ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

Series on the Safety of Manufactured Nanomaterials
No. 21

REPORT OF THE WORKSHOP ON RISK ASSESSMENT OF MANUFACTURED NANOMATERIALS
IN A REGULATORY CONTEXT
REPORT OF THE WORKSHOP ON RISK ASSESSMENT OF MANUFACTURED NANO MATERIALS IN A REGULATORY CONTEXT
Also published in the Series of Safety of Manufactured Nanomaterials:


No. 3, Current Developments/Activities on the Safety of Manufactured Nanomaterials: Tour de table at the 2nd Meeting of the Working Party on Manufactured Nanomaterials (2007)


No. 5, Current Developments/Activities on the Safety of Manufactured Nanomaterials: Tour de table at the 3rd Meeting of the Working Party on Manufactured Nanomaterials(2008)

No. 6, List of Manufactured Nanomaterials and List of Endpoints for Phase One of the OECD Testing Programme(2008)


No. 8, Preliminary Analysis of Exposure Measurement and Exposure Mitigation in Occupational Settings: Manufactured Nanomaterials(2009)

No.9, EHS Research Strategies On Manufactured Nanomaterials: Compilation Of utputs(2009)

No.10, Identification, Compilation and Analysis of Guidance Information for Exposure Measurement and Exposure Mitigation: Manufactured Nanomaterials(2009)

No.11, Emission Assessment for the Identification of Sources and Release of Airborne Manufactured Nanomaterials in the Workplace: Compilation of Existing Guidance(2009)

No.12, Comparison of Guidance on Selection of Skin Protective Equipment and Respirators for Use in the Workplace: Manufactured Nanomaterials (2009)


No. 15, Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials (2009)
No. 16, Manufactured Nanomaterials: Work Programme 2009-2012 (2009)

No. 17, Current Developments in Delegations and other International Organisations on the Safety of Manufactured Nanomaterials- Tour de Table (2009)

No. 18, Manufactured Nanomaterials: Roadmap for Activities during 2009 and 2010 (2009)

No. 19, Analysis of Information Gathering Initiative on Manufactured Nanomaterials (2009)


© OECD 2010
Applications for permission to reproduce or translate all or part of this material should be made to: Head of Publications Service, RIGHTS@oecd.org, OECD, 2 rue André-Pascal, 75775 Paris Cedex 16, France
ABOUT THE OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 30 industrialised countries in North America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD’s work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD’s workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

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

This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organizations. The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The participating organisations are FAO, ILO, OECD, UNEP, UNIDO, UNITAR and WHO. The World Bank and UNDP are observers. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.
This publication is available electronically, at no charge.

For this and many other Environment, Health and Safety publications, consult the OECD’s World Wide Web site (www.oecd.org/ehs/)

or contact:

OECD Environment Directorate, Environment, Health and Safety Division

2 rue André-Pascal
75775 Paris Cedex 16
France

Fax: (33-1) 44 30 61 80

E-mail: ehscont@oecd.org
FOREWORD

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

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

Based on the conclusions and recommendations of the Workshop [ENV/JM/MONO(2006)19] it was recognised as essential to ensure the efficient assessment of manufactured nanomaterials so as to adverse effects from the use of these materials in the short, medium and longer term. With this in mind, the OECD Council established the OECD Working Party on Manufactured Nanomaterials (WPMN) as a subsidiary body of the OECD Chemicals Committee in September 2006. And as part of its programme of work, the WPMN has a project on Co-operation on Risk Assessment.

As agreed at the 5th meeting of WPMN, the Workshop on Risk Assessment of Manufactured Nanomaterials in a Regulatory Context was organised with the objective of: i) to obtain expert input into the critical issues specific for the risk assessment of nanomaterials in a regulatory context; ii) to identify possible approaches for risk assessment based on the current state of knowledge; and iii) to identify issues which may be addressed through Sponsorship Programme.

This document is the report of the workshop held on 16-18 September 2009 in Washington D.C., United States, co-hosted by Business and Industry Advisory Committee (BIAC) and Society for Risk Analysis (SRA). It intends to provide information on outcomes and discussions of the workshop, as well as a number of recommendations for the WPMN activities. The Working Party endorsed this document and this document is published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology of the OECD.
# TABLE OF CONTENTS

ABOUT THE OECD ............................................................................................................................. 6  
FOREWORD ......................................................................................................................................... 8  
THE WORKING PARTY ON MANUFACTURED NANOMATERIALS (WPMN).................................11  
PROJECT ON CO-OPERATION ON RISK ASSESSMENT ............................................................12  
EXECUTIVE SUMMARY ..................................................................................................................13  
THE OECD WORKING PARTY ON MANUFACTURED NANOMATERIALS (WPMN) REPORT OF THE WORKSHOP ON RISK ASSESSMENT OF MANUFACTURED NANOMATERIALS IN A REGULATORY CONTEXT ..........................................................14  
  
  
  
  
  
  
Background ...................................................................................................................................... 14  
Introduction ...................................................................................................................................... 14  
Objectives of the Workshop ............................................................................................................. 15  
Presentations and Discussions .......................................................................................................... 15  
  General Presentations: Setting the Scene ..................................................................................... 15  
  Case Study Presentations and Discussion .................................................................................. 15  
  Summary ................................................................................................................................... 15  
  Summary ................................................................................................................................... 16  
  Summary ................................................................................................................................... 17  
Breakout sessions ............................................................................................................................. 18  
  Plenary discussion ......................................................................................................................... 18  
  Chair Summaries Breakout Sessions ........................................................................................ 18  
  (1) Assessment Problem Formulation ....................................................................................... 18  
  (2) Exposure – Public, Occupational and Environment ............................................................ 19  
  (3) Hazard – Human Health ....................................................................................................... 19  
  (4) Ecological Toxicity and Fate ............................................................................................... 20  
  (5) Determining Risk and Linkage between Assessment and Management ............................. 21  
Conclusions ...................................................................................................................................... 22  
ANNEX I (AGENDA FOR WORKSHOP) ............................................................................................23  
ANNEX II (GENERAL PRESENTATIONS) .........................................................................................25  
  (1-1) Overview of WPMN activities ............................................................................................... 25  
  (1-2) Critical Issues ...................................................................................................................... 29  
  (2) Presentation from SRA ........................................................................................................ 32  
  (3) Presentation from industrial perspective ............................................................................... 38  
  (4) Presentation from regulatory perspective ............................................................................ 41  
  (5) Presentation from NGO perspective .................................................................................... 45  
ANNEX III (CASE STUDY PRESENTATIONS) ....................................................................................49  
  (1) TiO2 case study ....................................................................................................................... 49  
    (1-1) Presentation from BIAC .................................................................................................... 49  
    (1-2) Presentation from US EPA ............................................................................................... 52  
    (1-3) Report from chair of TiO2 case study ............................................................................. 57  
  (2) Nano-Ag case study ................................................................................................................. 58
(2-1) Presentation from Global Sales & Marketing NanoHorizons Inc. and HeiQ Materials Ag 58
(2-2) Presentation from Germany ................................................................. 69
(2-3) Presentation from Netherland ...............................................................72
(2-4) Report from chair of Nano-Ag case study ........................................... 75
(3) CNT case study .................................................................................... 75
(3-1) Presentation from Bayer Schering Pharma (to be confirmed) ............... 75
(3-2) Presentation from US NIOSH ............................................................. 80
(3-3) Presentation from Japan NIOSH ......................................................... 84
(3-4) Report from chair of CNT case study ................................................ 87

ANNEX IV (BREAKOUT SESSIONS) ............................................................. 88
(0) Questions to Breakout Groups .............................................................. 88
(1) Assessment Problem Formulation ....................................................... 89
(2) Exposure – Public, Occupational and Environment ............................. 92
(3) Hazard – Human Health ..................................................................... 94
(4) Ecological Toxicity and Fate ............................................................... 98
(5) Determining Risk and Linkage between Assessment and ManagementTiO2 .................................................. 101

ANNEX V (PARTICIPANTS LIST) ............................................................... 103
THE WORKING PARTY ON MANUFACTURED NANOMATERIALS (WPMN)

1. The Working Party on Manufactured Nanomaterials was established in 2006 to help member countries efficiently and effectively address the safety challenges of nanomaterials. OECD has a wealth of experience in developing methods for the safety testing and assessment of chemical products.

2. The Working Party brings together more than 100 experts from governments and other stakeholders from: a) OECD Countries; b) non-member economies such as Brazil, China, the Russian Federation, and Thailand; and c) observers and invited experts from UNEP, WHO, ISO, BIAC, TUAC, and environmental NGOs.

3. Although OECD member countries appreciate the many potential benefits from the use of nanomaterials, they wished to engage, at an early stage, in addressing the possible safety implications at the same time as research on new applications is being undertaken.

4. The Working Party is implementing its work through specific projects to further develop appropriate methods and strategies to help ensure human health and environmental safety:

   - OECD Database on Manufactured Nanomaterials to Inform and Analyse EHS Research Activities;
   - Safety Testing of a Representative Set of Manufactured Nanomaterials;
   - Manufactured Nanomaterials and Test Guidelines;
   - Co-operation on Voluntary Schemes and Regulatory Programmes;
   - Co-operation on Risk Assessment;
   - The role of Alternative Methods in Nanotoxicology;
   - Exposure Measurement and Exposure Mitigation; and
   - Environmentally Sustainable Use of Nanotechnology.

5. Each project is being managed by a steering group, which comprises members of the WPMN, with support from the Secretariat. Each steering group implements its respective “operational plans”, each with their specific objectives and timelines. The results of each project are then evaluated and endorsed by the entire WPMN.

6. This document was prepared by the WPMN steering group six leading the work on Co-operation on Risk Assessment and was endorsed by the WPMN.

---

1 Updated information on the OECD’s Programme on the Safety of Manufactured Nanomaterials is available at: [www.oecd.org/env/nanosafety](http://www.oecd.org/env/nanosafety)

2 The Business and Industry Advisory Committee to the OECD

3 Trade Union Advisory Committee to the OECD.
PROJECT ON CO-OPERATION ON RISK ASSESSMENT

The overall objectives of this project are to evaluate risk assessment approaches for manufactured nanomaterials through information exchange and to identify opportunities to strengthen and enhance risk assessment capacity. This project is led by the steering group 6 (SG6) which will serve to integrate outputs from other WPMN steering groups into an overall framework within which risks of manufactured nanomaterials are assessed, ensuring good practice across OECD.

There are three detailed objectives with this project:

- Consider risk assessment strategies, methodologies, and supporting tools that offer the potential to underpin risk assessment.
- Identify and consider any unique issues that manufactured nanomaterials present for risk assessment.
- Make recommendations to WPMN for addressing and filling identified gaps.

These recommendations will also consider the need for provision of guidance on key issues that should be considered when undertaking risk assessments for manufactured nanomaterials as well as development of empirical evidence to support this guidance.

This document is the report of the OECD Workshop on Risk Assessment of Manufactured Nanomaterials in a Regulatory Context, which was held on 16-18 September 2009, in Washington D.C., United States. This report includes a summary conclusion of the discussion as well as the presentations that were given.

More information about the work of the WPMN, as well as publications and updates on efforts of governments and other stakeholders to address safety issues of nanomaterials is available at http://www.oecd.org/env/nanosafety.
EXECUTIVE SUMMARY

At the 5th meeting of the Working Party on Manufactured Nanomaterials (WPMN), it was agreed to hold an OECD Workshop on Risk Assessment of Manufactured Nanomaterials in a Regulatory Context. The objectives of the workshop were: i) to obtain expert input into the critical issues specific for the risk assessment of manufactured nanomaterials in a regulatory context; ii) to identify possible approaches for risk assessment based on the current state of knowledge; and iii) to identify issues which may be addressed through the sponsorship programme.

The workshop took place September 16th – 18th, 2009 in Washington D.C., United States, and was co-hosted by the Business and Industry Advisory Committee (BIAC) and the Society for Risk Analysis. Seventy (70) participants representing OECD member countries, non-member economies, industries, academia and environmental NGOs attended.

Following general presentations and discussions, case studies on Titanium dioxide nanomaterials, Silver Nanomaterials and Carbon Nanotubes were presented. Workshop attendees then participated in one of five parallel break-out sessions to discuss specific issues of risk assessment methodology including i) Assessment Problem Formulation; ii) Exposure – Public, Occupational and Environment; iii) Hazard – Human Health; iv) Ecological Toxicity and Fate; and v) Determining Risk and Linkage between Assessment and Management.

Workshop participants concluded that the risk assessment paradigm for chemicals will continue to guide approaches to the risk assessment of nanomaterials. However, because of the limited amount of empirical data on nanomaterials, many of the assumptions and estimations employed in chemical risk assessments need to be evaluated for nanomaterials. Research is also needed to determine what characteristics of nanomaterials may pose unique hazards. In terms of the application of uncertainty factors in risk assessments, there does not appear to be a scientific rational to justify employing a nano-specific risk assessment uncertainty factor. Application of standard risk assessment uncertainty factors should also undergo validation; justification should also be provided when using invalidated uncertainty factors in risk assessments. Lastly in terms of employing units of measurement used to communicate test results used in risk assessment, it is expected that empirical results will continue to be reported in terms of mass based units. However, risk assessments should include a discussion of any limitations this metric may present.
THE OECD WORKING PARTY ON MANUFACTURED NANOMATERIALS (WPMN) REPORT OF THE WORKSHOP ON RISK ASSESSMENT OF MANUFACTURED NANOMATERIALS IN A REGULATORY CONTEXT

Background

The aim of the Working Party on Manufactured Nanomaterials (WPMN) is to promote international co-operation on human health and environmental safety aspects of manufactured nanomaterials, in order to assist in their safe development.

One of the main projects included in the Programme of Work of the WPMN is led by Steering Group Six on Co-operation on Risk Assessments. The overall objective of Steering Group Six is to evaluate risk assessment approaches for chemicals that currently apply or may be extended to cover manufactured nanomaterials, identify critical issues for risk assessment and make recommendations to the WPMN with regards to how these issues should be addressed.

At the 5th meeting of the OECD WPMN held in March 2009, it was agreed to hold a workshop on the risk assessment of manufactured nanomaterials in a regulatory context that included participation from OECD member-countries, invited risk analysis experts and others.

The workshop was intended to provide expert input in the critical issues specific for the risk assessments of nanomaterials in a regulatory context, and provide information useful for the revision of the SG6 draft report entitled “Risk Assessment of Manufactured Nanomaterials: Critical Issues” which was prepared at the 4th meeting of the OECD WPMN.

The output of the workshop follows, and is a report of the opinions expressed during structured breakout sessions and plenary discussions.

Introduction

The OECD Workshop on Risk Assessment of Manufactured Nanomaterials in Regulatory Context took place on 16th – 18th September 2009 in Washington D.C., United States. This event was co-hosted by the Business and Industry Advisory Committee (BIAC) and the Society for Risk Analysis (SRA).

The workshop programme was prepared by the Organising Committee involving delegates from Canada, Germany, Japan, United States, European Commission, BIAC, and SRA.

The workshop was chaired by Andy Atkinson (Canada, co-chair of SG6). There were 70 participants from 14 delegations, including OECD member countries, and other stakeholders from non-member economies, industry, academia and environmental NGOs. In addition to the welcome remarks of SRA and the Secretariat, the workshop chair set the scene by giving an overview of WPMN activities as well as the critical risk assessment issues identified by SG6.
Objectives of the Workshop

The agreement to hold the workshop was made at the 5th meeting of the WPMN and the organising committee agreed to the objectives. There were three main objectives: i) to obtain expert input into the critical issues specific for the risk assessments of nanomaterials in a regulatory context; ii) to identify possible approaches for risk assessment based on the current state of knowledge; iii) to identify issues which may be addressed through the sponsorship programme.

Presentations and Discussions

General Presentations: Setting the Scene

The workshop started with a number of presentations which set the scene for starting the discussion on the importance of addressing risk assessment of manufactured nanomaterials. The introductory presentations provided perspectives from SRA, industry, government, and NGOs.

JoAnne Shatkin (CLF Ventures, Inc.) introduced SRA and its activities, as well as giving background information on the workshop for nanomaterial risk management organised by SRA in September 2008. William Gulledge (BIAC) made a presentation from the industrial perspective in which he highlighted the difficulties of assessing uncertainty in risk characterisation. Maila Puolamaa (European Commission) introduced the audience to the European regulatory perspective on nanomaterials under REACH. Finally, Caroline Baier-Anderson (Environmental Defense) addressed the challenges that need to be addressed in conducting a risk assessment of manufactured nanomaterials.

Case Study Presentations and Discussion

The workshop used case studies, presented from both a government / regulatory and industry perspective, to generate discussions. Materials that were discussed included: i) nano-sized titanium dioxide (TiO₂); ii) nano-silver (Ag); and iii) carbon nanotubes (CNTs). A number of presentations were made on each nanomaterial with the aim of providing a range of perspectives on risk assessment approaches and challenges. Each presentation was followed by comments from discussants and then by general discussion from all participants.

Titanium dioxide nanomaterials

This session was chaired by Jo Anne Shatkin (SRA).

- Shaun Clancy (Evonik, BIAC) presented “Risk Assessment Considerations for a Low Hazard Material”.
- J. Michael Davis (US EPA) presented “EPA Nanoscale Titanium Dioxide Case Studies”.
- Discussants
  - Robert Landsiedel (BASF, BIAC)
  - Margaret MacDonnell (SRA)

Summary

Three case studies presented data and analysis on nanoscale titanium dioxide. These case studies were narrowly focused and sought to address specific questions. The first focused on occupational exposure issues, while the two EPA cases evaluated specific applications of nanoscale titanium dioxide—as a water

---

treatment agent and in sunscreen—using Comprehensive Environmental Assessment (CEA), proposed as a life cycle approach to risk analysis useful for identifying research needs for risk assessment.

Discussants suggested the presentations did identify nano-specific material properties, but not their relationship to toxicity, and considered nano-specific aspects, but with an uneven comparison to bulk materials. Much of the discussion focused on the issue of general nano-related uncertainties vs. specific concerns. For example, understanding which material properties are responsible for a toxic effect will allow determination of the correct metrics for expressing exposure and dose. It was suggested that the toxic effects must be related to functionality, not only to nano-size. Participants raised issues regarding preparation of materials for study that may not reflect real world exposures, but do allow study of nanoparticle behavior. The experimental media can also affect interpretability of results (e.g., suspension media influencing the agglomeration state of the particles). Use of different media in different test protocols, including OECD test protocols, impacts particle behavior and comparability of results, and should be revisited for nanomaterial testing.

**Silver Nanomaterials**

This session was chaired by William Gulledge (BIAC).

- Murray Height (HeiQ Materials Ltd.) presented “Risk Assessment Case Study / Silver Nanoparticles”
- Mario Goetz (Germany) presented “Risk Assessment Case Study / Nano-Ag”.
- Eric Bleeker (Netherlands) presented “Nanoparticles under REACH / Nanosilver as a case study”.
- Discussants:
  - James Delattre (NanoHorizons, Inc.)
  - Mary Gulumian (NIOH, South Africa)
  - George Gray (SRA)

**Summary**

The presentations on silver nanomaterials included three case studies using data specific to the nano range and supplemented where needed by data in the macro scale and other forms of silver. Height and Delattre presented information on silver nanomaterials from the perspective of historical exposure as well as more current data addressing releases of silver from textiles during washing and the potential release of silver nanoparticles in wastewater. They also talked about historical toxicology data that already informs EPAs limit values for silver as directly derived from nanoscale silver and not from bulk silver. Also, they noted that EPA has regulated nanoscale silver products throughout a period of over 50 years and these applications have not been associated with any adverse health effects. A discussion point was the need to determine how new nanoscale silver formulations may compare to the historical data with regard to physical and chemical characterization. Goetz presented human health hazard data which was collected in the context of the risk assessment of two nanoscale silver products. In addition, a proposal for the derivation of nano-specific acceptable external exposure levels relating to medium-term and chronic inhalation scenarios was made. Finally, the issue of using nano-specific uncertainty factors to cover nano-to-nano variability was raised. Bleeker examined nanosilver as a case study to determine the applicability of the REACH risk assessment framework. The case studies provided excellent data rich examples to compare risk assessment derivation.

The importance of problem formulation (framing the scope of the risk assessment) was identified during the discussion of the silver case studies. Comparing data from bulk or ionic silver and nanoscale silver was also an important element of the case studies. Participants identified the importance of having additional fate, transport, and exposure information, particularly for particulates. The case studies also
included excellent examples of the beneficial uses of silver nanomaterials. Possible translocation and persistence of silver nanomaterials as well as the need to explore epidemiology studies were discussed as areas where additional information would be useful for risk assessment purposes.

**Carbon Nanotubes (CNTs)**

This session was chaired by Vladimir Murashov (US NIOSH).

