanomaterials.

Furthermore, European Committee for Standardisation (CEN) TC 352 has accepted a mandate (M461) from the EU Commission to develop standards relevant for nanotechnologies that will also address this[19].

The characterisation of nanomaterials within hazard testing is also crucial. To ensure adequacy and comparability of test data, a minimum set of physico-chemical characteristics, as well as careful sample preparation, are necessary. The relevance of particle size measurements, as well as other parameters for sample characterisation for testing has been addressed by the OECD Working Party on Manufactured Nanomaterials (WPMN) in its draft guidance on sample preparation and dosimetry[20].

Finally, the characterisation of nanomaterials during their life cycle, and the potential exposure of people and the environment to nanomaterials are important. It is recognised that nanomaterials may be incorporated into a variety of matrices depending on their use.

Furthermore, nanomaterials have a tendency to aggregate/agglomerate; however, the stability of such aggregates/agglomerates over their life cycle, and the potential release of smaller particles cannot be neglected. Therefore, it is relevant to consider:

a. how to measure and characterise the release of nanomaterials during their life cycle; and

b. how to measure the stability of aggregated/agglomerated particles and their potential for releasing smaller particles during the entire life cycle of the substance.

17 Requirements on measurements for the implementation of the European Commission definition of the term "nanomaterial" available at http://ec.europa.eu/dgs/jrc/index.cfm?id=2540
18 http://www.nanosafetycluster.eu/eu-nanosafety-cluster-projects/seventh-framework-programmeprojects/enanomapper.html
19 M/461 MANDATE ADDRESSED TO CEN, CENELEC AND ETSI FOR STANDARDISATION ACTIVITIES REGARDING NANOTECHNOLOGIES AND NANOMATERIALS available at http://ec.europa.eu/enterprise/standards_policy/mandates/database/index.cfm?fuseaction=search.detail&id=443#
20 Guidance on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials available at ENV/JM/MONO/(2012)40

4.2 PRESENTATIONS

For Topic 2 of the workshop, the following presentations were made:

- "Implementation of the risk-neutral, wide-scope EC nanodefinition: Practical concepts and test cases" - Dr Wendel Wohlleben, BASF, Germany
- "Testing the test in NANoREG: Nanomaterial characterisation and technical guidance for toxicological testing" - Dr Keld Jensen, National Research Centre for the Working Environment, Denmark
- "Characterisation of nanomaterial release during their life cycle" - Prof. Michael Stintz, Technische Universität Dresden, Germany

4.2.1 "Implementation of the risk-neutral, wide-scope EC nanodefinition: Practical concepts and test cases"

Dr Wendel Wohlleben (BASF), in his presentation entitled "Implementation of the risk-neutral, wide-scope EC nanodefinition: Practical concepts and test cases", outlined:

As context, first estimates by BiPRO and Öko-Institut of the impact of the EC's recommendation on a definition of a nanomaterial are that about 2 000 – 5 000 substances, 80 000 – 160 000 preparations and 800 000 – 1 300 000 articles alone in Belgium fall within scope of the definition. 35 000 – 45 000 enterprises (15-20% of all enterprises in Belgium) would be affected in sectors as diverse as cosmetics, health care, food and feed, coatings and inks, cleaning and disinfection, tyres and rubber products, plastic products, building and construction, textiles, paper and wood products, sporting goods, electronics, etc.[21]. Pigments, fillers, and anticaking agents are clearly particulate and product performance is linked to their relatively well-defined morphology. There is, however, no technical relevance of size in number metrics. Datasheets typically specify size in volume metrics or specific-surface area. An even higher number of materials need to be screened among the non-engineered particulates, whose product performance is after melting or dissolution: mortars, solidified waxes, polymer granulates, salts etc., which were all excluded in the BiPRO study.

Electron microscopy (EM) is generally accepted as the reference counting method for the size distribution of particulate materials. For reasonably well dispersible powders, transmission electron microscopy (TEM) can be performed on monolayer preparations, such that the remaining uncertainty is the attribution of an external diameter to irregularly-shaped primary particles (Linsinger et al. 2012) and the counting of small agglomerates of non-separated primary particles. Further method development needs for electron microscopy, for example, addressing in-dispersible materials, platelets, etc. have been highlighted[22].

However, a drastically simpler method performs well for mono-constituent powder materials: volume specific surface area (VSSA) was acknowledged as an agglomeration-tolerant ensemble method with low costs and wide availability to identify nanomaterials[23-24]. VSSA has the important advantage over classifying and counting techniques (including TEM) that it does not involve dispersion protocols and achieves few-percent precision[25].

21 BiPRO (2013) Study of the scoping of a Belgian national register for nanomaterials and products containing nanomaterials
22 Brown, S. C., Boyko, V., Meyers, G., Voetz, M., & Wohlleben, W. (2013). Towards Advancing Nano-object Count Metrology - A Best Practice Framework. Environ Health Perspect, doi:10.1289/ehp.1306957
23 Allen T (1997) Particle size measurement - vol. 1: Powder sampling and particle size measurement. vol. 2: Surface area and pore size determination. Chapman & Hall, London
24 Kreyling W, Semmler-Behnke M, Chaudhry Q (2010) A complementary definition of nanomaterial. Nanotoday. 5:154:168
25 Hackley VA, Stefaniak AB (2013) Real-world precision, bias, and between-laboratory variation for surface area measurement of a titanium dioxide nanomaterial in powder form. J Nanopart Res 15:1-8.

The International Organisation for Standardisation (ISO) standard ISO 9277:2014-01 lists 19 certified reference materials with Brunauer–Emmett–Teller (BET) surfaces between 0.104 ± 0.012 and 550 ± 5 m^2/g.

In a pilot round robin, the VSSA measurements from six labs were reproducible within a scatter of 10% on this substance (Eurocolor / JRC, 2013). In a further assessment on a representative portfolio selection of BASF pigments, VSSA and TEM achieved identical classification. The VSSA cut-offs adapted to the dimensionality of the material as proposed by JRC-report #2 (2014) were used. This result was not compromised by the various compositions, irregular shapes or strong agglomeration.

In contrast, the same Eurocolor / JRC round robin on eight pigments with laser diffraction (LD), characteristic loss spectroscopy (CLS), dynamic light scattering (DLS), VSSA, TEM and standardised sonication protocols did not recommend any simple, widely available method after re-dispersion in liquid.

In a closer investigation on a representative portfolio selection of BASF pigments, it turns out that the "smallest dispersible unit" classifies 60% of those pigments as non-nano that are nano by EM and VSSA (BASF, 2014, see slides).

In summary, a measurement of "smallest dispersible units" is technically feasible, delivers a size distribution in number metrics, and achieves the same ranking of materials – but it integrates an element of risk assessment (dispersability) and is in general in disagreement with "smallest external dimension" (EM, BET). As a result, even some materials with product performance directly linked to structures (pigments, fillers) would be non-nano.

The opinion from the NanoDefine consortium suggests that only EM and VSSA (by BET) cover the entire size range 1nm – 10µm. All other techniques miss parts of the relevant size range. Further, the research suggests that only small-angle

x-ray scattering (SAXS), x-ray diffraction (XRD), scanning electron microscopy (SEM), BET can measure sizes without pre-dispersion in a liquid. These techniques can thus serve as validation of techniques that measure after dispersion in a liquid, where the quality of dispersion is the biggest source of uncertainty.

Manufacturers seek to meet the spirit of the definition given the challenges it presents in terms of its high degree of inclusiveness and in terms of metrology. A screening approach is needed as it is just not possible to perform an indepth analysis on thousands of materials. With a suitable screening approach and methods, materials that are clearly nano- and clearly not nano- (not addressed within the definition) could be identified.

4.2.2 "Testing the test in NANoREG: Nanomaterial characterisation and technical guidance for toxicological testing"

Dr Keld Jensen (National Research Centre for the Working Environment), in his presentation entitled "Testing the NANoREG: Nanomaterials characterisation and technical guidance for toxicological testing", outlined:

A general semi-automatic procedure for determining the minimum diameter primary particle size-distributions for granular and fibrous/tubular nanomaterials as requested in the EC recommendation on a definition of a nanomaterial. The method works for both aggregated and agglomerated nanomaterials and the method relies on image-processing of well-calibrated transmission electron microscopes.

A draft protocol for discriminating specific surface area from porosity has been established to address the volume-specific surface area criterion in the EC definition recommendation. Work is underway on the general testing of the ability to characterise a wider suite of nanomaterials with different physicochemical characteristics, including organic coatings.

The NANoREG project is allocating significant resources to test and propose revisions of the existing OECD test guidelines (TGs) to become suitable for manufactured nanomaterials. Currently, the review and desktop analysis of suitability and revision needs has been completed. New methods are also underway to address currently un-addressed characterisation needs on chemical surface modifications, reactivity and fate.

A technical guidance document has been developed to harmonise the in vitro and in vivo toxicological exposure and exposure characterisation in the NANoREG project. The technical guidance document specifies specific standard operating procedures (SOPs) to prepare batch dispersion for in vitro (NANOGENOTOX dispersion protocol), in vivo (NANOGENOTOX or ENPRA dispersion protocol or inhalation), and ecotoxicology (water or water with natural organic matter) testing. Dynamic light scattering is selected as the common basic tool characterisation of dispersions. In vitro and ecotoxicology studies have additional requirements to measure the hydrodynamic size-distribution in the exposure media at the start and the end of the experiment. Additional detailed information and other characterisation end-points are also recommended. A standard operation procedure was also developed to calibrate the probe-sonicators used. This is essential to achieve comparable dispersions entering the different test systems.

Based on the current state of technology and methods developed, it appears possible to implement the EC recommendation for definition of a nanomaterial, although it will be method and matrix dependent.

It also appears possible to have automated techniques (e.g. electron microscopy) and harmonise testing and measurement requirements in toxicological testing. However, it is certain that some challenges will emerge for some materials and some systems, and that the need for characterisation exists across different stages of testing. These will be lessons learnt after testing the test.

4.2.3 "Characterisation of nanomaterial release during their life cycle"

Prof. Michael Stintz (Technische Universität Dresden), in his presentation entitled "Characterisation of nanomaterial release during their life cycle", provided some examples of standardisation activities pertinent to nanomaterials testing:

ISO/TC 229/JWG 2/PG 10 has developed in a first step the technical specification (TS) ISO/TS 12025:2012, which is a general framework for determining the airborne release of nano-objects from nanostructured powders by means of aerosol analysis. The TS provides information on the methodology for nano-object release quantification that covers, beside necessary measures and process parameters, the presentation of measurement results by specific release numbers. It also supports the standardisation of nano-object release testing of nanocomposites, e.g. by abrasion procedures.

Standardisation in nanoparticle characterisation is performed in 15 working groups within ISO/TC 24/SC 4. In addition to imaging methods for morphology inspection of single particles, aerosol measurement devices have some benefits for exposure analysis compared with particle measurement techniques for liquid dispersions (i.e. emulsions, suspensions or combinations of them), for instance, the ability of providing absolute count numbers or the independency from specific material properties (e.g. from the index of refraction).

A fundamental aerosol measurement principle that allows the characterisation of particles down to a few nanometres is the electrical mobility analysis as described within ISO 15900:2009. One problem from metrological view, which still exists for aerosol measurement technology, is the lack of a concentration reference material. An important step in this direction represents the draft international standard (DIS) ISO/DIS 27891:2013 for the calibration of condensation counters.

In the field of liquid dispersion characterisation, a fundamental challenge is the characterisation of the dispersion stability, i.e. the absence of change in specified properties over a given timescale. Therefore, the technical report (TR) ISO/TR 13097:2013 was issued by Working Group (WG) 16, which describes two different approaches to determine relative property changes.

It has been acknowledged for some time that sample preparation is an important aspect in fate, exposure, hazard and risk assessment of substances. For example, zeta potential measurement proved to be a necessary tool for checking dilution and stabilisation protocols. Therefore, WG 17 issued methods for zeta potential determination within ISO 13099, which currently consists of two standards and one final draft of an ISO standard (FDIS).

4.3 SUMMARY OF PRESENTATIONS FROM THE SPEAKERS

A collated summary of the main aspects from the presentations is provided below.

In general, characterisation and the use of reference materials are required for many steps of the risk assessment process, from identification and hazard assessment through to grouping/ranking, and a number of available methods and reference nanomaterials are fit for purpose for key properties.

