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No. 21

REPORT OF THE WORKSHOP ON RISK ASSESSMENT OF MANUFACTURED NANOMATERIALS IN A REGULATORY CONTEXT

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REPORT OF THE WORKSHOP ON RISK ASSESSMENT OF MANUFACTURED NANOMATERIALS IN A REGULATORY CONTEXT

IOMC
INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
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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.

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FOREWORD

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

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

Based on the conclusions and recommendations of the Workshop [ENV/JM/MONO(2006)19] it was recognised as essential to ensure the efficient assessment of manufactured nanomaterials so as to 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.

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THE WORKING PARTY ON MANUFACTURED NANOMATERIALS (WPMN)

1. The Working Party on Manufactured Nanomaterials[1] 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[2], TUAC[3], 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

[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[4]. 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 (TiO_2); 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

[4] http://www.sra.org/docs/SRA_Nano_prog_9_9.pdf

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 focussing 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 focussing 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.

5. Mechanisms of bioaccumulation and determination of methods for predicting bioaccumulation.

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.

	DAY 1 *September 16 – starting at 10h00*	
	Registration	
1.	**Welcome Remarks**	*Mar Gonzalez, OECD* *Jo Anne Shatkin, SRA*
2.	**Introduction**	*Andy Atkinson, Canada, Co-chair SG6*
	Chair: Andy Atkinson	
3.	**Overview of WPMN activities**	*Andy Atkinson*
4.	**Presentation from SRA**	*Jo Anne Shatkin, SRA*
5.	**Presentation from industry perspective**	*William Gulledge* *American Chemistry Council, BIAC*
6.	**Presentation from regulatory perspective**	*Maila Puolamaa* *European Chemicals Agency (ECHA)*
7.	**Presentation from NGO perspective**	*Caroline Baier-Anderson* *Environmental Defense*
	LUNCH	
	Chair: Jo Anne Shatkin	
8.	**TiO2 case study 1**	*Shaun Clancy, Evonik, BIAC*
9.	**TiO2 case study 2**	*Mike Davis, US EPA*
11.	**TiO2 discussants**	*1. Robert Landsiedel (BASF, BIAC)* *2. Carlos Peña (US FDA)* *3. Margaret MacDonnell (SRA)*
12.	**TiO2 general discussion**	*All*
	BREAK	

	Chair: William Gulledge, American Chemistry Council, BIAC	
13.	**Nano-Ag case study 1**	*Murray Height, HeiQ Materials Ag*
14.	**Nano-Ag case study 2**	*Mario Goetz, Germany*
15.	**Nano-Ag case study 3**	*Eric Bleeker, Netherlands*
16.	**Nano-Ag discussants**	*1. James Delattre (NanoHorizons, Inc.)* *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	
18.	**CNT case study 1**	*Gisela Stropp, Bayer Schering Pharma*
19	**CNT case study 2**	*Eileen Kuempel, US NIOSH*
20.	**CNT case study 3**	*Mariko Ogasawara, Japan NIOSH*
21.	**CNT discussants**	*1. To be determined* *2. Jim Willis (US EPA)* *3. Rick Canady (SRA)*
	BREAK	
22.	**CNT general discussion**	*All*
23.	**Introduction to breakout sessions**	*Andy Atkinson*
	LUNCH	
24.	**Breakout session**	*All*
	BREAK	
25.	**Breakout session**	*All*
	DAY 3 *September 18 – starting at 09h00*	
	Chair: Andy Atkinson	
26.	**Plenary discussion**	*All*
	BREAK	
27.	**Path forward**	*All*
28.	**Closing remarks**	

ANNEX II (GENERAL PRESENTATIONS)

(1-1) Over view of WPMN activities

OECD Work on the Safety of Manufactured Nanomaterials

Environment, Health and Safety Division
Environment Directorate
OECD
September 2009

1

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)

2

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.

3

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

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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

Project 1 and 2: OECD Database on Manufactured Nanomaterials to Inform and Analyse EHS Research Activities

- Objective: 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
- Co-Chairs: Australia, Germany and Japan
- Status:
  - Publicly launched in April 2009
  - A comprehensive compilation document "EHS Research Strategies on MNs" was published in May 2009

6

Project 3: Safety Testing of a Representative Set of MNs

- Objective: to agree and test a representative set of manufactured nanomaterials (MNs) using appropriate test methods.
- Co-Chairs: United States and European Commission
- Status:
  - Launched Sponsorship Programme (November 2008) to test representative MNs for a base set of endpoints

7

Project 4: MNs and Test Guidelines

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

8

Project 5: Co-operation on Voluntary Schemes and Regulatory Programmes

- Objectives:
  - To identify common elements of the various information gathering initiatives, in place or planned.
  - 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.
- Chair: Canada
- Status:
  - Completed initial comparisons of information gathering.
  - Issued questionnaire (August 2008) on regulatory regimes and how they address information requirements

9

Project 6: Co-operation on Risk Assessment

- Objective: to evaluate risk assessment approaches for manufactured nanomaterials through information exchange and identify opportunities to strengthen and enhance risk assessment capacity.
- Co-Chairs: Canada and Germany
- Status:
  - Reviewing existing risk assessment schemes and their relevance to nanomaterials

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Project 7: The Role of Alternative Methods in Nano Toxicology

- Objective: to address the use of alternative test methods and testing strategies (in parallel with the Sponsorship Programme) t
- Chair: Germany and European Commision
- Status:
  - Reviewing alternative test methods which may be applicable to manufactured nanomaterials
  - Developing guidance material on alternative methods in the Sponsorship Programme

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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

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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)

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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

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Implementation - Two Stages

Stage 1

Agreement on:

i) A list of MNs (based on materials which are now, or soon to enter, commerce) ; and

ii) 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

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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

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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)

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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

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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)

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	Lead sponsor(s)	Co-sponsor(s)	Contributors
Fullerenes(C60)	Japan, US		Denmark, China
SWCNTs	Japan, US		Canada, France, Germany, EC, China, BIAC
MWCNTs	Japan, US	Korea, BIAC	Canada , Germany, France, EC, China, BIAC
Silver nanoparticles	Korea, US	Australia, Canada, Germany, Nordic Council of Ministers	France, EC, China, Netherlands
Iron nanoparticles	China	BIAC	Canada, US, Nordic Council of Ministers
Carbon black			Denmark, Germany, US
Titanium dioxide	France, Germany	Austria, Canada, Korea, Spain, US, EC, BIAC	China, Denmark, Japan, UK
Aluminium oxide			Germany, US, Japan
Cerium oxide	US, UK/BIAC	Australia, Spain	Denmark, Germany, Switzerland, EC, Japan, Netherlands
Zinc oxide	UK/BIAC	Australia, Spain, US, BIAC	Canada, Denmark, Japan, Germany, Netherlands
Silicon dioxide	France, EC	Belgium, Korea, BIAC	Denmark, Japan
Polystyrene			Austria, Korea
Dendrimers		Spain, US	
Nanoclays			Denmark, US, EC

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

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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

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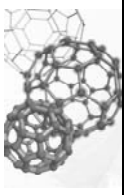
(1-2) Critical Issues

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

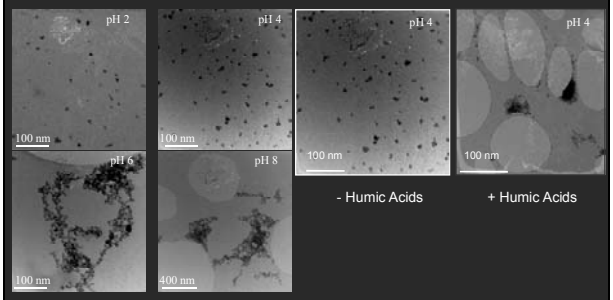
↓

High aspect ratio (>20μm length <3μm width, biopersistent)
Fibre / pathogenicity paradigm:
function of shape, size, persistence and physiological interaction

↓

Read across to other fibres e.g. CNT

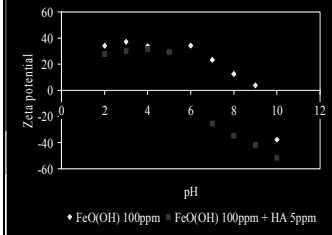
How: Key Issues for Environmental Risk Assessment
1. Complexity of behaviour in natural systems



Agglomeration of Iron oxide nanoparticles

Images courtesy of Jamie Lead and Mohammed Baalousha, University of Birmingham

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



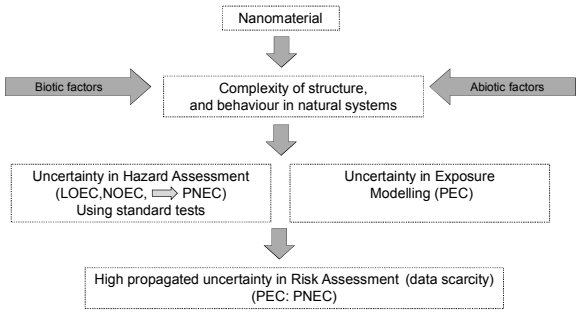
Abiotic factors include

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, ecotox) – SG4 should consider

2. Complexity and data scarcity leads to risk uncertainty



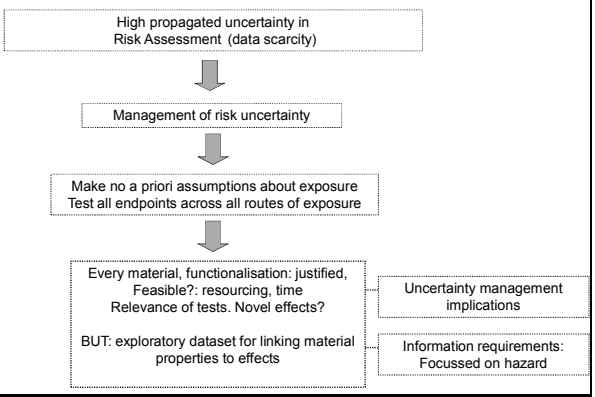
Critical issue 2. Complexity
Leads to risk uncertainty

: potentially high (data scarcity)
: probably not uniform across nanomaterials

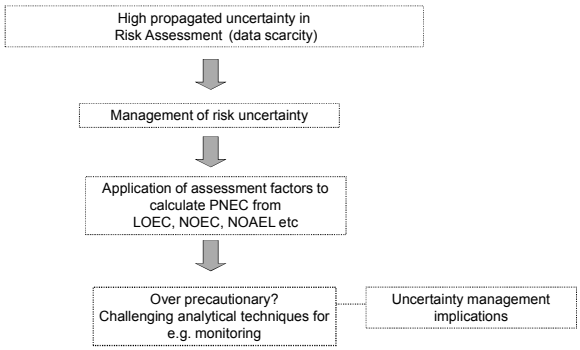
Critical issue 3.

How do we manage high risk uncertainty?
Strategy?

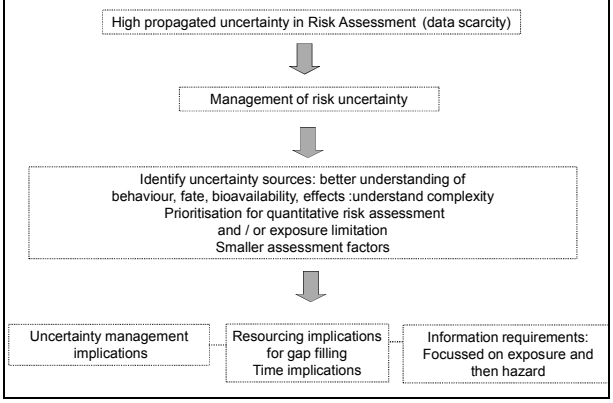
Managing risk uncertainty: make no a priori assumptions about exposure
Due to high exposure uncertainty



Managing risk uncertainty: approaches from 'conventional chemicals'



Managing uncertainty in risk assessment – exposure driven risk assessment



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

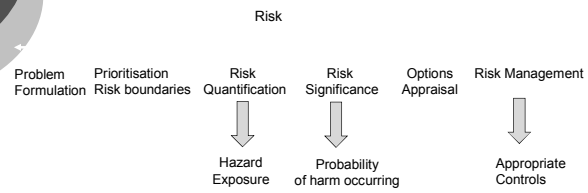
Speciation, bioavailability

Source–pathway–receptor connectivity

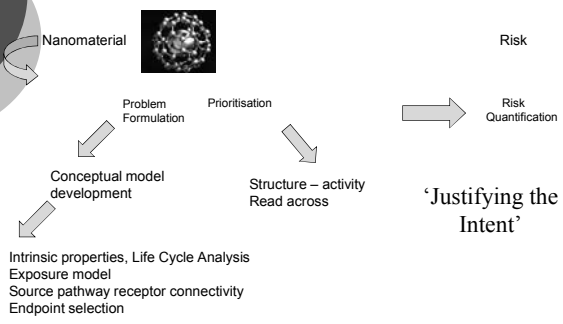
Endpoint selection

Boundaries for quantitative risk assessment

Problem formulation for risk assessment of nanomaterials



Tiered risk assessment and problem formulation



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 (WPMN) 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

2

Society for Risk Analysis

27 year old professional society

2000 member international organization

Interdisciplinary – breadth of expertise in risk specialty groups for disciplines

In December 2006 formed the Emerging Nanoscale Materials Specialty Group (EMNMS) with 75 founding members.