- Gisela Stropp (Bayer Schering Pharma AG) presented “Risk Assessment Case Study / MWCNT (Baytubes®)”.
- Eileen Kuempel (US NIOSH) presented “Risk Assessment Case Study / Carbon Nanotubes”.
- Mariko Ogasawara (Japan NIOSH) presented “Risk Assessment Case Study / (MW) CNT”.
- Discussants:
  - Jim Willis (US EPA)
  - Rick Canady (SRA)
  - Ron White (John Hopkins University)

**Summary**

The carbon nanotubes panel featured three presentations on risk assessment of carbon nanotubes by Gisela Stropp (Bayer Schering Pharma), Eileen Kuempel (US NIOSH), and Mariko Ogasawara (Japan NIOSH). CNTs can have wide variations in structure, size, shape and chemistry (including impurities) affecting their hazard properties, exposure potential and ultimately risk. To facilitate risk assessment of carbon nanotubes through model approaches one needs to correlate such variations with hazard and exposure potential. In the meantime, it is sometimes recommended to conduct risk assessment on a case-by-case basis. However, for practical purposes, one needs to determine the minimum differences that would make two CNT materials distinct (i.e., physico-chemical differences; or variations by batch, process, plant, etc.).

Dose and exposure metrics are determined by the biological mechanism of action for a given hazard; however, there is still no consensus on the best metrics. For example, the studies presented by Stropp indicate that for the Bayer CNT material, the dose-response relationship was best described when dose was expressed as a volume concentration, while other published studies with other materials seem to suggest mass-based and number-based metrics. Until this issue is resolved, it is often recommended to conduct a detailed characterization of CNT material in hazard and exposure studies in order to be able to make conversions between different metrics if necessary. In addition, discrimination of CNT material from background carbon-containing particles has not been completely resolved.

Another outstanding issue relevant to risk assessment is the effect of agglomeration/de-agglomeration processes on hazard and exposure potential. Carbon nanotubes like other nano-objects and nanostructured materials can act as carriers for other chemicals present in formulations or captured in transport and, therefore, could potentially have unexpected additive or synergistic effects. This potential should be accounted for in risk assessment when data characterising these properties are available.

Most of the issues around risk assessment of CNT materials arise from our desire to assess and manage risk pro-actively, that is in the absence of complete information for quantitative risk assessment analysis. Some of the solutions presented at the panel include conducting: 1) hazard-centric risk assessment focusing on acute toxicological studies; however, it is not clear how to address potential for long-term effects in this model; 2) exposure-centric risk assessment focusing on minimizing exposure; however, even
in this approach a minimum hazard characterization is necessary; and 3) quantitative risk assessment extrapolating from available data; however, questions remain about uncertainties and selection of toxicological endpoints. Given that new data are constantly generated, interim risk assessments and tentative exposure limits combined with regular re-evaluation of available data could provide a solution.

**Breakout sessions**

The workshop held a number of parallel breakout sessions to focus discussions on specific issues of risk assessment methodology and to develop approaches to address those issues. Each session was led by a chair and outcomes were reported in plenary. The sessions addressed: (1) Assessment Problem Formulation; (2) Exposure – Public, Occupational and Environment; (3) Hazard – Human Health; (4) Ecological Toxicity and Fate; and (5) Determining Risk and Linkage between Assessment and Management.

**Plenary discussion**

The last session of the workshop was a plenary discussion which summarized the outcomes from each breakout group and invited further discussion from participants on the breakout topics.

**Chair Summaries Breakout Sessions**

**(1) Assessment Problem Formulation**

Problem formulation is a critical but often under-utilized step in risk assessment that establishes the scope of assessment in consideration of risk management decision needs. The problem formulation breakout group agreed that there was generally no evidence yet of unique problem formulation considerations for risk assessment of nanomaterials; however, the group agreed that there are “particle specific” and quantitative needs that should be considered during risk assessment problem formulation for nanomaterials. Key points raised by the group with regard to particle-specific and quantitative needs included:

- Consider the “particle nature” of the material, such as the surface properties and interactions, the relation of metrics used, the characteristic of the material, and the risk outcome and application to decisions.
- Assess and accommodate risk assessment approaches to the effects of test methods and exposure matrix (e.g., dispersion methods) on testing outcomes and inter-comparability of the data used in the assessment.
- Include particular attention to the mixture nature of the material (e.g., variation in size, surface properties, and composition that create a heterogeneous range of particle types) and its interaction with environmental components and transport mechanisms in exposure and toxicity contexts.

In addition, during the workshop it became apparent that the relationship between existing data on formulations of materials that have nanoscale characteristics and formulations that are predominantly non-nanoscale is difficult to describe. Furthermore, the relationship is not clear between current data sets and older data sets where measurements were less precise. This relationship between data sets is a consideration at the problem formulation step because the risk assessment should take advantage of existing information where possible, and methods to “bridge” to existing data would need to be included in planning. Similarly, and as a general consideration, problem formulation should identify, or call for evaluation of, the level of generalization that can and should occur across information sources and data types. For example, studies
with dissimilar materials, methods, or reporting should be combined only where it is scientifically appropriate toward elucidating decision alternatives.

(2) Exposure – Public, Occupational and Environment

This breakout group reported on three key points from their discussions:

- More exposure data is needed. OECD should develop a database of published exposure information involving all routes of exposure and promote publication of exposure data from companies, etc. The database should be stratified by routes of exposure.

- The detection limit of conventional methods to measure particles in the environment may be limited. Therefore, it may be necessary to develop more sensitive methodologies to measure and characterize nanoparticles.

- OECD in collaboration with ISO should define standardized exposure measurements for various media and exposure types that could be used to validate exposure metrics and instrumentation.

(3) Hazard – Human Health

As the session notes reflect, there was general agreement within the human health break-out group that there is already a “toolbox” of testing approaches that can be applied to nanomaterials. However, in most instances modifications or augmentations will need to be made to those approaches to accommodate nanoparticle testing. There was also agreement that while much focus is on toxicology, exposure and epidemiology are important areas of research that also deserve significant attention. The break-out group identified the following four areas as those being the highest priority for further development:

- Focusing testing approaches and the building of databases on enabling and advancing modeling, QSAR, computational, etc. approaches that advance our ability to categorize and otherwise efficiently group materials for decision making. Key to this is linking material properties to effects.

- Understanding the particle nature of nanomaterials, and in particular, particle kinetics.

- Identifying whether there are nanoparticle-specific endpoints or nano-specific considerations for currently identified endpoints.

- Advancing epidemiological approaches, including taking advantage of existing data and developing biomonitoring techniques.

In summary, the human health break-out group acknowledged that there are a number of nanoparticle-specific considerations that need much further development before human health assessments can be developed that are of the same quality as those currently developed for many chemicals. That said, the group also noted that the basic human health approaches are sound; in general the current set of test guidelines is adequate; and our existing knowledge gained from the study of chemicals and particulates provides us with a sound basis of knowledge from which to investigate the special considerations related to manufactured nano-scale materials.
(4) Ecological Toxicity and Fate

The Ecological Fate and Effects break-out group began discussions by examining the current risk assessment paradigm for chemicals, and discussing how analogous assessments could be undertaken for nanomaterials. Following this process, the group addressed a series of questions designed to better understand how to address current ecological risk assessments nanomaterials. Ecological risk assessments (ERAs) were discussed in terms of the following 7 components for which interim approaches could assist risk assessors.

1. Behaviour of nanomaterials in various media: In the absence of empirical data, assessments could assume “worst case” behaviour, (i.e. the nanomaterial does not agglomerate, but is monodispersed).

2. Persistence: Predictive techniques currently exist to predict dissolution of certain nanomaterials, and these approaches could be applied when examining persistence of nanomaterials.

3. Transportation/Distribution: As in the ERA paradigm for traditional chemicals, information on behaviour and persistence should be used to address transport/distribution.

4. Predicted Environmental Concentrations (PECs): Metrics of PECs remains a challenge and ERAs should include a justification for why a particular metric was used. In addition, the PEC could include various forms of the nanomaterial (e.g., single particle, agglomerate, ions, etc.)

5. Transformation Products and Impurities: Transformations of the coatings of nanoparticles in the environment may change the particles’ properties. The importance of these changes to fate, transport, bioaccumulation, and toxicity should be determined. Nanomaterials may also act as carriers for other substances, and the potential for this should be addressed in assessments.

6. Bioaccumulation: No methods for quantitative prediction of bioaccumulation exist. In the absence of empirical bioaccumulation data, qualitative judgments could be made based on information on bulk material or actual data on similar substances.

7. Effects: The basis for effects assessment must be empirical data on nanomaterial or analogue data, given that no predictive capacity exists. In addition, the use of acute data to predict chronic toxicity is not recommended, as uncertainty factors are not available. Assessment could consider the use of margin of safety rather than employing uncertainty factors.

The discussion also highlighted the following key issues for further research:

1. Comparison of acute to chronic data for all trophic levels.
2. Toxicity as a function of size of the nanomaterial.
3. Disposition of nanomaterials (ADME) in all trophic levels.
4. Identification of the most sensitive species, potentially different from the current fish, daphnia, algae paradigm.
6. Toxicity metrics providing the best comparability and regulatory relevance.
In summary, the breakout group agreed generally that the basic risk assessment paradigm for nanomaterials is essentially the same as for traditional chemicals. However, the limited empirical data has left gaps in how this paradigm is applied to nanomaterials; interim approaches for conducting assessments were identified, and research priorities were identified to resolve these gaps.

(5) Determining Risk and Linkage between Assessment and Management

The group's focus was on the interface between risk assessment and risk management, in view of the scientific uncertainty on nanomaterial hazard. The group agreed that the focus of these considerations would be on public authorities, and the discussion would be restricted to how decisions could be made today, i.e. not to focus on what data are still missing.

The group did not identify a need for a general adjustment of the approaches to determining and managing chemical risks; however, it was acknowledged that there are certainly unique or important attributes in the context of nanomaterials. These attributes include considerations of the specific physical and chemical aspects (form, functional characteristics etc) and the current state of knowledge about the potential interactions between nanomaterials and biological systems. Risk communication is a key component in the linkage between risk assessment and risk management and can also affect the public perception of nanotechnology safety. As with any chemical or physical hazard, prudent risk management measures can be based on an evaluation of existing data and uncertainties prior to the availability of sufficient data to develop a comprehensive risk assessment.

In the discussion on whether there is anything unique to nanomaterials that will affect risk management or require new risk assessment policies, the group emphasised the need to have a metric to support identification of the risk management measures. Ideally, this metric would relate to the mode of action and the prediction of adverse effects and be measureable in the workplace and ambient environment. The group was not able to identify a specific metric given the current state of the science, but some proposed that airborne mass concentration could continue to be used (e.g., in occupational exposure sampling) if the limitations (e.g., detection limits and specificity) were made clear. Others suggested that particle number concentration would be more appropriate.

The challenges of quantifying exposures to nanomaterials differ in workplace assessment compared to human health assessment or in the environment (e.g., measurement media, background interferences, detection limits). Generally the group agreed that authorities must use what data and information exist today and avoid being paralysed by the inability to fully characterise or monitor reliably.

In an initial assessment of nanomaterial hazard, some suggested that in the absence of nanomaterial-specific data, information may be derived from the “bulk” material of the same chemical composition, as long as the limitations are acknowledged and taken into account (e.g., potential greater biological activity of the nanoscale material relative to that of the bulk material). This approach could prove useful in a risk assessment context. Initially, hazard and risk assessment will likely be applied on a case-by-case basis, although the need for better understanding of nanomaterial properties that influence biological activity was also discussed in the context of developing hazard group approaches to more effectively manage the potential risks across a wide range of specific nanomaterials.

A major challenge in assessing the risk of exposure to nanomaterials is understanding the kinetic processes in biological systems (i.e., adsorption, distribution, metabolism, and excretion) which influence the internal dose, biopersistence and bioaccumulation. It was also clear that nanomaterials could have different effects which in turn should influence the risk management measures.
The group discussed the lessons learned from the individual case studies presented in the plenary sessions. While old data should not necessarily be dismissed, there was some unease with the data quality from older studies, which may have used poorly characterized materials or materials with different chemical or physical formulations. As such, data from these studies may be of limited relevance in a risk assessment context, unless accompanied with a thorough analysis of the data quality. It was also the impression that the scientific literature includes studies that are relevant to assessing and managing the risks of exposure to some nanomaterials (e.g., particles and fibers in the workplace), but that the existing literature is more limited with respect to studies on the potential environmental hazards of nanomaterials.

Finally, the group took the view that risk management decisions often need to be made in the absence of complete data. However, the development of appropriate risk management strategies based on an evaluation of existing data and uncertainties was considered to be prudent practice and not unique to nanomaterials.

Conclusions

1. The risk assessment paradigm for chemicals will continue to guide approaches to the risk assessment of nanomaterials, and no fundamental changes to this paradigm are envisioned. However, because of the limited amount of empirical data on nanomaterials, many of the assumptions and estimations employed in chemical risk assessments (e.g., acute to chronic ratios, estimation of bioaccumulation potential, estimation of persistence) need to be evaluated for nanomaterials.

2. As with any risk assessment, extrapolation approaches for nanomaterials should be based on mechanistic data where available and additional research is needed to support the validity of default assumptions. Furthermore, limiting exposures and releases of nanomaterials should be encouraged where ever possible as an interim measure in order to compensate for the current limitations in the science.

3. Although the basic risk assessment paradigm for nanomaterials is essentially the same as for traditional chemicals, research is needed to determine what characteristics of nanomaterials may pose unique hazards.

4. There does not appear to be a scientific rational to justify employing a risk assessment uncertainty factor specifically addressing materials at the nanoscale. In addition, application of standard risk assessment uncertainty factors in nanomaterial risk assessments should undergo validation; justification should also be provided when using invalidated uncertainty factors in risk assessments. Identification of a “margin of exposure” may be an alternative approach to understanding likelihood of risk.

5. It is recognised that there is uncertainty concerning the units of measurement (i.e., metrics) used to generate test results employed in risk assessments. It is expected that empirical results will continue to be reported in terms of mass based units; however, risk assessments should include discussion of any limitations this metric may present (e.g., limit of detection, specificity). Characterization of nanomaterials by various dose metrics (e.g., particle surface area, number concentration, etc) would facilitate evaluation of the metrics most closely associated with mechanism of action and improve risk estimation.
**ANNEX I (AGENDA FOR WORKSHOP)**

OECD Working Party on Manufactured Nanomaterials (WPMN)

**WORKSHOP ON RISK ASSESSMENT OF MANUFACTURED NANOMATERIALS IN A REGULATORY CONTEXT**

Co-hosted by the Business and Industry Advisory Committee to the OECD (BIAC) and the Society for Risk Analysis (SRA)

Organized by Steering Group 6 – Co-operation on Risk Assessment

September 16-18, 2009

Washington D.C.

**AGENDA**

Objectives: i) to obtain expert input into the critical issues specific for the risk assessments of nanomaterials in a regulatory context; ii) to identify possible approaches for risk assessment based on the current state of knowledge; and iii) to identify issues which may be addressed through the Sponsorship Programme.

<table>
<thead>
<tr>
<th>DAY 1</th>
<th>September 16 – starting at 10h00</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Registration</strong></td>
</tr>
<tr>
<td>1.</td>
<td>Welcome Remarks</td>
</tr>
<tr>
<td></td>
<td><em>Mar Gonzalez, OECD</em></td>
</tr>
<tr>
<td></td>
<td><em>Jo Anne Shatkin, SRA</em></td>
</tr>
<tr>
<td>2.</td>
<td>Introduction</td>
</tr>
<tr>
<td></td>
<td><em>Andy Atkinson, Canada, Co-chair SG6</em></td>
</tr>
<tr>
<td></td>
<td><strong>Chair: Andy Atkinson</strong></td>
</tr>
<tr>
<td>3.</td>
<td>Overview of WPMN activities</td>
</tr>
<tr>
<td></td>
<td><em>Andy Atkinson</em></td>
</tr>
<tr>
<td>4.</td>
<td>Presentation from SRA</td>
</tr>
<tr>
<td></td>
<td><em>Jo Anne Shatkin, SRA</em></td>
</tr>
<tr>
<td>5.</td>
<td>Presentation from industry</td>
</tr>
<tr>
<td></td>
<td>perspective</td>
</tr>
<tr>
<td></td>
<td><em>William Gulledge</em></td>
</tr>
<tr>
<td></td>
<td><em>American Chemistry Council, BIAC</em></td>
</tr>
<tr>
<td>6.</td>
<td>Presentation from regulatory</td>
</tr>
<tr>
<td></td>
<td>perspective</td>
</tr>
<tr>
<td></td>
<td><em>Maila Puolamaa</em></td>
</tr>
<tr>
<td></td>
<td><em>European Chemicals Agency (ECHA)</em></td>
</tr>
<tr>
<td>7.</td>
<td>Presentation from NGO</td>
</tr>
<tr>
<td></td>
<td>perspective</td>
</tr>
<tr>
<td></td>
<td><em>Caroline Baier-Anderson</em></td>
</tr>
<tr>
<td></td>
<td><em>Environmental Defense</em></td>
</tr>
<tr>
<td></td>
<td><strong>LUNCH</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Chair: Jo Anne Shatkin</strong></td>
</tr>
<tr>
<td>8.</td>
<td>TiO2 case study 1</td>
</tr>
<tr>
<td></td>
<td><em>Shaun Clancy, Evonik, BIAC</em></td>
</tr>
<tr>
<td>9.</td>
<td>TiO2 case study 2</td>
</tr>
<tr>
<td></td>
<td><em>Mike Davis, US EPA</em></td>
</tr>
<tr>
<td>11.</td>
<td>TiO2 discussants</td>
</tr>
<tr>
<td></td>
<td>1. Robert Landsiedel (BASF, BIAC)</td>
</tr>
<tr>
<td></td>
<td>2. Carlos Peña (US FDA)</td>
</tr>
<tr>
<td></td>
<td>3. Margaret MacDonnell (SRA)</td>
</tr>
<tr>
<td>12.</td>
<td>TiO2 general discussion</td>
</tr>
<tr>
<td></td>
<td><em>All</em></td>
</tr>
<tr>
<td></td>
<td><strong>BREAK</strong></td>
</tr>
<tr>
<td>No.</td>
<td>Session Title</td>
</tr>
<tr>
<td>-----</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>13.</td>
<td>Nano-Ag case study 1</td>
</tr>
<tr>
<td>14.</td>
<td>Nano-Ag case study 2</td>
</tr>
<tr>
<td>15.</td>
<td>Nano-Ag case study 3</td>
</tr>
</tbody>
</table>
|     |                                                  | 2. Mary Gulumian (NIOH, South Africa) 
|     |                                                  | 3. George Gray (SRA)               |
| 17. | Nano-Ag general discussion                        | All                               |

**RECEPTION**

**DAY 2**  
*September 17 – starting at 09h30*

**Registration**  
*Chair: Vladimir Murashov, US NIOSH*

<table>
<thead>
<tr>
<th>No.</th>
<th>Session Title</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.</td>
<td>CNT case study 1</td>
<td>Gisela Stropp, Bayer Schering Pharma</td>
</tr>
<tr>
<td>19.</td>
<td>CNT case study 2</td>
<td>Eileen Kuempel, US NIOSH</td>
</tr>
<tr>
<td>20.</td>
<td>CNT case study 3</td>
<td>Mariko Ogasawara, Japan NIOSH</td>
</tr>
</tbody>
</table>
| 21. | CNT discussants                                   | 1. To be determined               
|     |                                                  | 2. Jim Willis (US EPA)             
|     |                                                  | 3. Rick Canady (SRA)              |

**BREAK**

<table>
<thead>
<tr>
<th>No.</th>
<th>Session Title</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22.</td>
<td>CNT general discussion</td>
<td>All</td>
</tr>
<tr>
<td>23.</td>
<td>Introduction to breakout sessions</td>
<td>Andy Atkinson</td>
</tr>
</tbody>
</table>

**LUNCH**

<table>
<thead>
<tr>
<th>No.</th>
<th>Session Title</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.</td>
<td>Breakout session</td>
<td>All</td>
</tr>
</tbody>
</table>

**BREAK**

<table>
<thead>
<tr>
<th>No.</th>
<th>Session Title</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.</td>
<td>Breakout session</td>
<td>All</td>
</tr>
</tbody>
</table>

**DAY 3**  
*September 18 – starting at 09h00*

**Chair: Andy Atkinson**

<table>
<thead>
<tr>
<th>No.</th>
<th>Session Title</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.</td>
<td>Plenary discussion</td>
<td>All</td>
</tr>
</tbody>
</table>

**BREAK**

<table>
<thead>
<tr>
<th>No.</th>
<th>Session Title</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27.</td>
<td>Path forward</td>
<td>All</td>
</tr>
<tr>
<td>28.</td>
<td>Closing remarks</td>
<td></td>
</tr>
</tbody>
</table>
## ANNEX II (GENERAL PRESENTATIONS)

### (1-1) Overview of WPMN activities

#### OECD Work on the Safety of Manufactured Nanomaterials

- **Environment, Health and Safety Division**
- **OECD**
- **September 2009**

#### Manufactured Nanomaterials and Chemical Safety

In 2006, the OECD established the Working Party on Manufactured Nanomaterials (WPMN).

**Objective:**

To promote international co-operation in human health and environmental safety related aspects of manufactured nanomaterials (MNs), in order to assist in the development of rigorous safety evaluation of nanomaterials.