Given the enormous number of particulate materials (and the absence of an upper size limit in the EC definition recommendation), both industry and regulators need a screening procedure for identification of both nano and non-nano materials, with cases of uncertainty subject to further in-depth evaluation.

Possibilities and procedures exist to determine whether a material is a nanomaterial or not, but there are clearly different experiences and positions taken between "academic" and industrial characterisation specialists.

The NANoREG project is predominantly a top-down controlled development and documentation project. Several methods exist at technical draft-levels with limited or no analysis of general applicability and variability between laboratories. It is important to evaluate the results from the current exercise to identify further development needs in characterisation and testing. In this project, a harmonised characterisation and testing approach for nanomaterials is being sought for the first time.

However, to make progress with the categorisation of nanomaterials, there remain issues regarding the simple categorisation/classification even by chemical composition, compounded by the fact that nanomaterials may increasingly become more and more complex as second and third generation materials become high-volume compounds.

On identification of substances under the EC definition, EM and VSSA can provide discrimination between nano and non-nano forms, thus lending support to the use of the VSSA criterion not only as a proxy but also potentially for screening for certain materials and with the support of reference materials.

VSSA may fulfil this requirement at least for mono-constituent powders. However, the uncertainty margin still needs to be explored. The JRC report[26] that assessed collected information concerning the experience with the definition, provides a framework of VSSA screening, and suggests VSSA threshold values based on dimensionality ("M" adapted into Figure 1). JRC suggest M = 20 for platelets and 40 for fibres; BASF propose X = 6 for an uncertainty factor of 10 and is easy to measure, or X = 0.6 for an uncertainty factor of 100, equivalent to PM10, but this may challenge the measurement range of BET. The concept was further detailed and extended by the BASF presentation, for future implementation e.g. in the NanoDefine e-tool as tier-1-option. Alternative screening procedures are anticipated to be needed for other materials classes.

26 https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/towards-review-ec-recommendation-definition-term-nanomaterial-part-2-assessment-collected

VSSA > 60	Nano, unless "baseline EM" shows inner or coating porosity
60 > VSSA > M	Cannot decide by VSSA, need EM or validated counting on this specific product
M > VSSA > X	Non-nano, if "baseline EM" on similar products shows no extraordinary shape or bimodality
X > VSSA	Non-nano without any further evidence

Figure 1: Framework for VSSA screening as proposed by JRC report #2 (2014)

In technical terms, the VSSA methodology is currently being further developed by NANoREG WP2 and by NanoDefine WP3, including cooperation and data sharing between the projects. VSSA can also be determined by techniques other than BET, and the NanoDefine project explores these. Existing data shows that TEM and VSSA provide the same discrimination between nano and non-nano forms, such as for the OECD NM series, metal oxides, pigments and fillers, representative portfolio selection of BASF pigments. This lends support to the screening use of VSSA.

At a policy level, it should be recognised that VSSA screening reduces the by-catch of large particulates that are "usually not considered a nanomaterial"26, in practice with a cut-off at 10µm diameter.

Irrespective of the wording in the revised definition ("contain" vs "consist of"), one could argue that a liquid containing a single nanoparticle should not be listed as nanomaterial, but one may want to ensure that nanoparticles remain classed as nano in regulatory terms when wetted by a liquid. Specifically, the following may be a reasonable guidance: "Mixtures, suspensions, formulations are nanomaterials, if one or more ingredient is a nanomaterial, and if these ingredients constitute more than N% of the solids mass." The CLP legislation would provide justification for N = 1% or 0.1%.

Formulations and liquids with particulate traces are conceptually very vague in the present EC definition. In test cases, the non-particulate components such as surfactants dominate the appearance after drying onto TEM grids, and thus interfere with the image evaluation. With current methodology, these samples cannot be reproducibly measured as a whole, but only by ingredients.

Regarding exposure assessment procedures, the potential use of control-banding-like systems for precautionary occupational exposure management continue to be important, as well as the considerations of using exposure waiving to prioritise the documentation requirements.

Published studies on nano-object release into air still suffer more or less from three problems, i.e. a consistent terminology, standardised metrological procedures and the kind of data evaluation. An uncertainty also exists about whether studies are conducted under realistic or worse-case scenario conditions. Thus, a quantitative comparison between the different studies was often impossible, if necessary parameters are missing. This also hinders the conclusion on real exposure situations.

The release scenarios and the mechanical treatment processes must be defined and agreed concerning their parameters by the involved stakeholders; the influence of the processing conditions often dominates over any influences from the physico-chemical nature of the samples tested.

There are no real online methods available for nanoparticle size and concentration measurement; electrical mobility analysis is only applicable for very small aerosol concentrations. There is, especially for liquid suspensions, no counting method in the nanometre range available so far, which could be used as a pendant to the condensation particle counters for aerosols.

Standardisation of emission/release testing, to derive reliable source-strength data, is important and it is crucial to establish applicable methods and quickly expand the knowledge to enable reliable modelling.

In summary for the topic of measurement and characterisation of nanomaterials:

- In practice, most characterisation resources are spent on particulate materials, whose product performance is conveyed following melting or dissolution, where shape can be complex, size is not specified (with particulates often up to micrometres in size), and the material may be soluble, and/or reactive. Solubility, composition, release and dispersibility require a combined assessment as part of a testing strategy, to identify the influence that these properties may have on safe use. For the characterisation of airborne nanomaterial release during their life cycle, a methodology is now available and the subject of international standardisation.
- The measurement of aggregate/agglomerate size distributions under defined conditions (e.g. dispersing procedures, release scenarios) is essential for characterising particulate systems. A need exists for a screening approach that enables the identification of both nano and non-nano forms of a substance, with cases of uncertainty subject to in-depth evaluation; to reduce the analytical uncertainty, formulations and mixtures should be assessed by ingredients, not as a whole.
- Apart from granulometric analyses by imaging methods (SEM, TEM), the metrological determination of characteristic properties allowing the classification of a material as a nanomaterial in accordance with the recommendation of the European Commission is still a complex scientific and technical challenge. However, implementation of the EC-recommendation for definition of a nanomaterial and harmonised testing requirements seems possible, but for some materials challenges may still be ahead. A semi-automatic transmission electron microscopy procedure for sizing manufactured nanomaterials, according to the EC recommendation, has been established and is undergoing inter-laboratory validation.
- Supported by the NanoDefine method evaluation, VSSA seems best suited to screen both for nano and non-nano forms in mono-constituent powders. Classification was seen to be identical by VSSA and by TEM in the Eurocolor/JRC round robin and in BASF pigments. A draft protocol for discriminating specific surface area from porosity has been established and is underway for testing the applicability for the volume-specific surface area criterion in the EC recommended definition.
- NANoREG is expected to provide a review and suggest revisions to key OECD technical guidelines for characterisation of manufactured nanomaterials and methods for new endpoints. A technical guidance document and associated standard operation procedures for calibration of probe-sonicators, dispersion in liquids, and characterisation in batch- and test dispersions has been developed to harmonise exposure characteristics and key exposure characterisation to test comparability of test results and grouping principles.
- Regarding dustiness, release, dispersibility, solubility, and reactivity, various talks and discussions at the workshop have shown that none of these properties alone can discriminate safe uses, but all of them need to be considered in testing strategies that screen for hazardous substances among the nanomaterials group.

5 TOPIC 3: METROLOGY AND DOSE METRICS FOR HAZARD AND EXPOSURE ASSESSMENT THROUGHOUT THE LIFE CYCLE

5.1 BACKGROUND

The agreement of the most appropriate metrics for each type of nanomaterial within each specific route of exposure and (eco)toxicological endpoint is one of the most important gaps regarding the regulatory testing of nanomaterials.

The most optimal dose metrics to be used for nanomaterials are still under discussion. Dose-response relationships have been reported in several studies, especially in vitro studies, using nanomaterials such as single- and multiple carbon nanotubes and various forms of nano-metals[27].

In general in these studies, dose refers to "dose by mass". However, for nanomaterials this may not sufficiently describe the dose that determines a particular response in a biological system. A specific mass of a variety of nanomaterial consisting of the same chemical substance but with different properties such as particle size may have completely different toxicity profiles[28]. Oberdörster et al.[29] suggested that the biological activity of nanoparticles might not be mass-dependent, but dependent on physical and chemical properties not routinely considered in toxicity studies. For example, several studies[30], [31], [32] , [33] found that the surface area of the nanoparticles is a better descriptor of the toxicity of low-soluble, low-toxicity particles. For inhaled insoluble spherical particulate matter, it was suggested that the particle displacement volume rather than surface area appears to be the most critical metric for these types of nanomaterials[34].

Other studies[35],[36] found that the particle number was the best dose metric while others[37],[38] found that the number of functional groups in the surface of nanoparticles influenced their toxicity.

The dose metrics that are most appropriate to compare the risks of nanomaterials are probably variable, but seem to depend on the type of nanomaterial, the route of exposure, the kinetics and/or the (eco)toxicological

27 Hansen S.F. and Baun A. (2012) European Regulation Affecting Nanomaterials – Review of Limitations and Future Recommendations, Dose Response. 10(3): 364–383.
28 Park, M. V. D. Z., de Jong, W. H., Oomen, A. G., & Delmaar, C. J. (2012). Nanotoxicology – an in vitro approach: A practical way forward to determine appropriate dose metrics for engineered nanomaterials. Maastricht University, Maastricht, The Netherlands.
29 Oberdörster G., Maynard A., Donaldson K., Castranova V., Fitzpatrick J., Ausman K., Carter J., Karn B, Kreyling W, Lai D, Olin S, Monteiro-Riviere N, Warheit D, Yang H. (2005). Principles for characterising the potential human health effects from exposure to nanomaterials: Elements of a screening strategy. Particle Fibre Toxicol.2:8.
30 Oberdörster G. (1996). Significance of particle parameters in the evaluation of exposure dose-response relationships of inhaled particles. Particu Sci Technol. 14:135– 151
31 Oberdörster G, Oberdorster E, Oberdorster J. (2007). Concepts of Nanoparticle Dose Metric and Response Metric. Environ Health Perspect. 115(6):A 290
32 Stoeger T, Reinhard C, Takenaka S, Schroeppel A, Karg E, Ritter B., Heyder J., Schultz H. (2006). Instillation of six different ultrafine carbon particles indicates surface area threshold dose for acute lung inflammation in mice. Environ Health Perspect. 114(3):328–333.
33 Stoeger T, Schmid O, Takenaka S, Schulz H. (2007). Inflammatory Response to TiO2 and Carbonaceous Particles Scales Best with BET Surface Area. Environ Health Perspect. 115(6):A290–A291.
34 Pauluhn, J. (2011). Poorly soluble particulates: Searching for a unifying denominator of nanoparticles and fine particles for DNEL estimation. Toxicology 279: 176-188
35 Wittmaack K. (2007). In search of the most relevant parameter for quantifying lung inflammatory response to nanoparticle exposure: Particle number, surface area, or what? Environ Health Perspect. 115:187–194.
36 Wittmaack K. (2007). Dose and Response Metrics in Nanotoxicology: Wittmaack Responds to Oberdörster et al. and Stoeger et al. Environ Health Perspect.115(6):A290–A291.
37 Warheit DB, Webb TR, Colvin VL, Reed KL, Sayes CR. (2007). Pulmonary bioassay studies with nanoscale and fine-quartz particles in rats: Toxicity is not dependent upon particle size but on surface characteristics. Toxicol Sci. 95(1):270–280.
38 Warheit DB, Webb TR, Reed KL, Frerichs S, Sayes CM. (2007). Pulmonary toxicity study in rats with three forms of ultrafine-TiO2 particles: Differential responses related to surface properties. Toxicology. 230:90–104.

endpoint studied. More data from toxicokinetics and in vivo toxicity studies would aid further progress on establishing the most appropriate dose metrics for nanomaterials. For example, for multi-walled carbon nanotubes (MWCNT) attempts were made to identify common mechanistic denominators between higher and lower density, bio-persistent nanosized and sub-micron sized insoluble particles. It appears that the potency of these particles to induce inflammation-related sustained lung injury is solely dependent on biokinetics rather than the particles inherent properties[34].

Furthermore, nanomaterials interact strongly with their surroundings during their life cycle as well as during their preparation, sample collection or during contact with cellular media, biological fluids and environmental media, and may see their physical, chemical and biological properties evolving. This makes it even more difficult to assign a single physical qualifier for unequivocal characterisation.

5.1.1 Issues to be addressed

This session discussed the state of the art regarding the most appropriate metrology and dose metrics that should be used in the context of the risk assessment of nanomaterials.