3

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.

4

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

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Nano Risk Analysis:

***Advancing the Science for Nanomaterial Risk Management* Sept 2008, 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?

6

Nano Risk Analysis: *Advancing the Science for Nanomaterial Risk Management*

Workshop Co-Sponsors

National Science Foundation · Johns Hopkins University · NanoGram · inbt · American Chemistry Council · SRA National Capital Area Chapter Society for Risk Analysis · SRA nano · HESI · EVONIK · BASF · SERDP · WCEE · NIOSH National Institute for Occupational Safety and Health

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Nano Risk Analysis:
Advancing the Science for Nanomaterial Risk Management

Repeated themes

- Considerable uncertainty in understanding of nano-specific 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

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Nano Risk Analysis: *Advancing the Science for Nanomaterial Risk Management*

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

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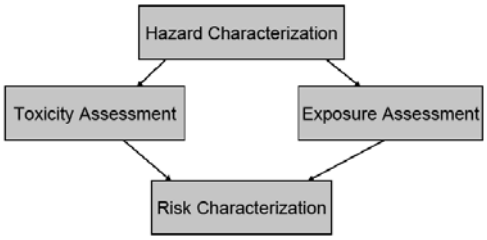
Framing the Issues for Health/ Environmental Risk Assessment of Engineered Nanoscale Materials



(NRC 1983)

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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?

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NanoRisk Analysis:
Advancing the Science for Nanomaterial Risk Management

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.

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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

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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?

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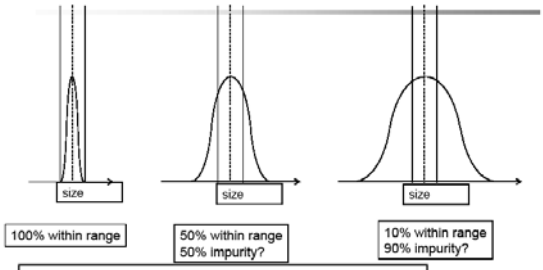
Framing the Issues: Dose Response for Nanotechnology

- 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

18

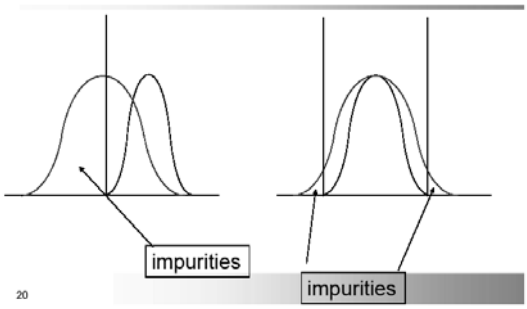
Size tolerances and "purity"



What does 99% pure mean for a nanomaterial?

19

When are populations different for extrapolation purposes?



20

Framing the Issues: Characterizing Risks of Nanomaterials

- Several deliberations conclude that current frameworks 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?

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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

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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

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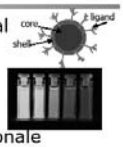
Nanoscale particles vs. Nanotechnology



- 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?

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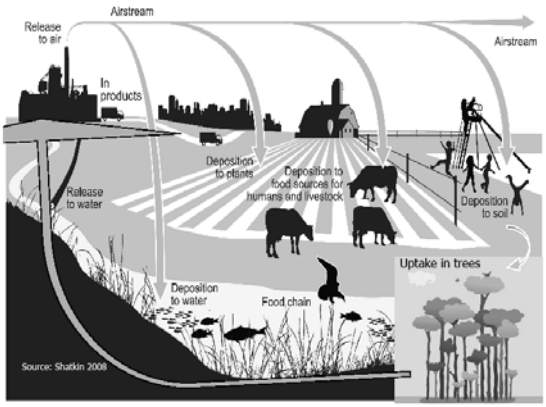
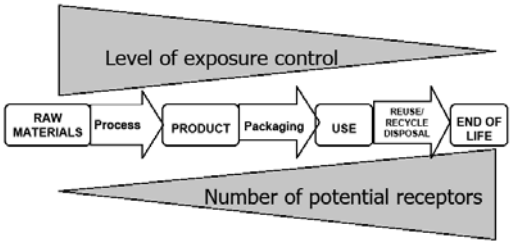


In the product life cycle, environmental exposures are less easily assessed and managed



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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)

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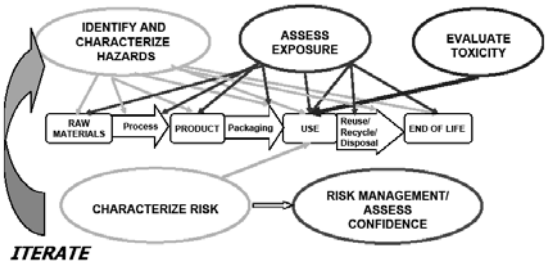
NANO SLCRA

Adaptive Streamlined Life Cycle/ Risk Assessment Framework for Nano Materials (Shatkin 2008)



ITERATE

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NANO SLCRA

Case Example Nanocrystalline Cellulose for Packaging Application

Analysis

Hazard Identification
- No nanomaterials in raw materials
- Extract released during isolation process
- Uncontained disposal practices for Nano-containing wastes
- Product contains unbound crystalline particles
- Post application recycling distributes nanoparticles

Exposure Assessment
- Material production process not enclosed
- Packaging process is very dusty
- Use exposes consumers to nanoparticles
- Disposal practices create secondary human exposure pathways

Recommendations

Toxicity Assessment
- Material characterization
- Design protocol to assess toxicity of packaging product in vivo and in vitro

Inhalation and Dermal Exposures
- Develop tracking system
- Work with solutions not particles
- Contain process releases
- Provide PPE/training for handling production materials
- Conduct training
- Develop MSDS
- Assess use/disposal exposures

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Comprehensive Environmental Assessment (CEA)

CEA ≈ LC + RA

LC = Product Life Cycle framework
RA = Risk Assessment paradigm

See: Davis, J. M. "How to assess the risks of nanotechnology: learning from past experience" *J. Nanosci. Nanotechnol.* 7(2): 402-409, 2007

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Comprehensive Environmental Assessment (CEA)

Life Cycle Stages	Environmental Pathways	Fate & Transport	Exposure	Effects
Feedstocks	Air	Primary contaminants	Biota	Eco-systems
Manufacture	Water			
Distribution	Soil	Secondary contaminants	Human populations	Human Health
Storage	Food chain			
Use				
Disposal				

Source: adapted from Davis, J. M. and Thomas, V.M. Annals N.Y. Academy of Science 1076: 498-515, 2006

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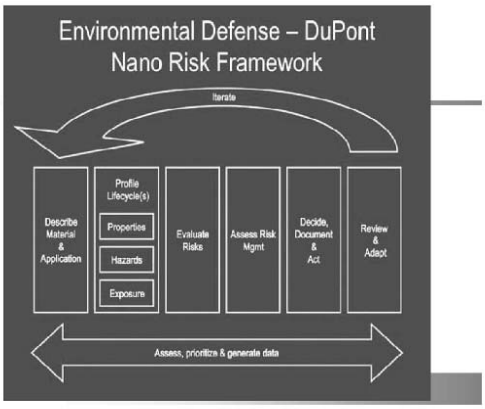

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In Summary

- 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

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Thank You Very Much!

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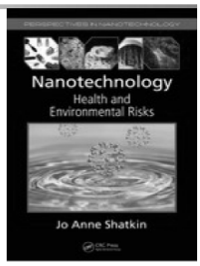

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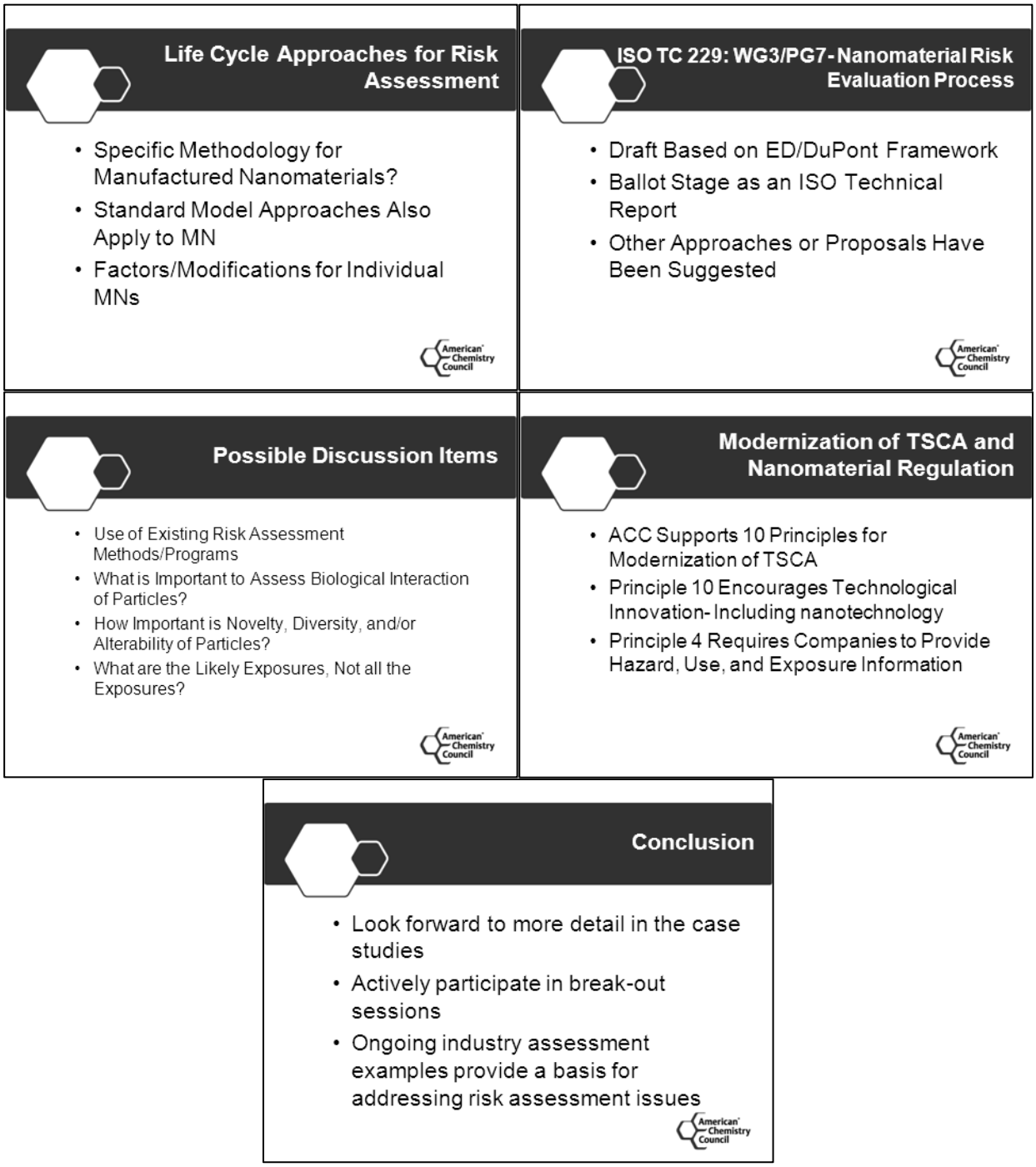
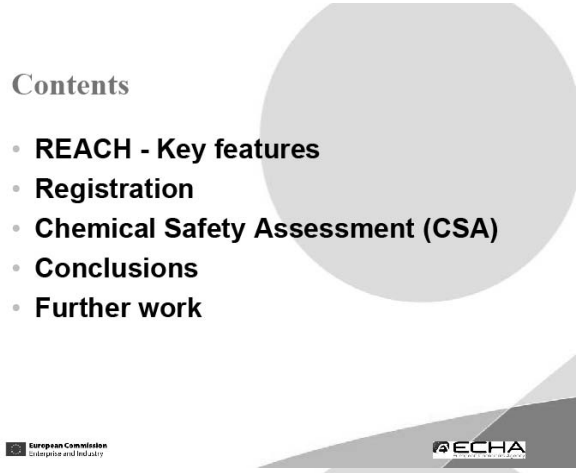
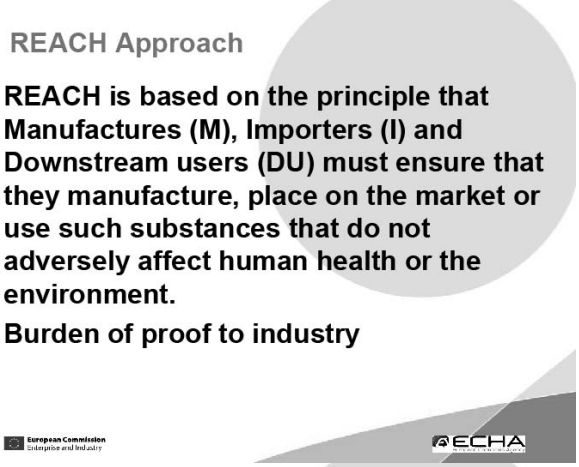
(3) Presentation from industrial perspective