#### Current WPMN Projects

- OECD database on Manufactured Nanomaterials to Inform and Analyse EHS Research Activities;
- Safety Testing of a Representative Set of Manufactured Nanomaterials;
- Manufactured Nanomaterials and Test Guidelines;
- Co-operation on Voluntary Schemes and Regulatory Programmes;
- Co-operation on Risk Assessment;
- The Role of Alternative Methods in Nano Toxicology;
- Co-operation on Exposure Measurement and Exposure Mitigation; and
- Environmentally Sustainable Use of Nanotechnology

#### Background of the OECD's activities on the safety of manufactured nanomaterials

- The safety of nanotechnologies was first raised in the OECD Chemicals Committee in November 2004. This was followed by two events:
  - Special Session on the “potential implications of manufactured nanomaterials for human health and environmental safety” (June 2005)
  - Workshop on the Safety of Manufactured Nanomaterials (December 2005)

#### Who participates?

- 30 OECD Member Countries and the European Commission
- Non-members: Brazil, China, Singapore, Thailand, and Russia
- Inter-governmental organizations: IOMC, FAO, UNEP, UNITAR and WHO
- ISO/TC229
- Other stakeholders: BIAC, TUAC and Environmental NGOs
<table>
<thead>
<tr>
<th>Project 1 and 2: OECD Database on Manufactured Nanomaterials to Inform and Analyse EHS Research Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective:</strong> to develop a global resource (Database), which details research projects and identifies research needs; and to provide opportunities to identify the similar fields, and lead to create new collaboration and networks</td>
</tr>
<tr>
<td><strong>Co-Chairs:</strong> Australia, Germany and Japan</td>
</tr>
<tr>
<td><strong>Status:</strong></td>
</tr>
<tr>
<td>- Publicly launched in April 2009</td>
</tr>
<tr>
<td>- A comprehensive compilation document “EHS Research Strategies on MNs” was published in May 2009</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Project 3: Safety Testing of a Representative Set of MNs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective:</strong> to agree and test a representative set of manufactured nanomaterials (MNs) using appropriate test methods.</td>
</tr>
<tr>
<td><strong>Co-Chairs:</strong> United States and European Commission</td>
</tr>
<tr>
<td><strong>Status:</strong></td>
</tr>
<tr>
<td>- Launched Sponsorship Programme (November 2008) to test representative MNs for a base set of endpoints</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Project 4: MNs and Test Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objectives:</strong></td>
</tr>
<tr>
<td>- To review existing OECD Test Guidelines for adequacy in addressing MNs</td>
</tr>
<tr>
<td>- To identify the need for development of new or revision of existing test guidelines or guidance</td>
</tr>
<tr>
<td><strong>Co-chairs:</strong> United States and European Commission</td>
</tr>
<tr>
<td><strong>Status:</strong></td>
</tr>
<tr>
<td>- Completed the Preliminary Review of the existing guidelines for potential applicability</td>
</tr>
<tr>
<td>- Preliminary Guidance Notes on Sample Preparation and dosimetry will be published in 2010</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Project 5: Co-operation on Voluntary Schemes and Regulatory Programmes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objectives:</strong></td>
</tr>
<tr>
<td>- To identify common elements of the various information gathering initiatives, in place or planned.</td>
</tr>
<tr>
<td>- To identify applicable current and proposed regulatory regimes and how they address information requirements, hazard identification, risk assessment and exposure mitigation/ risk management of MNs.</td>
</tr>
<tr>
<td><strong>Chair:</strong> Canada</td>
</tr>
<tr>
<td><strong>Status:</strong></td>
</tr>
<tr>
<td>- Completed initial comparisons of information gathering.</td>
</tr>
<tr>
<td>- Issued questionnaire (August 2008) on regulatory regimes and how they address information requirements</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Project 6: Co-operation on Risk Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective:</strong> to evaluate risk assessment approaches for manufactured nanomaterials through information exchange and identify opportunities to strengthen and enhance risk assessment capacity.</td>
</tr>
<tr>
<td><strong>Co-Chairs:</strong> Canada and Germany</td>
</tr>
<tr>
<td><strong>Status:</strong></td>
</tr>
<tr>
<td>- Reviewing existing risk assessment schemes and their relevance to nanomaterials</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Project 7: The Role of Alternative Methods in Nano Toxicology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective:</strong> to address the use of alternative test methods and testing strategies (in parallel with the Sponsorship Programme)</td>
</tr>
<tr>
<td><strong>Chair:</strong> Germany and European Commission</td>
</tr>
<tr>
<td><strong>Status:</strong></td>
</tr>
<tr>
<td>- Reviewing alternative test methods which may be applicable to manufactured nanomaterials</td>
</tr>
<tr>
<td>- Developing guidance material on alternative methods in the Sponsorship Programme</td>
</tr>
</tbody>
</table>
Project 8: Co-operation on Exposure Measurement and Exposure Mitigation

- Objective: to exchange information on guidance for exposure measurement and exposure mitigation for MNs
- Chair: United States
- Status:
  - Evaluating data and provide recommendation on measurement technologies and sampling protocols for determining concentrations of manufactured nanomaterials in air (led by Australia)
  - Comparing exposure mitigation guidance for laboratories (led by Germany)

Project 9: Environmentally Sustainable Use of Nanotechnology

- Objective: to enhance the knowledge base about life cycle aspects of manufactured nanomaterials as well as positive and negative impacts on environment and health of certain nano-enabled applications at their different stages of development
- Co-Chairs: United States and European Commission
- Status:
  - To finalize the Operational Plan (2009-2012) and start the implementation of the project (1st report July 2010)

Current focus

Safety Testing of a Representative Set of MNs (Project 3)

- Objective: To test an agreed representative set of manufactured nanomaterials using appropriate test methods.
- Aim: To understand the types of information on intrinsic properties that may be relevant to exposure and the effects assessment of MNs.
- In close co-ordination with other OECD work on Chemical Safety: Test Guidelines, Mutual Acceptance of Data

Implementation - Two Stages

Stage 1
Agreement on:
- A list of MNs (based on materials which are now, or soon to enter, commerce)
- A list of endpoints for which these MNs should be tested.

Stage 2
Development of a programme to test MNs for a base set of endpoints relevant to human health and environmental safety

Stage 1: List of Manufactured Nanomaterials (14)

- Fullerenes (C60)
- Single-walled carbon nanotubes (SWCNTs)
- Multi-walled carbon nanotubes (MWCNTs)
- Silver nanoparticles
- Iron nanoparticles
- Carbon black
- Titanium dioxide
- Aluminium oxide
- Cerium oxide
- Zinc oxide
- Silicon dioxide
- Polystyrene
- Dendrimers
- Nanoclays

Stage 1: List of Endpoints

- Nanomaterial Information/Identification (9 endpoints)
- Physical-Chemical Properties and Material Characterization (17 endpoints)
- Environmental Fate (15 endpoints)
- Environmental Toxicology (6 endpoints)
- Mammalian Toxicology (9 endpoints)
- Material Safety (3 endpoints)
Stage 2: Sponsorship Programme

- The sponsorship programme is an international effort to share the testing of an agreed set of manufactured nanomaterials selected by the WPMN.

Two phases:
- Phase 1: To test selected MNs for the selected endpoints (officially launched: November 2007)
- Phase 2: Examine cross-cutting issues or tests identified in phase 1 and that will need further consideration by the WPMN

Sponsorship Programme

Work in Progress Phase 1

- Launched November 2007
- OECD Secretariat is the clearing house to ensure co-ordination
- Development of a guidance manual for sponsors to guide the testing
- Development of a review mechanism for dossier development plans
- Workshop in Korea will assist Sponsors in their development of dossier development plans (November 2008)
- Draft dossier development plans to be considered by the 5th WPMN (March 2008)

Meetings Schedule

- Workshop on Exposure Assessment and Exposure Mitigation, 20 October 2008, Frankfurt, Germany
- Meeting of SG8, 21 October 2008, Frankfurt, Germany
- Workshop on the Safety Testing of Manufactured Nanomaterials, 19-21 November 2008, Busan, Korea
- Meeting for the Sponsorship Programme, 2-3 March 2009, Paris, France
- 5th Meeting of the Working Party on Manufactured Nanomaterials, 4-6 March 2009, Paris, France
- 6th Meeting of the Working Party on Manufactured Nanomaterials, 28-30 October 2009, Paris, France

More information

Safety of Manufactured Nanomaterials
- www.oecd.org/env/nanosafety
- www.oecd.org/env/nanosecurite

Nanosafety team: Peter Kearns, Mar Gonzalez, Hiroyuki HANAWA, Beobjeong KIM, Patric AMCOFF, Charis FEENEY-ORCHARD
E-mail: Nanosafety@oecd.org
29

(1-2) Critical Issues

Steering Group 6
Critical Issues for Risk Assessment of Nanomaterials

OECD Paris June 12th

Critical issue 1. Complexity
(of nanomaterials behaviour in natural systems)

Complexity, bioavailability and effects
Interaction between nanomaterials and living systems

Asbestos
Respiratory exposure
High aspect ratio (>2µm length <3µm width, biopersistent)
Fibre / pathogenicity paradigm:
function of shape, size, persistence and physiological interaction
Read across to other fibres e.g. CNT

Physico chemical behaviour of nanoparticles in natural systems is influenced by numerous abiotic and biotic factors

Abiotic factors include:
pH, ionic strength, organic matter etc..

Implications:
Environmental Exposure: agglomeration, form, surface chemistry
Bioavailability and direct toxicity
Indirect toxicity (e.g. through dissolution - some metal nanoparticles)
Relevance of some tests (e.g. in vitro, ecotoxic) – SG4 should consider

2. Complexity and data scarcity leads to risk uncertainty
Critical issue 2. Complexity
Leads to risk uncertainty
- potentially high (data scarcity)
- probably not uniform across nanomaterials

Managing risk uncertainty: make no a priori assumptions about exposure
Due to high exposure uncertainty

- High propagated uncertainty in Risk Assessment (data scarcity)
- Management of risk uncertainty
- Make no a priori assumptions about exposure
  Test all endpoints across all routes of exposure
- Every material, functionalisation: justified, Feasible?: resourcing, time
  Relevance of tests: Novel effects?
- BUT: exploratory dataset for linking material properties to effects
- Uncertainty management implications
- Information requirements: Focussed on hazard

Critical issue 3.
How do we manage high risk uncertainty?
Strategy?

Managing risk uncertainty: approaches from 'conventional chemicals'

- High propagated uncertainty in Risk Assessment (data scarcity)
- Management of risk uncertainty
- Application of assessment factors to calculate PNEC from LOEC, NOEC, NOAEL etc.
- Over precautionary? Challenging analytical techniques for e.g. monitoring
- Uncertainty management implications

Development of conceptual model of exposure and bioavailability to drive risk assessment

- Intrinsic properties
- Conceptual exposure model development: sources, pathways etc
  (e.g. Biotic Ligand Model for metals): bioavailability
  Speciation, bioavailability
  Source–pathway–receptor connectivity
  Endpoint selection
  Boundaries for quantitative risk assessment
Problem formulation for risk assessment of nanomaterials

Risk
Prioritisation
Risk boundaries
Risk Quantification
Risk Significance
Options Appraisal
Risk Management

Hazard Exposure
Probability of harm occurring
Appropriate Controls

Tiered risk assessment and problem formulation

Risk
Nanomaterial

‘Justifying the Intent’

Intrinsic properties, Life Cycle Analysis
Exposure model
Source pathway receptor connectivity
Endpoint selection

Closing Thoughts (1)

- Complexity of structure, form and behaviour in natural systems
- Uncertainty in hazard, exposure and risk assessment
- Management of uncertainties: which approach should we adopt and what information should be assembled – and validated in SG3?

Closing Thoughts (2)

- Development of exposure model: problem formulation, prioritisation / exposure management: exposure driven?
- No a priori assumptions of exposure: all endpoints, hazard driven? Sets a precedent.
- Application of assessment factors to hazard data?
- How does this sit with SG3 studies, guiding the information requested in phase 1 and phase 2.
(2) Presentation from SRA

Risk Analysis: SRA Nano Risk Workshop Findings

Jo Anne Shatkin, Ph.D.
Emerging Nanoscale Materials Specialty Group
Society for Risk Analysis
and Managing Director, CLF Ventures Boston

OECD Working Party on Manufactured Nanomaterials (WPtHN) SG 6
WORKSHOP ON RISK ASSESSMENT OF MANUFACTURED
NANOMATERIALS IN A REGULATORY CONTEXT
Washington, DC
September 16, 2009

Overview

- Society for Risk Analysis Expert Workshop Findings
- Nano challenges to risk assessment
- Adopting a life cycle approach in risk assessment

The Emerging Nanoscale Materials Specialty Group (EMNMS) aims to:

- Facilitate the exchange of ideas and knowledge among practitioners, researchers, scholars, teachers, and others interested in risk analysis and emerging nanoscale materials.
- Encourage collaborative research on risk analysis and emerging nanoscale materials.
- Provide leadership and play an active role in advancing issues related to risk analysis and emerging nanoscale materials.

SRA Emerging Nanoscale Materials Specialty Group (EMNMS)

- 135 Current Members from 22 Countries
- Diverse interests and expertise
- Affiliations
  - Academia
  - Government
  - Non-profits
  - Trade organizations
  - Industry
  - Students
  - Others
- Website www.sra.org

Nanorisk Analysis:
Advancing the Science for Nanomaterial Risk Management Sept 2006, Washington DC

- Public expert workshop organized by the Society for Risk Analysis Emerging Nanoscale Materials Specialty Group
- Brought together risk analysts with nano-experts in to advance our understanding and build new networks
- A deliberative workshop to address:
  - What is "nano" about risk assessment for nanoscale materials?
  - What tools in the field of risk analysis can be used for managing nanomaterials?
  - What are the needs for communicating about risks?
  - How to consider the benefits of nanotechnology for risk reduction?
**Nanorisk Analysis: Advancing the Science for Nanoscale Risk Management**

**Workshop Co-Sponsors**

**Session on Data Gaps**

**Nanorisk Analysis: Advancing the Science for Nanoscale Risk Management**

**Repeated themes**

- Considerable uncertainty in understanding of nanoscale attributes and relevance to biological and environmental effects
- Size matters, but its not clear there is a bright line, e.g. at 100 nm
- Regulatory approaches are likely to be case-by-case in the near term
- Perceptions outside of industry and the government are critical, and proactive measures to communicate with the public are critical to successful development of nano-products

**Key Issues Identified**

- Many previously identified concerns are not specific to nanomaterials or nanotechnologies
- Can address some concerns “by design”
  - Engage risk analysts to work with product designers
- Need for a long-term plan/framework to answer questions with pending data
- Conduct case-by-case evaluations to elicit key concerns
- Also conduct expert workshops more broadly to raise overarching issues
- Test/compare adaptive approaches to risk analysis that incorporate the product life cycle
Framing the Issues for Health/Environmental Risk Assessment of Engineered Nanoscale Materials

Hazard Characterization

Toxicity Assessment

Exposure Assessment

Risk Characterization

Framing the Issues: Hazard Characterization for Nanotechnology

- How to define nanomaterials
  - Distinguish engineered from other nanoparticles?
  - Are agglomerated or aggregated particles “nano”?
  - Is a composite material containing nanoparticles “nano”?
- Do we characterize the particle, or the product?
- What are the appropriate measurement units?
- How to characterize variability, uncertainty?

Framing the Issues: Units of Material Characterization

- It’s possible that once we get the units right, there will be no nano-specific issues in risk assessment.
- However nanoparticles are dynamic – this drives decisions about units for a breadth of contexts.
- May need more than one set of units, but it may also be possible to build relationships across units to unify them.
- There may be a role for applying a nano-specific uncertainty factor in some situations.

Framing the Issues: Exposure Assessment for Nanotechnology

- Need new ways to characterize exposure
  - Mass may not be most useful measure
  - When does size trigger new measures?
  - How does the matrix affect exposure?
- Limitations of available analytical techniques
  - Methods require low detection limits
  - Also need to characterize “background” exposures
- Limited data on transport and fate

Framing the Issues: Dose Response for Nanotechnology

- Uncertainty in defining dose
- Different mechanisms of nanoparticles
  - Are there novel effects?
- Difficulty in measuring responses
  - Data are equivocal; assays, reporting not standardized
- Differences in absorption, distribution, metabolism, excretion
- Diversity of materials and characteristics
  - When are particle distributions different?
  - What are the tolerances?

Framing the Issues: Dose Response for Nanotechnology

- Limited data available from well-designed studies
  - Most is in vitro or inhalation studies to particles
- Reactive oxygen formation (ROS) is a commonly observed mechanism of toxicity; physical effect on cells
  - Leads to inflammation
- Study conditions affect results
  - Data are equivocal
- Surface coating/particle size/surface charge/surface area/contamination and aggregation may be important
Size tolerances and “purity”

When are populations different for extrapolation purposes?

Framing the Issues: Characterizing Risks of Nanomaterials

- Several deliberations conclude that current frameworks are adequate and appropriate
  - but significant model and parameter uncertainty
- Still much research to be done to quantify risks
- Need to address uncertainty and variability
- Still a limited ability to conduct quantitative assessments
- New metrics and endpoints for risk?

Framing the Issues: Uncertainty Analysis

Haven’t we been here before?

- Foodborne vs. nosocomial antimicrobial resistance
- Chemical mixtures
- Climate change impacts
- Cellular phones and non-ionizing radiation
- Nutrient requirements
- Vitamin and mineral fortification of food
- Fish consumption advisories

Risk Analysis is a robust approach for assessing and managing uncertain hazards and risks

Regulatory Implications from the State of the Science

- Lack of tools for measurement (and lack of data) prohibit exposure measurements; limit ability to conduct risk assessments; and prevent monitoring
- Safe levels for existing nanomaterials are unknown and prohibit standard setting
- Significant research is required to understand whether nanomaterials pose novel risks
- Slow pace of scientific research could slow the regulatory process and create greater risk for nanotech entries to market – case law may prevail

Nanoscale particles vs. Nanotechnology

- Long history of using physical and chemical methods to create small molecules
- Emerging nanoscale materials are novel
  - E.g. quantum dots
- Is this a reasonable distinction?
- Why focus on size—is there a scientific rationale
  - No biological basis for 100 nm cutoff
- Is there a need for regulatory distinction
  - Are existing nanoparticles demonstrated to be safe?
- Can the public discern the difference?
Consider Adaptive Life Cycle Approaches to Risk Assessment and Risk Management

- Provide a framework for assessing biological and environmental exposure: a significant advance
- How to implement these approaches: not part of the current risk management paradigm
- A variety of frameworks exist/proposed
  - Nano LCRA (Shatkin 2008, Nanotechnology Health and Environmental Risks CRC Press)
  - Comprehensive Environmental Assessment (Davis 2007)
  - Nano Risk Framework (EDF/DuPont 2007)

NANO SLCRA

Comprehensive Environmental Assessment (CEA)

$$ CEA \approx LC + RA $$

**LC = Product Life Cycle framework**

**RA = Risk Assessment paradigm**

Comprehensive Environmental Assessment (CEA)

<table>
<thead>
<tr>
<th>Life Cycle Stages</th>
<th>Environmental Pathways</th>
<th>Fate &amp; Transport</th>
<th>Exposure</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feedstock</td>
<td>Air, water</td>
<td>Primary contaminant</td>
<td>Plate</td>
<td>Bio-systems</td>
</tr>
<tr>
<td>Manufacture</td>
<td>Soil</td>
<td>Secondary contaminant</td>
<td>Human populations</td>
<td>Human Health</td>
</tr>
<tr>
<td>Distribution</td>
<td>Food chain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Storage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disposal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In Summary

- Risk assessment is a valid paradigm for evaluating risks of nanoscale materials
- Several outstanding issues, that relate in part to defining exposure/dose metrics
- Some issues are not specific to nanoscale, but relate to emerging nature of ENMs
- These are complicated messages, but critical to communicate
- Incorporating life cycle aspects into risk analysis is an important next step for ENMs

Thank You Very Much!