From the current knowledge, several important findings emerge:

- The best choice of metrics or measurements heavily depends on (eco)toxicological considerations;
- A single metric is generally not sufficient to characterise and quantify nanomaterial exposure for all types of nanomaterials;
- Exposure is best characterised by multiple parameters and thus should be described by a set of information;
- Size distribution is important for understanding the likelihood of deposition of particles in certain parts of the airways;
- Particle size and surface area concentration are associated with the potential toxicity of a nanomaterial;
- Particle (or fibre) number concentration is important as, in some cases, this metric may be more relevant than the mass metric in determining potential risk from exposure to nanomaterials. Furthermore, the mass of airborne nanoparticles will usually be very small and therefore can be much more difficult to measure than the particle number;
- The mass concentration is important because there is already a large body of research on exposure to and (eco)toxicity of particles and conventional chemicals in the mass-based metric;
- Since the mass-based metric is currently a fundamental cornerstone in all chemical regulations, any change will also require further thoughts on how existing legal thresholds can be applied and harmonised;
- A common understanding and harmonisation of the most appropriate metrics used to describe exposure and hazard characterisation for nanomaterials is needed. To design and perform the studies using appropriate dosing, it is important to take into account the likelihood and degree of human and environmental exposure in terms of the physicochemical nature, possible physicochemical alteration, and concentration (number, mass, surface area) of the manufactured nanomaterial.

5.2 PRESENTATIONS

For Topic 3 of the workshop, the following presentations were made:

- “Concepts of nanoparticle toxicology, dosimetry and risk assessment” - Prof. Günter Oberdörster, University of Rochester, United States (US)
- “Metrology and metrics for exposure assessment throughout the life cycle” - Prof. Thomas Kuhlbusch, Institut für Energie- und Umwelttechnik (IUTA), Germany
- “State-of-the-science in metrology and metrics for nanomaterials regulation” - Dr Steve Hankin, Institute of Occupational Medicine (IOM), United Kingdom (UK)

5.2.1 "Concepts of nanoparticle toxicology, dosimetry and risk assessment"

The presentation of Prof. Günter Oberdörster (University of Rochester), entitled "Concepts of nanoparticle toxicology, dosimetry and risk assessment" covered key concepts addressing:

- Key parameters of nanomaterials affecting hazard properties as a basis for testing and for using metrics;
- Mode of action and choice of dose metrics;
- Approaches involving dosimetry and dose metrics for regulatory purposes.

Prof. Oberdörster explained that after the spike in what he terms 'nano-hype' and safety concerns for nanomaterials, we are moving towards a more realistic view and analysis of nanomaterial toxicity. A key basis of previous concerns was that animal dose ranges were often far in excess of human exposure ranges which can trigger artifactual and biologically irrelevant endpoints. This shows the need for proper consideration of dose, the dose metrics, as well as the consideration of the nature of the dose response. For example, looking at the crystalline silica and amorphous silica, it appears there is no in vitro-in vivo correlation, yet when you consider the shape of the dose response and consider the choice of metric you may see correlation (for example, unit response per unit surface area).

The surface reactivity can be another important metric. As a good correlation between reactive oxygen species (ROS) per cm3 and inflammation was found, this parameter can be used as a screening tool for hazard identification. Prof. Oberdörster also touched upon other important issues such as the importance of the retained lung burden for finding a dose-response relationship and the usefulness of the benchmark approach for the comparative hazard and risk characterisation of inhaled nanoparticles.

5.2.2 "Metrology and metrics for exposure assessment throughout the life cycle"

Prof. Thomas Kuhlbusch (IUTA), in his presentation entitled "Metrology and metrics for exposure assessment throughout the life cycle", outlined:

In the domain of exposure assessment, significant improvements have been made during the last decade. While the problem of background particle distinction from engineered nano-objects or nanostructured materials is still a tedious task, some new instrumentation and tiered approaches have been developed to facilitate a more systematic approach to measurements and exposure assessments. Test procedures to allow the assessment of particle release during various handling, processing and environmental processes have been tested and discussions on their applicability and improvements are currently on-going.

Different metrics are currently being used for the various tasks within the testing and evaluation of nanomaterial-related environment, health and safety issues. A concept and recommendations on which metric, which purpose and the best to be used as an overarching one is still lacking.

5.2.3 "State-of-the-science in metrology and metrics for nanomaterial regulation"

Dr Steve Hankin (IOM), in his presentation entitled "State-of-the-science in metrology & metrics for nanomaterial regulation", outlined:

Metrology (characterisation) plays an important role in many stages along the value chain of a product or material's development including product and process R&D, quality control and product labelling, as well as in the science of assessing its safety and meeting the risk assessment dossier requirements of regulations in the EU and other jurisdictions.

In particular, metrology is essential for:

i. substance identification in terms of chemical composition and physical structure;
ii. possible categorisation;
iii. informing the selection of techniques for, and the interpretation of, benchmarked hazard assessments, exposure assessments, and functional assays showing the action of a substance's properties in biological or environmental systems; and

iv. potential read-across using structure/property-activity relationships.

Whilst there remains some uncertainty about the suitability of the current regulatory frameworks for nanomaterials, for example, in the context of the notification triggers and information requirements, efforts have been made to improve the understanding and feasibility of gathering the information requested by regulators for safety assessments, to promote standardised practices, and to gather information on nanomaterials currently on the market.

However, knowledge gaps still exist, particularly in linking the physico-chemical characteristics and exposure data with toxicology assessments to make risk assessment and risk management as informed as possible. This is particularly applicable to some of the intrinsic properties and behaviours of nanomaterials observed in research studies which have still to be shown to be sufficiently robust and relevant to the regulatory-world. This landscape begets the adoption of precautionary approaches, some of which may be more or less than what's required.

It is true to say that in addition to the extensive longer-term research programmes on nanomaterials safety in Europe and elsewhere around the world, a number of seminal activities have contributed to moving the state-of-the-science on. These include, but are of course not limited to, two of the European Commission's REACH Implementation Projects on Nanomaterials (RIP-oN 2 and 3), the OECD's publication series on the safety of manufactured nanomaterials, the development and publication of standards from ISO and other national standardisation bodies (e.g. British Standards Institution (BSI), American Society for Testing and Materials (ASTM)).

It is generally considered that there is no unique response to the question of which is the "best" metric for nanomaterials. Mass-based metrics are embedded in regulatory testing and may well be expected to remain so for some time. At least for inhalation, surface area and number-based metrics are also important in some circumstances, but that there is insufficient evidence for these additional metrics in relation to environmental exposure and ecotoxicology. A number of measurement approaches are available and suitable for nanomaterials, but the conversion between metrics is challenging and sufficient characterisation is essential to the relevance of metrics chosen in safety assessment.

In more recent times, the publication and review of the EC's definition of a nanomaterial and the on-going review of the REACH legal text and annexes may be anticipated to have an impact on the regulation of nanomaterials in Europe. (The outcomes of these considerations were still awaited at the time of the workshop.)

Broader and deeper evidence gathering has been taking place through a number of activities including those examining:

i. possible modifications across the breadth of EU safety & health at work legislation for nanomaterials;
ii. scientific technical support on the assessment of nanomaterials in REACH registration dossiers and the adequacy of available information (Nano Support Project - Task I); and
iii. the impact on industry, consumers, human health and the environment from possible options for changing the REACH Regulation (Nano Support Project - Task II).

A potential strategy for enhancing the components of nanomaterials risk assessment has been developed (ITS-Nano), but it needs widespread consideration, further development of operational processes, and adoption for successful implementation.

5.3 SUMMARY OF PRESENTATIONS FROM THE SPEAKERS

A collated summary of the main aspects from the presentations is provided below.

Although a great deal of information has been produced from research projects studying nanomaterials, greater linkage needs to be established between the different communities and scientific disciplines producing and using the data to make its use as effective as possible in assessing and appropriately regulating the safety of a product/substance.

An approach based on linking release processes to exposure scenarios is one which it may be possible to implement in the fields of exposure assessment, risk management and workplace safety. The potential exists for data to be gathered to underpin release rates for use in predictive models, etc.

Significant development and harmonisation tasks are still to be tackled and finalised, including:

- Harmonised and accepted pragmatic exposure assessment.
- Guidelines on how exposure reductions can be successfully assessed and implemented.
- Which nanomaterial metric should be used for the assessment of particles released during various tasks (e.g. handling, processing and environmental processes)?
- Can we develop a release process concept and corresponding test methods to be used for the assessment of all exposure scenarios?
- How can we practically link release of nano-objects and nanostructured materials to exposure?
- The concepts may be first developed for working areas and workers but extension to consumers, the public and the environment still have to be developed or improved.

Three pertinent questions that can be asked, concerning what still has to be addressed, concern establishing confidence exists in:

i. whether the data currently gathered is appropriate for risk assessment;
ii. whether registrants can meaningfully gather and report the data expected by regulators; and
iii. whether the data informs regulatory decision-making?

These questions can be considered in the context of the notion of a metric's 'value chain' (Concept -> Theory / Principle -> Practice -> Value) and the extent to which academia, industry and regulators cooperate and have common interests in developing, establishing, validating and using the metric.

It is arguable whether many metrics have reached the stage of providing value to the regulatory decision-making process, although it is clearly acknowledged that the size of regulatory datasets on nanomaterials to afford such an appraisal is limited at this time.

Asking the aforementioned questions on both the outputs from research and dossiers compiled for regulatory purposes is considered to be an important step in the review and refinement of regulatory processes to ensure the data gathered and evaluated serves the intended purpose of informing regulatory decision-making. It remains to be seen whether activities purporting to address this will prove fruitful.

In summary, for the topic of metrology and dose metrics for hazard and exposure assessment throughout the life cycle:

- Metrology plays an essential role in the development of nanomaterials, not least in facilitating and integrating the interpretation of components of risk assessments.
- Release is the prerequisite for any exposure and the metric(s) to be used in release, exposure and hazard assessment may vary depending on the tasks being characterised and the sensitivity needed.
- Extensive data is being gathered on nanomaterials, and experience-based learning in doing so is emerging, but whether the data gathered brings true value for regulatory risk assessment is not clear. It is arguable whether unlinked data on a substance's properties and behaviours can ever meaningfully inform regulatory risk assessment decision-making.
- It is feasible for release processes to be grouped and simulation tests to be defined, with combinations of release processes being set-up for specific exposure scenarios.
- A potential strategy for enhancing the components of nanomaterials risk assessment exists (i.e. ITS-Nano) but it needs widespread consideration, further development of operational processes, and adoption for successful implementation.
- A tiered approach specifically for exposure assessment has been developed, which now requires adoption and evaluation to establish and harmonise the approach and identify the extent to which it can be employed meaningfully.
- A greater and more focused interaction between different communities and scientific disciplines producing and using data is needed to make its use as effective as possible in assessing and appropriately regulating the safety of a product/substance through the components of risk assessment paradigm.

6 TOPIC 4: ENVIRONMENTAL FATE, PERSISTENCE AND BIOACCUMULATION THROUGHOUT THE LIFE CYCLE

6.1 BACKGROUND

In the REACH Regulation, the assessment of environmental fate is primarily based on a number of standard information requirements; among others, physicochemical characteristics of the substance, biotic and abiotic degradation, and bioaccumulation.

Due to the wide range of nanomaterials and their variety of different forms, sizes, shapes and surface characteristics, their environmental fate assessment can become very complex. REACH testing strategies and standard test guidelines are in principle applicable for assessing the fate of nanomaterials[39], [40]. Nevertheless, there seems to be a clear need for adaptation and development of test guidelines and discussion on the necessity of introducing nano-specific information into the environmental fate assessment.

The unique properties of nanomaterials bring new challenges to the applicability of harmonised test guidelines for chemicals. A preliminary review of OECD test guidelines outlines that the majority of the OECD TGs for chemicals are generally applicable for nanomaterials[41]. However, the applicability of individual test methods depends on the physical and chemical properties of nanomaterials in different environmental media.

In 2013 at the OECD meeting on "Ecotoxicology and environmental fate", further recommendations on the development needs regarding the OECD TGs for assessing the environmental fate and behaviour of nanomaterials were given by experts[42]. For example, there is a need for the development of new test guidelines for specifying dissolution behaviour, adsorption-desorption and partitioning properties of nanomaterials and guidance on the determination of agglomeration behaviour and transformation processes in environmental media. Furthermore, limitations in aquatic bioaccumulation tests predicting the bioaccumulation of nanomaterials were observed.