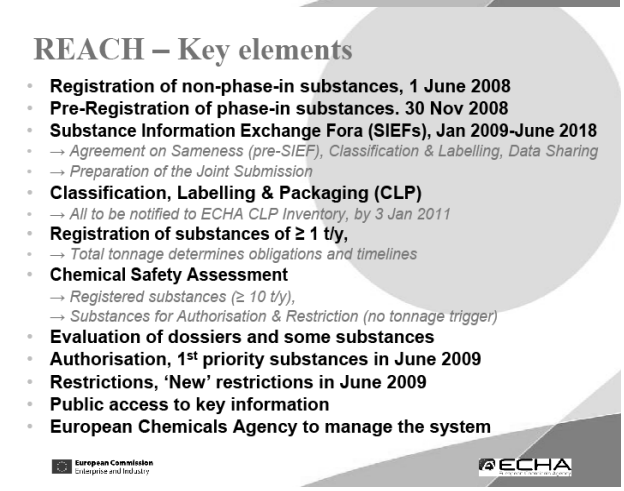

Product Stewardship and Responsible Care®
• Assess Uses, Exposures, Toxicity
• Prioritize Risks
• Conduct Risk Characterizations on Priorities (risk, uses, life cycle)
• Prepare Product Stewardship Summary (By 2012)
American Chemistry Council
OECD WPMN SG6: Risk Assessment
• BIAC participation since 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- less so on environmental assessment
– Issues identified: complexity of nanoparticles in natural systems; management of uncertainty; and problem formulation for nano risk assessment
American Chemistry Council
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 characterisation, although the magnitude of uncertainty may not be uniform across different nanomaterials".
American Chemistry Council
Securing the Promise of Nanotechnologies: Towards Transatlantic Regulatory Cooperation
• September 2009 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
American Chemistry Council
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
American Chemistry Council
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
American Chemistry Council

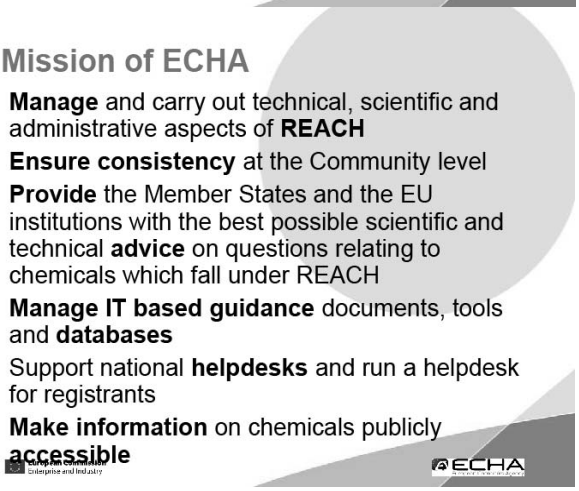

Life Cycle Approaches for Risk Assessment
• Specific Methodology for Manufactured Nanomaterials?
• Standard Model Approaches Also Apply to MN
• Factors/Modifications for Individual MNs
American Chemistry Council
ISO TC 229: WG3/PG7 - Nanomaterial Risk Evaluation Process
• Draft Based on ED/DuPont Framework
• Ballot Stage as an ISO Technical Report
• Other Approaches or Proposals Have Been Suggested
American Chemistry Council
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?
American Chemistry Council
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
American Chemistry Council
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
American Chemistry Council

(4) Presentation from regulatory perspective









Communication in REACH

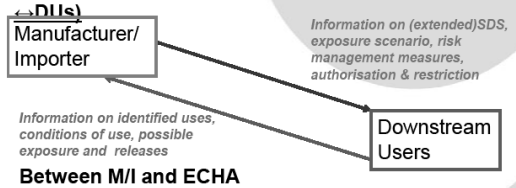
Betweeen suppliers (M/I ↔ M/I)

- *Pre-SIEF: Agreement of the sameness of a substance*
- *SIEF: Classification and labelling, Data sharing & Joint submission*

Between users (DU ↔ DU)

- *Uses and Conditions of use*

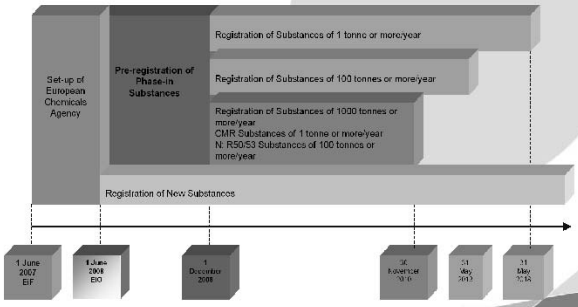
Between Suppliers and Downstream Users (M/I ↔DUs)



Between M/I and ECHA

- Pre-Registration, Registration, Evaluation and Authorisation/Restriction

REACH Timelines



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 (CASG Nano) to advice on NM issues**

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 nanoapplications*
- *Information needs*

Other issues of relevance

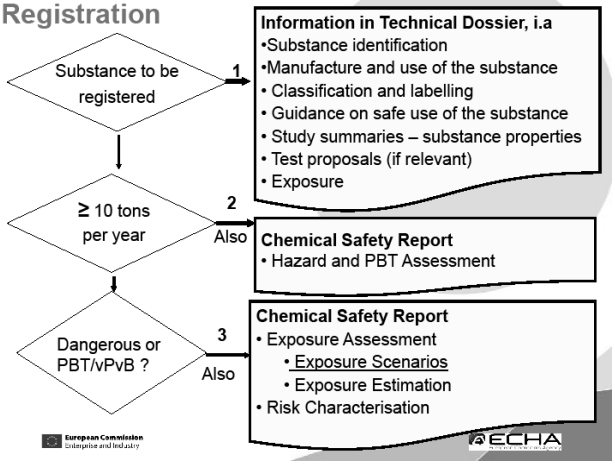
- *Test methods and test guidelines (JRC, FPs, OECD-WPMn)*
- *Member State activities*
- *Other*

Outputs: Nanomaterials in REACH, December 2008

Registration

- **Who: Manufacturers and Importers of ≥ 1 t/y**
  - *Tonnage triggers are based on the total volume*
  - *Chemicals 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**

Registration



REACH – Substance identification

Name or other identifier of each substance

- *Name(s) in the IUPAC nomenclature or other international chemical name(s)*
- *Other name(s) (usual name, trade name, abbreviation)*
- *EINECS or ELINCS number*
- *CAS name and CAS number*
- *Other identity (if available)*

Information related to molecular and structural formula of each substance

- *Molecular and structural formula*
- *Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)*
- *Molecular weight or molecular weight range*

Composition of each substance

- *Degree of purity*
- *Nature of impurities, including isomers and by-products*
- *Precentage of (significant) main impurities*
- *Nature and order of magnitude (…ppm, …%) of any additives (e.g. stabilising agents or inhibitors)*
- *Spectral data (ultra-violet, infra-red, nuclear magnetic resonance or mass spectrum)*
- *High-pressure liquid chromatogram, gas chromatogram*
- *Description of analytical methods or the appropriate bibliographical references (substances and impurities and additives) This information shall be sufficient to allow the methods to be reproduced)*

CSA:Hazard Assessment – Info. requirements

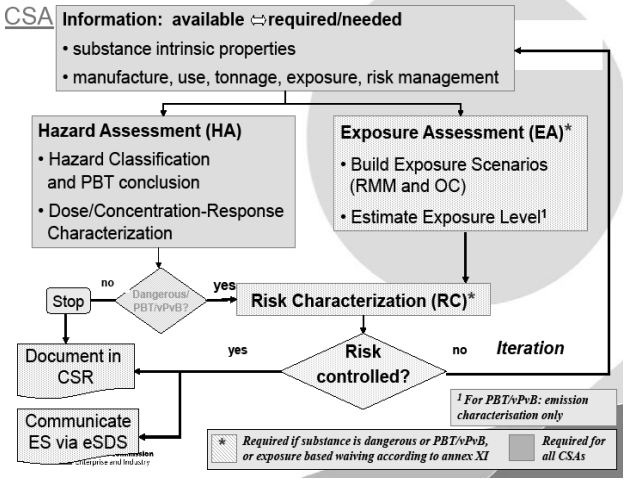
	Physico-chemical properties	
1-10t prioritised	• State of the substance at 20° C, 101.3 kPa • Melting point • Boiling point • Relative density • Vapour pressure • Surface tension/surface activity • Water solubility	• Partition coefficient n-octanol/water • Flash point • Flammability • Explosive properties • Self ignition temperature • Oxidising properties • Granulometry
≥100t	• Stability in org. solvents, identity of rel. degradation products	• Dissociation constant • Viscosity

CSA: Hazard Assessment – Info. requirements

	Health	Environment
1-10t prioritised	• *In vitro* skin and eye irritation • Skin sensitiation • *In vitro* mutagenicity • Acute toxicity (one route)	• Acute aquatic toxicity – Daphnia • Biodegradation – biodegradability and hydrolysis • Acute aquatic toxicity – Algae
10-100t	• *In vivo* skin and eye irritation • Further *in vitro* mutagenicity • Sub acute toxicity (28 days) • Reproductive toxicity screen	• Acute aquatic toxicity – Fish • Activated sludge • Adsorption/desorption screening
100-1000t	• Further mutagenicity tests • Sub-chronic toxicity (90-days) • Further reproductive toxicity tests	• Long-term aq. toxicity Daphnia and fish • Further degradation and fate/behaviour • Short-term effects on terrestrial organisms
> 1000t	• Further mutagenicity tests • Carcinogenicity • Chronic toxicity • Further reproductive toxicity tests	• Further degradation and fate/behaviour studies • Long-term effects on terrestrial organisms

OECD-WPMN Sponsorship Programme

	Additional information compared to REACH	
Phys. – chem. properties	• Basic morphology • Description of surface chemistry • Known catalytic activity • Agglomeration/aggregation • Crystalline phase • Dustiness • Crystalline size • Representative TEM picture(s)	Specific surface area Zeta potential (surface charge) Surface chemistry Photocatalytic activity Pour density Porosity Redox potential Radical formation potential Dispersion stability in water
Toxicity	• Phototoxicity	



Build Exposure Scenarios

Initial Exposure Scenarios

- **Short title**
- **Operational conditions (OC)**
- **Risk management measures (RMM)**

Final Exposure Scenarios

- **Short title**
- **Operational conditions (OC)**
- **Risk management measures (RMM)**

If risk not demonstrated to be controlled

Decisions by M/I

- **Refine Hazard Assessment**
- **Refine Exposure Estimate**
- **Modify RMM or OC**
- **Advise against use**

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 DMELs (Derived Minimal Effect Levels)
- Comparing exposure levels to derived no-effect levels (DN(M)ELs)
- Populations (workers, consumers, humans exposed via the environment) by routes of exposure
- Cover all end points (including phys-chem: explosivity, flammability, oxidising potential)

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 – 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)

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 dosemetrics needed
  - exposure assessment methods need review
  - no clear view on environmental effects
  - case-by-case assessment

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

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

Cal Baier-Anderson
Environmental Defense Fund

OECD Workshop on Risk Assessment of Manufactured Nanomaterials in a Regulatory Context
September 16-18, 2009
Washington D.C.

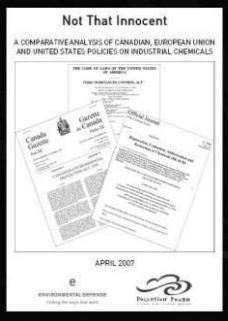
Overview:
What is Important to EDF?

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

2

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?



www.environmentaldefense.org/documents/6653_HighHopesLowMarks.pdf

3

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

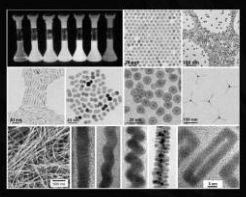


Photo from: Dmitri Talapin web page, http://chemistry.uchicago.edu/fac/talapin.shtml

4

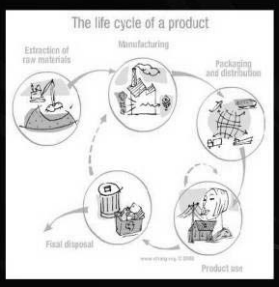
Source of Frustration:
Still not Playing with a Full Deck

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

5

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



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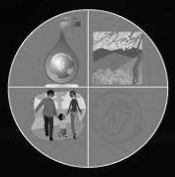
Lifecycle Pitfalls

- Oversimplification

Energy efficiency + Toxic Waste ≠ Green Product

- Understand green tradeoffs

e.g., decreased hazard vs. greater water use



www.bostonherald.com

7

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

8

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

9

Hazard Considerations

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

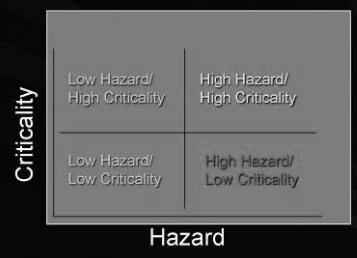
10

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

11

Weighing Hazard



12

Exposure Considerations

- Notable failures in exposure assessment decreased trust in risk assessment
  - Brominated flame retardants, Perfluorinated chemicals, Bisphenol A
- 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***

13

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

14

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

15

Some NM Applications may be Reasonably Safe…

- No claims without data!
- Need publicly available assessments before market

16

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?