Jo Anne Shatkin, Ph.D.
CLF Ventures
jshatkin@clf.org
+1 617-850 1715
(3) Presentation from industrial perspective

Today- An Introduction

- Introduce a Perspective on Risk Assessment From a Former Insurer
- No Mention of Specific Nanomaterials- that’s the case studies later
- Items to Consider for Later Discussions

American Chemistry Council (ACC)

- Represent Over 130 Companies Engaged in the Business of Chemistry
- Subset of Those Companies Produce, Use, or Otherwise Handle Manufactured Nanomaterials
- Industry is a Substantial Investor to Research and Development

ACC Nanotechnology Panel: Founded 2005

- Producers and Users- Variety of Nanomaterials (Less than 10% of ACC Member Companies)
- Primarily Focus on EHS Issues- Implications of Nanotechnology (Including Research and Risk Issues)
- National and International in Scope
- Task Groups: Technical, Product Stewardship, Communications, Policy

ACC and Nanotechnology- Board Position, Adopted 2005

- Support Global Coordination of Regulatory, Research, and Standard-Setting Activities
- Assess Existing Legislative and Regulatory Frameworks. For Application to the Characterization and Properties of Nanomaterials
- Apply Product Stewardship Principles of the Global Chemicals Management Policy and Responsible Care® to Nanotechnology-Related Activities
- Support the Increased Funding of Methods to Assess Impacts of Nanotechnology on Environment, Health, and Safety and for Research Programs to Apply Those Methods
### Product Stewardship and Responsible Care®

- Assess Uses, Exposures, Toxicity
- Prioritize Risks
- Conduct Risk Characterizations on Priorities (risk, uses, life cycle)
- Prepare Product Stewardship Summary (By 2012)

### OECD WPMN SG6: Risk Assessment

- BIAC participation since inception
- Produced Draft Report: Critical Issues (June 2008)
  - Describes general risk assessment framework primarily based on chemicals assessment
  - Focuses on human health and occupational exposures without so on environmental assessment
  - Issues identified: complexity of nanoparticles in natural systems, management of uncertainty, and problem formulation for nano risk assessment

### SG6 Draft Risk Assessment Report: Partial Initial Conclusions

- “In principle, the globally accepted tiered approach for chemical risk assessment appears to be appropriate for nanomaterials”
- “However, nanomaterials pose issues for the implementation of current methods of risk assessment”
- “Uncertainty in hazard and exposure will be propagated as potentially high uncertainty in risk characterization, although the magnitude of uncertainty may not be uniform across different nanomaterials”

### Securing the Promise of Nanotechnologies: Towards Transatlantic Regulatory Cooperation

- September 2008 Report Identifies Uncertainties Associated With:
  - Diverse Commercial and Regulatory Paths
  - Hazard and Exposure Pathways Associated With Certain Nanomaterials
  - Regulatory Oversight
  - Scientific Expertise and Resources
- Risk Assessment Cannot Be Conducted in Isolation

### Handling of Uncertainty in MN Risk Analysis

- Case by Case Hazard and Exposure Evaluation
- Dealing with Mixtures
- Product Evaluation or Particle Evaluation
- Use of Uncertainty Factors
- Importance of Particle Characterization
- Close Knowledge Gaps

### What is Nano? What is Important?

- ACC Panel identified (2007) the following factors (all should be included):
  - Size and Content
  - Dimensions
  - Intentionally Produced
  - Properties
  - Aggregates and Agglomerates
  - Solubility
**Life Cycle Approaches for Risk Assessment**

- Specific Methodology for Manufactured Nanomaterials?
- Standard Model Approaches Also Apply to MN
- Factors/Modifications for Individual MNs

**ISO TC 229: WG3/P7 - Nanomaterial Risk Evaluation Process**

- Draft Based on ED/DuPont Framework
- Ballot Stage as an ISO Technical Report
- Other Approaches or Proposals Have Been Suggested

**Possible Discussion Items**

- Use of Existing Risk Assessment Methods/Programs
- What is Important to Assess Biological Interaction of Particles?
- How Important is Novelty, Diversity, and/or Alterability of Particles?
- What are the Likely Exposures, Not all the Exposures?

**Modernization of TSCA and Nanomaterial Regulation**

- ACC Supports 10 Principles for Modernization of TSCA
- Principle 10 Encourages Technological Innovation-Including nanotechnology
- Principle 4 Requires Companies to Provide Hazard, Use, and Exposure Information

**Conclusion**

- Look forward to more detail in the case studies
- Actively participate in break-out sessions
- Ongoing industry assessment examples provide a basis for addressing risk assessment issues
(4) Presentation from regulatory perspective

**REACH and Nanomaterials**

Risk assessment and Risk Management

OECD Working Party on Manufactured Nanomaterials
Risk Assessment of Manufactured Nanomaterials in a Regulatory Context
16-18 September 2006, Washington

Matteo Pusilamas, European Commission
Marcella Luistomo, Jack de Bruin and Andreas Ahrens, European Chemicals Agency (ECHA)

**REACH Aims**

- Regulation on the Registration, Evaluation, Authorisation and Restrictions of Chemicals
- REACH aims at:
  - Ensuring a high level of protection of human health and environment
  - Promotion of alternative test methods
  - Free circulation of substances on internal market
  - Enhancing competitiveness and innovation

**REACH – Key elements**

- Registration of non-phase-in substances, 1 June 2008
- Pre-Registration of phase-in substances, 30 Nov 2008
- Substance Information Exchange Fora (SIEFs), Jan 2009-June 2010
  - Agreement on Similar Chemicals (pre-SIEF), Classification & Labelling, Data Sharing
  - Preparation of Joint Submission
- Classification, Labeling & Packaging (CLP)
  - All to be notified to ECHA CLP Inventory, by 3 Jan 2011
- Registration of substances ≥ 1 t/yr
  - Total tonnage determines obligations and timelines
- Chemical Safety Assessment
  - Registered substances ≥ 10 t/yr
  - Substances for Authorisation & Restriction (no tonnage trigger)
- Evaluation of dossiers and some substances
- Authorisation, 1st priority substances in June 2009
- Restrictions, ‘New’ restrictions in June 2009
- Public access to key information
- European Chemicals Agency to manage the system

**Contents**

- REACH - Key features
- Registration
- Chemical Safety Assessment (CSA)
- Conclusions
- Further work

**REACH Approach**

- REACH is based on the principle that Manufactures (M), Importers (I) and Downstream users (DU) must ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment.
- Burden of proof to industry

**Mission of ECHA**

- Manage and carry out technical, scientific and administrative aspects of REACH
- Ensure consistency at the Community level
- Provide the Member States and the EU institutions with the best possible scientific and technical advice on questions relating to chemicals which fall under REACH
- Manage IT based guidance documents, tools and databases
- Support national helpdesks and run a helpdesk for registrants
- Make information on chemicals publicly accessible

41
Communication in REACH
Between suppliers (M/I → M/I)
• Pre-2007: Agreement of the same interpretations of a substance
• 2007: SIEF: Classification and labelling; Data sharing & Joint submission
Between users (DU → DU)
• Uses and Conditions of use

Between Suppliers and Downstream Users (M/I → DU)

Manufacturer/Importer
Information on identified users, conditions of use, possible exposure and releases

Downstream Users

Between M/I and ECHA
• Pre-Registration, Registration, Evaluation and Authorisation/Restriction

REACH and nanomaterials

• REACH applies to nanomaterials (NM) that are like any other form of a substance or a distinct substance

• March 2008: REACH Competent Authorities subgroup on nanomaterials (CASY Nano) to advice on NM issues

Registration

Who: Manufacturers and Importers of ≥ 1 t/y
• Tonnage triggers are based on the total volume of chemicals
• Chemical Safety Report, ≥ 10 t/y

What: All relevant information (incl. specific NM properties not mentioned in REACH) demonstrating that risks are controlled
• Substance identification
• Hazard assessment
• Exposure assessment
• Risk Characterisation
• Risk Management

Registrant should update registration to include the information generated and adapt CSA / CSR

CASG Nano Mandate
REACH applicability to nanomaterials
REACH implementation issues such as
• Substance identification
• Registration of nanomaterials
• Chemicals Safety Assessment
• Risk management measures
• Communication in the supply chain
• Current and evolving nanomaterials
• Information needs

Other issues of relevance
• Test methods and test guidelines (JRC, PPs, OECD-WP6/n)
• Member State activities
• Other

Outputs: Nanomaterials in REACH, December 2008
REACH – Risk Characterisation (1/2)

Human health –
characterisation of dose/concentration-response
- Deriving DNELs (Derived No-Effect Levels) for threshold effects
- When no DNEL can be derived, including where possible for some non-threshold effects, aspects to be considered when deriving DNELs (Derived Minimal Effect Levels)
- Comparing exposure levels to derived no-effect levels (DNM/ELs)
- Populations (workers, consumers, humans exposed via the environment) by routes of exposure
- Cover all end points (including phys-chem; explosivity, flammability, oxidising potential)

Conclusions – General (1/2)
- Manufacturers and importers obtain and/or generate information for their substances
- This enables well-informed management of the risks that substances may cause throughout their life cycle
- Exposure Scenarios are:
  - Developed in the iterative Chemical Safety Assessment (CSA), based on cooperation with Downstream Users
  - Documented in the Chemical Safety Report (CSR)
  - Communicated to Downstream Users as annexes to extended Safety Data Sheets (SDSs)
- Managing risks is an integral part of the Chemical Safety Assessment
- Basic principles apply to NMs
- IND responsibility to investigate safe use of NMs and develop relevant Exposure Scenarios (ESs)

Further CASG Nano activities

REACH-CLP Competent Authorities, June 2009:
- To adjust the existing guidance to better address nanomaterials, CASG Nano will start a REACH Implementation Project for nanomaterials (RiPoN) on
  - substance identification,
  - Information requirements and
  - chemical safety assessment
- Cooperation with the Member States, industry & NGOs
- Makes use of on-going research and work in OECD-WPMN and ISO
- Timelines, by mid-2011, intermediate results earlier

REACH – Risk Characterisation (2/2)

Environment –
Characterisation of dose/concentration-response
- Deriving the predicted no-effect concentrations (PNECs)
- Environmental compartments (aquatic: freshwater and marine, micro-organisms in sewage treatment plants (STP), sediments, terrestrial (soil), air, Secondary poisoning)
- Comparing (predicted) exposure levels to PNECs
- PBT and vPvB substances

Conclusions – Nanomaterials (2/2)

SCENIHR opinion on RA Test Guidelines, 2007 (old legislation):
- The RA principles apply, but guidance needs further adjustment for NMs:
  - insufficient knowledge
  - likely identify hazards associated to nanomaterials
  - appropriate dosmetics needed
  - exposure assessment methods need review
  - no clear view on environmental effects
  - case-by-case assessment

Thank you for your attention!

http://ec.europa.eu/enterprise/sectors/chemicals/reach/nanomaterials/index_en.htm
http://echa.europa.eu
(5) Presentation from NGO perspective

Risk Assessment for Nanomaterials: An NGO Perspective
Cap Baier-Anderson
Environmental Defense Fund

Overview:
What is Important to EDF?
- Risk assessment challenges: how unique for nanomaterials?
- Life cycle perspectives
- The case for hazard-driven decision making
- Exposure considerations
- Managing uncertainty
- Recommendations

Many Nano Challenges are Same for other Chemicals
- How do we handle toxicity and exposure data gaps?
- How do we assess hazard and risk?
- How do we rank or prioritize chemicals?
- How can we incentivise green chemistry decisions?

Source of Frustration:
Still not Playing with a Full Deck

But do we ever have the luxury of a full deck?

There are Unique Challenges in Nano Risk Research
- Variability of nanomaterials
  - By design
  - Throughout lifecycle
- Instruments and methods for detection & measurement
  - Environment & humans
- Defining relevant physical-chemical parameters
  - General principles relating to hazard
- Biological and environmental fate and transport

Life Cycle Perspectives
- Assessment of hazards, exposures and benefits throughout product life cycle stages
- Comprehensive environmental assessment - combines a product life-cycle framework with the risk assessment paradigm

Photo from Daisi Taksapan web page: http://www.chemistry.queensland.edu.au/3275/lecture_10.html

www.environmentdefense.org/documents/0553_HighHopesLowMarks.pdf
Lifecyle Pitfalls

- Oversimplification
  Energy efficiency ≠ Toxic Waste ≠ Green Product
- Understand green tradeoffs
  e.g., decreased hazard vs. greater water use

Is Risk the Only Basis for Decision-Making?

- Risk is a function of hazard & exposure
  - Human considerations: sensitive populations, age, life stage, etc.
  - Uncertainties and data gaps: assumptions and ranges
  - Need to avoid unintended consequences
- Risk can be controlled by reducing hazard or reducing exposure
- Science-based decision can be driven by hazard, exposure or risk

Importance of Hazard

- Green chemistry focus
  - Design safer nanomaterials and products
  - Design chemicals and products to degrade after use
- Compare nano to conventional chemicals
- Identify safer alternatives
  - Replacement with less hazardous chemical;
  - Elimination of the need for the chemical through material change, product re-design, or product replacement;
  - Eliminating the chemical by altering the functional demands for the product through changes in consumer demand, workplace organization or product use
- Reduce concern for exposure

Hazard Considerations

- Mortality/morbidity
- Reproduction
- Development
- Immune system
- Endocrine system
- Brain or nervous system or
- Any other biological functions in humans or animals

Hazard, Use & Alternatives

- Functional use for alternatives assessment
- Use as a proxy for exposure and basis of comparison
  - What is its industrial function? (e.g., catalyst) or function within the consumer product (e.g., binding agent)
  - What chemical(s) does it replace?
  - How do the hazard profiles compare?
  - Identify & critically evaluate high hazard options

Weighing Hazard

<table>
<thead>
<tr>
<th>Criticality</th>
<th>Hazard</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Hazard High Criticality</td>
<td></td>
</tr>
<tr>
<td>Low Hazard Low Criticality</td>
<td></td>
</tr>
<tr>
<td>High Hazard Low Criticality</td>
<td></td>
</tr>
</tbody>
</table>
Exposure Considerations
- Notable failures in exposure assessment decreased trust in risk assessment
  - Brominated flame retardants, Perfluorinated chemicals, Biphosphor
- Exposure prediction
  - Life cycle exposure considerations
  - Nanomaterial use, release & disposal
  - Environmental fate & transport
  - Disposition in biological organisms
- Special considerations for children’s exposures, other sensitive populations
- Aggregate exposures
- These exposure considerations can modify hazard-driven decisions

Managing Uncertainties
- Good to know:
  - What are the key uncertainties that risk assessors may face?
  - Where in the lifecycle and/or under what use scenarios is there greatest uncertainty?
- Better to bound uncertainties
- Use sensitivity analyses to determine impact of range of potential alternatives

Putting it All Together
- Assessments must be data driven
- Go for maximum transparency
- Involve stakeholders early & often
- Identify & bound assumptions
- Examine potential impacts if the assumptions are incorrect
  - Can help identify critical check points

Some NM Applications may be Reasonably Safe...
- No claims without data!
- Need publicly available assessments before market

Interim Safety Steps: Overarching Considerations
- Does the use of this nanomaterial reduce hazard?
- Does the hazard profile change during material or product lifecycle?
- What are likely environmental fate & transport properties during different stages?
- Are there “green” tradeoffs?

Interim safety steps - Workplace
- Assume toxicity of materials, wastes until shown otherwise
- Implement effective worker training, industrial hygiene, PPE as last resort
- Monitor workplace, worker health
Interim safety steps - Environment

- Avoid dispersive uses until hazard and exposure/fate data available
- Identify, assess and disclose lifecycle hazards and risks in advance of commercialization
- Conduct release/environmental monitoring
(1) TiO2 case study

(1-1) Presentation from BIAC

Key Points

- "Titania" ≠ all Titania ≠ P25
- P25 is not Nanoscale though it is Nanostructured.
- P25 is highly aggregated & agglomerated.
- There are many years of experience from the use of P25.
- P25 is a material of low hazard.
- Good hygiene practices are sufficient to mitigate known hazards.
- We routinely search for new pertinent information.

What is P25?

Aeroxide P25 is an Evonik product composed of Titanium Dioxide (Titania). (79% Anatase, 21% Rutile)
It is not the only Titania in the marketplace.
It has been manufactured for over 35 years and the manufacturing process has not changed significantly during that time.
The manufacturing process is based on the flame hydrolysis of Titanium Tetrachloride.

Key Physical Properties

- "Primary Particle Size" is about 21 nm.
- Primary Particle Lifetime: <200 milliseconds
- Aggregate Particle Size about >100 nm – 1 μm.
  Agglomerate Size about 1-20 microns (1000 – 250,000 nm)
- Fused/Melted "primary particles"
- Surface Area is about 50 m²/gm

Particle Growth

TEM of P25
“Nano before Nano was Big!”

Known Application Areas

- Catalyst Support – High surface area
- Heat stabilizer in silicone rubber – Bound in matrix
- Photocatalyst – Sometimes bound to surfaces

"Färbe & Lacke" April 1949

Known Acute Hazards

- Physical irritant to eyes
- Desiccant in contact with skin
- May be irritating to the respiratory tract if inhaled
- Not known to be toxic by ingestion, inhalation or absorption

Known Chronic Hazards

- Classified as IARC 2B carcinogen
- Not supported by experience or epidemiology
- Evonik workplace monitoring has not indicated increased incidence of health problems

Most Likely Exposures

Path:
- Inhalation
- Dermal

Place
- Manufacturing workplace
- Processing workplace

Practices to mitigate hazards

- Automated manufacturing – Few workers exposed
- Engineering controls – Manufacturing performed at slightly reduced pressure to contain particles
- Packaging performed using enclosed, reduced pressure systems
- Recommended PPE – Glasses & Gloves
- Goggles and Respiratory Protection recommended if dusts present or OEL exceeded
What else?

- Monitor literature for relevant information
- Monitor literature for new information, even if not relevant
- Ongoing medical surveillance
- Engaged with peer companies
- Participate in and contribute to pertinent activities such as NanoSafe, NanoCare, ISO and OECD WPMN

Key Points

- "Titania" ≠ all Titania ≠ P25
- P25 is not Nanoscale though it is Nanostructured.
- P25 is highly aggregated & agglomerated. - Big particles
- There are many years of experience from the use of P25
- P25 is a material of low hazard.
- Good hygiene practices are sufficient to mitigate known hazards.
- We routinely search for new pertinent information.
(1-2) Presentation from US EPA

**EPA Nanoscale Titanium Dioxide Case Studies Document and Workshop**

**J. Michael Davis**  
T. U. S. EPA, Research Triangle Park, NC  
&  
Jeffrey Morris  
U.S. EPA, Washington, DC  
OECD Workshop on Risk Assessment of Manufactured Nanomaterials in a Regulatory Context  
September 16-18, 2009  
Washington, DC

**Outline**

- **Content**
- **Objectives & Goals**
- **Approach**
- **Comprehensive Environmental Assessment (CEA)**
- **Case Studies**
- **Workshop**
- **Conclusions?**

**Disclaimer:** This presentation does not necessarily reflect the views or policies of the U.S. Environmental Protection Agency

**EPA Context**

- **EPA (2007) Nanotechnology White Paper recommendations:**
  - Use Case Studies to:
    - Identify unique risk assessment considerations for nanomaterials
    - Identify research needed to support risk assessment
    - Hold series of workshops
  - Substantial number of multidisciplinary experts
  - Identify what is known and needs to be known to support risk assessments
- **EPA (2009) ND Nanomaterials Research Strategy**
  - Research Theme: Developing Risk Assessment Methods
  - Key Science Question 6: How may risk assessment approaches used to be modified to incorporate special characteristics of manufactured nanomaterials?

**Approach**

- Case studies based on Comprehensive Environmental Assessment (CEA)
  - Holistic approach combines product life cycle framework with risk assessment paradigm
- Case studies focus on specific uses of selected types of nanomaterials
  - Complex, often unique properties make generalizations difficult
- Structured workshop
  - User-case studies and Decision Analytic approaches with diverse group to identify and prioritize research needs

**CEA = LC + RA**

**LC** = Product Life Cycle framework
**RA** = Risk Assessment paradigm

Case Studies

- Selected by EPA internal workgroup based on:
  - “Nano-nuts”
  - EPA-relevance
  - Data availability
  - Exposure potential
  - Both human and ecological effects

- Specific uses of nano-TiO₂ with overlapping but different product life cycles:
  - CS1: Drinking water treatment to remove arsenic
  - CS2: Topical sunscreen

Chapter 2: Life Cycle Questions

Feedbacks
2.8.1. Are certain feedstocks more relevant to producing nano-TiO₂ specifically for water treatment or sunscreen applications?

Manufacturing
2.8.2. What manufacturing processes for nano-TiO₂ affect their physicochemical properties?
2.8.3. Are certain manufacturing processes used specifically for nano-TiO₂ in a water treatment agent or as a topical treatment?
2.8.4. What waste products or by-products, both nanoscale and larger, might be released, and in what quantities, for nano-TiO₂ manufacturing processes?
2.8.5. Where is nano-TiO₂ manufactured? What is the potential for general population exposure to nano-TiO₂ if there are?

Distribution and Storage
2.8.1. How is nano-TiO₂ shipped (i.e., what are the relative frequencies for shipments in bulk, paper bags, or drums, or by truck or rail)? How is it stored? In what quantities? Are any guidelines available on whether protective packaging (e.g., additional polyethylene lining) is warranted?
2.8.2. Could water treatment facilities or consumers of nano-TiO₂ release water treatment facilities or consumer releases be stored under such conditions as to prevent environmental exposure pathways?
2.8.3. How would products made with nano-TiO₂ be disposed of by the end user or by the manufacturer?
Chapter 2: Life Cycle Questions (continued)

Use
2.4.3. To what extent is nano-TiO₂ used or could be used for water or waste water treatment? Are data available (e.g., volume of water currently treated in the United States for sanitary, amount of nano-TiO₂ needed to treat a given volume of water) that would permit an estimate of potential use?

2.4.3. Which nano-TiO₂ treatment processes are used or could use nano-TiO₂, and in what quantities? Would the type of process depend on the size of the treatment facility or the size of the population served, or both?

2.4.3. What percentage of the nano-TiO₂ would settle out in floe or become part of the filter matrix? What percentage would be released into finished water? Are measurement or monitoring methods adequate to detect such particles?

2.4.4. Water distribution systems often have substantial facilities or周恩來 development, despite the implementation of control practices. Would the presence of nano-TiO₂ influence the bacterial biofilm community or the occurrence of odors?

(Continued next slide)

Disposal
2.5.1. How much residual nano-TiO₂ is present in packaging of the primary material or derived product? How is such packaging disposed of?

2.5.2. If nano-TiO₂ were to become more widely used and produced at a much higher volume, would packaging and shipping methods of nano-TiO₂ change? If so, how would such changes affect the potential release and exposure during transport, storage, and disposal?