In addition, a lack of harmonised methods in sample preparation, characterisation of the test substance and its different forms may reduce the reliability of the environmental fate assessment of nanomaterials in general.

Due to the complex interactions of nanomaterials with their environment and potentially changing physico-chemical characteristics during their life cycle, many uncertainties in understanding their behaviour in the environment remain. Especially extrapolation of fate data across media, biological species and

39 Hankin SM, Peters SAK, Poland CA, Hansen SF, Holmqvist J, Ross BL, Varet J, Aitken RJ. 2011. Specific advice on fulfilling information requirements for nanomaterials under REACH (RIP-oN 2) - final project report. http://ec.europa.eu/environment/chemicals/nanotech/pdf/report_ripon2.pdf.

40 Kűhnel D, Nickel C. 2014. The OECD expert meeting on ecotoxicology and environmental fate — Towards the development of improved OECD guidelines for the testing of nanomaterials. Sci Total Environ. 472: 347-353.

41 OECD 2009. Organisation for Economic Co-operation and Development: Environment Directorate: Preliminary review of OECD test guidelines for their applicability to manufactured nanomaterials. ENV/JM/MONO(2009)21, Series on the Safety of Manufactures Nanomaterials, No. 15.

42 OECD 2014. Organisation for Economic Co-operation and Development: Ecotoxicology and environmental fate of manufactured nanomaterials, ENV/JM/MONO(2014)1, Series on the Safety of Manufactures Nanomaterials, No. 40.

across nanomaterials with different properties is challenging. Based on these identified challenges and development needs, it has been stated that the environmental fate of nanomaterials cannot be reliably assessed with the currently available standards[43]. Therefore, updates in guidance for environmental fate assessment and harmonisation of the regulatory risk assessment approaches may be necessary.

Degradation and transformation assessment

Degradation is an important process that may result in the reduction or transformation of a chemical substance in the environment. A pre-requisite for biodegradation is that the test material is based on organic carbon chemistry. As a result, fully inorganic nanomaterials will not require testing in the biotic degradation tests. The OECD TGs for biodegradability that are recommended in the ECHA Guidance on information requirements and chemical safety assessment (R.7b, November 2012) measuring carbon dioxide production or oxygen uptake are, in principle, applicable for nanomaterials to the same extent as for bulk materials.

These OECD TGs have been developed and validated for the assessment of organic compounds whereas many nanomaterials are primarily inorganic and even carbon-based nanomaterials arguably tend to be of an inorganic nature. There is evidence of single-walled carbon nanotubes (SWCNT), multi-walled carbon nanotubes (MWCNT) and fullerene (C60) degradation by oxidative enzymes[44],[45]. Degradation of organic coatings or functional groups of some inorganic nanomaterials may be assessed by these traditional biodegradation tests, but this still needs to be validated.

Simulation tests for biological degradation in various environmental compartments are applicable in principle, but again the detection and quantification of the nanomaterial is the challenge. The possible degradation to carbon dioxide, integration into biomass or other partitioning can be followed e.g. using labelled test materials. In addition to the biodegradation; hydrolysis, photo-degradation, oxidation and reduction plays an important role in environmental fate assessment. For hydrolysis testing, the chemical structure of the material and whether it contains groups that could be subject to hydrolysis dictate whether this test is necessary or appropriate. It has been suggested that degradation of nanomaterials may also be identified as changes at the nanomaterial surfaces (e.g. by oxidation processes or changes of coatings) and transformation and/or degradation (assessed by appropriate analysis approaches) as basic changes in composition or form (e.g. dissolution or hetero-aggregation)40.

Bioaccumulation assessment

To determine if and under which circumstances nanomaterials accumulate in the environment and environmental species, more knowledge on the key characteristics that influence the fate, behaviour and kinetics of nanomaterials and implementation of this knowledge within the risk assessment approaches and regulatory frameworks is needed.

For organic substances, there is an established relationship between the octanol/water partition coefficient (Kow) and bioaccumulation or bio-concentration factor (BCF). With regard to nanomaterials, it is not possible to make log Kow or solubility estimations, since they are dispersed and not in solution. Therefore, estimation based on log Kow for assessing the potential for bioaccumulation of nanomaterials is not acceptable. Furthermore, current possibilities for using non-testing approach (e.g. quantitative structure–activity relationships (QSAR)) are limited while no generally accepted approached are available for nanomaterials (Appendix R7-2 Recommendations for nanomaterials applicable to Chapter R7c Endpoint specific guidance).

43 Schwirn K, Tietjen L, Beer I. 2014. Why are nanomaterials different and how can they be appropriately regulated under REACH?. Environmental Sciences Europe 2014, 26:4.
44 Allen BL, Kichambare PD, Gou P, Vlasova II, Kapralov AA, Konduru N, Kagan VE, Star A. 2008. Biodegradation of single-walled carbon nanotubes through enzymatic catalysis. Nano Letters. 8:3899–3903.
45 Schreiner KM, Filley TR, Blanchette RA, Bowen BB, Bolskar RD, Hockaday WC, Masiello CA, Raebiger JW. 2009. White-Rot Basidiomycete-Mediated Decomposition of C60 Fullerol. Environ Sci. Technol 43: 3162-3168.

Bioaccumulation testing in aquatic organisms according to OECD TG 305 (bioaccumulation in fish) is generally considered to be applicable, but the calculation of the BCF has been critically discussed with regard to nanomaterials. Recommendations from the OECD expert meeting were to examine dietary exposure for nanomaterials and to develop a guidance document for the testing of nanomaterials in accordance with TG 305[46] (OECD 2014). Nanomaterials have a tendency to aggregate, and thus their likelihood of ending up associated with sediment is high[47].

Bioaccumulation in sediment-dwelling organisms according to OECD TG 315 is generally considered an applicable approach for nanomaterials as well as OECD TG 317 for terrestrial bioaccumulation. For these TGs and others, there may still be a need to develop new standard approaches, application of new nano-relevant endpoints (uptake rate, internalisation rate, and attachment efficiency) and general agreement of the bioaccumulation testing strategies for nanomaterials[40]. One of the main challenges in testing the bioaccumulation of nanoparticles is their detection, quantification and characterisation in the various test guidelines that exist.

6.1.1 Issues to be addressed

Within the regulatory frameworks, assessment of the environmental fate of the nanomaterials should be based on the generally accepted and scientifically-valid techniques. It has been commented that the REACH Guidance does not fully cover the specific environmental fate of nanomaterials (e.g. alterations, dissolution and distribution) and adjustments have been recommended by Meesters et al.[48]. Is there a need for further information on the environmental fate of nanomaterials to address the existing uncertainties that go beyond those requirements laid down in REACH to date?[38]

6.2 PRESENTATIONS

The fourth topic of the workshop was focused on environmental fate, persistence and bioaccumulation throughout the life cycle and was addressed in the following presentations:

- Environmental fate modelling and measurement of nanomaterials - Dr Geert Cornelis, University of Gothenburg, Sweden
- Bringing it all together: Comparing a "classical" ERA based on standard endpoints and approaches with a more informed and nano-specific ERA for ZnO and Ag nanoparticles - Dr Claus Svendsen, Centre of Ecology and Hydrology, United Kingdom
- Challenges for effect assessment of nanomaterials in the environment - Prof. Teresa Fernandes, Heriot-Watt University, United Kingdom

6.2.1 "Environmental fate modelling and measurement of nanomaterials"

Dr Geert Cornelis (University of Gothenburg), in his presentation entitled "Environmental fate modelling and measurement of nanomaterials", stated:

Fate descriptors

Developments in hazard identification of engineered nanomaterials (ENM) have not been met with

46 OECD 2014. Organisation for Economic Co-operation and Development: Ecotoxicology and environmental fate of manufactured nanomaterials, ENV/JM/MONO(2014)1, Series on the Safety of Manufactures Nanomaterials, No. 40.
47 Klaine SJ, Alvarez PJ, Batley GE, Fernandes TF, Handy RD, Lyon DY, et al. Nanomaterials in the environment: behavior, fate, bioavailability, and effects. Environ Toxicol Chem 2008;27:1825–51.
48 Meesters JAJ, Veltman K, Hendriks AJ, Van De Meent D. 2013. Environmental exposure assessment of engineered nanoparticles: why REACH needs adjustment. Integr Environ Assess Manag 2013: 15–26.

proper fate descriptors to calculate travel distances and the bioavailable concentration of engineered nanoparticles (ENP). Many of the hazard assessments have, for instance, been performed without assessing the interactions with the surrounding medium (e.g. a rare exception Waalewijn-Kool et al.[49]). Overlooking the interactions between ENMs and the medium may lead to high uncertainty in risk assessments due to the variability in the fate and bio-availability of ENM[50]. It is therefore important to take this variability into account. Looking at conventional chemicals, this has been done using partitioning coefficient (Kd) values, that have been related e.g. to soil properties leading to much less conservative risk assessments because the accuracy increased drastically when accounting for the partitioning of chemicals to solid phases in the environment.

An alternative fate descriptor to the Kd value is thus required to describe the behaviour of ENM in the environment. Three possible fate descriptors for ENM discussed were batch partitioning coefficients (Kd values), batch retention coefficients (Kr values) and column attachment efficiency. Analysis of the applicability of these fate descriptors should be looked at in view of both technical and practical aspects of environmental risk assessments of ENM[51].

Kd values are not appropriate fate descriptors for ENP because the equilibrium assumption is not valid. The processes that govern the fate of ENM are all kinetic processes and ENM particles will never reach equilibrium in the environment. Hence, their fate can never be described by one static parameter such as Kd values. ENM require an entirely different fate descriptor and an entirely different modelling approach to go with it[52].

The kinetic interpretation of batch studies by Kr values offer some improvement. Kr values are in essence obtained in the same way as Kd values, but they do not assume equilibrium. It has been found that this approach bears a link to relevant ENP processes in the environment, but interpretation may be confounded by the conditions of high shear during batch tests complicating direct use in transport or bioavailability calculations.

The attachment efficiency of ENMs in a particular environmental compartment can be obtained from column experiments. Attachment efficiency is a kinetic parameter that, contrary to Kr values, can be used directly in transport modelling. It expresses the likelihood that a particle will "stick" when it passes an environmental surface. High attachment efficiency implies limited transport and most likely a limited bio-availability. This parameter has already been used in transport models in rivers as well as for soils.

Monitoring of ENM in the environment

Monitoring of ENM in the environment is complicated by the low expected concentrations and the presence of other naturally occurring particles in the environment. At the same time, it has been claimed that the size of ENM matters in terms of their hazard and that number concentration (e.g. number of particles per mL-1) is a more appropriate dose metric of ENM instead of just the total mass concentration (e.g. mg L-1). The wish list for monitoring ENM in the environment is thus long: we require a highly sensitive, selective technique that can measure size and number concentrations. The technique should also be cost-effective, fast and easy to use. The most promising technique in this respect is single-particle inductively coupled plasma mass spectrometry (ICP-MS) that has been shown to measure number-based size distributions of ENM in real environments (e.g. wastewater treatment plant effluents and freshwaters) at environmentally

49 Waalewijn-Kool PL, Ortiz MD, Lofts S, van Gestel CAM. The effect of pH on the toxicity of zinc oxide nanoparticles to Folsomia candida in amended field soil. Environmental Toxicology and Chemistry 2013; 32: 2349-2355.
50 Cornelis G, Hund-Rinke KM, Kuhlbusch T, Van den Brink N, Nickel C. Fate and bioavailability of engineered nanoparticles in soils: a review. Critical Reviews in Environment Science and Technology 2014; 44: 2720–2764.
51 Cornelis G. Fate descriptors for engineered nanoparticles: the good, the bad, and the ugly. Environmental Science: Nano 2014: In press: DOI: 10.1039/C4EN00122B.
52 Praetorius A, Tufenkji N, Goss K-U, Scheringer M, Von der Kammer F. The road to nowhere: Equilibrium partition coefficients for nanoparticles. Environmental Science: Nano 2014; In press. DOI: 10.1039/C4EN00043A.

relevant concentrations (i.e. ng L^{-1} or a few thousands particles per mL^{-1} [53].

The spICP-MS technique uses existing equipment (normal ICP-MS machines) and is thus not particularly costly and when the data is collected and treated properly, number-based size distributions can be obtained. The technique has now been sufficiently explored so that accuracy can be guaranteed or at least the limitations are known. One such limitation has been the size detection limit, which has been reduced using advanced data treatment e.g. down to a few nm for "ideal" elements such as Ag and Au. Other ENM such as titanium dioxide (TiO2) still have detection limits of a few tenths of nm.