17

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

Photo credit: Albany Nano Tech http://www.siteselection.com/ssinsider/incentive/IBMs-NY-investment.htm

18


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
19

ANNEX III (CASE STUDY PRESENTATIONS)

(1) TiO2 case study

(1-1) Presentation from BIAC

Risk Assessment Considerations for a Low Hazard Material

Shaun F. Clancy, Ph.D.
September 16, 2009

EVONIK INDUSTRIES

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.

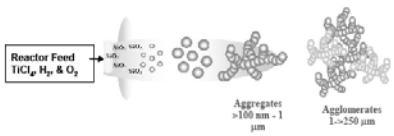
It has been manufactured for over 35 years and the manufacturing process has not changed significantly during that time.

The manufacturing process is based on the flame hydrolysis of Titanium Tetrachloride.

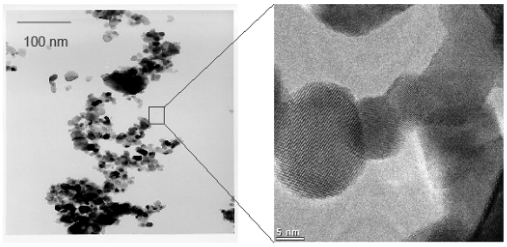
Key Physical Properties

- "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 m^2/gm

Particle Growth



TEM of P25



TME HRTEM

"Nano before Nano was Big!"

"Farbe & Lacke" April 1949

Known Application Areas

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

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
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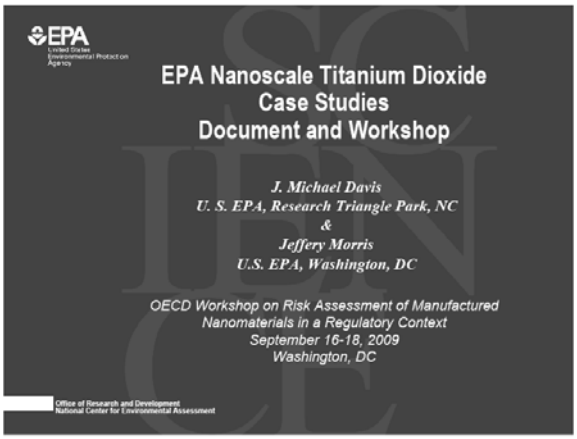
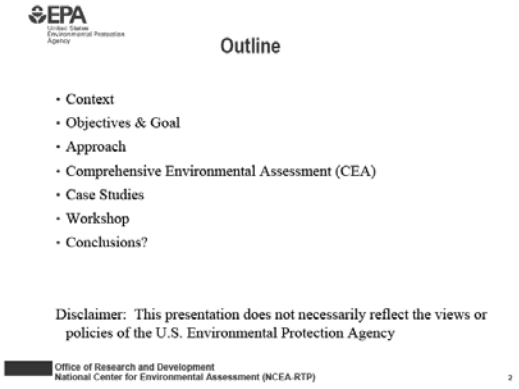
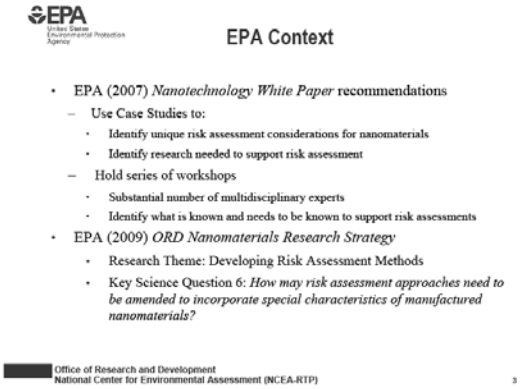
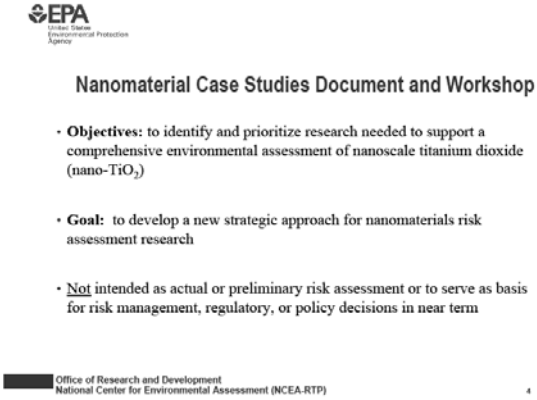
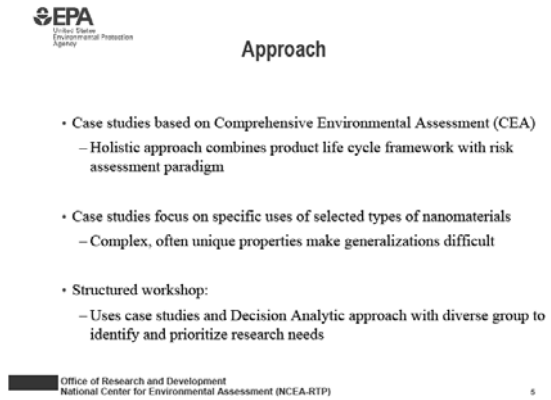
(1-2) Presentation from US EPA

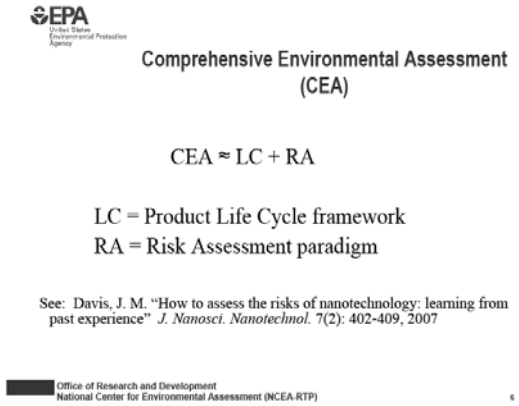


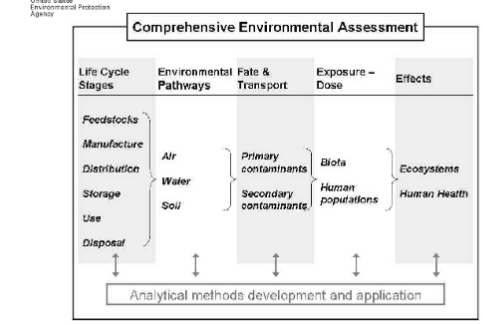












Adapted from Davis (2007), Davis & Thomas (2006)

Case Studies

- Selected by EPA internal workgroup, based on:
  - "Nano-ness"
  - EPA-relevance
  - Data availability
  - Exposure potential
  - Both human and ecological effects
- Specific uses of nano-TiO_2 with overlapping but different product life cycles:
  - CS1: Drinking water treatment to remove arsenic
  - CS2: Topical sunscreen

Nanomaterial Case Studies: Nanoscale Titanium Dioxide in Water Treatment and Topical Sunscreen (External Review Draft)

www.epa.gov/ncea

- Team effort
- Contents:
  - Introduction (including characterization, analytic methods)
  - Product life cycle stages
  - Fate and transport
  - Exposure-dose
  - Effects:
    - Ecological
    - Human health
  - Appendices
- Each chapter has list of questions (research/information needs):
  - To be refined by workshop participants and reviewers
  - Starting point for prioritization process

Nanomaterial Case Studies: Nanoscale Titanium Dioxide in Water Treatment and Topical Sunscreen (External Review Draft)

www.epa.gov/ncea

- Number of Questions (research / information needs) related to:
  - Characterizing nano-TiO_2: 11
  - Product life cycle stages: 26
  - Fate and transport: 18
  - Exposure-dose: 18
  - Effects:
    - Ecological: 13
    - Human health: 11
- Total: 97 (reviewers may add to or modify these)

Chapter 2: Life Cycle Questions

Feedstocks

2.1-1. Are certain feedstocks more relevant to producing nano-TiO_2 specifically for water treatment or sunscreen applications?

2.1-2. What contaminants, nanoscale and larger, might be released, and in what quantities, in relation to the procurement and processing of feedstocks for nano-TiO_2?

Manufacturing

2.2-1. How do various manufacturing processes for nano-TiO_2 affect their physicochemical properties?

2.2-2. How are manufacturing processes likely to evolve with increasing demand for nano-TiO_2?

2.2-3. Are certain manufacturing processes used specifically for nano-TiO_2 as a water treatment agent or as topical sunscreen?

2.2-4. What waste products or other by-products, both nanoscale and larger, might be released, and in what quantities, for nano-TiO_2 manufacturing processes?

2.2-5. Where is nano-TiO_2 manufactured? What is the potential for general population exposure to nano-TiO_2 in these areas?

Chapter 2: Life Cycle Questions (continued)

Distribution and Storage

2.3-1. How is nano-TiO_2 shipped (i.e., what are the relative frequencies for shipments in bulk, paper bags, or drums, or by truck or rail)? How far is it shipped? In what quantities?

2.3-2. Are data available or can they be collected or estimated for accident rates and routine product releases associated with various modes of shipping and storage? To what degree could best practices reduce such occurrences?

2.3-3. How is nano-TiO_2 stored (e.g., in warehouses, sunscreen manufacturing plants, and water treatment facilities)?

2.3-4. Does the use of "ventilated paper bags" increase the possibility of accidental spillage during shipment and storage? Are any guidelines available on whether protective packaging (e.g., additional polyethylene lining) is warranted?

2.3-5. Could vermin breach storage containers and contribute to environmental releases or become part of an environmental exposure pathway?

2.3-6. Would prolonged storage in adverse or less than ideal climates (e.g., cold or humid environments) alter nano-TiO_2 characteristics and behavior?

2.3-7. How much nano-TiO_2 could be released under various routine and accidental scenarios of distribution and storage?

Chapter 2: Life Cycle Questions (continued)

Use

2.4-1. To what extent is nano-TiO_2 used or could be used for either drinking water or waste water treatment? Are data available (e.g., volume of water currently treated in the United States for arsenic, amount of nano-TiO_2 needed to treat a given volume of water) that would permit an estimate of potential use?

2.4-2. Which water treatment processes use or would use nano-TiO_2 and in what quantities? Would the type of process depend on the size of a treatment facility or the size of the population served, or both?

2.4-3. What percentage of the nano-TiO_2 would settle out in floc 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 biofilm or corrosion development, despite the implementation of control practices. Would the presence of nano-TiO_2 influence the bacterial biofilm community or the occurrence of corrosion?

(Continued next slide)

Chapter 2: Life Cycle Questions (continued)

Use (continued)

2.4-5. What is the total quantity of nano-TiO_2 used in topical sunscreen products in the United States and worldwide?

2.4-6. What is the maximum quantity and frequency of personal sunscreen use in relation to season, geographic location, demographics, and other variables?

2.4-7. How much nano-TiO_2 enters the environment under different scenarios and conditions of sunscreen use (e.g., ambient air and water temperature, swimming, bathing)? Under what conditions would nano-TiO_2 be released from the sunscreen matrix?

Chapter 2: Life Cycle Questions (continued)

Disposal

2.5-1. How much residual nano-TiO_2 is present in packaging of the primary material or derived products? How is such packaging disposed of?

2.5-2. If nano-TiO_2 were to become much more widely used and produced at a much higher volume, would packaging and shipping methods of nano-TiO_2 change? If so, how would such change affect the potential release and exposure during transport, storage, and disposal?

2.5-3. In water treatment, how are filter materials and associated waste/waste water containing nano-TiO_2 disposed of or recycled?

2.5-4. How are large quantities of sunscreen (e.g., sub-par batches rejected during manufacturing) handled?

2.5-5. How much nano-TiO_2 is present in sunscreen containers that are discarded? Are there any circumstances where such discarded product could enter a microenvironment at significant levels?

Workshop

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

Workshop (continued)

- Decision analytic method (Nominal Group Technique) to rank priority research needs:
  - Equitable
  - Interactive
  - Independent judgments
- Identify and prioritize research needs for:
  - specific applications of nano-TiO_2
  - nano-TiO_2 regardless of application
  - nanomaterials generally

Workshop (continued)

- First of series / iterative process
- Conducted under aegis 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

1-1. To evaluate nano-TiO_2 (in these or other applications) or to compare products containing nano-TiO_2, is further standardization or refinement of terminology needed? If so, is such an effort underway and/or what terminology is most important to standardize?

1-2. Have the properties of nano-TiO_2 in different applications been adequately characterized? If not, is the problem that methods are not generally available or that existing methods have not been widely applied? If new methods are needed, what properties should they measure?

1-3. Which coatings, dopings, carriers, dispersants, and emulsion types are most prevalent in different applications of nano-TiO_2?

1-4. What are the potential implications (e.g., in terms of physical and chemical properties) of differences in the composition and mineralogy of different forms of nano-TiO_2 (e.g., rutile and anatase)?

1-5. How do coatings applied for different purposes (e.g., to disperse particles or to decrease photocatalysis) interact or affect other properties of nano-TiO_2?

Chapter 1: Characterization Questions (continued)

1-6. What factors determine whether and to what extent aggregation or agglomeration of nano-TiO_2 occurs?

1-7. Are data available that indicate the level of agglomeration or aggregation or dispersion of nano-TiO_2 in specific products? If so, what do the data show?

1-8. Is there a difference between the opacity of nano-TiO_2 aggregates and conventional TiO_2 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 flow fractionation (FFF) be used for characterization of particle size and elemental 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

3-1. What are the relative contributions of different stages of the life cycles of water treatment and sunscreen products to environmental levels of nano-TiO_2 and associated contaminants in air, water, and soil?