2.5.3. In waste treatment and in the environment, how are waste stream and associated waste water containing nano-TiO₂ disposed of or recycled?

2.5.4. How are large quantities of nano-TiO₂ released (e.g., sub-pan batches expected during manufacturing) handled?

2.5.4. Is nano-TiO₂ present in waste containers that are not disposed of? Are there any circumstances where such disposed product would enter the environment at significant levels?

Workshop
- Diversity of technical and stakeholder perspectives
- 20 invited participants balanced across sectors/disciplines:
  - Academia, Government, Industry, NGOs, others
  - Technical, scientific, policy, other
- Pre-workshop review and making of research/information needs:
  - Rank order top 10
  - Identify top 25
  - Identify lowest 10
  - Modify existing or add new needs

Workshop (continued)
- First of series / iterative process
- Conducted under auspices of EPA Board of Scientific Counselors
  - Report describing workshop process and outcomes
  - BOSC will review report in public forum
- Research Strategy
  - Form, scope, timing depend on workshop outcomes
Conclusions

- To be continued

ADDENDUM

Questions from Chapters 1, 3, 4, and 5

Chapter 1: Characterization Questions (continued)

1.6. What factors determine whether and to what extent aggregation or agglomeration of nano-TiO₂ occurs?

1.7. Are data available that indicate the level of agglomeration or aggregation or dispersion of nano-TiO₂ in specific products? If so, what do the data show?

1.8. Is there a difference between the opacity of nano-TiO₂ aggregates and conventional TiO₂ particles of nominally similar size (e.g., because of light passing through pores in aggregates)? If so, what are the implications of such a difference?

1.9. Regarding the properties of aggregates and agglomerates and proper characterization of particle size, what insight is available from study of other nanoparticles?

1.10. What existing or emerging analytical techniques might be relevant or useful for material characterization? For example, could field transmission (FT) be used for characterization of particle size and composition?

1.11. Do surface area measurements in air (e.g., BET analysis) correlate to surface area in an aqueous environment? If so, what is the extent of their accuracy and precision?

Chapter 3: Fate & Transport Questions (continued)

3.7. What is the bioavailability of nano-TiO₂ in land-applied sludge to both terrestrial and aquatic organisms? Is bioavailability likely to change when nano-TiO₂ is incorporated into sludge and is allowed to age (i.e., weathering)?

3.8. What effect, if any, do coatings, dispersants, carriers, and surfactants have on biopersistence and biocumulation?

3.9. Can the photodegradability properties of nano-TiO₂ cause other unintended substances to form, for example, degradation products, in various environmental media?

3.10. Will nano-TiO₂ affect the efficiency of other major elements of water treatment processes (e.g., chemical coagulation)? The contaminant concentrations necessary for effective organics removal?

3.11. What influence could water drinking water treatment, including taste, have on the chemical properties or behavior of nano-TiO₂?

3.12. Irradiation photodegradable nano-TiO₂ is potentially biocidal and antimicrobial. What is the potential for interactions of nano-TiO₂ with microbes needed in water treatment systems?
Chapter 2: Fate & Transport Questions (continued)

3.43. What are the key environmental factors (e.g., pH, natural organic matter type and concentration, temperature) that facilitate or hinder nano-TiO₂ stability in the aqueous environment? Would human feces or other common contaminants or constituents in water undergoing treatment affect the fate, including agglomeration/aggregation properties, of TiO₂?

3.44. What is the impact to nutrient and metal cycling and microbial diversity when sewage with nano-TiO₂ is applied to soils?

3.45. How do sunscreen ingredients affect nano-TiO₂ fate and transport?

3.46. Can agglomeration/aggregation in the environment be predicted on the basis of physical properties of the particle, for example, size, shape, or charging?

3.47. What is the likelihood that nano-TiO₂ in house dust will become part of the food web and ground water contamination?

3.48. What is the potential for plant uptake of nano-TiO₂ from contaminated soil and irrigation water?

Chapter 4: Exposure-Dose Questions (continued)

4.13. Since nano-TiO₂ may increase the uptake of other pollutants, such as mercury, would nano-TiO₂ be a greater concern for exposure and ecological effects in areas with high concentrations of certain pollutants than in other areas? If so, how do we predict or identify such “hot spots”?

4.14. Which physiologically-based pharmacokinetic models are optimal for understanding absorption, distribution, and elimination of nano-TiO₂ in humans?

4.15. Are exposure-dose models available (and adequate) to quantitatively extrapolate the exposure used in animal toxicology studies (by inhalation, instillation, oral, dermal, and in vitro) to the human exposure that would result in an equivalent dose to the target of interest?

4.16. What is the potential for nano-TiO₂ to transfer to or accumulate in the food web and cause adverse effects on ecological receptors?

4.17. Nano-TiO₂ has been shown to attach to the surface of algae and fish as well as bioaccumulate in fish. Does nano-TiO₂ biomagnify?
(1-3) Report from chair of TiO2 case study

NTiO2 Case Study Discussion

- Did identify nano-specific properties, but not their relationship to toxicity
- On the issue of metrics, it may be related to functionality, rather than size
- Considered nano-specific aspects, but did not compare these to bulk materials
- May want to look to PBPK modeling in specific media to identify issues
(2) Nano-Ag case study

(2-1) Presentation from Global Sales & Marketing NanoHorizons Inc. and HeiQ Materials Ag

Material Background

- Silver nanoparticles:
  - CAS #: 7440-22-4

- There are many actual and potential applications for silver nanoparticles:
  - Antimicrobial
  - Conductive and antistatic
  - Pigment
  - Catalyst
  - etc.

- Silver nanoparticles as an antimicrobial:
  - Textiles
  - Medical articles & devices
  - Coatings
  - Plastics
  - eg. sportswear, socks
  - eg. plasters, wound care
  - eg. wall paint
  - eg. keyboards

Ecology Risk Assessment

- Primary questions for silver nanoparticles in textiles:
  1. Eco-exposure: Are silver nanoparticles released during laundry?
  2. Eco-toxicity: Do silver nanoparticles impact wastewater treatment plants?

Published Protocol: Arizona State Silver Sock Study

- Seven commercially available silver socks were washed under aggressive conditions
- Silver particle and ionic silver release was measured

<table>
<thead>
<tr>
<th>Sock Brand</th>
<th>Wash Cycle</th>
<th>Silver Nanoparticle Release</th>
<th>Silver Particle Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longhorn (Black)</td>
<td>7</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Longhorn (Black)</td>
<td>7</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Arizona State (Black)</td>
<td>7</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Arizona State (White)</td>
<td>7</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Arizona State (Black)</td>
<td>7</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Arizona State (White)</td>
<td>7</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

- Conclusions:
  - Socks with silver nanoparticles (SmartSilver EPA 93687-3) showed no silver nanoparticle release
  - X-Static, a "conventional bulk silver", released silver nanoparticles

* This document is a partial summary of the content from the presentation by NanoHorizons Inc. and HeiQ Materials AG, as mentioned in the presentation title.
Results – Glass substrate

- Glass substrate used for SEM

Results – Nanosilver reference

- Nanosilver as positive control
Results – Nanosilver reference
- Nanosilver as positive control

Results – Sample 1
- Negative control – polyester without silver

Results – Sample 2
- Polyester with HeiQ AGS-20 inside coating layer

Results – Sample 3
- Polyester with HeiQ AGS-20 inside fibers

Polyester reference sample confirmed to contain no silver.

Sample treated with HeiQ AGS-20 TF (textile coating) shows no release of silver nanoparticles during laundry.
Results – Sample 3
• Polyester with HeiQ AGS-20 inside fiber

Results – Sample 3
• Polyester with HeiQ AGS-20 inside fibers

Results – Sample 4
• Commercial nanosilver sock** (also in Benn et al. paper)

Case Study: Silver Nanoparticle Release During Laundry?
• Results summary:

Ecology Risk Assessment
• Primary questions for silver nanoparticles in textiles:
  1. **Toxicity**: Are silver nanoparticles released during laundry?
  2. **Efficacy**: Do silver nanoparticles impact wastewater treatment plants?
**Ecology Risk Assessment**

- Primary questions for silver nanoparticles in textiles:
  1. Eco-exposure: Are silver nanoparticles released during laundry?
  2. Ecotoxicity: Do silver nanoparticles impact wastewater treatment plants?

- **No release of silver nanoparticles during laundry:**
  - Eco-exposure risk is low from textiles
  - Why?
    - Silver nanoparticles are effectively bound to fabric structure.

- **No impact of silver nanoparticles on wastewater treatment plant:**
  - Low potential for impact on wastewater plant flora
  - Why?
    - Silver ion load with high ambient loadings of common waste components such as microbes, solutes and particulate as well as organic carbon. Silver-exceded cells particulate material also effectively binds silver, removing it from the wastewater.

**Risk Assessment Perspective**

The Nanomaterials Risk Assessment Narrative:

1. Nanomaterials (eg. nanosilver) are new and exhibit unique physical and chemical properties compared to 'conventional' materials (eg. macroscale silver)

2. Existing risk assessments have been based on a dataset derived from conventional materials, so they do not apply to nanoscale materials

3. New data and risk assessments are necessary to determine if exposure limits developed for conventional materials apply to nanomaterials

**Risk Assessment Perspective**

On the 'newness' of nanomaterials: Lessons from colloidal chemistry

"We have only recently come to learn that every structure assumes special properties and a special behaviour when its particles are so small that they can no longer be recognised microscopically, while they are still too large to be called molecules."

Carl Wolfgang Debye, Colloid Chemistry in World of Neglected Dimensions, 1922.

---

**Risk Assessment Basis**

- **Case study:** silver nanoparticles in textiles
  - "Worst-case" example
  - Potential for ecological and human exposure

---

**Risk Assessment Perspective**

The Nanomaterials Risk Assessment Narrative:

- Assumption #1: The nanomaterials under investigation are new.

- Assumption #2: The current dataset was derived from conventional materials.

These assumptions clearly hold for a number of nanomaterials, eg. carbon nanotubes.

Is this the case for silver nanoparticles?

**Risk Assessment Perspective**

**Colloidal Silver: A Relevant History**

- Colloids are ultrafine particle dispersions, typically 1-1000 nm diameter

- Nanoscale silver colloids (Colloidal, Argynol, etc.) sold continuously since early 1990s; extensive database of toxicological data is available

- All major 'conventional' silver toxicity limits are in fact based on nanoscale silver colloids or ionic silver:
  - EPA drinking water limit
  - OSHA 8 hr inhalation limit
  - Dietary exposure EPA IRL

- Challenge: How well characterized?
Risk Assessment Perspective

Particle Sizes of Common Colloidal Silver Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Use</th>
<th>Particle Size (nm)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lugol</td>
<td>Anti-infective</td>
<td>20-80 (4-400)</td>
<td>15</td>
</tr>
<tr>
<td>Colloidal</td>
<td>Anti-infective</td>
<td>10-40 (2-80)</td>
<td>101</td>
</tr>
<tr>
<td>Sodium Hypochlorite</td>
<td>Disinfectant</td>
<td>100-300 (10-300)</td>
<td>209</td>
</tr>
</tbody>
</table>


Risk Assessment Perspective

Nanoscale Silver: Regulatory History

1954: Nanoscale colloidal silver (10-70 nm) first registered by EPA

1955: EPA registered silver impregnated carbon filters (2-15 nm) widely used to protect municipal water supply

1998: First FDA approved nanoscale/Silver second care devices are approved

2002: First nanosize silver diodes approved by EPA (5-10 nm)

Present: Estimated 90% (75 of 82) of EPA-registered products contain nanoscale particles or ions (precipitated silver)

Risk Assessment Perspective

EPA-Registered Nanosilver Algaeides

Product: nu-eo Silveroxide
Particle size: 25-95 nm
FIFRA Reg # 7124-101
Type: 3.0% Colloidal Silver
First Registered: 01/15/1993


Risk Assessment Perspective

Nanosilver Algaeides: EPA-Registered Since 1994

Product: Silver Algaeides
Particle size: 20-110 nm
FIFRA Reg # 68151-1
Type: 0.8% Colloidal Silver
First Registered: 12/31/1994

Risk Assessment Perspective

EPA-Registered Filter Media: Nanoscale Silver-Impregnated Carbon

- Of all EPA silver registrations, 40% (37 of 92) are silver-impregnated filters
- Nanosilver-carbon water filters have been commercial for over 40 years
- Silver particles >50 nm are inefficient; particles <15 nm are required

"... for proper efficiency, the silver must be dispersed as particles of colloidal size (less than 250 A (2.5 nm) in crystalline size..."

<table>
<thead>
<tr>
<th>FIFRA Reg #</th>
<th>First registered</th>
</tr>
</thead>
<tbody>
<tr>
<td>58295-1</td>
<td>12/01/1988</td>
</tr>
<tr>
<td>58295-2</td>
<td>11/01/1989</td>
</tr>
<tr>
<td>58295-3</td>
<td>01/16/1990</td>
</tr>
</tbody>
</table>

Risk Assessment Perspective

EPA-Registered Nanosilver Disinfectants: American Biotech Labs

"These engineered silver particles currently vary in size between about 10-50 nanometers in diameter..."

Inman D. Models, President, American Biotech Laboratories
Science on nanoscale particles has a U.S. Patent No. 6,890,695

Product: ASAP-AGX
Particle size: 10-50 nm
FIFRA Reg # 73495-1
Type: 0.001% Silver
First Registered: 2/27/2002

Product: ASAP-AGX-32
Particle size: 10-50 nm
FIFRA Reg # 73495-2
Type: 0.022% Silver
First Registered: 4/23/2003

Risk Assessment Perspective

EPA-Registered Antimicrobial Additives: Ciba / Bio-Gate

Product: Hygida 4000
Particle size: 50-200 nm
Agglomerate size: 2-5 μm
FIFRA Reg # 70404-10
Type: 100% Silver
First Registered: 05/05/2008

Product: MicroSilver BG-R
Particle size: 50-200 nm
Agglomerate size: 2-5 μm
FIFRA Reg # 64146-1
Type: 100% Silver
First Registered: 03/15/2008

Risk Assessment Perspective

EPA-Registered Nanomaterials: NanoCopper Wood Preservatives

Product: CORS-3272 / Micro Pro 200
Particle size: 50-100 nm
FIFRA Reg # 10305-80
Type: 32% Copper (as carbonate)
First Registered: 5/12/2005

Risk Assessment Perspective

EPA-Registered Nanosilver Disinfectants: Dental Line Cleaners

"The Maintenance Treatment contains a controlled, minute amount of colloidal silver to keep things clean."

Product: H2Pro™ Maintenance Treatment
Particle size: 1-500 nm (avg)
FIFRA Reg # 73929-1
Type: 0.001% Silver
First Registered: 5/9/2004

Risk Assessment Perspective

FDA-Approved Nanosilver Products

- Acticoat Wound Care with Nanocrystalline Silver
  - FDA approved in 1998
  - Clinically proven to reduce wound infection
- i-Flow SilverCoated Nanosilver Catheters
  - FDA approved in 2005
  - Recommended by NGOs to reduce hospital acquired infections
- Other FDA approved nanosilver products:
  - Baxter Needleless IV Connectors
  - SilverSol Nanosilver Wound Care Gel
  - Bard Silver-coated Endotracheal Tubes

Human Toxicity

Review of Silver Threshold Limits: Inhalation

- All silver exposure limits are based on argyria which is considered a cosmetic condition, not toxic.
- Not all forms of silver have the same propensity to cause argyria.
- American Conference of Governmental Industrial Hygienists (ACGIH) has established separate threshold limit values (TLVs) for metallic silver and soluble compounds of silver.

  Dust or fume of metallic silver ......... 0.1 mg/m³

  Soluble silver salts (silver nitrate) ........ 0.01 mg/m³

- "The available data on soluble compounds of silver demonstrate that silver salts have a greater propensity to cause argyria than does the dust or fume of metallic silver."
  (ACGIH: 1291).
Human Toxicity

Nanotoxicology in 1976:
Relative toxicity of nanoscale silver to silver nitrate

- Silver nitrate is 20 times more toxic than colloidal silver when given intraperitoneally. 1
  

- 'Based on total Ag concentration, toxicity was 18 times higher for AgNO3 than for AgNPs (silver nanoparticles).'' 2


The historical risk assessment data bridges to present day silver nanoparticles.

Human Toxicity

What datasets have EPA and OSHA used to set current exposure limits?

- Referring to Gaul and Staudt (1935): "One in 70 patients developed argyria after receiving an intravenous dose of 1 gram. This intravenous dose was converted to an oral dose of 0.014 mg/kg/day and was considered a lowest observed effect level. Other patients did not develop argyria until doses five times higher were administered." 1

- Referring to Hill and Hillsbury (1929): "Both of the US standards for silver in drinking water and in workplace air have been based on a presumed 1 g minimum dose of silver that has caused argyria." 2

1 EPA HSG 628 650 2008 Federal Register Vol. 74, No. 116 June 16, 2009
2 EPA HSG 628 650 2008 Federal Register Vol. 74, No. 116 June 16, 2009

Human Toxicity

Nanosilver Toxicology: Exposure Summary

The Gaul and Staudt (1935) and Hill and Hillsbury (1929) argyria 1 gram threshold value is the basis for:
- ACGH's Inhalation Threshold Limit Value (TLV)
- OSHA Inhalation Permissible Exposure Limit (PEL)
- Mine Safety and Health Administration PEL
- EPA RIS oral reference dose (RfD)
- EPA Office of Water's Secondary Maximum Contamination Level

Every major exposure limit set over the last 50 years is based on these 2 reviews of argyria (a non-toxic effect from nanosilver solvents or outside silver compounds).

No studies on micron-sized silver powders were referenced. Very little is known about the toxicity of micron-sized silver particles.

1 EPA HSG 628 650 2008 Federal Register Vol. 74, No. 116 June 16, 2009
2 EPA HSG 628 650 2008 Federal Register Vol. 74, No. 116 June 16, 2009
3 EPA HSG 628 650 2008 Federal Register Vol. 74, No. 116 June 16, 2009
Risk Assessment Basis

Case Study

Ecology  Sustainability  Human Health

Perspective

- Case study - silver nanoparticles in textiles:
  - "Worst-case" example
  - Potential for ecological and human exposure

How Do Silver-based Antimicrobials Work?

- All silver-based antimicrobials act against bacteria through the action of silver ions (Ag⁺).
  - The effect of silver ions against microorganisms is well established and is referred to as the allogenic effect [1].
  - Silver ions interact with bacteria cells through 3 mechanisms (see Figure):
    1. Damage cell membranes [2]
    2. Disrupt Ca²⁺ and Mg²⁺ ions [3]
    3. Interact with sulphur, oxygen or nitrogen [4]
  - Silver ions are active against a broad range of gram-positive and gram-negative bacteria.
  - Unique qualities of silver ions:
    - Low risk for bacteria resistance [5]
    - Effective in very low concentrations [6]
    - No human toxicity

Silver as an Antimicrobial

General advantages of silver antimicrobials:
- Can be directly integrated into polymers, coatings and formulations
- Easily processable - robust and temperature resistant
- Replace synthetic chemical antimicrobials
- Can be used in low concentrations to protect substrates from action of microorganisms

Example application - Textiles:
- Unpleasant odours from synthetic fibers
- Discoloration and stains
- Reduced service lifetime of textile
- Silver provides straightforward way to provide antimicrobial effect

Risk Assessment Perspective

Sustainability:
- Antimicrobials are not new:
  - Protection of everyday articles from the effects of microorganisms has long been achieved through use of antimicrobial agents.
- Antimicrobial agents give longer useful lifetime and improved utility for many everyday articles.
- This useful and widespread functionality should use the most sustainable antimicrobial agents available.
- Silver nanoparticle antimicrobial additives offer sustainability advantages:
  - Compared to:
    1. Ionic silver additives
    2. Organic chemicals (eg. chlorinated phenols, quaternary ammonium

Silver Additives Deliver Silver Ions

Antimicrobial effect:

Threshold concentration of Ag⁺ required for antimicrobial effect

Silver Additives in Use

- Silver antimicrobials derive activity from release of silver ions (Ag⁺)
  - Extent of Ag⁺ release varies over a wide range
    - Can be roughly considered as having different "solubilities"
      - Silver nitrate is totally soluble in water - highest possible extent of Ag⁺ release
      - Silver sulfide is totally insoluble - lowest possible extent of Ag⁺ release
      - Various silver antimicrobials lay in-between these extremes

Silver metal particles (example: Ag₂S)

- Because of the higher surface area per mass of silver, nanosilver has a higher release capability than bulk silver metal.
Nanosilver versus Conventional Silver Materials

Compared to other silver additives, silver nanoparticles generally have:
- Lower antimicrobial activity
- Longer durability
- Less silver needed in a treated article - combination of durability and activity is achieved at lower concentrations

Application Example - Textiles

- Textiles have unique potential to benefit from silver-based antimicrobial additives.
- Synthetic fibers (e.g. polyester or polyamide) offer overall a better environmental profile than natural fibers (e.g. cotton or wool). However, synthetic fibers have a tendency to develop strong odors when colonized by skin bacteria and so their use has limitations.
- Silver-based antimicrobials can be integrated directly into textile fibers or as part of a durable coating on the outside of the fabric.
- The integrated silver antimicrobial protects the textile from colonization by bacteria and therefore reduces odor development during textile use.
- In addition to achieving higher user comfort, the silver-functionalised textile can be washed less frequently, at lower temperatures, and with less detergent since odor resistance in synthetic textiles after usage is no longer a concern.
- Improved environmental profile through lower energy and detergent use and extended useful life of the textile.
- The preservative action of the silver antimicrobial enables synthetic fibers to achieve a better environmental profile and a wider field of application.