6.2.2 "Bringing it all together: Comparing a 'classical' ERA based on standard endpoints and approaches with a more informed and nano-specific ERA for ZnO and Ag nanoparticles"

Dr Claus Svendsen (Centre of Ecology and Hydrology), in his presentation entitled "Bringing it all together: Comparing a "classical" ERA based on standard endpoints and approaches with a more informed and nano-specific ERA for zinc oxide (ZnO) and silver (Ag) nanoparticles", stated:

It has been established from the mass-based flow modelling of Gottschalk and Nowack[54] what the major flows and entry routes into the environment outside direct application are likely to be, namely; through consumer products into waste waters, where upon treatment NMs mainly go to soils through sludge application and a fraction to waters with the effluent.

Mechanistic models of nano-relevant fate processes can be coupled with classical fate and transport models and get reasonable worst-case models for predicted environmental concentration (PEC) estimates that are "nano employable", but they must include accounting for NP fate and transformation processes. An example of turning such mass usage estimates into local predicted environmental concentrations at the EU scale can be found in Dumont et al (2014)[55] and also in very local scale models for specific water causes that include sedimentation, re-suspension and turbulence[56].

Good predicted no effect concentration (PNEC) estimates can be obtained from using slightly modified standard tests where media are modified to present nanomaterials in a realistic yet as stable as possible form and using standard Environmental Risk Assessment (ERA) data analysis. The key modifications needed are to control exposure and ensure it is "real world" relevant.

Under the current EU scale of risk assessment for down the drain ENMs (e.g. NanoFATE), in the worst-case scenario the PEC gets to within one to two orders of magnitude of the PNEC in EU water courses, while for soils the gap between the PEC and the PNEC in EU water courses is two or more orders of magnitude. With more detailed consideration of how media chemistry affects transformations, fate and bioavailability of NMs these gaps will become larger. The major environmental sinks for ENMs are sediments and soils, where due to the low availability and slow removal rates the most pressing question is long-term - low dose fate, availability and long-term effects.

Addressing release and exposure relevant nanomaterial forms is becoming a priority. From the few completed studies, it appears that, in the short-term, standard toxicology test aged nanomaterials generally have proven to be less toxic than pristine nanomaterials. In contrast, experiments using longer term mesocosms or aged sewage sludge exposures within the UK-US TINE project[57] showed that sludge

53 Tuoriniemi J, Cornelis G, Hassellöv M. Size discrimination and detection capabilities of single-particle ICP-MS for environmental analysis of silver nanoparticles. Analytical Chemistry 2012; Accepted for publication (doi: 10.1021/ac203005r).
54 Gottschalk F, Sun T, Nowack B. Environmental concentrations of engineered nanomaterials: Review of modeling and analytical studies. Environmental Pollution 2013; 181: 287-300.
55 Egon Dumont, Andrew C. Johnson, Virginie D.J. Keller, Richard J. Williams (2014) Nano silver and nano zinc-oxide in surface waters - Exposure estimation for Europe at high spatial and temporal resolution, Env Poll, in press.
56 Quik JTK (2013) Fate of nanoparticles in the aquatic environment. Removal of engineered nanomaterials from the water phase under environmental conditions. PhD thesis, Radboud University Nijmegen, The Netherlands.
57 http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.highlight/abstract/9145

from waste water dosed with metals in nanoform caused higher effects than those doses with ionic metals at the same concentration. This illustrates that long-term fate is of major importance.

For metal NPs, there is some evidence that organisms exposed to nano forms accumulate internal metal levels that exceed those seen in severely affected organisms exposed to the ionic form of the metal, without those excessive levels of nano derived metal in their tissues causing the same effects[58],[59]

6.2.3 "Challenges for effect assessment of nanomaterials in the environment"

The presentation of Prof. Teresa Fernandes (Heriot-Watt University, United Kingdom) entitled "Challenges for effect assessment of nanomaterials in the environment" reported that:

Knowledge concerning environmental fate and effects of nanomaterials has increased enormously over the last few years. Nevertheless, there are still many knowledge gaps, including general environmental exposure, how environmental conditions may affect exposure and effects, and the applicability of standard tests. Therefore, further effort needs to be dedicated to these areas. Given the knowledge of dynamic interactions that take place between organisms, nanomaterials and the environment, consideration needs to be given to the importance of realistic vs standardised approaches.

Modifications to the composition of growth media used in ecotoxicity experiments and data interpretation (e.g. bioconcentration factor), to try and improve the value of hazard assessments was highlighted. For example, with the OECD TG 201 algal test, appropriate test measurements must be considered to avoid artefacts; the media composition (i.e. salts, pH, organic matter) has been shown to affect the results, as do suspension/mixing protocols and the light conditions. Lastly, regarding challenges to overcome in grouping and read-across, the same materials of the same size may lead to different toxicity, and not all test species will respond similarly.

6.3 SUMMARY OF PRESENTATIONS FROM THE SPEAKERS

A collated summary of the main aspects from the presentations is provided below.

It was recommended that future efforts should be placed on the investigation and development of tests that strike a better balance between operational simplicity and technical accuracy. For example, column tests entail significant costs and, although the attachment efficiency they predict bear a close relation to real processes in the field, column experiments are to some extent also operationally defined and require a more experimentally dedicated approach that does not necessarily lead to a widely carrying physical parameter. There is thus a need for a simpler test. Even though it might deliver a less accurate parameter, this test could be more easily standardised and thus, similarly to Kd values produce high volumes of data allowing the parameter to be extrapolated to scenarios in which the parameter, whatever it may be, was not determined per se.

Comparison of Kr values with attachment efficiencies from column experiments show that such useful information can still be obtained from batch tests and different types of tests can be envisaged where a lower shear force exists so that the process of ENM sticking to surfaces is simulated as closely as possible to the situation in the field, while still leading to a relatively simple and cheap test.

It is also unclear how fate descriptors for transport (e.g. attachment efficiency) relate to bio-availability (as is also the case for conventional chemicals). This field is entirely unexplored, because fate assessment has

58 Heggelund, L.R. et al. 2013. Soil pH effects on the comparative toxicity of dissolved zinc, non-nano and nano ZnO to the earthworm Eisenia fetida Nanotoxicology, 8, 559-72

59 . Hooper, H.L., Jurkschat, K., Morgan, A.J., Bailey, J., Lawlor, A.J., Spurgeon, D.J., Svendsen, C. (2011) Chronic toxicity of nanoparticulate zinc oxide and dissolved zinc chloride to the earthworm Eisenia veneta in a soil matrix. Environment International 37(6): 1111-1117

not been met with the same level of attention in the research and regulatory domain. It is, however, required to establish a relation between whatever descriptor is deemed appropriate for fate, whether it is also appropriate to calculate bio-availability.

While spICP-MS has been developed a lot, it does not address all monitoring needs for ENM. Foremost, organic ENMs (e.g. fullerenes) cannot be analysed using spICP-MS. Techniques for such ENMs are at their infancy and currently have detection limits in the order of mg L-1, i.e. higher than currently predicted concentrations in the environment.

Even in the case of inorganic ENMs that can be analysed using spICP-MS, many hurdles still remain. Firstly, naturally occurring particles exist that contain the same element (e.g. Ti) as ENMs and these cannot be distinguished using spICP-MS. spICP-MS only analyses liquids that have to be extracted from, for example, soils.

The effect of these extraction methodologies has not been assessed for soils and nor has the implications for bio-availability assessment. In summary, it can be stated that model outcomes can today not sufficiently be validated using the available equipment *(see e.g. Gottschalk et al. 201349). Future developments such as coupling spICP-MS to field flow fractionation or using TOF-spICPMS, where many elements can be monitored may improve this situation much in the near future. Finally, the widespread usage of spICP-MS has been halted by lack of experience and training in the technique, but this situation can be resolved in the very short-term by software that has been developed in-house by manufacturers (e.g. Perkin-Elmer) or at Gothenburg University.

Currently, the major weakness of environmental ENM risk assessments are that the majority of data available on both exposure and hazard, are so far gathered from work undertaken using "pristine/as manufactured" ENM forms, which are most likely more reactive than the "release/exposure relevant" forms. This has consequences for the major important fate, bioavailability and hazard parameters[60],[61],[62],[63], and hence the fate chemistries, bio-availabilities, and hazard estimates are possibly more worst-case than required.

There is a need to compare results from testing of pristine particles with more relevant testing of the exposure relevant particles. For this, we need to know the release and fate routes plus how particles have been transformed, as it is most relevant to test the particles in the media where they end up in the environment (e.g. solid, sewage sludge etc.) and in the exposure relevant forms.

There are also technical developments needed to be able to really characterise environmentally-relevant exposures. Currently, many of the suitable techniques for nanomaterials have detection limits and media requirements (i.e. needs to be run in clean media) that currently means they operate at concentrations beyond those of even artificially high toxicological experiments. As such, they are incapable of addressing a heteroaglomeration state, dissolution rates, and acquired coatings at realistic environmental exposure conditions. Long-term, low dose exposures may reveal that some of the odd nanoparticle effects seen at high doses do not represent the chemistries and therefore resultant effects seen under realistic exposure conditions.

In summary for the topic of environmental fate, persistence and bioaccumulation throughout the life cycle:

- While some progress has been made in elucidating environmental hazard of engineered nanomaterials

60 Tourinho, P. S., et al. 2012. Metal-based nanoparticles in soil: fate, behaviour and effects on soil invertebrates Environ. Toxicol. Chem. 31, 1679-1692
61 Cornelis, G.; Hundy et al. Fate and Bioavailability of Engineered Nanoparticles in Soils: A Review 2014. Crit. Rev. Environ. Sci. Tech. DOI:10.1080/10643389.2013.829767.
62 Cornelis, G. et al. 2013. Transport of silver nanoparticles in saturated columns of natural soils. Sci. Total Environ. 463-464. 120-130
63 Hammes, J., et al. 2013. Geographically distributed classification of surface water chemical parameters influencing fate and behaviour of nanoparticles and colloid facilitated contaminant transport. Water Res., 47, 5350-5361

(ENMs), predicting exposure and bio-availability has been lagging behind.

- The chemistry of the environment has a significant effect on the transport and bio-availability of ENMs. The risk of ENMs will thus also vary as a function of the environmental characteristic of the receiving medium (water, soil, sediment).
- Mass-based and detailed models have been developed for environmental ENM fate, but no agreed fate descriptors that can be used routinely to calculate transport or bio-available ENM concentrations from total ENM concentrations are available.
- Use of Kd values to calculate environmental interactions of ENMs will lead to false predictions, because the processes that control ENMs are not in equilibrium.
- Progress in analytical chemistry now allows measuring sizes and number concentrations of inorganic ENMs, albeit with some size limitations, at environmentally relevant concentrations using single particle ICP-MS (spICP-MS). This is not possible for organic ENMs and even interferences with natural particles do not allow spICP-MS to truly validate model outcomes presently.
- Currently, the major weakness of environmental ENM risk assessments are that the majority of data available on both exposure and hazard is not undertaken using "pristine/as manufactured" ENM forms, which are more reactive than the "release/exposure relevant" form. Hence, the fate, bio-availabilities, and hazard estimates may be worst-case scenarios.
- Mechanistic models of nano-relevant fate processes can be coupled with classical fate and transport models and reasonable worst-case models obtained for PECs estimates that are "nano employable", but they must include accounting for NP fate and transformation processes.
- Good PNEC estimates can be obtained by using slightly modified standard tests and data analysis. The key modifications needed are to control exposure and to gain reproducible and comparable test results.
- Under the current EU scale of risk assessment for down the drain ENMs (e.g. NanoFATE); in the worst-case scenario the PEC gets to within one to two orders of magnitude of the PNEC in EU water courses, while for soils the gap between the PEC and the PNEC in EU water courses is two or more orders of magnitude. With more detailed consideration of how media chemistry affects transformations, fate and bioavailability of NMs these gaps will become larger. The major environmental sinks for ENMs are sediments and soils, where due to the low availability and slow removal rates, the most pressing question is long-term - low dose fate, availability and long-term effects.
- There is a need to compare results from testing of pristine "as made particles" with testing of the exposure relevant particles, including information on the release and fate routes and transformation of the particles. In short-term tests, aged NMs have generally proven less toxic than pristine NMs. Experiments using aged sewage sludge showed that sludge from waste water dosed with metals in nano form caused higher effects than those doses with ionic metals at the same concentration, hence, illustration that long-term fate is of major importance.
- Despite many efforts and costs in research on risks of ENMs, it appears that the needs of the regulators have not been fully addressed. There is a need to develop protocols, frameworks, and approaches to group ENMs to obtain widely carrying datasets that can serve to resolve this uncertain situation. The workshop clearly called for a much closer collaboration between academia, industry and regulators to shortcut towards practically useable tools.