3-2. How do specific physicochemical properties, including particle surface treatments and aggregation/agglomeration, affect the fate and transport of nano-TiO_2 in various environmental media?

3-3. Are available fate and transport models applicable to nano-TiO_2? If not, can they be adapted, or are new models required?

3-4. Is information on environmental fate and transport of other substances available that might provide insights applicable to nano-TiO_2?

3-5. If nano-TiO_2 production were to increase greatly, the packing and transport methods are likely to be changed as well. How would this affect the fate and transport of nano-TiO_2?

3-6. How might nano-TiO_2 affect the fate and transport of metals and other potentially toxic substances in water or other environmental media?

Chapter 3: Fate & Transport Questions (continued)

3-7. What is the bioavailability of nano-TiO_2 in land-applied sludge to both terrestrial and aquatic organisms? Is bioavailability likely to change when nano-TiO_2 is incorporated into sludge and is allowed to "age" (in-situ weathering)?

3-8. What effect, if any, do coatings, dopings, carriers, dispersants, and emulsion types have on biopersistence and bioaccumulation?

3-9. Can the photocatalytic properties of nano-TiO_2 cause other unintended substances to form, for example, degradation products, in various environmental media?

3-10. Will nano-TiO_2 affect the efficacy of other major elements of water treatment processes (e.g., chemical disinfection, the coagulant concentration necessary for effective organics removal)?

3-11. What influence could other drinking water contaminants, including arsenic, have on the chemical properties or behavior of nano-TiO_2?

3-12. Irradiated photocatalytic nano-TiO_2 is potentially biocidal and antimicrobial. What is the potential for interactions of nano-TiO_2 with microbes needed in water treatment systems?

EPA United States Environmental Protection Agency

Chapter 3: Fate & Transport Questions (continued)

3-13. What are the key environmental factors (e.g., pH, natural organic matter type and concentration, temperature) that facilitate or hinder nano-TiO_2 stability in the aqueous environment? Would humic acids or other common constituents or contaminants in water undergoing treatment affect the fate, including agglomeration/aggregation properties, of TiO_2?

3-14. What is the impact to nutrient and metals cycling and microbial diversity when sludge with nano-TiO_2 is applied to soils?

3-15. How do sunscreen ingredients affect nano-TiO_2 fate and transport?

3-16. Can agglomeration/disagglomeration in the environment be predicted on the basis of physical properties of the particle, for example, size, shape, or coating?

3-17. What is the likelihood that nano-TiO_2 in biosolids will become part of the food web and ground water contamination?

3-18. What is the potential for plant uptake of nano-TiO_2 from contaminated soil and irrigation water?

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National Center for Environmental Assessment (NCEA-RTP) 25

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Chapter 4: Exposure-Dose Questions

4-1. Which sources, pathways, and routes pose the greatest exposure potential to nano-TiO_2 for biota? …for humans?

4-2. What is the potential for biota and human (both occupational and general population) exposure to secondary contaminants (e.g., waste or transformation products) associated with the entire life cycle of water treatment or sunscreen applications of nano-TiO_2?

4-3. Do particular species of biota and populations of humans have greater exposure potential (e.g., high-end exposures due to unusual conditions or atypical consumption)? In particular, do children get a higher exposure and/or dose?

4-4. What is the total population that could be exposed to nano-TiO_2 via drinking water? …via topical sunscreens?

4-5. Approximately how many workers are involved in nano-TiO_2 production, distribution, and use?

4-6. What concentrations, routes, frequencies, and durations characterize worker exposures to nano-TiO_2 across the life cycle and within certain stages (e.g., manufacturing)?

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Chapter 4: Exposure-Dose Questions (continued)

4-7. What management practices exist to control occupational exposures to nano-TiO_2?

4-8. What personal protective equipment do workers use at the various life cycle stages of nano-TiO_2 applications? How effective is such equipment in controlling exposures by all routes?

4-9. Are occupational monitoring methods available or in place for all relevant stages of the life cycle for nano-TiO_2 applications?

4-10. Are available methods adequate to characterize nano-TiO_2 exposure via air, water, and food? What properties of nano-TiO_2 should be included in such exposure characterizations?

4-11. Given the potential for greater uptake of certain substances in the presence of nano-TiO_2, should monitoring and exposure studies include a suite of substances that might interact with nano-TiO_2?

4-12. What happens when nano-TiO_2 is trapped in the stratum corneum and the dead skin flakes off? Is there a potential for dead-skin nano-TiO_2 to settle around households, or be inhaled? How much might accumulate after a day (or a few days) in the sun (and numerous reapplications)?

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Chapter 4: Exposure-Dose Questions (continued)

4-13. Since nano-TiO_2 may increase the uptake of other pollutants, such as arsenic, would nano-TiO_2 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, if any, exposure models have been evaluated for applicability to nano-TiO_2?

4-15. Which physiologically-based pharmacokinetic models are optimal for understanding absorption, distribution, and elimination of nano-TiO_2 in humans?

4-16. 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?

4-17. What is the potential for nano-TiO_2 to transfer to or accumulate in the food web and cause adverse effects on ecological receptors?

4-18. Nano-TiO_2 has been shown to attach to the surfaces of algae and fish as well as bioaccumulate in fish. Does nano- TiO_2 biomagnify?

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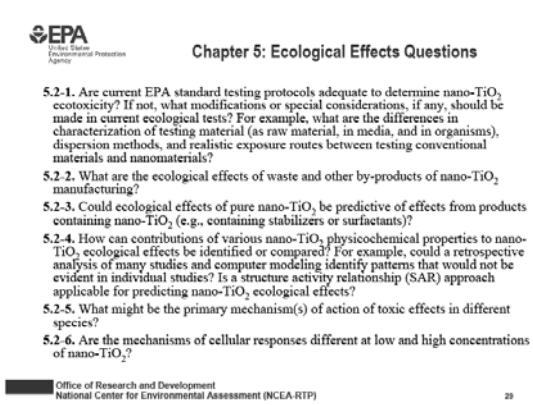

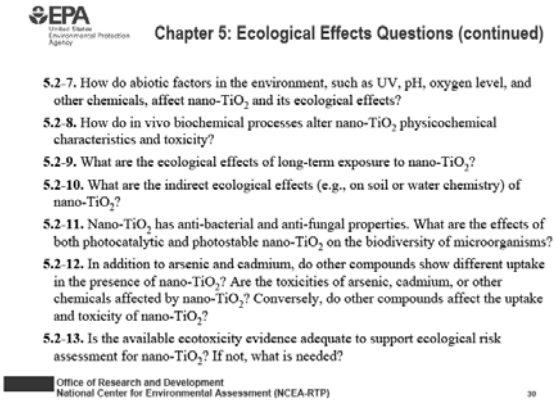

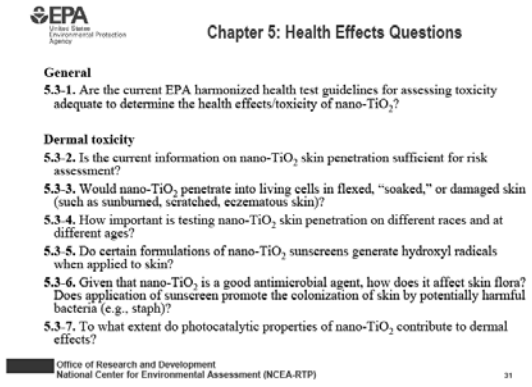

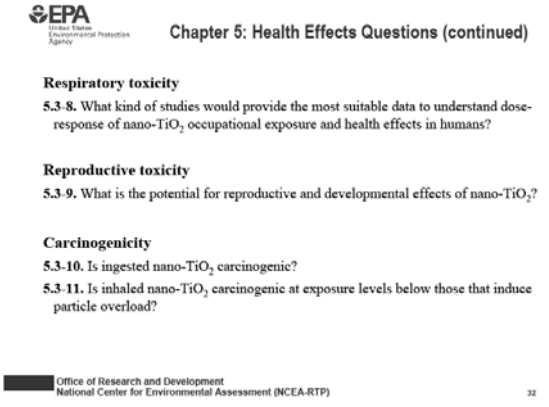

(1-3) Report from chair of TiO2 case study

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

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

Risk Assessment Case Study:

Silver Nanoparticles

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*Presented on behalf of the **Silver Nanotechnology Working Group (SNWG)**, an industry effort intended to foster the collection of data on silver and nanotechnology in order to advance the science and public understanding of the beneficial uses of silver nanoparticles in a wide-range of consumer and industrial products.*

OECD Workshop on Risk Assessment of Manufactured Nanomaterials in a Regulatory Context
September 16-18, 2009
Washington D.C.

Outline

- Material background
- Risk assessment basis
- Case studies
- Risk assessment perspective
- Conclusions and needs

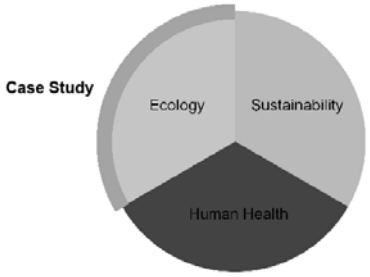
2

Material Background

- Silver nanoparticles:
  - Metallic silver
  - 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 — *eg. sportsclothing, socks*
  - Medical articles & devices — *eg. plasters, wound care*
  - Coatings — *eg. wall paint*
  - Plastics — *eg. keyboards*

3

Risk Assessment Basis



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

5

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?

7

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

Sock Style	EPA Reg	Silver in Sock	Silver Nanoparticle Released	Silver Ion Conc (ppm)
Lounge Sock (Green)	?	✓	Yes	836
Lounge Sock (Blue)	?	✓	No	1845
Athletic Sock (White)	?	×	n/a	n/a
Foxfiber / X-Static	# 70527-1	✓	Yes	165
Arctic Shield / SmartSilver(s47)	# 83587-3	✓	No	below detection
Basketball Sock	?	×	n/a	n/a
Casual Black Sock	?	×	n/a	n/a

- **Conclusions:**
  - Socks with silver nanoparticles (SmartSilver EPA 83587-3) showed **no silver nanoparticle release**
  - X-Static, a "conventional bulk silver", released silver nanoparticles

* TM. Benn and P. Westerhoff, "Nanoparticle Silver Released into Water from Commercially Available Sock Fabrics", Environmental Science and Technology, 42 (2008) 4133–4139.

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Case Study: Silver Nanoparticle Release During Laundry?

Protocol Step		Benn et al. study *	Current study
1. Exposure to water	Washing medium	Ultrapure water	Ultrapure water
	Fabric:water ratio	ca. 1:19	1:19
	Agitation method	Orbital shaker for 24 hour periods	Orbital shaker for 24 hour periods
2. Measurement of released silver ions (Ag^+)	Detection method	Ion-selective electrode on unfiltered sample aliquot	Ion-selective electrode on unfiltered sample aliquot
3. Measurement for released silver particles	Preparation	Washwater evaporated to concentrate nanoparticles. Drops of the concentrated washwater evaporated on the TEM stub substrates.	Washwater thoroughly stirred 2ml Aliquot of water removed and centrifuged to concentrate particles Droplet placed onto glass SEM substrate and evaporate washwater
	Measurement	Transmission electron microscope (TEM) and energy dispersive x-ray spectroscopy (EDX).	Scanning electron microscope (SEM) and energy dispersive x-ray spectroscopy (EDX).
	Analysis	Check area of sample for presence of silver particles and analyse composition using EDX.	Check area of sample for presence of silver particles and analyse composition using EDX.
Control materials	Negative control (Sample without silver)	None	Polyester fabric without silver
	Positive control (Reference nanosilver)	None	Analytical nanosilver reference (Sigma Aldrich, "silver nanopowder" <100nm 99.5% purity, Prod# 576832, CAS# 7440-22-4)

* TM. Benn and P. Westerhoff, "Nanoparticle Silver Released into Water from Commercially Available Sock Fabrics", *Environmental Science and Technology*, 42 (2008) 4133–4139.

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Case Study: Silver Nanoparticle Release During Laundry?