Risk Assessment Basis

Conclusions

- Ecology
  - Case study: Are silver nanoparticles released from textiles during laundry?
    - No
      - The studied silver treated textiles show strong affinity of particles to the fabric.
  - Case study: Do silver nanoparticles impact wastewater treatment plants?
    - No
      - Studies using dosing systems showed no impact from silver nanoparticles and textile-related formulations.

- Human health
  - Significant bodies of toxicity data for silver nanoparticles stretching back 8 decades
  - All “conventional” exposure guidelines are in effect based on nanoscale silver.

- Sustainability
  - Silver nanoparticles offer significant sustainability benefits compared to ionic silver and synthetic chemical antimicrobials

Challenges & Needs

- Silver Nanoparticle Human toxicity:
  - Review of the wide body of historic published data for silver nanoparticles (also equivalently known as colloidal silver, micronized silver etc.) prior to performing essentially repeat studies and to avoid unnecessary animal testing.

- Silver Micronizations:
  - Regulatory limits are currently based on an extensive body of data derived directly from nanoscale silver particles.
  - Data is actually needed for micron size silver particles.
  - Microscale data would assist in bridging the existing pool of nanoscale data.

- Sustainability life cycle analysis:
  - An analysis considering the relative impact of all antimicrobial technologies (silver nanoparticles, ionic silver, synthetic chemicals) is needed to assist an informed selection of the most sustainable antimicrobial additives.

Conclusions

- An established regulatory track record based on a wide body of silver nanoparticle data
  - EPA
    - EPA first registered silver nanoparticles in 1994
    - 82% of all EPA registered silver antimicrobials are based on silver nanoparticles (also equivalently referred to as colloidal particles)
    - For 6 decades the EPA has successfully managed the registration of silver nanoparticles that are used across every sector of commercial antimicrobial products
    - This long experience of regulated use, with an extraordinarily low rate of incidents, suggests that EPA and other regulatory bodies have adequately managed risks associated with commercial applications of silver nanoparticles.
  - FDA
    - The FDA has also registered a wide range of products that contain silver nanoparticles

Sustainability

68
(2-2) Presentation from Germany

Risk Assessment Case Study
nano-Ag

Marie E. Goede and Carsten Knaack
Federal Institute for Risk Assessment
(Germany)

Human Health Risk Assessment for two nano-Ag products
in the context of §31 German Plant Protection Law

Additional product information from REMEDEE
performed at Federal Environmental Agency (UBA)

Primary particle size: approximately 10-25 nm

Additional product information from DUBL / Zara
commissioned by Federal Inst. for Risk Assessment (BfR)

Key studies: Acute Toxicity

Key studies: Local Effects

- Skin Irritation
- eye irritation
- oral Irritation
- Inhition of growth
- Genotoxic effects

- Skin irritation
- eye irritation
- Oral irritation
- Inhition of growth
- Genotoxic effects
Repeated Dose Toxicity: Oral

Species: C57BL/6 and ICR mice (Hakim, 2009) for male and female poisoning (Hakim, 2009). The data were from the study by Hakim et al. (2009).

Results:

- Male mice: 30 days administration of the compound at the dose of 30 mg/kg body weight.
- Female mice: 30 days administration of the compound at the dose of 30 mg/kg body weight.

Regressed Dose Toxicity: Inhalation

Species: C57BL/6 and ICR mice (Hakim, 2009) for male and female poisoning (Hakim, 2009). The data were from the study by Hakim et al. (2009).

Results:

- Male mice: 30 days administration of the compound at the dose of 30 mg/kg body weight.
- Female mice: 30 days administration of the compound at the dose of 30 mg/kg body weight.
(2-3) Presentation from Netherlands

Nanomaterials under REACH

• Explore the key questions on hazard, exposure and risk assessment of a nanomaterial under REACH, using nanosilver as a case study
• To identify the (additional) information needs for REACH

REACH*

• Gathering and generating information
  - Substance identification
  - Classification and labelling
  - Chemical Safety Assessment
  - Exposure-related information
  - Guidance / communication on safe use (SDS)

Nanosilver case study

• Metallic silver, in nanof orm and bulk form
• Nanoform: particles 15 ± 5 nm
  - Used in bathroom cleaning product (1% nanosilver)
  - Environmental emission during all life cycle steps
  - Consumers dermal and inhalation exposure
  - Workers possible exposure (not considered)
• Hypothesis: nanosilver dissolves to Ag⁺
  - Comparison with bulk silver or silver salts
• Not a complete survey

Available REACH information

<table>
<thead>
<tr>
<th>Annexes VII + VIII</th>
<th>Nano</th>
<th>Bulk / salts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety data sheet</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Technical data sheet</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Environmental behaviour</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Toxicological properties</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Environmental fate</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ecotoxicological properties</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Human health effects</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Urgency classification</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Overall classification</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Registration, Evaluation, Authorisation and restriction of Chemicals

Disclaimer

- This case study is purely a scientific exercise with the aim to generate recommendations for future guidance on how to deal with the chemical safety assessment of first generation nanomaterials under REACH
- (Nano)silver was chosen because it is rich on data which was easily available (e.g. Wijnhoven et al 2009)
- This report does not pretend to provide a complete overview of all available toxicity data on (nano)silver
- This report is not to be used as an actual registration under REACH

Classification & Labelling / Chemical Safety Assessment?
Nanosilver case study: No insuficient information

- Physicochemical / Environmental fate
  - granulometry (e.g. surface area, aspect ratio)
  - surface chemistry (e.g. charge)
  - dissolution kinetics
  - distribution coefficients (Kd values)

- Ecotoxicity
  - long term toxicity in fish or Daphnia (dissolution kinetics)
  - (effects on microbiological activity in STP - nano and bulk)

- Human Health
  - data on the kinetics of dissolution to Ag+ (rate and extent)
  - data on transplacental passage/developmental toxicity
  - in vitro gene mutation in mammalian cells

Classification & Labelling / Chemical Safety Assessment?
Nanosilver case study: No insuficient information

- Exposure Assessment
  - environmental exposure
  - EUSES limitations for metals (Kd not available)
  - rapid, 100% dissolution to Ag+ ions in water not realistic
  - consumer exposure
  - large differences between models
  - only very rough estimates possible
  - worker exposure
    - not estimated here

Lessons learned: Nanosilver

- Data-rich, but insufficient to assess “sameness”™
- Measurements of the nanoform were often made as Ag (structure?, Ag+?)
- In vitro information is not (yet) suitable (sameness, chemical safety assessment)
- Existing risk assessment proposals insufficient
  - information needs?
  - what is low/negligible exposure?
  - first step based on exposure (in REACH only > 10 Ly)

Further lessons learned

- No definition of nanomaterials under REACH
- Characterisation of nanomaterial
  (information lacking / nanoparticles outside range?)
- Dose metrics (mass may be not sufficient)
  (low/negligible exposure?)
- Exposure models not validated for nano
- Comparative studies lacking
  (nano/bulk comparison: sameness)
- Information on kinetics of nanomaterials
  (exposure)

Proposed approach

- REACH framework applies
  - Providing Information for registration (base-set)
  - Depending on base-set further information
- Adaptation of base set information
  (independent of tonnage)
- Reconsider tonnage bands
  (1 tonne/year for registration)
Physicochemical properties

- Annex VII on physicochemical plus
  - Dissolution kinetics in addition to water solubility
- Nano-specific requirements
  - Dustiness
  - Fat solubility/oleophilicity
  - Hydrodynamic size/particle size measurements/distribution
  - Length
  - Shape
  - Specific surface area
  - Surface charge/Zeta potential
  - Surface chemistry

Exposure information*

- Developing exposure scenarios and generating exposure estimates (Annex I) with special attention to:
  - Frequency, duration and level (all populations and compartments exposed)
  - Life cycle (form in which human/environment are exposed)

Toxicological information*

- Toxicokinetics
- Repeated dose (incl. nano-specific parameters)
- In vitro gene mutation and in vitro cytogenicity

Ecotoxicological information*

- Algal growth test
- Chronic Daphnia
- Information on fate and behaviour with special attention to:
  - Stability of the nanomaterial (biotransformation and biodegradation rates)
  - Distribution coefficients (Kd values)

Next tier

- Depending on outcome of base-set data gathering, further higher tier testing on a case-by-case basis

Acknowledgements

Marja Pronk
Susan Wijnhoven
Evelyn Heugens
Willie Peijnenburg
Robert Luttik
Betty Hakkert
Nano Silver Discussion Summary

- Consideration in risk assessments as particles, fibers, and/or silver ions
- Importance of problem formulation (framing the risk assessment): what are we trying to address?
- Did identify and consider nano specific properties, mode of toxicity, etc.
- Comparison to bulk materials was considered
- Data rich substance including uses but data may still not be adequate to address all issues

Nano Silver Summary (2)

- Long regulatory and use history: experience with risk management
- Uncertainties were addressed: how are the various database uncertainties linked?
- Fate, transport, and exposure must be considered
- How to address translocation and persistence of silver nano particles?
- Consideration of medical applications: wound care data base

(3) CNT case study

(3-1) Presentation from Bayer Schering Pharma

Risk Assessment Case Study
MWCNT (Baytubes®)

Dr. Gisela Strapper and Dr. Jacqueline Rappi
Bayer Schering Pharma AG and Bayer MaterialScience AG
Germany

Background and Approach

- This case study is an actual activity and part of our Product Stewardship program for nanomaterials and using:
  - Standard chemical hazard and risk assessment approaches
    - Hazard Identification
    - Exposure Assessment
    - Risk Characterization
    - Risk Assessment
- Standard test methods (OECD Guidelines)
  - Special care was taken for test substance characterization
  - Consideration of Mode of Action

Baytubes® – Characterization

- CNTs are a large family of distinct products
- Baytubes® are Multi-Walled Carbon Nanotubes:
  - Form large and stable agglomerates of high chemical purity
  - Purity >90%, Cobalt < 0.5%, NO < 0.5%
  - Short, thin & elongated tubes
  - Wall tube length in dispersion ca. 12.5mm
  - Display a respirable cutliness (EN15235-B)
  - Have an low agglomerate density
  - 5.2 g/m³ (ca. 10 times lower than Carbon Black)
Use Patterns

- What is the nanomaterial used for?
- Additive in polymers and metals
- What is its function?
- Mechanical reinforcement, electrical and thermal conductivity
- Is the nanomaterial used in consumer products?
  - High-tech sport equipment (e.g. tennis racket, hockey sticks)
  - Rotor blades of wind turbines
- Potential use in all applications where reduced weight is desired (e.g. automotive, aeronautic)
- Production capacity?
  - Current capacity at BMG: 90 metric tons/year

Hazard Assessment: Evaluation of the literature on CNTs

Examples from the literature demonstrating the complexity:
- SWCNT induce indirect cytotoxicity in vitro by medium depletion (Cary et al., Toxic Lett 173, 76-84, 2008)
- Protein is absorbed to SWCNTs (Jogessar et al., Carbon 45, 467-473, 2007)
- SWCNT interact with dyes used to assess cytotoxicity (Cary et al., Carbon 45, 1425-1432, 2007; Dueren et al., Toxicology in vitro 21, 435-448, 2007)
- Confounding factors need to be considered (see e.g. Task et al., Metalomics 34, 215-230, 2007; and Dybauer et al., Carbon 45, 2542-2551, 2007)

Specific Question: In vivo toxicity of MWNT compared to Asbestos after single i.p. or intracotital application

- Long and thick MWNT:
  - Fiber-like response in short term assay in C57Bl/6 mouse (7 days); Hazard et al., Nature Nanotechnology 3, 7, 471-475
  - Mesothelium in p3534-kb--heterozygous knock out mouse (up to 180 days; Hogan et al., J. Toxicol. Sci. 32, 1, 69-76)
- Short, thin and tangled MWNT:
  - No fiber effect in short term assay in C57Bl/6 mouse (7 days); Manes et al., Toxicology in vitro 21, 435-448, 2007
  - No carcinogenic response in long term study in Water rats (2 years); Nishio et al., J. Toxicol. Sci. 32, 1, 69-76

Hazard Assessment: Evaluation of the literature on CNTs - Summary

- Evaluation of the literature on CNTs:
  - There is a limited number of in vivo studies on some CNTs showing effects, but neither has reached the critical mass of action
  - Inhalation studies are regarded as of major importance for risk assessment and Occupational Exposure Limit setting
  - The materials tested in the literature are not identical to Baytubes® and may differ significantly in composition and a number of parameters that might influence the toxicological profile
- Single/Multi-Wall, Impurity profile, Diameter, Aspect ratio, Bulk density, Stability...

- Health and safety issues need to be evaluated specifically for each product.
- Product stewardship program is in place for Baytubes®
**Hazard Assessment: 2. Toxicological Test Program Baytubes®**

- Acute toxicity, oral (OECD 425, feeding, vehicle dosing cream).
  - LD50 rat: 1,500 mg/kg, no signs of toxicity and no mortality
- Acute toxicity, dermal (OECD 403, dry test substance and moulded wrapping).
  - LD50 rat: < 1,000 mg/kg, no local effects, no signs of toxicity and no mortality
- Primary skin irritation (OECD 444, moistened with water).
  - Non-irritant (guinea pig): no skin effects
- Primary eye irritation (OECD 467, dry test substance).
  - Non-irritant (rabbit): minimal conjunctival irritation in 3 animals; reversible within 72 hours, no ocular damage or corneal ulcerations
- Sensitisation (OECD 406, modified Guinea Pig Maximisation test; vehicle petroleum; formulated to yield a paste, warmed at 37°C, maximum achievable concentration 25.9% used for induction and challenge). No positive (no skin effects in all animals)
- Genotoxicity in vitro (vehicle dosed reaction, > 30 min batch-coculture, 25°C, 474 Hz, Shift of agglomerates size from 100 µm down to 10 µm under induction conditions).
  - No alterations in chromosome aberration test in vivo (OECD 478).
  - Not mutagenic in Ames Test (OECD 471)

---

**Toxicological Test Program: Acute Inhalation Study in Rats**

- Study design (adapted OECD 440).
  - Both genders, 7, 26 and 48 day post exposure observation, 11 and 341 mg/kg.
- Baytubes®: Reference substances: Quartz and Carbon Black (CB).
- Results: No mortality, 0/30 rats: 251 mg/kg.
- Class: >11 mg/kg: poorly soluble particle effect (personally responsible).
- Pulmonary toxicity is related to the MWNT.
- Baytubes® and CB are markedly different.
- Merkato compressed to CB is consistent with density-related overlapping.
- Less particle mass is needed to exceed the volumetric overlap limit for the inhibition of macrophage-mediated clearance (particle volume rather than surface area most critical)

---

**Toxicological Test Program: Subchronic Inhalation Study in Rats**

- Poorly soluble particle effect confirmed.
- Results: 0.1 mg/m³ was tolerated without changes in BAL considered to be adverse. This is in line with histopathological examinations:
  - Clear effects at 1.5 and 6 mg/m³, borderline effects at 0.4 mg/m³.
  - Comparative inflammatory response studies (pH in BAL, alveolar collapse, pathological changes in lung structure: no toxicity).
  - The findings match those observed in studies with poorly soluble particles of low specific density.
  - The inflammatory potency of Baytubes® is associated with its low bulk density leading to volumetric overlap of macrophages.
  - The conclusion of acute and pulmonary MWNTs may suggest that the MWNTs are the cause of the effects observed.
  - No evidence of any toxicity outside the respiratory tract.
  - Translocation/adsorption/uptake into small tubes or fibres does not occur (cytoplasm).
- Mode of Action: Findings suggest that a volumetric overload rather than specific structural features is causative for the effects observed.
  - Rat-like overload phenomena have no equivalence in humans.

---

**Toxicological Test Program Baytubes®: Inhalation Studies in Rats**

- The inhalation toxicity test program was developed to:
  - Cover regulatory aspects (dose-response relationship for acute and repeated dose toxicity; classification).
  - To gain insight in the principle mode(s) of action (e.g. reference materials, extended and hypothesis-driven study design).
- Baytubes® agglomerates are too large to be tested n.s.-l. They need to be processed (e.g. micronisation).
- In the inhalation studies only Baytubes® aerodisperse test substance was subject to grinding (centrifugal ball mill) to increase dustiness, however without determination of the typical agglomerate structure.
- Test materials in the lung were carefully characterized.
  - Enlarged agglomerates of tubes predominate in inhalation atmosphere.
  - Under the conditions of the studies with Baytubes® single tubes could not be identified in lung cells (cytoplasm).

---

**Exposure Assessment: Safe Use of Baytubes® over the Whole Life Cycle**

- **End of Life**
  - Production
    - e.g. Proper disposal, Baytubes® undergo complete combustion > 99%
    - e.g. Closed System, Automated filling, Exhaust gas incinerated
  - Use Phase
    - e.g. Nanoparticles embedded in a matrix have a negligible exposure potential
    - e.g. Proper use to ensure safe handling, use of implementing controls, use of personal protection measures (H2OS)

---

77
Risk Characterization and Assessment of Human Health

- Toxicity profile of Baytubes®:
  - Acute toxicity is low; not an skin and eye irritant, not a skin sensitizer, not mutagenic in the Ames Test and not clastogenic in the chromosome aberration test in vitro
  - Mode of Action after Ingestion
    - Effects consistent with "Potentially Soluble Particles"-like mode of action (PSP effect)
    - Findings suggest that a volumetric overload rather than specific structural features is causative for the effects observed after ingestion
    - No evidence of extraordinary toxicity after ingestion
  - Sub-chronic ingestion data will be set to an OEL (8 - 0.1 ~ 4 - 1.5 ~ 6 ppm)
- Exposure: no unreasonable exposure along the life-cycle (additive in polymers)
  - For further processing typical exposure to Baytubes® during compounding was lower than 0.8 mg/m³ (< 0.005 mg/m³; limit of detection)
- Based on all data available presently, Baytubes® is safe for its current intended use

Conclusions

- Based on the experience in the Product Stewardship Program with Baytubes®:
  - The available toxicological and ecotoxicological test methods are applicable for the test substance examined; for poorly soluble particles post-exposure observation as well as testrodsinsertion Laurel (BAL) are recommended for inhalation studies
  - Confounding factors due to physico-chemical interferences need to be considered especially in in vitro testing
  - Special care has to be taken for test substance characterization before and during testing
  - The data generated give no indication of a specific "nano"-toxicity not covered by the available methods
- This overall conclusion is in line with a recent document by the Working Group of Nanosized Nanomaterials

Eco-toxicological Test Program for Baytubes®

- Ecotoxicity test results for Baytubes®:
  - Acute bacterial toxicity (OECD 209)
  - EC50 = 100 mg/l (activated sludge)
  - Acute toxicity to fish (OECD 203)
  - LC50 = 100 mg/l (Brachydanio rubuze (zebra fish); 96 h)
  - Acute toxicity for daphnia (OECD 202)
  - EC20 = 100 mg/l (Daphnia magna (Water flea); 48 h)
  - Acute toxicity for algae (OECD 201)
  - EC50 104 mg/l (Desmodesmus subspicatus (green algae); 72 h)
- Exposure assessment in the environment
  - For the applications envisaged (Baytubes® embedded in polymer matrix) the exposure potential through ingestion can be considered as negligible
  - Further research on Baytubes® is ongoing (e.g. Project CarbonSafe within the Inno-CNT alliance)
  - First estimations support low Predicted Environmental Concentrations
- All standard studies performed so far with Baytubes show no relevant adverse effect at realistic exposure level (SLP studies according to OECD guidelines)

Thank you for your attention
Hazard Assessment: 1. Evaluation of the literature on CNTs

Specific Question: In vitro Toxicity of MWCNT compared to Asbestos after i.p. or intracutaneous application

- Takeda et al. (1) study in mice indicated:
  - More intense animal response for MWCNT than asbestos due to lower levels of inflammation in the treated groups.
  - No significant differences in the inflammatory response between MWCNT and asbestos.
  - Very high mortality rate for untreated animals (injection volume: 0.2 mL).
  - Intermediate high single dose (1 mg/mouse) vs. very strong local reaction, e.g., peritoneal.
  - Reference: non-carcinogenic and non-genotoxic.
  - Low and short MWCNT treated
  - Injection of non-carcinogenic

- Repeated 5x: short-term study in mice (7 days):
  - Mice injected intraperitoneally with the test substance.
  - Single dose 100 mg/kg.
  - Reference: short-term study, non-carcinogenic, non-genotoxic.
  - Different doses of MWCNT tested.
  - Injection of test substance (beige, white, black) in the local region.
  - No harmful effect for the mice, local, long-term studies.

References:
- Takeda et al. (1) Nanotechnology 2010, 11, 2009, 1930-1935
- Takeda et al. (1) Nanotechnology 2010, 11, 2009, 1930-1935
(3-2) Presentation from US NIOSH

Risk Assessment Case Study: Carbon Nanotubes

Dr. Emile D. Kunzinger, Ph.D.
National Institute for Occupational Safety & Health
Cincinnati, Ohio

OEC Workshop on Risk Assessment of Engineered Nanomaterials
Washington D.C.