7 TOPIC 5: READ-ACROSS AND CATEGORIES OF NANOMATERIALS

7.1 BACKGROUND

Read-across and categories of nanomaterials are valuable approaches used to predict specific properties of substances for which there is insufficient experimental data. In a read-across approach, endpoint information from one or many chemicals is used to predict the same endpoint, either qualitatively or quantitatively, for one or many other chemicals. In a category approach, a group of substances whose properties are likely to be similar or follow a regular pattern is constructed.

Within the group, a property can be estimated through, for example, read-across or trend analysis. For predictions of nanomaterial properties using read-across or categories, three main possible scopes of prediction are conceivable:

1. from bulk to all nano-forms,
2. from bulk to specific nano-forms,
3. from one or many nano-forms to one or many nano-forms (of the same chemical identity but with differences in physicochemical characteristics, differently coated nano-forms, or nano-forms of different chemical identity).

Read-across is recognised as one of the key issues in finding a pragmatic way to bridge existing data gaps in the hazard characterisation of nanomaterials. Therefore, there is a push from both academia and policy makers, to find a way forward in agreeing on key issues within read-across and categorisation of nanomaterials; for example, establishing criteria for when and how read-across may be acceptable. Currently, in several FP7 projects, read-across is an identified deliverable and the issue is also discussed at a global level in an OECD context.

Any read-across and category approach applied for nanomaterials in a regulatory context must not compromise the insurance of the safe use of the substance and thus must be based on a robust scientific justification. The approach should identify and consider the properties or parameters that drive the endpoint in question.

7.1.1 Issues to be addressed

Identified within the workshop background document, the main challenges in the regulator context are how to use available hazard information in acceptable read-across and categories of nanomaterials for prediction of the hazard endpoints related to, for example, fate, ecotoxicity and toxicity. At this point in time, establishing the criteria and validation approaches with a high enough certainty to provide confidence and not jeopardise safe use is crucial. The combination of key criteria and possible cut off points that determine whether read-across and/or categories can be used without making underestimations of hazards, and for which purpose, are still to be defined.

Further clarification is also needed on how to best evaluate and to appropriately take into account uncertainties associated with read-across and categories, and if any uncertainty would be different from that associated with conventional substances.

7.2 PRESENTATIONS

In the final session (5) of the workshop, the topic of read-across and categories was addressed in the following presentations:

- Safety assessment of nanomaterials. What about extrapolation between ENMs? Read-across and categorisation - Dr Wim De Jong, National Institute for Public Health and the Environment, The Netherlands
- Grouping of nanomaterials using short-term inhalation studies and related in vitro methods - Dr Robert Landsiedel, BASF, Germany

7.2.1 "Safety assessment of nanomaterials. What about extrapolation between ENMs? Read-across and categorisation"

Wim De Jong (National Institute for Public Health and the Environment), in his presentation entitled "Safety assessment of nanomaterials. What about extrapolation between ENMs? Read-across and categorisation." stated:

In general, knowledge on nanomaterial toxicity has increased and now there is a greater focus on the understanding of mechanisms of toxicity which may increase in the possibilities for grouping of nanomaterials. Not all nanomaterials are toxic and this raises the need to evaluate nanomaterials individually rather than take a blanket approach of assumed toxicity.

To facilitate time and resource efficient identification of nanomaterial hazard status, there is a need for categorisation/grouping of nanomaterials. This raises many challenges and one of these is that the "environment" of a nanomaterial (e.g. lung lining fluid, blood, mucus) can have a large influence on their toxicological behaviour. These include pH, ionic strength, biomolecules and macromolecules, which coat the surface of the once naked particle. Coatings and surface molecules of nanomaterials, either applied deliberately (e.g. attaching Polyethylene Glycol (PEG) functional groups to the particle surface to increase blood circulation time) or incidentally such as the formation of a protein corona after deposition in the lung, are important factors in nanomaterial behaviour and toxicity as these modify the point of cellular interaction, the particle surface.

It was also outlined, using carbon nanotubes as an example, that it is not necessarily the bulk chemistry of a particle (carbon in this case) that dictates toxicity but also other components such as length and shape which can have a profound effect on hazard.

An example of grouping was given based on the work done on TiO2 and ZnO by the European Commission's (EC) Scientific Committee on Consumer Safety (SCCS), which has demonstrated that even one type of nanomaterial (e.g. TiO2) when obtained from different suppliers may show large differences in physicochemical characteristics including shape, crystal composition and catalytic activity. However, based on extensive toxicological information it was possible to describe parameters for both TiO2 and ZnO nanomaterials to form a group that shows acceptable low risks when applied as anultraviolet (UV)-filter in sunscreens. So, when a sufficient amount of data is available, interpolation within a type of nanomaterials seems to be possible and a description of a group is obtainable.

An alternative way for investigating nanomaterial toxicity is the analysis of adverse outcome pathways (AOPs), which describe a sequential chain of causally linked events that lead to an adverse health or ecotoxicological effect. These may be used in the future to compare possible toxicity of different nanomaterials. Similarly, principle component analysis (PCA), a statistical approach to identifying strong patterns within datasets, may also be another way to approach extrapolation of effects between

nanomaterials. In relation to such statistical data-mining, it is important that toxicological (disease) outcomes or pathways are included in such analysis, including PCA

7.2.2 "Grouping of nanomaterials using short-term inhalation study and related in vitro methods"

Dr Robert Landsiedel (BASF), in his presentation entitled "Grouping of nanomaterials using short-term inhalation study and related in vitro methods", outlined:

That BASF already use categories in the risk assessment of applications using nanomaterials. As a result, they do not subject each nanomaterial, in each modification, to a fixed list of animal studies but instead, perform the studies needed for the risk assessment of the nanomaterial in its very application.

Here, Dr Landsiedel described the concept of 'multi-perspective grouping of nanomaterials' which was born out of the observation that no single property groups all materials and that instead, a multi-perspective strategy is needed for grouping and testing. It was also stated that the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) task force on nanomaterials recently reviewed and critically appraised the existing approaches and suggested a framework to pull together different concepts in a "multi-perspective approach". Publication of the concept is anticipated to be available in 2015.

As the second main component to the presentation, Dr Landsiedel described the BASF approach to short-term inhalation studies (STIS) which follow the approach of longer, 28-day exposure guideline studies however limit exposure to five days with the following 23 days used as a recovery period. Using pigments as an example, they have investigated a wide range of materials using the STIS approach and generally find inflammation/necrosis as an effect. In terms of translocation, ZnO showed Zn dissolution and transfer whilst silica did not, although silica with a coating did transfer to spleen. Potency can be also used for grouping and based on this, there is a suggestion of four groups ranging from no adverse effects to no observed adverse effect concentrations (NOAECs) < 0.5 µg m3.

Overall, the STIS approach examines effects in the lungs, persistence, progression or regression of the effects, effects outside the lung, lung burden and potential translocation to other tissues with less animals and resources.

7.3 SUMMARY OF PRESENTATIONS FROM THE SPEAKERS

A collated summary of the main aspects from the presentations is provided below.

Nanotoxicology has benefited from the wealth of knowledge conventional particle inhalation toxicology and, while inhalation is still one of the major routes of exposure with the highest risks, it is now known that there is a need to expand 'nanotoxicology' beyond our knowledge obtained from inhalation toxicology.

One area where this is apparent is in regulation and testing of nanomaterials, as although the regulations as such, can be applied to and are suitable for nanomaterials; there is a need for the adaptation of certain assays used in the safety evaluation. Indeed there is a lack of validated and standardised methodologies for assessing toxicity as well as well-defined benchmark data based on reference nanomaterials.

A careful evaluation of the various assays used for the safety evaluation of classical chemicals is needed as nanoparticles do show different behaviours. This is most clear in the difference in toxicokinetics between chemicals (concentration driven) and nanoparticles (not concentration driven). Indeed the bio-distribution of nanoparticles is not dependent on concentration but on active filtering of the particles from the blood circulation, especially by organs from the so-called mononuclear phagocytic system (MPS), notably the liver and spleen.

A key issue facing nanotoxicology and the regulation of nanomaterials is the importance of careful and proper characterisation of the nanomaterials for registration especially in relation to the identification of the materials. This issue of characterisation and substance identity is crucial when considering if the nanomaterials presented within a registration or being used are the same as the ones on which the safety evaluation was performed. If these are not and the materials differ, it raises the question of the suitability of the use of such information for a registration. One area in which this may be important is in modifications of surface chemistry by coatings of functionalisation, which may alter the behaviour and thus potential toxicity of nanomaterials.

There is now a shift from earlier years of basic scientific research on nanomaterials to a greater focus on addressing what information regulators need for safety assessment.

While a framework for grouping may be within reach, a major challenge will be the design of a decision-tree and the definition of criteria to serve it. Some criteria for grouping, based on material properties (for example, solubility), biokinetics (for example, dermal absorption), bio-physical interactions (for example, surface reactivity) or early biological effects (for example, inflammation), are obvious to apply, while others, such as long-term effects, are currently being investigated.

The definition of groups and sub-groups will require reference materials and case studies of nanomaterial examples. While several reference materials will almost immediately be available, it will take more consideration, and probably experimental work, to find them for other grouping criteria. The multi-perspective grouping offers, however, a flexible decision-making framework, which can be used and further developed, at the same time.

Another challenge will be the generation of data to assign nanomaterials to groups. A substantial amount of data is, however, already available from physico-chemical characterisation of the materials and from short-term inhalation studies (generated by several research projects, such as nanoCare, NanoGEM, NanoSafe2 and NanoMILE).

Short-term inhalation studies serve grouping approaches by providing information on the organ's particle-burden as well as early lung effects, extra pulmonary effects, and the recovery or progression of these effects. On other levels, the cytochrome c assay and the macrophage assay in vitro may be useful to serve grouping criteria based on physico-biological interactions and cellular effects, respectively.

In summary for the topic of read across and categories of nanomaterials:

- Not all nanomaterials have identifiable hazardous properties; each nano-material has to be evaluated on its own to establish its hazard characterisation profile. While there are physico-chemical indicators of potential toxicity such as shape (i.e. fibre length in comparison with asbestos fibres), generalisations must be made with caution and on the basis of evidence; for example, there is no general rule that smaller particles are more hazardous as other factors can influence toxicity.
- Toxicokinetics are important for understanding particle distribution throughout the body, the identification of target organs, the dose organs receive and ultimately which organs are at risk of toxicity.
- Extrapolation between different engineered nanomaterials is still difficult.
- There can be considerable differences in physico-chemical characteristics of ostensibly the same engineered nanomaterials yet from different suppliers.
- Nanomaterials largely behave like other particles in the body; often with a higher biological activity due to their higher specific surface area and sometimes with an increased mobility in the body due to their smaller size. There is no general toxicity associating nanomaterials collectively but instead, toxic effects can be and are apparent within different nanomaterials.
- A comprehensive understanding of how the properties of nanomaterials dictate adverse health outcomes

has not yet been developed. Hence, classical QSAR (quantitative structure activity relationship) approaches are not yet capable of providing a sufficient grouping concept. A multi-perspective approach is proposed which looks at the life cycle of a nanomaterial as well as using information on the exposure, uptake, distribution, biophysical interactions as well as cellular and organ responses.

- Four major groups of inhaled nanomaterials with similar concerns related to human health are proposed by industry:

    i. granular insoluble particles without specific chemical toxicity;
    ii. granular insoluble particles of toxicity owing to their chemical composition;
    iii. soluble particles; and
    iv. insoluble, fibre-like particles.

Furthermore, industry also suggests that sub-groups can be formed based on exposure as well as bio-physical interactions and cellular effects of the assigned nanomaterials. Finally, short-term studies can further refine the information requirements needed for a risk assessment. Most nanomaterials will be assigned to a (sub-)group by either of these criteria, while others may undergo targeted testing based on the information requirements evolving in this process.