- Reference materials:
  - Glass substrate without washwater (Background reference)
  - Dispersed reference nanosilver (Positive control)
  - Polyester fabric without silver (Negative control) – *Sample 1*
- Sample materials (after 24hrs shaking):
  - Polyester fabric with silver inside coating layer (HeiQ AGS-20 TF) – *Sample 2*
  - Polyester fabric with silver inside fibers (HeiQ AGS-20 MB) – *Sample 3*
  - Commercial nanosilver sock sample (X-systems sock**) – *Sample 4*

** Contains Nanohorizons SmartSilver - a nanosilver material registered by EPA under registration number 83587-3.

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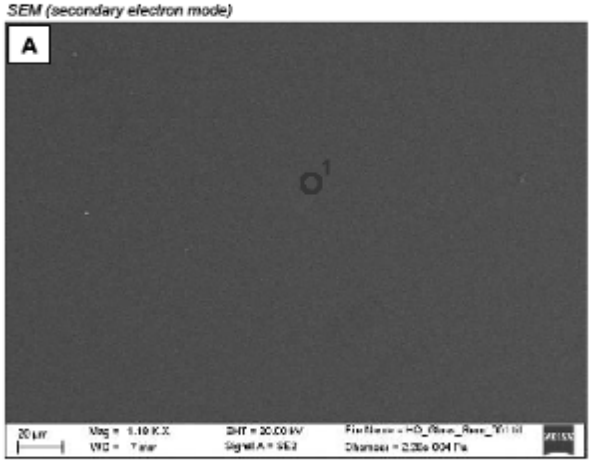
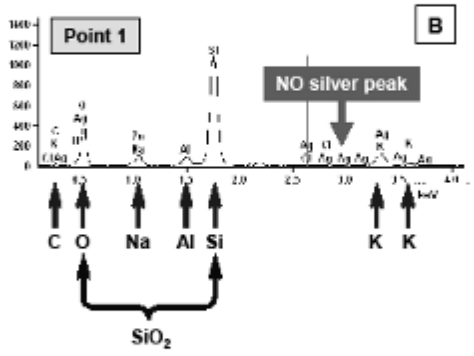
Results – Glass substrate

- Glass substrate used for SEM

SEM (secondary electron mode)





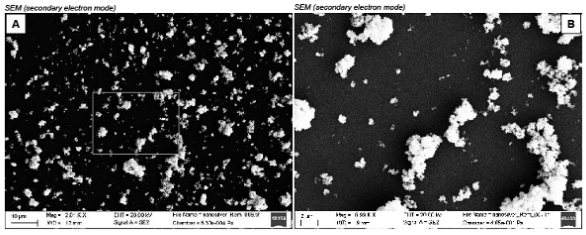
Glass substrate has dominant peaks for Si, O
Smaller peaks also for Na, Al, K
Glass has no Ag peak

18

Results – Nanosilver reference

- Nanosilver as positive control

SEM (secondary electron mode) *SEM (secondary electron mode)*

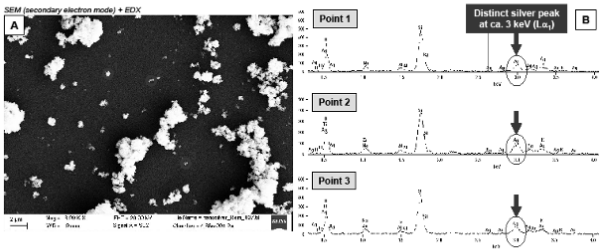


19

Results – Nanosilver reference

- Nanosilver as positive control

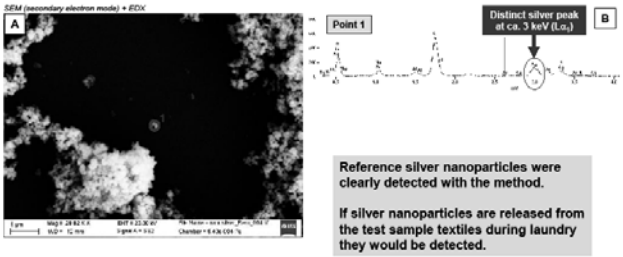
SEM (secondary electron mode) + EDX



20

Results – Nanosilver reference

- Nanosilver as positive control



Reference silver nanoparticles were clearly detected with the method.

If silver nanoparticles are released from the test sample textiles during laundry they would be detected.

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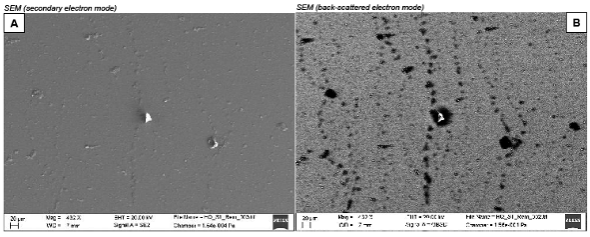
Results – Sample 1

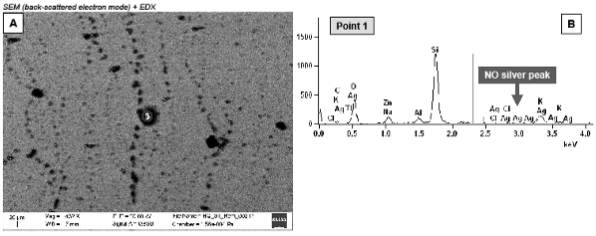
- Negative control – polyester without silver



22

Results – Sample 1

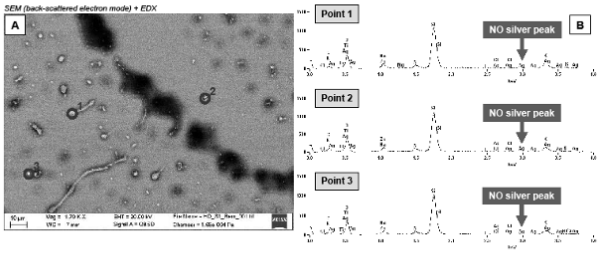
- Negative control – polyester without silver



23

Results – Sample 1

- Negative control – polyester without silver

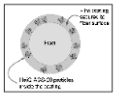


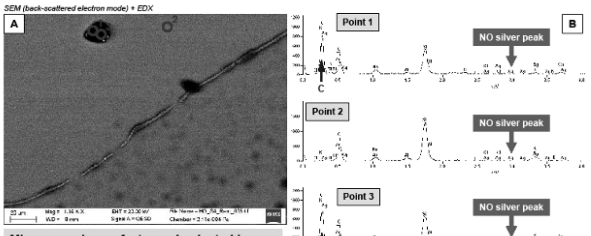
Polyester reference sample confirmed to contain no silver.

24

Results – Sample 2

- Polyester with HeiQ AGS-20 inside coating layer



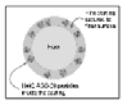


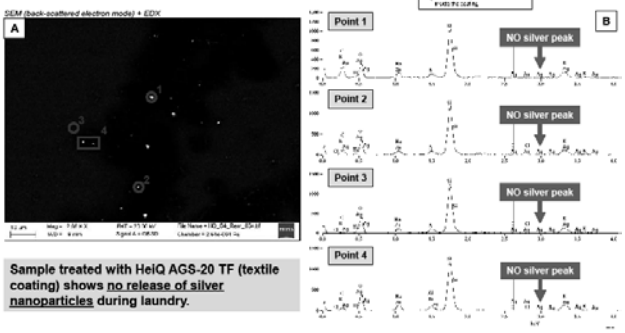
Microscope image features dominated by salts & organic residues - no silver present.

25

Results – Sample 2

- Polyester with HeiQ AGS-20 inside coating layer

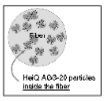


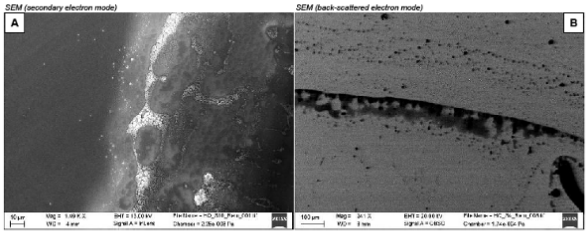


Sample treated with HeiQ AGS-20 TF (textile coating) shows no release of silver nanoparticles during laundry.

Results – Sample 3

- Polyester with HeiQ AGS-20 inside fibers





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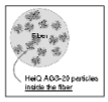
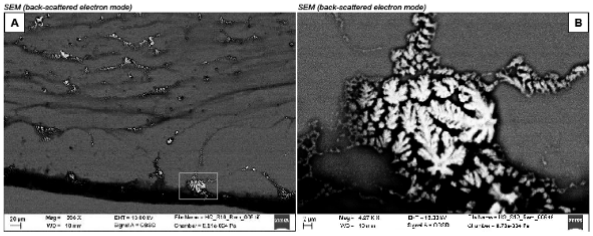
Results – Sample 3

- Polyester with HeiQ AGS-20 inside fiber





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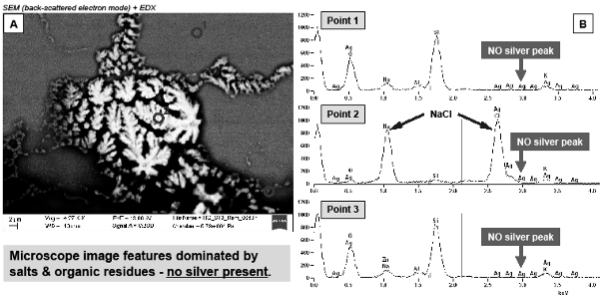
Results – Sample 3

- Polyester with HeiQ AGS-20 inside fiber

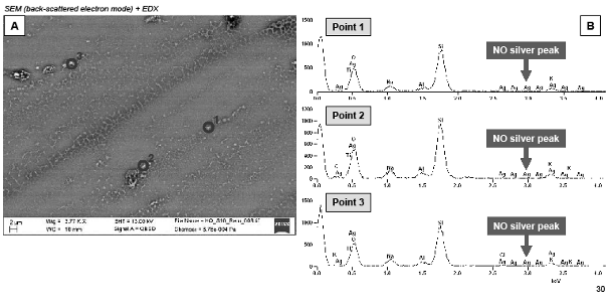


Microscope image features dominated by salts & organic residues - no silver present.

29

Results – Sample 3

- Polyester with HeiQ AGS-20 inside fibers



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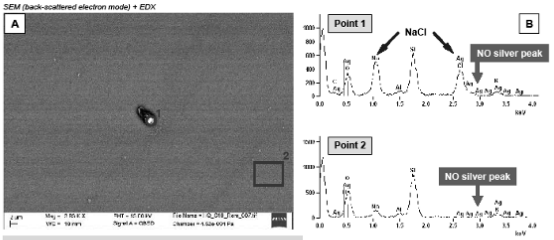
Results – Sample 3

- Polyester with HeiQ AGS-20 inside fibers



Sample treated with HeiQ AGS-20 MB (inside fibers) shows no release of silver nanoparticles during laundry.

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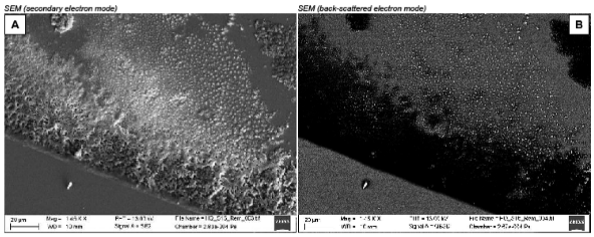
Results – Sample 4

- Commercial nanosilver sock** (also in Benn et al. paper)



** Contains Nanohorizons SmartSilver - a nanosilver material registered by EPA under registration number 83587-3.

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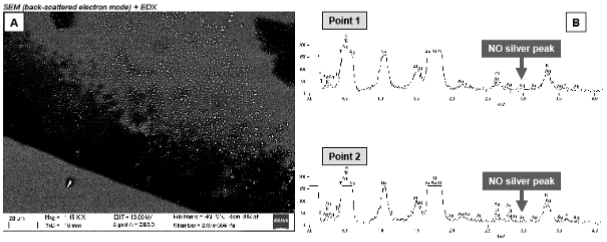
Results – Sample 4

- Commercial nanosilver sock** (also in Benn et al. paper)



Sample treated with Nanosilver (EPA 83587-3) shows no release of silver nanoparticles during laundry.

** Contains Nanohorizons SmartSilver - a nanosilver material registered by EPA under registration number 83587-3.

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Case Study: Silver Nanoparticle Release During Laundry?

- Results summary:

Sample analysis	Nanosilver reference	Sample 1	Sample 2	Sample 3	Sample 4
	-	Standard polyester fabric	HeiQ AGS-20 in coating	HeiQ AGS-20 in fiber	Commercial nanosilver sock**
Free silver nanoparticles?	Yes	No	No	No	No
Organic particles?	No	Yes	Yes	Yes	Yes
Salt particles?	No	Yes	Yes	Yes	Yes

- **Fabrics treated with HeiQ AGS-20 or Nanosilver EPA 83587-3 show no release of silver nanoparticles during laundry.**
- In agreement with findings of Benn et al. paper.

** Contains Nanohorizons SmartSilver - a nanosilver material registered by EPA under registration number 83587-3.

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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?

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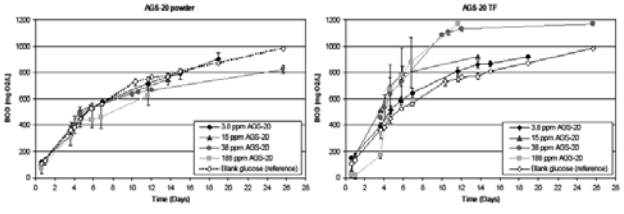
Case Study: Silver Nanoparticles impact MWTP?

- BOD (Biological Oxygen Demand) bottle test with sludge from a local sewage treatment plant.
- Four different concentrations tested with highest recommended application concentrations (worst case) as starting point for dilution series.
- Glucose (COD = 600 mg O_2/l) was used as a substrate for growing the bacteria in the bottle test.



- **High concentrations of HeiQ AGS-20 powder and HeiQ AGS-20 TF textile finish show no hazard to wastewater viability (as measured by BOD).**

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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?
- **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 ions bind with high ambient loadings of common waste components such as chloride, sulfide and thiosulfite as well as organic carbon. Suspended solid particulate material also effectively binds silver, removing it from the wastewater.*

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Risk Assessment Basis

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

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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

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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?

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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 recognized microscopically, while they are still too large to be called molecules."