Background

- **Objective**: Evaluate the toxicology data, methods, and uncertainties in assessing hazards of carbon nanotubes (CNTs).
- **Overall Goal**: Support development of NIOSH occupational safety and health recommendations and identify research needs.
- **Purpose of this presentation**: Provide an overview of toxicology and worse-case exposure data, and examples of risk assessment methods and issues.

--

NIOSH Role

- NIOSH is authorized to develop recommended occupational safety and health standards (OSHA).
- Conducts toxicological research, risk assessment, exposure assessment, and health surveillance.
- Develops criteria for recommended standards.
- Forecasts recommendations to OSHA.

--

Substance Description & Uses

- **SWCNT**: Single-walled carbon nanotubes
  - 1.4 nm diameter, 10-300 nm length
  - MWCNT: Multiple-walled carbon nanotubes
- **CMF**: Carbon nanofibers
  - Surface or dispersed metal catalysts & reaction by-products
- **CNTs**: Carbon nanotubes

--

Potential Nano-specific Components of Risk Assessment of CNTs

- Close metric
  - Size & structure may influence dose response relationship compared to other materials
- Non-CNTs are not similar
- Non-CNTs may show different toxicity
- Nanoparticles may not exist at CNTs

- Coating & decoration: Particle characteristics, including hydrophobicity & low density, may alter dispersion, clearance, and retention
- Reactivity: Nano-size & structure may influence bioavailability, toxicity, and elimination
- Response: Nano-characteristics may affect mechanisms

--

CNT Occupational Exposure Data

<table>
<thead>
<tr>
<th>Material &amp; Process</th>
<th>Concentration: ppm</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWCNT in source</td>
<td>12–53</td>
<td>Maynard et al. 2004</td>
</tr>
<tr>
<td>MWCNT in source</td>
<td>37–40</td>
<td>A. S. N. 1998</td>
</tr>
<tr>
<td>MWCNT before &amp; after</td>
<td>642</td>
<td>K. D. 1998</td>
</tr>
<tr>
<td>CNT composite in encapsulation</td>
<td>8.1–1.9</td>
<td>McDonald et al. 2007</td>
</tr>
<tr>
<td>MWCNT composite post-synthetic</td>
<td>2.1–0.5</td>
<td>Raffo et al. 2006</td>
</tr>
</tbody>
</table>

*Data are from NIOSH, NIOSH Report 505.211

--

CNT Hazard and Risk Assessment

- **Qualitative approaches**: Use of Control Banding
  - Strategy: control chemical & physical properties
  - Comparison to similar processes
  - Relative ranking of processes

- **Quantitative Risk Assessment (QRA)**: Develop Exposure Limits
  - NOAEL, LOAEL, with uncertainty factors
  - Benchmark dose and exposure-attribute risk estimates

--

"Classic" Risk Assessment Paradigm (adapted from NRC 2005)

--

80
Example: Deriving Human-equivalent Dose (continued)

- Human working lifetime equivalent concentration = 
  Dose (human) / [gt (human) x (3.6 kg / 70 kg) x (1.8 cm x 2 cm)] 
  = 14.8 mg / (3.6 kg x 1.8 cm x 2 cm) 
  = 0.0001 mg/cm² (assumes same deposition fraction as rodent) 
  or, 
  = 1 mg/cm² as a 24 hour weighted average [TWA] concentration 
    before applying uncertainty factors of 10-15% / 
    Note: Assuming equal long exposure fraction in cat & human, 
    and so long duration

(3) Benchmark Dose Method

- Model dose-response relationships to determine the dose (BMD) associated with a specified level of response (P, 10%) 
  - BMD Benchmark dose - maximum biologically estimated 
  - BMDL Lower 95% confidence limit of the BMD 
  - (the BMDL is the point of departure (POD) to estimate risk at P = 0%)
  - Extrapolate BMDL to humans 
    - by accounting for species-specific differences in neurogenesis, 
      physiology, & revelations of aging 
    - Evaluate human exposure to characterize risk

Example: Extrapolating Rat BMDL to Humans

- Chronic respiratory inflammation [Lee et al. 1998] 
  - 10% BMDL 37 ng/kg bw/week 
  - Human-equivalent lung burden to rat BMDL 
    - Dose (human) = 
      Deposition in respiratory surface area (Human Retrofit) 
      X 3.5 (3.5 mg/kg/week) 
  - Note: Estimate the workplace airborne concentration that would result in this lung burden...

Example: Extrapolating Rat BMDL to Humans

- Human working lifetime equivalent concentration 
  - 0.1 mg/kg body weight / 70 kg x 0.0001 cm² / 70 kg x 150 cm² / 70 kg 
  - 14.8 mg/cm² (assumes same deposition fraction as rodent) 
  - or, 
  - 1 mg/cm² as a 24 hour weighted average [TWA] concentration 
    before applying uncertainty factors of 10-15% / 
    Note: Assuming equal long exposure fraction in cat & human, 
    and so long duration

Example: Extrapolating Rat BMDL to Humans

- Chronic respiratory inflammation [Lee et al. 1998] 
  - 10% BMDL 37 ng/kg bw/week 
  - Human-equivalent lung burden to rat BMDL 
    - Dose (human) = 
      Deposition in respiratory surface area (Human Retrofit) 
      X 3.5 (3.5 mg/kg/week) 
  - Note: Estimate the workplace airborne concentration that would result in this lung burden...

Example: Extrapolating Rat BMDL to Humans

- Human working lifetime equivalent concentration 
  - 0.1 mg/kg body weight / 70 kg x 0.0001 cm² / 70 kg x 150 cm² / 70 kg 
  - 14.8 mg/cm² (assumes same deposition fraction as rodent) 
  - or, 
  - 1 mg/cm² as a 24 hour weighted average [TWA] concentration 
    before applying uncertainty factors of 10-15% / 
    Note: Assuming equal long exposure fraction in cat & human, 
    and so long duration

Quantitative Risk Assessment Methods to Derive Recommended Exposure Limits for Inhaled Particles

<table>
<thead>
<tr>
<th>BreathingZone</th>
<th>Human</th>
<th>Recommended exposure limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indoor air</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outdoor air</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambient air</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respired air</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhaled air</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk Assessment Data & Information Needs — To Reduce Uncertainty & Improve Risk Estimation

- Develop validated models of CNT deposition and disposition in rodent and human lungs 
  - Determine long-term effects of CNT in the lungs and 
    other organs, including pneumonia & cancer 
  - More accurately predict long-term exposure; e.g., early effects on 
    lung diseases 
  - Evaluate human-equivalent lung response to those 
    observed in animal studies 
  - Compare CNT exposures in animal studies and 
    workplace, qualitative & quantitative

CNT Risk Management — Data & Information Needs

- Assess worker exposures 
  - to nanomaterials and other hazards 
    - by task 
    - by downstream users 
  - Determine sensitivity of sampling & analytical 
    methods 
  - Assess adequacy of exposure controls & 
    personal protective equipment 
  - Assess need for medical screening & surveillance
Summary - CNT Risk Assessment Case Study

- Standard methods for hazard and risk assessment using toxicology data are available and appear feasible.
- Short-term studies of various types of CNTs by various nodes in several rodent species & strains, indicate inhalation hazards.
- Toxicological data appear to be sufficient to develop initial risk estimates for mesothoracic lung impairment.
- Further data are needed for risk characterization, including workplace exposure assessment & control.
Background(1)

- This case study is about a topic relating to Japanese regulatory system, especially exposure assessment.
  (http://www.jniosh.go.jp/joho/nano/index_e.html)
  - Information document for attention
  - Less than 100nm at least one dimension of PM, even if only some part of size distribution is this size
  - Strict control is (strongly) recommended.
  - Ordinary risk assessment system for chemical substances and particulate matter is encouraged to introduce.
- This presentation is not reflecting the policy of Japanese MHLW.

Outline

- Risk assessment system in Japanese regulatory context for occupational setting.
  - Exposure assessment
  - Risk assessment
- CNT case study
  - Potential exposure
  - Uncertainties
  - EC analysis
- Conclusion

Statistical risk evaluation in Japanese administrative method

\[
\begin{align*}
\log E_{A1} &= \log M + 1.645 \log \sigma \\
E_{A1} &= 95\% \text{ value of concentration distribution} \\
M &= \text{geometrical mean, } \sigma &= \text{geometrical standard deviation} \\
\log E_{A2} &= \log M + 1.151 \log \sigma \\
E_{A2} &= \text{equivalent to arithmetic mean} \\
\end{align*}
\]

Constants 1.645 and 1.151 are determined empirically from the data for traditional PM.

Problem: spatial distribution of NM is same as traditional PM?

Statistical risk evaluation in Japanese administrative method

<table>
<thead>
<tr>
<th>Risk class of workplace</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$E_{Source} \leq E$</td>
</tr>
<tr>
<td>Class 1: well controlled</td>
<td>Class 1</td>
</tr>
<tr>
<td>Class 2: fairly controlled</td>
<td>Class 2</td>
</tr>
<tr>
<td>Class 3: severe control measures needed</td>
<td>Class 3</td>
</tr>
</tbody>
</table>

$E$: the administrative control value

$E_{Source} < E$: well controlled = risk very low
Concentrations in 95% of the area are lower than ACL

Class 1: well controlled = risk very low
Class 2: fairly controlled = risk low
Class 3: severe control measures needed

Problem: ACL and measured data necessary
CNT case study

Substance Identification

- Core composition: Carbon
- Size, shape: width 10 – 150 nm, length 1- 100 µm
- Impurities: depending on each MWCNT

Process dependent:
- Synthesis - raw materials, catalyst, by-products, products
- Handling - Products
- Maintenance - depending on the facilities

Manufacturers usually have information about what kind of substances are present.

Use Patterns

- Used for secondary batteries, composite, etc.
- Improving conductivity, durability, strength of plastics
- Production volume of CNTs in Japan (TORAY Research Center, 2008)
  - SWCNT: 100 kg/year
  - MWCNT(10-70 nm): 60 t/year
  - Carbon fiber (<150 nm): 60-70 t/year
- Problem: CNTs of width>100nm NM?

Occupational Exposure

- Processes of potential high-risk exposure
  - Synthesis, Maintenance, Packing/Weighing/Mixing
- Number of workers: not large
- Manual process
  - Duration of one process = duration of exposure
- Automated process
  - Duration of one process ≠ duration of exposure
- Metric
  - On-line: Mass, Size, Surface area
  - Off-line: Mass, Carbon amount (EC: Han, et al, 2008) by size selected sampling
  - Off-line: Morphology
  - Off-line: Counting number of fibers (Han, et al, 2008) depending on the shape of CNTs

Why do you measure exposure?

- For emission control and external exposure
  - Any metric applicable
  - Suitable for existing state of PM
    - Nano-particle, aggregates/agglomerates
- For internal exposure
  - What is dose metric?
  - Off-line method might be better for personal exposure

Occupational Exposure to MWCNT

<table>
<thead>
<tr>
<th>Process</th>
<th>Exposure</th>
<th>CNT</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesis</td>
<td>Closed</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Automated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>Manual</td>
<td>High</td>
<td>Soot, PM2.5, Metals, Vapors, nano-PM*</td>
</tr>
<tr>
<td></td>
<td>Automated</td>
<td>Medium</td>
<td></td>
</tr>
<tr>
<td>Packing/Weighing</td>
<td>Manual</td>
<td>Low</td>
<td>Ambient PM</td>
</tr>
<tr>
<td></td>
<td>Automated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>w/o work</td>
<td>ND</td>
<td>ND</td>
<td>- very low</td>
</tr>
<tr>
<td>Outside</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Nanoparticles generated from condensation of vapors

Uncertainties (1) Measurement

- The key uncertainties for exposure assessment
  - CNT’s major component is carbon - Sensitivity of analysis is lower than metal based PM.
  - Effect of background PM especially on off-line mass measurement and on-line method at low concentration
  - Difficulty in establishing a general method for exposure assessment of CNTs, because size, shape, impurity, etc are different for different processes or MWCNTs.
  - Agglomerates can brake into small PM by impaction at size-selected sampling.

- Practical solutions:
  - For MWCNT, Carbon is one of the best metric for off-line method.
  - Experienced hygienist, and person who knows production process are needed.
  - Collection particles by different principal (ex. Cyclone, DMA)
Uncertainties (2) Dose metric

The key uncertainties for exposure assessment
- What exposure metric associates dose or health effects?
- Most of toxicological studies evaluated dose with mass concentration and size (observed by electron microscopy).
- Also, surface area or number of particles.

Practical solution:
Several metric should be measured.
- Off-line data of mass, carbon and size are practical metric for both environmental and personal measurement.
- Time resolution is not good.
- Not suitable for personal exposure measurement
- Effects from background PM and shape of PM
- Surface area can be calculated from above data.

Examples of Carbon analysis

MWCNT (Sigma-Aldrich)
Width 110-170 nm, Length 5-9 µm
Method: IMPROVE (final 920 °C)

Amount of MWCNT can be estimated by EC3.
Sensitivity is better than mass measurement.
10 µg/m³ (1m³ sampling)
Background effect is smaller than mass.

Conclusions

- Hazard evaluation plays a key role for risk evaluation.
- Exposure can be measured with combination of several metrics. Dose might be estimated from measured data.
- Japanese risk assessment system for occupational setting is applicable, even when personal exposure cannot be measured, if the ACL is set.
- If a certain level of the ACL is preliminary set, the workplace environment can be evaluated.

Examples of ACL
Be: 0.002 mg/m³, Cd, Pb: 0.05 mg/m³, MWCNT: <0.1 ??
- To evaluate MWCNT exposure, EC3 is helpful for both environment and personal exposure measurement.
(3-4) Report from chair of CNT case study

CNT case studies

- CNT can be considered to have unique chemical identity in addition to nanoscale features
- Wide variations in structure, size, shape and chemistry (impurities) affecting hazard, exposure and risk
- Issue:
  - how to relate variations to risk?
  - What are the minimum differences that would make two CNT materials distinct?

CNT case studies (cont)

- Metrics for dose and exposure are determined by the mechanism of hazard (volume?)
- Critical need for comprehensive characterization in hazard and exposure studies
- Agglomerations/de-agglomeration issues are not resolved
- Synergistic effects in mixtures? Carriers?

CNT case studies (cont)

- Pro-active Risk Assessment
- Solutions:
  - Hazard-based: conduct tox studies – chronic?
  - Exposure-based: minimize exposure - hazard characterization? Measurements?
  - Mixed: extrapolation existing data – uncertainties?
- Interim RA; Tentative limits; re-assessments
ANNEX IV (BREAKOUT SESSIONS)

(0) Questions to Breakout Groups

### Session A - Addressing Current Risk Assessments

<table>
<thead>
<tr>
<th>Assessment Problem Formulation</th>
<th>Exposure - Public, Occupational &amp; Environmental</th>
<th>Hazard - Human Health</th>
<th>Ecological toxicity and Fate</th>
<th>Determining Risk and Linkage between Assessment and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify unique aspects (if any exist) that should be considered for risk assessment of nanomaterials. For example, are there nano-specific physical or chemicals properties (size, aggregation) that will require adjusting the approach to assessing risk.</td>
<td>Identify unique aspects (if any exist) that should be considered for risk assessment of nanomaterials. For example, are there nano-specific physical or chemicals properties (size, aggregation) that will require adjusting the approach to assessing risk.</td>
<td>Identify unique aspects (if any exist) that should be considered for risk assessment of nanomaterials. For example, are there nano-specific physical or chemicals properties (size, aggregation) that will require adjusting the approach to assessing risk.</td>
<td>Identify unique aspects (if any exist) that should be considered for risk assessment of nanomaterials. For example, are there nano-specific physical or chemicals properties (size, aggregation) that will require adjusting the approach to assessing risk.</td>
<td>Identify unique aspects (if any exist) that should be considered for risk assessment of nanomaterials. For example, are there nano-specific physical or chemicals properties (size, aggregation) that will require adjusting the approach to assessing risk.</td>
</tr>
</tbody>
</table>

### Session B - Resolving Uncertainties

<table>
<thead>
<tr>
<th>Assessment Problem Formulation</th>
<th>Exposure - Public, Occupational &amp; Environmental</th>
<th>Hazard - Human Health</th>
<th>Ecological toxicity?</th>
<th>Determining Risk and Linkage between Assessment and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can exposure pathways typically be eliminated or emphasized as part of the problem formulation?</td>
<td>Generally speaking should we employ the same predictive techniques used for examining exposure to chemicals?</td>
<td>Have other end points been identified which should be considered over and above those used for chemicals?</td>
<td>Have other end points been identified which should be considered over and above those used for chemicals?</td>
<td>Can risk management be used to compensate for a lack of data, or uncertainty?</td>
</tr>
<tr>
<td>What uncertainties are relevant to nano risk assessment?</td>
<td>What uncertainties are relevant to nano risk assessment?</td>
<td>What uncertainties are relevant to nano risk assessment?</td>
<td>What uncertainties are relevant to nano risk assessment?</td>
<td>What uncertainties are relevant to nano risk assessment?</td>
</tr>
<tr>
<td>How can research resolve outstanding risk assessment methodology issues?</td>
<td>How can research resolve outstanding risk assessment methodology issues?</td>
<td>How can research resolve outstanding risk assessment methodology issues?</td>
<td>How can research resolve outstanding risk assessment methodology issues?</td>
<td>How can research resolve outstanding risk assessment methodology issues?</td>
</tr>
</tbody>
</table>
(1) Assessment Problem Formulation

Assessment Problem Formulation

Chair: Richard Canady
Rapporteur: Iseult Lynch

What is Problem Formulation

• Establishment of the scope of RA
  – what the RA is used for determines how the RA is performed
• Ensuring that RA supports decision making
• Focus on quantitation

• Can Problem Formulation be generalised?
  – Not yet ready for generalisation, but moving towards QSARs
  – Standard setting assessments
  – Consideration of the benefits of the proposed use also

Q1: Unique nanospecific aspects for RA?

Generally, No, but RA should consider particulate-specific issues such as:

• Relevant physicochemical properties
• Surface properties and co-transport issues
• Reactivity & photocatalytic effects
• Comparison to bulk and ionic/molecular forms

Session A – Addressing Current Risk Assessments

Q2: Current RA Approaches

• Hazard, exposure, uncertainty
• Nothing nano-specific in terms of the RA approach
• RA process is a whole – cannot be performed separately – entry point may be
• If exposure is low, don’t need to perform RA (FDA)
• Thresholds – same issues as for all chemicals

Q3: Quantitative challenges specific to NPs

• Not nanospecific but include:
  – Determination of background levels

Nano-specific issues that emerged include:
  – Distributional aspects – n-dimensions (size, charge, coatings, biomolecule interactions etc.)
  – Impurities (could be tails of distributions)
  – Variability in time, sample representation, batch-to-batch
  – Mixture analysis – stabilizer / vehicles / matrix effects
  – Dispersant effects – OECD tests based on variety of dispersion protocols...
Q4: What concepts from case studies should be captured?
• Need to be able to generalise the data
• Lot more borrowing of data than usual in RA
• Lot more information available than commonly understood
• How much uncertainly are we willing to accept?

Q5: How to define Persistence / Bioaccumulation of NPs?
• Transport issue – co-transport & organ-specific
• Active versus passive transport
• Different biological fate mechanisms?
• How to measure bioaccumulation?
  – Octanol-water distribution?
  – Solubility / insolubility as critical decider
  – Challenges in measuring, but not nano-specific - Hand this issue to exposure group!!

3 Additional Issues for Nano-RA
• Need to determine appropriate dose metrics for nano – not mass!
• Monitoring / Modelling of NP fate & behavior
  - exposure models
  - quantitative uncertainly analysis
• Quantitative variability / reproducibility of NP characteristics
  – Matrix dependency (water quality, buffer, NOM etc.)
  – Time-dependent transformation
  – Distribution & statistical analysis of uncertainty.

Session B – Resolving Uncertainty
Q1: Can exposure pathways be eliminated?

- No!
- Need to consider end of life-cycle issues
- Dispersant effects (water composition, buffer, NOM etc.)

Q2: Nano-specific uncertainly factors?

- No!
- Nanoparticles are not more hazardous, just more uncertainty surrounding them to date!
- Use database uncertainty factors where there is a lack of data – a way of capturing uncertainly.

Q3: How can research resolve outstanding RA methodology issues?

- Need to focus on establishing an adaptive RA process
- Need to enable utilisation of QSARs as additional data becomes available
- Noted that ahead of the game on many nanomaterials!
(2) Exposure – Public, Occupational and Environment

Exposure – Public, Occupational, and Environmental
Breakout Session Summary
Group 2
Session Leader: Paul A. Schulte
Rapporteur: Rosalind Volpe

1. • It is important to understand the difference between exposure conditions in animal studies and exposure conditions in the workplace when conducting occupational exposure assessments.
   • For example, dispersed aerosols may be measured in animal studies and agglomerates may be measured in workplace studies.

2. • It is possible to assess workplace exposure based on the airborne behavior of nanoparticles. This involves using a cascade impactor and diffusion sampler.
   • However the instrumentation is only available for area samples, not for personal breathing zone samples which we need. This is because of the lack of appropriate sampling equipment to capture enough air volume.