- Although the regulations as such can be applied and are suitable for nanomaterials, adaptation of certain assays, especially in vitro screening methods, used in the safety evaluation of nanomaterials is needed. A careful evaluation of the various assays used for the safety evaluation of classical chemicals is needed as (nano)particles show a different behaviour. This is most clear in the difference in toxicokinetics between chemicals (concentration driven) and nanoparticles (not concentration driven). The biodistribution of (nano)particles is not dependent on concentration but on active filtering of the particles from the blood circulation, especially by organs from the so-called mononuclear phagocytic system (MPS) notably the liver and spleen as main organs.

8 PANEL DISCUSSIONS

8.1 TOPICS 1, 2 AND 3

Panel Members: Dr Wendel Wohlleben, Dr Keld Jensen, Professor Michael Stintz, Professor Günter Oberdörster, Professor Thomas Kuhlbusch, Dr Steve Hankin

Chaired by: Prof. Wim de Coen and Dr Violaine Verougstraete

The panel discussion at the end of day 1 of the workshop was introduced by Violaine Verougstraete, (Eurometaux) and Wim De Coen (ECHA) who summarised some of the key points arising from the presentations and discussions of topics 1-3.

Looking back across the issues discussed, there were many areas of agreement, and one key area of agreement was that proper physico-chemical characterisation is both important and needed. This was seen as a cross-topic issue, needed for the proper registration and evaluation of materials as well as fundamental research into nanoparticle hazard and exposure. However, such characterisation should be appropriate so as not to become overly burdensome and be accessible to all and therefore must not be too specialist or too expensive. In addition, while characterisation and test methods should be specific and sensitive, they should not be too sensitive so as to cause false positives, meaning that there is a need to strike a balance to ensure the safe use. This issue of reflecting the real world was again a cross-topic issue: in simulating exposures or conducting toxicity testing, materials should at least consider, and preferably reflect, real life conditions.

As part of this wider consideration of improved testing and characterisation methods and approaches, there is a distinct need for more guidance on how to collect, explain, and justify data. When considering better guidance as well as needs for particle physicochemical characterisation, there should be a focus on emphasising and establishing the value of data in relation to the primary objective which is the safe use of nanomaterials.

None of these points raised can be addressed immediately, however to facilitate efficient and safe progress of nanotechnologies, clear approaches (and guidance) are needed sooner rather than later, which will require a pragmatic approach to addressing uncertainty.

One of the Chairs raised the issue that we have a definition for a nanomaterial and that the definition needs to be implemented, possibly through the use of a tiered or matrix approach. In relation to this, the panel discussion considered the volumetric specific surface area (VSSA) approach to defining nano and non-nano forms of a substance.

A panel member stated that a combined approach of VSSA is important but that there are concerns about the consideration of agglomerate size and how this may effect discrimination between nano and non-nano forms. Taking the example of polyvinylpyrrolidone (PVP) coated silver nanoparticles, outside of a liquid they may be largely aggregated; however, when placed in a fluid they immediately disperse to primary particle sizes due to the PVP coating. Given this issue of changeable aggregation state, it was the opinion of the panel member that it is important to disperse particles as fully as possible.

In relation to dispersing materials fully before use, a member of the panel raised the pertinent point that perhaps two separate issues were being discussed, namely metrology and preparation for (eco)toxicological testing; the former of which has greater relevance for the VSSA approach while the latter may require particle dispersion.

The overall issue of sample preparation/modification before testing (whatever the test may be) to facilitate the gathering of measurements calls into the question relevance to (eco)toxicology and (nano)particles in the real-world. There are characterisation techniques such as establishing surface area using Brunauer–Emmett–Teller (BET) which do not require sample modification; however, in the process of the technique the sample is de-gassed at certain temperatures which potentially could cause effect. Therefore, even techniques considered as not requiring extensive sample preparation may indeed cause modification thereby raising the question of relevance to the real-world. Considering this point of relevance to the real-world further, a panel member used the example of using BET to establish surface area of zeolites, which due to the presence of a high porous structure have a very high surface area using this technique yet not all the surface is biologically accessible and therefore not wholly biologically relevant.

Considering other schemes for metrology, the Chair drew the panel's attention to an overview of the metrology methods and ranking presented by Thomas Kuhlbusch in topic 3 (shown in Appendix 3). The schemes author explained that in reading the table, simply focusing on which cells have the most crosses would be overly simplistic. Instead, the table should be used to identify metrics based on the requirements/uses.

Considering the metrics collectively, a panel member stated that although they agreed that the selection of metrics must be governed by requirements/uses within the matrix, due to the historical uses of the mass metric this practice will continue, but we need to add in other metrics, ideally not just calculated but ideally measured in a complimentary way.

This issue of the retention of mass as a metric received agreement and a panel member pointed out that we need to keep track of the mass because looking back in history, it is mass that will tell us what has happened. The relevance and importance of considering historical data was exemplified by an industry delegate from the audience who raised the issue that in previous aerosol inhalation studies (>10 years ago), measurements were relatively basic with a focus on gravimetric analysis. In more modern studies using the same materials and more technologically advanced monitoring instruments, analysis showed that there are mixtures of agglomerates and primary particles. Their argument was that this mix of agglomerates and primary particles would likely raise the question of whether there is a need to test again.

Whilst in theory this may be true, a panel member explained that the way in which aerosols are produced can cause significant differences in particle size distribution (PSD) as well as other aerosol parameters. This creates many challenges to the issues of reproducibility. In certain cases, equipment from historical studies are still available and so the possibility exists to re-test materials with better characterisation to fully characterise the PSD and other key aerosol parameters with a view to avoiding re-testing using animals.

Maintaining mass as part of a metric matrix was further reinforced by a member of the panel who argued that mass is one of the most robust metrics as while we can do particle size distribution (PSD) analysis, we are not 100% sure if it is exactly true.

This issue of the link between instrument measurements and what is really there was similarly in relation to high aspect ratio nanomaterials (HARN). Here, where equipment such as a fast mobility particle sizers (FMPSs) are used to monitor HARN, what we think we are seeing with the measurement and what really is there is quite different and this needs to be considered during data interpretation.

In relation to this point, an industry delegate from the audience pointed out that if the focus is on primary particle size then that raises problems but if we consider a PSD then this is simpler. A key and overriding point to these issues is that we should understand the material; characteristics (e.g. primary) and the exposure conditions (e.g. agglomeration states). It was also raised that if the focus is on primary particle size then the technique needs to be electron microscopy and whilst there are considerable developments in electron microscopy, a key issue is that you can only measure what is on your microscope stage and this is

where the greatest degree of error comes from as you need size and number.

In relation to a point raised regarding understanding the material of interest, a question of which is more important - primary particle size or agglomerate size - was posed. In response, a member of the panel raised the point that the agglomeration state (single particle vs. different sized agglomerates) influences the site and efficiency of deposition in the lung. However, we do not know what happens to agglomerates once they deposit in the lung; does de-agglomeration occur and if so, does primary particle size become very important? The point was reiterated that it is the particles' characteristics at the point of exposure that are most relevant and while ideally we would have detailed exposure scenarios – that is still in the future.

The discussion then moved on to specific points around the metrics and why they may be selected. An academic delegate from the audience put forward the suggestion that the concept that the selection of metric may depend on why you measure the exposure.

Specifically, the parameters listed (see Appendix 3) are very good for measuring exposure in occupational settings/environments; however, if exposure is being monitored for the purpose of risk assessment, perhaps the focus should be on PSD in relation to deposition in the lung rather than external exposure. In doing so, the risk assessment would be for internal exposure (i.e. the amount that really deposits in the lung or has further systemic distribution) and therefore of greatest relevance to health impact.

In terms of the technical points around the measurement of different metrics, a governmental delegate from the audience raised the issue of distinguishing nanoparticles of interest from background particles, and asked how we can distinguish the information in the matrix table presented. In response, a panel member explained that the matrix table of technique and metrics was an early concept and that it is not an answer to the issues of looking between background and the particle and interest.

8.2 TOPICS 4 AND 5

Panel Members: Dr Geert Cornelis, Dr Claus Svendsen, Professor Teresa Fernandes, Dr Wim De Jong, Dr Robert Landsiedel

Chaired by: Dr David Carlander and Jenny Holmqvist

The panel discussion at the end of day 2 of the workshop was introduced by David Carlander (Nanotechnology Industries Association) and Jenny Holmqvist (ECHA).

One of the Chairs asked the panel where the focus should be when it comes to modelling of nanomaterials. A panel member stated that the focus should be on hazards, which is not an easy or quick area to address but that here is a need to move forward to a summary of what we know now in relation to the hazards different forms of nanomaterial pose and consolidate the information. Furthermore, there are areas of conflict within the literature; however despite this, there should be some routes of generalisation and areas in which the literature can be used to draw conclusions.

While there is agreement on the focus on hazard, a panel member added that a key issue for generating hazard information, and indeed information of fate, is the development and availability of standardised test methods validated for nanomaterials.

A panel member put forward the point that the focus should be somewhere between understanding the fate and the hazard of different nanomaterials and how nanomaterials behave in these test systems.

They drew on the example from the presentation of Teresa Fernandes showing that when using a standard

media, the particles sediment in suspension. Given this issue, the suggestion was that perhaps a range of media would be useful to assess what the effects are when the particles remain in suspension and also when they sediment. The relevance of this is that depending on where the particles are (in suspension or sedimented to the bottom of the tank), different organisms may be exposed differently.

Further to this issue, it was also argued by a panel member that efforts should be directed towards compartments where certain particles will come into contact rather than considering compartments where they will not. In addition, it was suggested by a panel member that progress would also increase if we stop focusing on pristine particles yet focus on how they will be seen in the environment. Another panel member suggested a preference to eradicate gaps rather than fill them; thereby taking out what does not fit in the risk assessment or is not needed for regulation.

In considering the above issue, one of the Chairs suggested that developments need to ensure that what is being tested in the lab is relevant for 'real' exposures. A panel member commented that a decision is needed on whether it is the characteristics of pristine particles or particles as exposed to that are needed. Another panel member commented that he supported a focus on particles as exposed to, but in contrast one of the Chairs stated that REACH is a substance-based regulation and that although it does take into account the life cycle, EACH clearly stipulates that information on degradation products can be asked for in within a substance evaluation by Member States where justified (e.g. components of the life cycle).

A panel member agreed that the issue of life cycle is very important but raises the question of how much does the pristine particle relate to the particles in the environment and the issue with life cycle is identifying the critical steps where there might be high exposure and hazard. This may become very complex and laborious and better if we can extrapolate from the pristine to fate in specific environments.

One of the Chairs asked what the current state is in terms of extrapolation from the pristine, and in response the panel member said that while we cannot yet fully extrapolate, there is some knowledge in this region but still much to do.

On the issue of modification during the life cycle, a panel member questioned if a registrant would be permitted to perform tests based on a pristine nanoparticle, but predict that the use of that nanoparticle will result in release into the drain (i.e. from a washing machine). The result of this release for nanoparticles such as silver would be sulfidation, which lowers the toxicity of the materials and so, could the registrant provide this data on this latter stage of the pristine nanomaterials life cycle?

In reply, a regulatory delegate from the audience informed the panel that it is currently relatively challenging to demand the sort of information that they have been discussing (i.e. on degradation products). They are currently awaiting updates in REACH annexes for nanomaterials but the information requirements are minimum requirements. For each requirement, there are often waivers that allow scientific data that is shown to be valid (i.e. based on models) to be used to fill in the information requirements in a more relevant way, such as has been described by the presenters. However, this does not mean pieces of information can be skipped; it has to be scientifically justified. Based on the description on information requirements and waivers, one of the Chairs asked the panel what information they would like to have if industry has to provide a lot more information; what should industry provide?

In response, it was suggested that work should not only focus on models for standard fate descriptors but also on what would be appropriate degradation models. To do this, there would first need to be agreement on what the dominant pathways for the majority of nanoparticles are and then possibly work towards some sort of model that enables industry to understand how a nanoparticle may change and perform more appropriate tests for toxicity or provide more appropriate information from the literature.

After the discussions on needs for modelling, and modification of nanomaterials during their life cycle, one of the Chairs asked the presenters of topic 5 for their views on the discussions and how they may relate to grouping possibilities. In response, it was suggested that within human health, there are some examples where you can come to some conclusions on grouping, as they showed with the SCCS evaluations.