Carl Wolfgang Ostwald, Colloid Chemist in *World of Neglected Dimensions*, **1922**.

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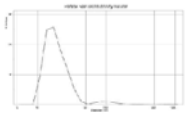
Risk Assessment Perspective

Colloidal Silver: A Relevant History

- Colloids are ultrafine particle dispersions, typically 1-1000 nm diameter
- Nanoscale silver colloids (Collargol, Argyrol, etc.) sold continuously since early 1900s; extensive database of toxicological data is available
- **All major 'conventional' silver toxicology limits are in fact based on nanoscale silver colloids or ionic silver:**
  - EPA drinking water limit
  - OSHA 8 hr inhalation limit
  - Dietary exposure EPA IRIS
- **Challenge: How well characterized?**



Average sizes are 10-20 nm
http://www.silver-colloids.com/Tables/Experiment.PDF

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Risk Assessment Perspective

Particle Sizes of Common Colloidal Silver Products

Product	Use	Particle Size (nm)	Ref
Argyrol	Anti-Infective (early 1900s)	35	DLS Study, NanoHorizons, 2009.
Collargol	Anti-Infective (early 1900s)	10-20	Muller, 1926 (1). Bogdanchikova, 1992 (2).
Mesosilver	'Dietary Supplement'	2	DLS Study, NanoHorizons, 2009.
Protargol	Anti-Infective (early 1900s)	2	Bogdanchikova, 1992 (2).

(1) Experimental Bone Marrow Reactions: I. Anemia Produced by Collargol. Muller, G.L. The Journal of Experimental Medicine, Vol 43, 533-553, **(1926)**.

(2) Activity of colloidal silver preparations towards smallpox virus, Pharmaceutical Chemistry Journal, N. E. Bogdanchikova, A. V. Kurbatov, V. V. Tretyakov, P. P. Rodionov. 26, 9-10, 778 **(1992)**.

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Risk Assessment Perspective

Nanotoxicology in 1926:
Bone Marrow Reactions with Nanoscale Silver

Experimental Bone Marrow Reactions: I. Anemia Produced by Collargol. by Muller, G.L. *The Journal of Experimental Medicine*, Vol 43, 533-553, 1926.

The collargol or colloidal silver employed is said to contain 78 per cent of metallic silver and a small percentage of egg albumin and its oxidation product (11). It is manufactured by the Hayden Chemical Works, and distributed by Schering and Glatz, New York. The size of the particles has been determined by Bechhold (12) to average 20 millimicrons ($\mu\mu$), the individual particle consisting of aggregates of metallic silver and the protective colloid. The concentration of the colloidal suspension, which was made up in small doses in sterile distilled water and filtered immediately before use, varied between 0.1 and 2 per cent. Physio-

IV administration of small amounts of collargol [20 nm metallic silver particles] *produced a stimulation of the endothelium. The animal's health remained unimpaired and the blood counts were normal.*

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Risk Assessment Perspective

Nanoscale Silver: Regulatory History

1954:
Nanosilver colloidal algaecides (~70 nm) first registered by EPA

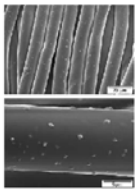
1960s:
EPA-registered silver-impregnated carbon filters (2-15 nm) widely used to protect municipal water supply

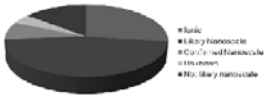
1998:
First FDA approved nanocrystalline silver wound care devices are approved

2002:
First nanosilver spray disinfectant approved by EPA (~50 nm)

Present:
Estimated **82%** (75 of 92) of EPA-registered products contain **nanoscale particles** or ionic (picoscale) silver

Kodak AGPET08 (EPA# 59441-9)
Particle size: 50.500 nm
Photo: KODAK Publication No. G2.1-2007





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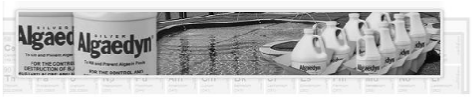
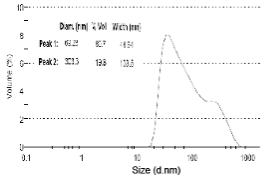
Risk Assessment Perspective

Nanosilver Algaecides: EPA-Registered Since 1954



Product: Silver Algaedyn
Particle size: **20-110 nm**
FIFRA Reg # 68161-1
Type: 0.8% Colloidal Silver
First Registered: 12/31/**1954**[1]



[1] *NPIRS Public* http://ppis.ceris.purdue.edu/npublic.htm

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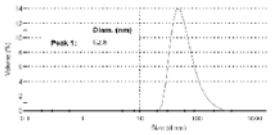
Risk Assessment Perspective

EPA-Registered Nanosilver Algaecides

Product: nu-clo Silvercide
Particle size: **25-95 nm**
FIFRA Reg # 7124-101
Type: 0.8% Colloidal Silver
First Registered: 6/15/**1993**[1]



[1] *NPIRS Public* http://ppis.ceris.purdue.edu/npublic.htm

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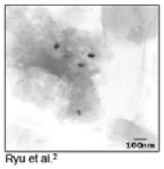
Risk Assessment Perspective

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 **2-15 nm** are required


Ryu et al.[2]

"…for proper efficiency, the silver must be dispersed as particles of colloidal size (less than 250 Å [25 nm] in crystallite size…)"[1]

FIFRA Reg #s	First registered
58295-1	12/01/**1988**[3]
58295-2	11/01/**1989**[3]
58295-3	01/16/**1990**[3]

[1] U.S. Patent #3,374,608 **(1968)**, "*Silver Impregnated Carbon*", Assigned to Pittsburgh Activated Carbon Co. (now Calgon Carbon)
[2] S.K.Ryu, S.Y.Eom, T.H.Cho, D.D.Edie, "*Distribution of Silver Particles in Silver-containing Activated Carbon Fibers*", *Carbon Science*, 4(4), 168-174 (2003).
[3] *NPIRS Public* http://ppis.ceris.purdue.edu/npublic.htm

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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…"

William D. Moeller, President, American Biotech Laboratories
*Testimony on Malaria before the U.S. House of Representatives, International Relations Committee, Subcommittee on Africa, Global Human Rights, and International Operations, April 26, **2005**.*

Product: ASAP-AGX
Particle size: **10-50 nm**
FIFRA Reg # 73499-1
Type: 0.001% Silver
First Registered: 2/27/**2002**[1]

Product: ASAP-AGX-32
Particle size: **10-50 nm**
FIFRA Reg # 73499-2
Type: 0.032% Silver
First Registered: 4/23/**2003**[1]

[1] *NPIRS Public* http://ppis.ceris.purdue.edu/npublic.htm

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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"[1]

Product: H2Pro™ Maintenance Treatment
Particle size: **1- 500 nm** (est)
FIFRA Reg # 75829 -1
Type: 0.0015% Silver
First Registered: 9/9/**2004**[2]

[1] http://www.garrisondental.com/
[2] *NPIRS Public* http://ppis.ceris.purdue.edu/npublic.htm

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Risk Assessment Perspective

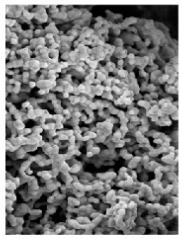
EPA-Registered Antimicrobial Additives: Ciba / Bio-Gate

Ciba

Product: HyGate 4000
Particle size: **50-200 nm**
Agglomerate size: 2-5 µm
FIFRA Reg # 70404-10
Type: 100% Silver
First Registered: 09/05/**2008**[1]

Bio Gate

Product: MicroSilver BG-R
Particle size: **50-200 nm**
Agglomerate size: 2-5 µm
FIFRA Reg # 84146 -1
Type: 100% Silver
First Registered: 03/18/**2008**[1]



Press Release: "Ciba Specialty Chemicals forms marketing cooperation with Bio–Gate for silver antimicrobial technology" 14.12.2005, Basel, Switzerland.

[1] *NPIRS Public* http://ppis.ceris.purdue.edu/npublic.htm

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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 SilverSoaker Nanosilver Catheters
  - FDA approved in **2005**
  - Recommended by NGOs to reduce hospital acquired infections
- Other FDA approved nanosilver products:
  - Baxter Needless IV Connectors
  - SilverSol Nanosilver Wound Care Gel
  - Bard Silver-coated Endotracheal Tubes

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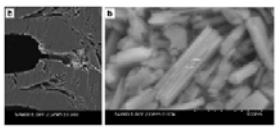
Risk Assessment Perspective

EPA-Registered Nanomaterials: NanoCopper Wood Preservatives

Product: ORD-X372 / MicroPro 200
Particle size: **50- 700 nm**
FIFRA Reg # 3008 -90
Type: 35% Copper (as carbonate)
First Registered: 5/12/**2005**[1]



"…Micronized copper wood preservatives are the latest generation wood preservative systems in which very small (sub-micron) particles of solid copper"[1]

The copper particle size used in the micronized copper products average about 300 nm. Particles <80 nm penetrate the wood.[2]

[1] http://www.treatedwoodtruth.com/Treated-Wood-Information-on-Osmose-MicroPro-Lumber.php
[2] "Microdistribution of copper-carbonate and iron oxide nanoparticles in treated wood." H. Matsunaga, M. Kiguchi, P. Evans. J Nanopart Res. 11,5. 1087-1098 (2009).

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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/m^3

  Soluble silver salts (silver nitrate) ..... 0.01 mg/m^3

- "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, 1991).

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Human Toxicity

Nanotoxicology in 1974:
Relative toxicity of nanoscale silver to silver nitrate

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

[1] Dequidt, J., P. Vasseur, and J. Gromez-Potentier. **1974.** Experimental toxicological study of some silver derivatives. Bull. de la Soc. de Pharm. de Lille. 1: 23-35.

- "Based on total Ag concentration, toxicity was 18 times higher for $AgNO_3$ than for AgNP [silver nanoparticles]."[2]

[2] Toxicity of Silver Nanoparticles to Chlamydomonas reinhardtii: Navarro et al. *Environ. Sci. Technol.* **2008**, 42, 8959–8964.

The historical risk assessment data bridges to present day silver nanoparticles

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Human Toxicity

Review of Silver Threshold Limits: Inhalation

- **Question:** The ACGIH inhalation TLV of 0.1 mg/m^3 applies to silver dust and fumes, but does it adequately reflect the argyria hazard for nanoscale silver?

- **Answer:** Yes. Ninety-day subchronic inhalation toxicity of 18-19 nm silver nanoparticles was studied in Sprague-Dawley rats and a no observable adverse effect level of 0.1 mg/m^3 was determined – in full agreement with existing ACGIH TLV.[1]

The data bridges…. Why?

[1] Sung, et al. Subchronic Inhalation Toxicity of Silver Nanoparticles. *TOXICOLOGICAL SCIENCES* 108(2), 452–461 (2009).

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Human Toxicity

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

- Referring to **Gaul and Staud (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 Pillsbury (1939)**: "Both of the US standards for silver in drinking waster and in workplace air have been based on a presumed 1 g minimum dose of silver that has caused argyria."[2]

[1] EPA–HQ–OPP–2007–0395 Federal Register / Vol. 74, No. 110 / June 10, 2009

[2] EPA-440/5-80-071 or PB81-117822 "Ambient water quality criteria for silver" U.S. EPA, 1980.

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Human Toxicity

Nanosilver Toxicology: Gaul and Staud (1935)

Summary: Seventy cases of argyria from nanosilver colloidals were reviewed.
Data was derived primarily from **Argyrol (35 nm)** and **Collargol (10-20 nm)**


1388 ARGYRIA—GAUL AND STAUD

Table I.—Generalized Argyria Cases following Peroral, Nasal and Pharyngeal Medication with Organic and Colloidal Silver Compounds

Gaul & Staud (1935) is the primary reference for all EPA documents on silver toxicity

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Human Toxicity

Nanosilver Toxicology: Exposure Summary

The Gaul and Staud (**1935**) and Hill and Pillsbury (**1939**) argyria 1 gram threshold value is the basis[1-3] for:

- ACGIH's Inhalation Threshold Limit Value (TLV)
- OSHA Inhalation Permissible Exposure Limit (PEL)
- Mine Safety and Health Administration PEL
- EPA IRIS 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 colloids or soluble 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–HQ–OPP–2007–0395 Federal Register / Vol. 74, No. 110 / June 10, 2009
[2] EPA-440/5-80-071 or PB81-117822 "Ambient water quality criteria for silver" U.S. EPA, 1980.
[3] Drake and Hazelwood: "Exposure-Related Health Effects of Silver and Silver Compounds: A Review" - Annals of Occupational Hygiene, vol. 49, p. 575-58-, 2005.

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Risk Assessment Perspective

Summary:

- **EPA has registered silver nanoparticles over a period of 6 decades**
  - Colloidal silver algaecides
  - Silver-carbon water filters
  - Nanosilver disinfectants
  - Antimicrobial additives

- This long history of regulated use in a wide range of applications, coupled with the extraordinarily low rate of recorded incidents, suggests that EPA and other regulatory bodies have adequately managed risks associated with commercial applications of silver nanoparticles.

- Newer studies on 'nanosilver' reveal no significant new risks because the database used for the last 50+ years is derived from studies of ionic or nanoscale silver. No significant studies on 'conventional' silver are available.