3. • While we can measure exposure, we don’t know what the best metric is.
   • Different metrics will be good for different purposes.
   • One size does not fit all.

4. • There is value in developing a decision logic for exposure assessment based on particle morphology.

5. • Although we have conventional methods to measure large particles in the environment, we may need different methods to measure nanoparticles.
Comparison of sampling on larger particles with nanomaterials

<table>
<thead>
<tr>
<th></th>
<th>Large particles</th>
<th>Nanomaterials</th>
</tr>
</thead>
<tbody>
<tr>
<td>size</td>
<td>500 nm - 10 μm</td>
<td>100 nm or less</td>
</tr>
<tr>
<td>respirable</td>
<td>Respirable + inhalable</td>
<td>respirable</td>
</tr>
<tr>
<td>sampling</td>
<td>personal/area</td>
<td>Personal/area</td>
</tr>
<tr>
<td>equipment</td>
<td>cyclone, impactor, filter</td>
<td>DMAS, CPC, OPC, APS, ELPI, filter</td>
</tr>
<tr>
<td>background</td>
<td>Usually not measured</td>
<td>measured</td>
</tr>
<tr>
<td>concentration</td>
<td>not usually analyzed</td>
<td>analyzed</td>
</tr>
<tr>
<td>size distribution</td>
<td>not usually analyzed</td>
<td>analyzed</td>
</tr>
<tr>
<td>TEM/SEM</td>
<td>not usually analyzed except asbestos analysis</td>
<td>often performed</td>
</tr>
<tr>
<td>process episode</td>
<td>not usually checked</td>
<td>checked and recorded</td>
</tr>
<tr>
<td>Emission source identification</td>
<td>easy</td>
<td>not easy to identify</td>
</tr>
</tbody>
</table>

6.
- There is a lack of sufficient published exposure data for exposure characterization of nanoparticles.
- It may be possible to assemble a database of published results that could stimulate development of instrumentation and sampling protocols.
- Building an exposure database of unpublished data may be more difficult due to factors such as author or corporate reluctance. However, using historical data as in the case of nanosilver and unpublished data when available is important.

7.
- Taking a lifecycle approach will help in identifying where to focus exposure assessments.
- We need to determine whether nanomaterials will move through different environmental media in different ways from their bulk counterparts.
(3) Hazard – Human Health

What’s in the Health Effects Toolbox and What Needs to be Added

The basic principles apply
- Routes of exposure – target organs
- Properties – hazard, behavior

Endpoints
- Need to investigate whether we need nano-specific endpoints
- May need to use satellite groups to identify early effects

Test methods (e.g., OECD) seem to work
- Sample preparation and dosimetry approaches need development
- Need to determine if refinements are needed to current tiered testing approaches

In vitro methods
- Validation, acceptability
- Link to risk context
- Relationship to in vivo methods

Histopathology approaches

Characterization
- Agreement on phys-chem parameters and how to measure them is needed.
- Particle-size distribution – percentage of "nano" in distribution
- When to (re) characterize material during testing program
PbPk/ADME

Detection and labeling of particles; what tracers will work
Lower limits of detection
How properties such as solubility and composition impact ADME

Mixtures

Secondary contaminants picked up by particles
Mixtures as part of nano formulation

Toxicogenomics and Computational methods:

Database
QSAR
Phys property – biological property relationships

Epidemiology approaches

Ability to use existing data
Tracking materials
Disease- v. exposure-driven approaches

Bioavailability

Mass-balance
Clearance

How to address background for hazard ID
Establishing Properties – Effects relationships (e.g., for bridging)
Translocation models (e.g. to identify size cut-offs)

"Rules" on determining the appropriate test substance; e.g., as produced or as transformed in environmental media and/or biological systems?

When do "nano effects" matter?

Comments from Plenary

- May be overstating applicability of existing in vitro methods
- Use of mode-of-action information (NAS Tox Testing in 21st Century) ought to be included in S06 report.
- Epidemiology approaches could be given greater focus
  - Developing worker cohorts
  - Setting up exposure registries
  - Look back at historical data on particles
- Look for opportunities to bridge to existing data
- Presence v. effects. Many statements from audience that presence of particles in organs (e.g., the brain) is an adverse "effect."
- How to relate mass to other particle properties is an area for study.

Our group's top four:

- Focus testing approaches and the building of databases on enabling and advancing modeling, QSAR, computational, etc approaches that advance our ability to categorize and otherwise efficiently group materials for decision making. Key to this is linking material properties to effects.
- Understanding particle kinetics and generally the particle nature of nanomaterials
• Identifying whether there are nano-specific endpoint considerations
• Advancing epidemiological approaches, including taking advantage of existing data and developing biomonitoring techniques.

SUMMARY

As the session notes reflect, there was general agreement within the human health break-out group that we already have a “toolbox” of testing approaches that can be applied to nanomaterials. However, in most instances modifications or augmentations will need to be made to those approaches to accommodate nanoparticle testing. There was also agreement that while much focus is on toxicology, exposure and epidemiology are important areas of research that also deserve significant attention.
(4) Ecological Toxicity and Fate

The Big Picture

1. Behaviour of nanomaterials in various media.
   - If not enough information is available then assume the worst case, i.e. the nanomaterial does not agglomerate but is monodispersed.

2. Persistence
   - Use current information to predict dissolution of nanomaterials.

3. Transportation/Distribution
   - Use information on behaviour and persistence to determine.

4. PEC
   - Expressed as: amount IN media/amount OF media
   - Metrics is an issue. A justification for why a particular metric was used.
   - The PEC could include various forms of the nanomaterial, i.e. single particle, agglomerate, ions etc.

5. Transformation Products and Impurities
   - Nanomaterials may also act as carriers for other substances.

6. Bioaccumulation
   - No methods for quantitative prediction of bioaccumulation. Qualitative judgments based on information on bulk material or actual data on similar substances.

7. Effects
   - Base effects assessment on empirical data on nanomaterial or analogue data.
   - No predictive capacity.
   - Use of acute data to predict chronic toxicity is not possible, as uncertainty factors are not available.
   - Instead of uncertainty factors, report a margin of safety, i.e. the difference between the effects concentration and the PEC.

Identify unique aspects (if any exist) that should be considered for risk assessment of nanomaterials?
   - Use similar methods as non-nano substances but conduct a complete evaluation of media effects (pH, humic acid, hardness, etc.) for every nanomaterial.
   - Consider how long it stays nano and in which nano form, i.e. nanomaterials will agglomerate or dissolve.

What approaches will we now use to address RA of NMs – should assessments be hazard, risk (uncertainty), exposure centric?
• Use the same risk paradigm.
• For hazard centric, we must have a comprehensive data set addressing acute and chronic endpoints of all likely impacted trophic levels. Unlike will have sufficient information to rely on this approach.
• For risk (uncertainty) centric, use of a margin of safety approach. Most frequently employed approach.
• Exposure centric, this approach is most appropriate for very limited and possibly regulated use.

Are there qualitative challenges specific to nanomaterials that should be considered at this stage of analysis? For example, what are the appropriate metrics for reporting effect on organisms (PNEC).
• The most appropriate metric is yet to be determined. The metric used should be justified in each case.
• The possible metrics are the mass, surface area, number of particles or some combination of these.
• The PNEC units must match the PEC units.

What concepts from the case studies should be captured for this stage of analysis?
• "Trojan horse" carrier concept. Arsenic adsorbed to the surface of a nanomaterial traveling across a cell membrane.
• Nanomaterials are going to distribute in an organism or the environment in way that is different from the bulk material.

How can information from bulk materials or other nanomaterials contribute to an assessment?
• Can contribute to a weight of evidence argument.
• May be used to determine general trends.
• Cannot be used instead of information specific to the nanomaterial.

How or can we define persistence and bioaccumulation in the context of nanomaterials?
• Dissolution kinetics are important and can be predicted.
• Persistence can be defined as persistence of effect, if the effect is retained or increased as result of transformation.
• In terms of bioaccumulation, forms of the nanomaterial are important, i.e. agglomerates versus ions, however, we have no quantitative means to predict the tendency to bioaccumulate. Therefore empirical data is required or information on bioaccumulation of bulk or ionic form. In the absence of these types of data, only the use of qualitative judgment remains.
What 3 additional questions or issues that were not addressed in the case studies should be considered by OECD in a discussion of risk assessment methods for nanomaterials?

Ecological toxicity?
1. Chronic toxicity. Acute toxicity test results have been reported as if that completed the story on the toxicity of the nanomaterial.
2. Bioaccumulation. Potential for bioaccumulation of nanomaterials was not addressed.
3. Transformation, possibly resulting in an increase in toxicity
4. Lack of transparency, although these assessments are completed by regulatory agencies, there is no mechanism for peer review. No opportunity for risk assessments to be critiqued by industry or academia.

Have other end points been identified which should be considered over and above those used for chemicals?
- Lower trophic levels have been hypothesized as being the most sensitive to nanomaterials. Effects on organisms such as nycornizal fungi and plants should be investigated.

Should we employ nano-specific uncertainty factors?
- Currently no, use of margin of safety approach could be employed.
- In the future, empirically determined uncertainty factors for nanomaterials could replace the chemical specific uncertainty factors.

What are some outstanding topics that could be researched to address risk assessment methodology issues?
1. Comparison of acute to chronic data for all trophic levels.
2. Toxicity as a function of size of the nanomaterial.
3. Disposition of nanomaterials (ADME) in all trophic levels.
4. Identification of the most sensitive species, potentially different from the current fish, daphnia, algae paradigm.
6. Toxicity metrics providing the best comparability and regulatory relevance.
(5) Determining Risk and Linkage between Assessment and Management

OECD Risk Assessment Workshop
Washington, DC
September 18, 2009

SG6 Break-out Group 5

Determining Risk and Linkage between Assessment and Management

+ What do we do / can we do NOW

Session A (Addressing current RA’s):

Question 1, 2 & 4 Answer 1

Question 3 Answer 2

Question 5 Answer 3

Question 6 Answer 4

Question 7 Answer 5

Answer 1

Preface: Debated who “we” was in context of question…. ….resolved to try to focus primarily on “Public Authorities”

• No need to adjust “approach” per se, but……
  ➢ acknowledge there are unique “attributes” in nano context
  ➢ PSD, Form (structural), Functional characteristics
  ➢ acknowledge that today, there are varying degrees of
    “uncertainty” → drive varying responses of “precaution”
  ➢ May drive conservative RMM’s until proven otherwise
  ➢ All “factors” taken in to account can directly drive
    RMM’s w/o a comprehensive RA
  ➢ important consideration today…..”Public Perception”
  ➢ Ion/Radical Dissolution and/or Translocation important
  • Correlations from bulk to nano are useful / good starting point
    ➢ May or may not be predictive or useful in RA context. OK
    ➢ Can inform (case by case / material by material bases):
      ➢ a “potency” position on nano form
      ➢ possibilities for short-term / long-term effects
      ➢ …then may translate in to initial RMM’s
    ➢ Understandings of “modes of action” may be gleaned
      from bulk forms (material dependent)
      ➢ different end points may require different references

Silver Case Study       CNT Case Study
Ion dissolution        Nothing apparent

Supports Case by Case Assessment

Answer 2

• Acknowledged need for metric to support ID of RMM’s
  ➢ Avoid different metrics if possible
  ➢ Concordance from RA to RMM’s is important
  ➢ Difficulty in recognizing a clear metric today, but….
    ➢ “mass” based metric could be used, with understanding
      of limitations (Particle # also discussed as possible):
      ➢ Detection Limits (are high) and Methods,
        Material specificities, non-Nano interferences
      ➢ Strength in WP setting, less clear on HH/Env media
  ➢ Benchmark Dose vs. Uncertainty Factors
  • Use what we have and can make work (“what’s reasonable”)
  ➢ Continue to improve methodology over time
  ➢ Avoid being paralyzed by inability to fully characterize or
    monitor reliably.

Answer 3

• Correlations from bulk to nano are useful / good starting point
  ➢ May or may not be predictive or useful in RA context. OK
  ➢ Can inform (case by case / material by material bases):
    ➢ a “potency” position on nano form
    ➢ possibilities for short-term / long-term effects
    ➢ …then may translate in to initial RMM’s
  ➢ Understandings of “modes of action” may be gleaned
    from bulk forms (material dependent)
  ➢ different end points may require different references

Silver Case Study       CNT Case Study
Ion dissolution        Nothing apparent

Supports Case by Case Assessment

Answer 4

• Question focused on persistence and bioaccumulation only
  • Defining P and/or B for a “nano” is no different than
    bulk or general chemical means
  • Translocation is an important additional consideration
  • Effects of course may be different, which can lead to
    differing RMM’s
Answer 5
Focused on “Issues”, NOT “questions” (as instructed!)

1. RE: Legacy (“old”) data cited in Case Studies
   Data Quality analysis would better inform “usability” in RA
   [e.g. Klimisch Ranking / Threshold of Acceptability]
2. Case Study emphasis was health “exposure” relevant……
   they could be further enhanced with a focus on Envmnt
3. Case Studies lacked “bridge” to RM/RMMs.

Session B (Resolving Uncertainties):

Question 1  Answer A
Question 2  Answer B
Question 3  Answer C

Answer A
• YES……
  ➢ it is used in practice today…..not Nano unique

Answer B
• NO……
  ➢ The issue is not unique to nano
    ➢ The threshold is “data availability” (or lack thereof) which is
      NOT “nano” specific – applies broadly
    ➢ Over time, “new” data may drive/require adaptations to
      RM/RMM’s, whether nano or not

Answer C
• This question may be a bit out of scope given focus on
  RM/RMM’s, but……
• Targeted research toward:
  ➢ establishing / closing gaps in “modes of action” by “nano” may
    help drive methodologies/improvements
  ➢ adoption/adaptation of socio-economic benefit analyses in to
    overall “nano” RA context
  ➢ continuing work of the form described by Mike Davis
    ➢ very helpful long term
  ➢ extrapolation of data from animals to humans
  ➢ Further refining “multi-criteria” decision analyses
ANNEX V (PARTICIPANTS LIST)

Participants list for WPMN: Workshop on Risk Assessment in a Regulatory Context
Washington D.C., United States
16 September 2009 – 18 September 2009

Australia/Australie

Dr. Janith WICKRAMARATNA  
Senior Regulatory Scientist  
Department of Health and Ageing  
National Industrial Chemicals Notification and Assessment Scheme (NICNAS)

Canada/Canada

Mr. Andy ATKINSON  
Head, Nanotechnology Science and Regulations  
New Substances Division, Science and Risk Assessment Directorate  
Environment Canada

Lie CHEN  
Chemist / Evaluator  
Nanotechnology Section  
Health CANADA

Myriam HILL  
Section Head  
Nanotechnology Section  
Health CANADA

Ms. Deborah RATZLAFF  
Environmental Assessment Unit  
Health Canada
Germany/Allemagne

Professor Mario GÖTZ  
Chemical Product Safety Toxicology  
Federal Institute for Risk Assessment

Japan/Japon

Dr. Masashi GAMO  
Research Scientist  
Research Institute of Science for Safety and Sustainability (RISS)  
National Institute of Advanced Industrial Science and Technology (AIST)

Ms. Mariko OGASAWARA  
Senior Researcher  
Japan National Institute of Occupational Safety and Health (JNIOSH)

Dr. Makoto OHNISHI  
Chief of Analytical Chemistry  
Analytical Chemistry Section, Division of Experimental Toxicology  
Japan Bioassay Research Center, Japan Industrial Safety and Health Association

Korea/Corée

Hye-Lim KIM  
Researcher  
Kyung Hee University

Professor Young Rok SEO  
Professor  
Department of Pharmacology  
Kung Hee University School of Medicine

Dr. Ilje YU  
Professor  
Hoseo University
Netherlands/Pays-Bas

Mr. Eric BLEEKER
RIVM - SEC

Mr. Cees DE HEER
Expertise Centre for Substances (RIVM-SEC)

United States/États-Unis

Dr. Linda ABBOTT
US Department of Agriculture

Nancy BECK
Toxicologist/ Risk assessor
Office of Management and Budget

Janet CARTER
Risk Assessor
Occupational Safety and Health Administration

Mr. Mike DAVIS
US Environmental Protection Agency

Suzanne FITZPATRICK
DHHS/FDA/OC/OSHC
Steve FROGGETT  
*AAAS Science & Technology Policy Fellow*  
*Office of Scientific & Technical Affairs*  
*Foreign Agricultural Service, USDA*

Dr. Maureen GWINN  
*ORD*  
*US EPA*

Paul HOWARD  
*National Center for Toxicological Research*

Dr. Eileen KUEMPEL  
*Senior Research Health Scientist*  
*National Institute for Occupational Safety and Health*

Mr. Jeff MORRIS  
*National Program Director for Nanotechnology*  
*US Environmental Protection Agency*

Dr. Vladimir MURASHOV  
*Senior Service Fellow*  
*NIOSSH/CDC/DHHS*

Mr. David O'CONNOR  
*Directorate of Standards and Guidance*  
*OSHA*

Carlos PENA  
*Food and Drug Administration*  
*US Department of Health and Human Services*
David ROSTKER  
*Policy Analyst*
*Office of Management and Budget*

Dr. Phil SAYRE  
*Associate Director*
*Office of Pollution Prevention & Toxics*
*US Environmental Protection Agency*

Valentine SCHAEFFER  
*Risk assessor*
*Occupational Safety and Health Administration*

Dr. Paul SCHULTE  
*Director of Education and Information Division*
*National Institute for Occupational Safety and Health*

Dr. Loretta SCHUMAN  
*U.S. Department of Labor*

Mr. Treye THOMAS  
*Toxicologist, Director for Health Services*
*U.S. Consumer Product Safety Commission*

Mr. Jim WILLIS  
*Director, Chemical Control Division*
*US Environmental Protection Agency*
Mr. Jack DE BRUIJN

Head of Unit - Risk Management
Joint Research Centre - Institute for Health and Consumer Protection
European Chemicals Agency - ECHA

Ms. Marita LUOTAMO

ECHA, European Chemicals Agency

Maila PUOLAMAA

DG Enterprise and Industry
European Commission

Mr. Henrik LAURSEN

Administrator
DG ENV, D1 Chemicals Unit
European Commission

Iseult LYNCH

School of Chemistry & Chemical Biology
University College Dublin

Mr. Philippe MARTIN

Principal Administrator
Directorate General Health and Consumer Protection
European Commission

Mr. Sazan PAKALIN

IHCP
European Commission
Thailand/Thaïlande

Junpen MEKA-APIRUK  
Minister Counsellor  
Office of Science and Technology  
Royal Thai Embassy

Business and Industry Advisory Committee (BIAC)/Comité consultatif économique et industriel (BIAC)

Dr. Richard CANADY  
McKenna Long & Aldridge LLP

Shaun CLANCY  
Director - Product Regulatory Services  
Evonik Degussa Corporation

Mr. William GULLEDGE  
Managing Director  
Chemical Products & Technology Division  
American Chemistry Council

Mr. Mark HERWIG  
Manager, Chemical Management Programs  
Corporate Environmental Programs  
General Electric Company

Mr. Matthew JAFFE  
Crowell & Moring LLP

Mr. Nils KRUEGER  
Evonik Degussa AG/Industriepark
Dr. Robert LANDSIEDEL  
*Product Safety*  
*BASF AG 2470*

Dr. Frédéric LUIZI  
*R&D General Manager*  
*Nanocyl SA*

Dr. Brian MAYES  
*Toxicology*  
*General Electric*

Dr. Jacques RAGOT  
*HSE Manager*  
*Bayer Material Science*

Dr. Gisela STROPP  
*Global Project Manager EI & IC*  
*Toxicology*  
*Bayer AG*

Dr. Rosalind VOLPE  
*Executive Director*
Environmental NGO/Environmental NGO

Dr. Caroline BAIER-ANDERSON
Health Scientist
Environmental Defense (NGO)

International Organization for Standardization (ISO)/Organisation internationale de normalisation (ISO)

Mr. Chris BELL
Sidley Austin Brown & Wood LLP

OECD/OCDE

Ms. Mar GONZALEZ
Administrator, Nanosafety
ENV/EHS
OECD

Other/Autre

Dr. Norris ALDERSON
Association Commissioner for Science
FDA

Dr. Elizabeth CASMAN
Department of Engineering & Public Policy
Carnegie Mellon University

Dr. Raymond DAVID
Manager, Toxicology
BASF - The Chemical Company

Dr. James DELATTRE
Nanohorizons Inc.
Dr. Georges GRAY

Professor Mary GULUMIAN
Head: Toxicology and Biochemistry Section
National Institute for Occupational Health

Dr. David HASSENZAHL
UNLV Env Studies

Dr. Murray HEIGHT
Chief Technology Officer
HEIQ MATERIALS AG

Dr. Kristen KULINOWSKI
Centre for Biological and Environmental Nanotechnology
Rice University

Dr. Margaret MACDONELL
Argonne Nat Lab

Mrs. Pat RIZZUTO
Chemical Regulation Reporter
BNA
Dr. Jo Anne SHATKIN  
Managing Director  
CLF Ventures, Inc.

Mr. Ron WHITE  
Univ of Bloomberg SPH -Epidemiology  
Johns Hopkins University