They found that they needed a great deal of information but that it also showed the diversity of the nanomaterial. This enormous diversity within a single nanomaterial type caused surprise during the SCCS evaluation but raised the possibility, perhaps also within other types of nanomaterials, to start to see if it is possible to start grouping within nanomaterials types. As the precedent has been set with TiO2 and ZnO, there may be other types of nanomaterials for which, either from the peer-reviewed literature or from previous regulatory submissions, sufficient information is available to allow the formation of a group to allow for marketing permission in certain areas of the regulations. In that sense, it can be considered that human toxicology is further ahead than ecotoxicology.

The commenter stated that what they still find difficult is considering the effect of variations of nanomaterials such as coating and the impact that may have on grouping. Overall, the key point is that information is required and currently, it cannot be done without testing, either in vitro or in vivo.

Supplementing this opinion, the other presenting author for topic 5 indicated that whilst not specific to human or environmental toxicology, there is some beauty in knowing beforehand what we have to do. The situation is that within industry there are projects and people wanting to use nanotechnology for different purposes but they want to know if they can use it safely or if not, what they have to do to be allowed and that question is currently quite difficult to answer.

It is not possible to tell if, in the future, certain products may fall under nano-specific regulation or what the requirements may be. As such, they currently have to give their best recommendation and to do this, they use grouping concepts but it would be preferable to have prior agreements so that they can provide more accurate information to internal customers etc. on what will happen. Currently, investments and decisions are partially based on a best guess but certainty provides far more stability and reassurance.

One of the Chairs asked the panel to elaborate on different purposes of performing read-across. In response, one panel member noted that when considering the various steps in the mode of action for nanomaterials, there is possibility for read-across or grouping between different nanomaterials. However, a key part of this is the providing of information and justification as to why specific read-across or groupings have been made.

There are assays and tests linked with properties or endpoints (that can form groups or points of read-across) that can facilitate decision making around grouping or read-across and so these require testing; it is not yet a paper exercise to provide the information to support the decision on whether or not you can group certain nanomaterials.

Following on from this, the Chair asked if the panel sees any differences when it comes to how you justify between making a category or performing read-across. One of the panel members stated that they see read-across as taking information on one substance and reading it across to another and this should be a specific case.

Categories, in their opinion, are generally based on predefined criteria, such as a hypothetical category of ‘soluble particles’ and there will be predefined criteria of how to perform categorisation that will require some fine tuning, especially in relation to defining when categorisation or read-across is acceptable and when it is not and what the limitations are. In general, for categorisation the schemes and concepts are probably rather straightforward. However, when it comes to defining criteria and finding methods to serve these criteria and find data then decision making becomes more challenging and harder to predefine.

They argued that to help this, reference materials are needed with which to benchmark materials against. Another panel member suggested that research generally is focused on issues relevant to grouping categorisation such as properties that drive inflammation. It is not focused on read-across which requires reference materials for which you know everything about to form the basis of a read-across.

Taking the point about grouping around solubility raised, a panel member discussed the dissolution of particles and explained that in terms of solubility, ZnO is fast, Cu slower than that and amorphous silica slower than that. These therefore show three groups of fast, medium and slow. In addition, in the context of the discussion on standards, reference materials and benchmark materials, it may be better to use benchmark materials as these fit the needs for grouping and categorisation better. This is because a standard can be anything, a benchmark tells you something.

A regulatory delegate in the audience provided clarification that within read-across, where a parameter is defined to allow data to be provided from one chemical to another, it is for a specific endpoint and cannot be generalised to all other endpoints for the chemical. A panel member indicated their agreement with this position and that there are boundaries and it is useful to know what these boundaries are, however he suggests that in some cases it might be more universal. The issue of defining boundaries is the start of a group because if you know the boundaries and you know the test outcomes you can establish if a material falls within set boundaries and therefore, falls within a group. This was what was done within the SCCS for TiO2 and ZnO.

A panel member suggested differences in the behaviour between particles in the environment and in the human body and how they may become modified, for example, with a protein corona. They raised the idea that perhaps when a huge array of particles with different properties enters the body or the environment, they become modified and so many of these properties are lost. They asked whether this concept has been considered and whether or not it can be used to reduce the complexity of considering such a wide array of particles and properties. A fellow panel member remarked on the protein corona concept and said it has not proven to be as important as it was once thought as, especially in vivo, it does not seem to have such a profound effect.

In relation to the need for high level advice on grouping and read-across, a panel member stated that whilst broad groups may not do the whole job, they will help. As an example, high aspect ratio nanoparticles could be formed into a group for the purposes of risk evaluation and while this would need fine tuning, such efforts can be performed later with more information but in the meantime, such a grouping would already have a benefit. The formation of such broad (interim) groups would be aided by the use of benchmark materials.

When considering the evaluations on nanoparticles, a panel member noted that it is important to consider the free, non-agglomerated particles. This is because these are often considered as posing the highest risk although in the environment, whilst some can be present as singlet nanoparticles, most will be aggregated. The major issues therefore are the potential for de-agglomeration into smaller units and this reflects back onto the importance of characterisation at every step. An academic delegate in the audience stated that ISO TC 229 tried to develop material specifications for grouping and asks the panel if they think that industry supplies would consider making more standardised types of particles (i.e. decrease in the number of TiO2 samples all doing the same job). In response, the panel member suggested probably not and that they are not aware of work in this area. He agreed in principle to the suggestion as he raised the point as to why a producer would develop a product that is not technically superior yet still requires toxicology testing (with associated costs). As such, there is, in theory, a financial driver to conform and reduce particle ranges.

An industry delegate in the audience asked the panel on the apparent contradiction between being told, as a consumer, how nanomaterials can have very diverse and specific effects yet the discussion within the workshop is on generalisations and groupings. Based on this apparent mismatch, is more data not needed first? In reply, a panel member argued that in actuality, we have a great deal of data but all too often, the data is not useful for the specific purposes and needs of risk assessment. Instead, what is needed is more data, but this needs to be the right data.

9 MAIN OUTCOMES

In his concluding remarks, the chairman of the Scientific Committee, Wim de Coen, acknowledged the contributions made by all involved with the workshop and the value ECHA has gained from the discussions in helping shape future activities in the Agency regarding the hazard, exposure and risk assessment of nanomaterials. Hosting the workshop under the auspices of ECHA's Topical Scientific Workshops series reflects the importance placed on the topic area and the on-going considerations through ECHA's working groups on nano issues.

The workshop met its intended goal of being 'a platform for academia and regulators to discuss how to address current challenges from the regulatory perspective, which can be reflected and employed in on-going and future research topics on nanomaterials.' The discussions were reinforced by information of the recent developments and of risk assessment methodologies applied in chemicals management both within and outside the European Union. He concluded the workshop by summarising the highlights and further considerations:

- Regarding characterisation, which ECHA considers crucial, the notion of VSSA combined with EM has been proposed as an elegant tiered approach, which has the potential benefit of also elucidating when a substance is not a nanomaterial (according to the scope of the current EC definition) albeit with acknowledgement that there may well always be ambiguities requiring bespoke consideration.he research community is encouraged to develop new methods, improve existing ones, and to develop standardised protocols and reference materials.
- Metrology and dose metrics are both critical issues and ECHA recognises the importance and use of different metrics. Moreover, a crucial aspect recognised is the prioritisation and integration of all information into risk assessment, using strategies and approaches that encourage those in the distinct hazard, exposure and risk assessment communities to coordinate efforts and continue to build bridges between disciplines.
- Benchmarking controls to enable comparative hazard analysis is recognised as useful and the emergence of surface area and reactivity (alongside established number and mass based metrics) is important but recognised as still to be fully developed and demonstrated for regulatory risk assessment purposes. During the workshop, it has been suggested that there is a lot of data on substances, particularly from hazard assessments, but argued that potentially half of which is not adequate. ECHA has a desire for data to be of high quality and useful for regulatory risk assessment.
- In relation to safety and risk assessment, giving consideration to the release of nanomaterials is important, which extends to understanding influencing factors associated with both the material and the processes and using a life cycle-based approach to developing exposure scenarios. A tiered approach to exposure assessment has some merits, again yet to be fully developed and demonstrated to be appropriate for regulatory risk assessment purposes.
- Regarding environmental aspects, opinions challenged the relevance of current fate descriptors. While ECHA believes in the current fate descriptors, if there is evidence that these are not relevant or appropriate then consideration should be given to amending them for specific materials or environmental conditions. Equally, it is recognised that new models bring new challenges and these need to be validated and the challenges they bring need to be addressed. Furthermore, understanding the influence of particle dynamics during ecotoxicity testing was highlighted to improve the realism of environmental risk assessment of nanomaterials.
- The question of whether the standard hazard assessment tools are appropriate was posed, and opinion suggested that mostly they do, but consideration of issues such as media influence, ageing etc. is warranted. Discriminating between particle and ionic effects, and the rationale for testing manufactured vs 'as exposed/released' forms need consideration. Similarly, the relevance of high test concentrations and what this can mean for effects seen both in ecotoxicity and human toxicity testing, begs the question of whether we are missing something at lower doses?

- Read-across, for the purposes of REACH and its aspirations, will provide an important economical and ethical means of addressing data gaps. However, read-across requires data and it goes without saying that it is nonsensical to attempt read-across from no data to no data. Hence, there is a high urgency here and a breakthrough is needed. It is recognised that a robust use and understanding of physico-chemical data on the properties and behaviour of substances, and the mechanisms of toxicity, will facilitate read-across and grouping. In vitro models and high throughput screening will play a role in hazard ranking and grouping, but it is important to know the limitations.

In terms of what ECHA considers to lie ahead, the workshop has given a good indication of many of the directions being pursued by the academic, industrial and regulatory communities involved with the risk assessment of nanomaterials. REACH is acknowledged to apply to nanomaterials and crucially the outcome is awaited on potential amendments to the annexes of the legal text relevant to nanomaterials. Further guidance for REACH registrants can then be anticipated with close support from ECHA's nanomaterial working group, informed by this workshop and involvement in other on-going activities in Europe and internationally.

Since 2014, ECHA has increased its activities at OECD level and accepted the opportunity to act as the Chair of the steering group under the OECD Working Party for Manufactured Nanomaterials (WPMN) responsible for hazard and assessment of manufactured nanomaterials. In particular, the steering group coordinates the revision and development of test guidelines for in vitro, in vivo, as well as alternative methods such as read-across.

The outcome of the current workshop will be utilised in the planned OECD work as well as provide important input for ECHA's future work in ensuring that the REACH guidance and advice is updated with new scientific development in a timely manner.

APPENDIX 1 – ADDITIONAL RESOURCES

In addition to their expert opinion on the progress and needs within the topics covered, the speakers also provided recommendations for additional sources of information. The resources are presented below according to the workshop topics.

1. Challenges in the regulatory risk assessment of nanomaterials

- New Substances Program Advisory Note 2014-02 - Assessment of nanomaterials under the New Substances Notification Regulations (Chemicals and Polymers)
- Publication of New Substances Risk Assessment Summaries
- Canada-United States Regulatory Cooperation Council (RCC) (Note: more documentation on the RCC Nanotechnology initiative will be available at this link shortly)

2. Measurements and characterisation of nanomaterials

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- ILSI Research Foundation NanoRelease Project Website: http://www.ilsi.org/ResearchFoundation/RSIA/Pages/NanoRelease1.aspx. The NanoRelease project will foster the safe development of nanomaterials by supporting development of methods to understand the release of nanomaterials used in products.
- NANOFutures initiative Website: http://www.nanofutures.eu. NANOFutures is a European initiative for sustainable development by Nanotechnologies which identifies the key nodes in strategic nano-activities and develop strategies to address nanotechnology challenges with an intersectorial approach.

3. Metrology and dose metrics for hazard and exposure assessment throughout the life cycle

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APPENDIX 3 – PARTICLE METRIC TABLE

Reproduced from the talk of Thomas Kuhlbusch (slide 5). The number of + symbols indicates the relative relevance or applicability

	Personal Monitors	Ease of Measure	Conserved between Release & Exposure	Sensitivity to Detect Exposure	Health Relevant
Particle Mass Concentration	+++	+++	+++	+	++
Particle Surface Area Concentration	+++	+++	-	++	++
Particle Number Concentration	++	+++	-	+++	+
Particle Size Distribution	o	+	-	+++	+++
Particle Reactivity	-	-	-	-	+++

	Ease of which to Distinguish from Background	Facilitates Grouping	Regulatory Experience	Feasibility for implementation into Regulation
Particle Mass Concentration	+	+	+++	+++
Particle Surface Area Concentration	+	+	+	+++
Particle Number Concentration	+	+	+	+++
Particle Size Distribution	++	+++	o	-
Particle Reactivity	-	+++	o	o

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