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Risk Assessment Basis

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

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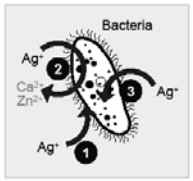
How Do Silver-based Antimicrobials Work?

- 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 oligodynamic effect [1]
- Silver ions interact with bacteria cells through 3 mechanisms (see Figure):
  1. Damage cell membrane[2]
  2. Displace Ca^{2+} and Zn^{2+} ions[2]
  3. Interact with sulphur, oxygen or nitrogen[3]
- 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 [4]
  - No human toxicity



1. US. EPA, "R.E.D. Facts – Silver", 1992.
2. Sondi I, et al. Journal of Colloid Interface Science, 2004, 275: 177-182.
3. Dowling DP, et al., Thin Solid Films, 2001, 398: 602-606.
4. Gilchrist T, et al., Biomaterials, 1991, 12: 76-78.
5. Damm, C. et al., Soft materials, 2006, 3:71-86.

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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*

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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)

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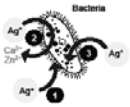
Silver Additives Deliver Silver Ions

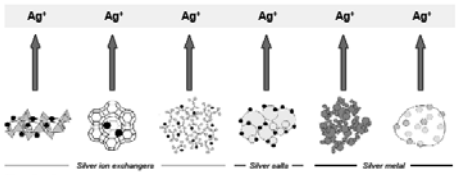
Antimicrobial effect solely from Ag^+

Threshold concentration of Ag^+ required to give antimicrobial effect



Liberation of Ag^+ from source antimicrobial additive

All silver-based antimicrobials "Store" silver ions



EPA registration numbers						
	EPA 11631-2 EPA 11631-3 EPA 74075-1	EPA 71227-1 EPA 72854-1 EPA 46810-18 EPA 82410-3	EPA 73148-1	EPA 59441-7 EPA 49403-34	EPA 70404-10 EPA 84146-1 EPA 83587-3	EPA 58295-1 EPA 58295-2 EPA 58295-3

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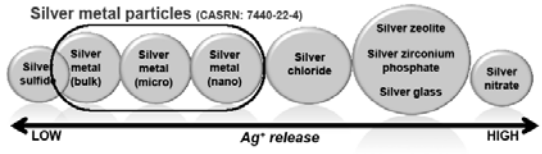
Silver Additives in Use

- 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



- Because of the higher surface area per mass of silver, nanosilvers have a higher release capability than bulk silver metal

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Silver Metal Antimicrobials

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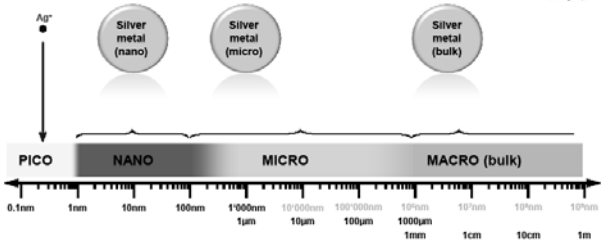
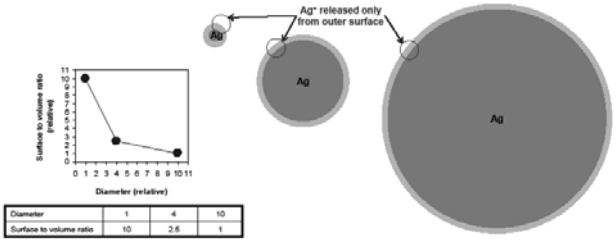
Silver Metal Antimicrobials – Size continuum



80

Silver Metal – Why go smaller?

- Antimicrobial effect from ionic silver (Ag^+)
- Efficient silver use considers Ag^+ release per mass of silver used
- Ag^+ release only from surface of metal on contact with water
- Efficiency is based on proportion of surface to volume (mass) of the particle



Diameter	1	4	10
Surface to volume ratio	10	2.5	1

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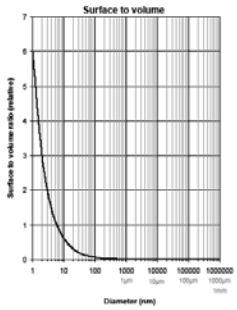
Silver Metal – Why go smaller?

- Ag^+ release proportional to surface to volume (mass) of the particle



Availability of Ag^+ ions per mass of silver is higher for smaller particles

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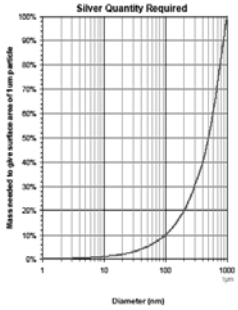
Silver Metal – Why go smaller?

- Ag^+ release proportional to surface to volume (mass) of the particle



Smaller particles allow much lower mass of silver to achieve a given Ag^+ dosing

Example:
For equivalent Ag^+ dosing

1µm particles	10'000 ppm Ag required
10 nm particles	100 ppm Ag required

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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*
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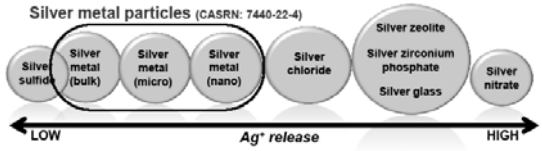

- Because of the higher surface area per mass of silver, nanosilvers have a higher release capability than bulk silver metal

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Silver Additives in Use

- A key factor in use of silver additives is the required **durability** which in turn dictates the amount of antimicrobial additive required.
- In general:
  - High Ag^+ release rate → low durability → high dosing levels required to **give durability**
  - Low Ag^+ release rate → high durability → high dosing levels to give **required activity**
  - Moderate release rate → good durability at low loadings

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Silver Additives in Use

- A key factor in use of silver additives is the required **durability** of silver ion release which in turn dictates the amount of antimicrobial additive required.
- In general:
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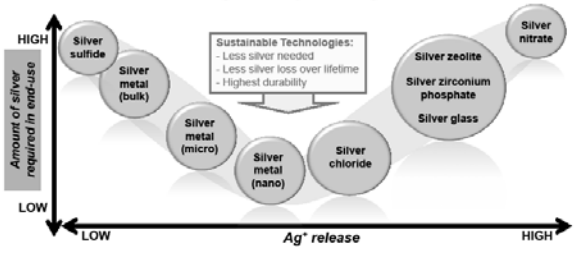
  - Moderate release rate → good durability at low loadings



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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

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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 colonised by skin bacteria and so their use has limitations.
- Silver-based antimicrobials can be integrated directly inside textile fibers or as part of a durable coating on the outside of the fabric.
- The integrated silver antimicrobial protects the textile from colonisation 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 resilience 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.

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Risk Assessment Basis

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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
    - Studied wastewater system 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-fact based on nanoscale silver
- **Sustainability**
  - Silver nanoparticles offer significant sustainability benefits compared to ionic silver and synthetic chemical antimicrobials

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Conclusions

- **An established regulatory track-record based on a wide body of silver nanoparticle data**
- **EPA**
  - EPA first registered silver nanoparticles in 1954
  - **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, suggesting 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

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Challenges & Needs

- **Silver Nanoparticle Human toxicity:**
  - Review of the wide body of historic published data for silver nanoparticles (also equivalently known as colloidal silver, millimicro silver etc.) prior to performing essentially repeat studies and to avoid unecessary animal tests.
- **Silver Microparticles:**
  - Regulatory limits are currently based on an extensive body of data derived directly from nanoscale silver particles
  - Data is actually needed for *microscale* silver particles
    - Microscale data would assist in bridging from 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.

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(2-2) Presentation from Germany

Risk Assessment Case Study
nano-Ag

Mario E. Goetz and Carsten Kneuer
Federal Institute for Risk Assessment, Germany

OECD Workshop on Risk Assessment of Manufactured Nanomaterials in a Regulatory Context
September 15-18, 2009
Washington D.C.

BfR

FEDERAL INSTITUTE FOR RISK ASSESSMENT

Human Health Risk Assessment for two nano-Ag products

in the context of §31 German Plant Protection Law

Mario E. Goetz and Carsten Kneuer

1

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§31 German Plant Protection Law

regulates listing of Plant Care Products (not PPPs!)

requires data on:
- the applicant
- trade name of product
- composition of product
- mode of action
- user instructions / manual
- packaging and labelling

allows the authority to:
- deny or withdraw marketing authorisation if there is reason for concern
- request further information available to the applicant
- request changes

Available product information

Composition:

Water		
Silver, colloidal	(CAS 7440-22-4)	8 ±2 ppm (mg/L)*
Ammonium nitrate	(CAS 6484-52-2)	< 1 mg/L
Ammonia	(CAS 7664-41-7)	< 1 mg/L
Sodium citrate	(CAS 6132-04-3)	< 1 mg/L

Other relevant substances:

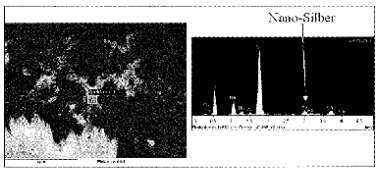
Silver, ionic	(CAS 14701-21-4)	max. 8 ±2 ppm (mg/L)

Relevant Exposure Path:
- Oral / residues
- Inhalation / spraying
- Dermal / mixing & loading, spraying

* 0.001 %, confirmed by ICP/MS at BfR

2

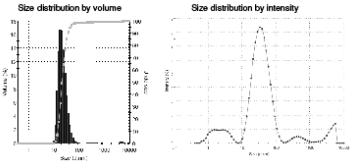
Additional product information from REM/EDX
performed at Federal Environment Agency (UBA)



Primary particle size: „approximately / mostly 10-30 nm"

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

Size distribution by volume | Size distribution by intensity



- average particle size confirmed
- limited amount of agglomerates / aggregates
- possibly particles 1-10 nm also present

3

Key studies Acute Toxicity

Oral

nano-Ag:	>1000 mg/kg bw, rat (highest dose of 28d study, Kim et al., 2008)
Bulk:	>2000 mg/kg bw, rat
Ionic silver:	1173 mg/kg bw, rat ($AgNO_3$)
	50 mg/kg bw, mouse ($AgNO_3$)
	473 mg/kg bw, guinea pig ($AgNO_3$)

Inhalation

nano-Ag :	no data (>0.5 mg/m³, rat, 90d study, Sung et al., 2008/2009)
Bulk:	no data
Ionic silver:	no data

Dermal

nano-Ag :	no data
Bulk:	no data
Ionic silver:	> 216 mg/kg bw, guinea pig ($AgNO_3$)

Conclusion: no classification triggered

(source: IUCLID, if not stated otherwise)

Key studies Local Effects

Skin Irritation

nano-Ag:	not available
Bulk:	not irritating, rabbit (TG 404) / human
Ionic silver:	corrosive

Eye Irritation

nano-Ag:	not available
Bulk:	not irritating, rabbit (TG 405) / human
Ionic silver:	corrosive

Sensitisation

nano-Ag:	not available
Bulk:	ambiguous (human), but traditional use of metallic silver
Ionic silver:	no data

Conclusion:
- no classification of product after application of generic classification limits (conc. below 0.1%)
- research need *(conflict bulk/ionic)*
- avoid exposure

(source: IUCLID)

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Repeated Dose Toxicity: Oral

nano-Ag: Kim et al., 28day Oral Toxicity ... Rats, 2008
(60 nm Ag-NP in 0.5% CMC)

LOAEL 300 mg/kg bw/d for liver toxicity
(M+F: ALP ↑, cholesterol ↑, bile duct hyperplasia)
(F only: RBC ↑, Hb ↑, HCT ↑, coagulation time ↓)

NOAEL 30 mg/kg bw/d
+ 26 (extrapolation from 4 to 104 weeks)
+ 100 (SF for intra- and interspecies variability)

proposed acceptable external exposure level
0.012 mg/kg bw/d

Repeated Dose Toxicity: Oral

Ionic Silver: Reference Doses proposed by WHO, US EPA, EFSA

US EPA LOAEL = 1 g (for argyrosis in humans, intravenously, single dose)
+ 3 (LOAEL / NOAEL extrapolation)
+ 0.04 (4% oral absorption)
+ 70 (70 kg body weight)
+ 25550 (70 yrs lifetime, 365 days/year)

RfD = 0.005 mg/kg bw/d

WHO / EFSA NOAEL = 10 g (epidemiol. data for argyrosis in humans, oral, lifetime)
+ 25550 (70 yrs lifetime)

tolerated dose = 0.39 mg/d (0.005 mg/kg bw/d)

Conclusion proposed value for nano-Ag higher than for ionic Ag
-> 0.005 mg/kg bw/d to be used

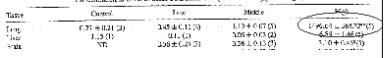
(to accout for nano -> ionic during lifecycle)

5

Repeated Dose Toxicity: Inhalation

nano-Ag: Ji et al., 28day inhalation Toxicity ... Rats, 2007
(~15 nm Ag-NP in air)

LO(A)EL 0.061 mg/m³, cumulative dose ~66 µg / animal
- silver residues in lung ↑↑↑

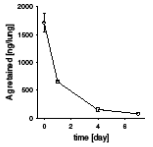


- possible liver effects (uncertain)

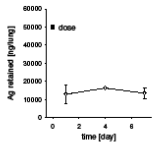
NOEL 0.0035 mg/m³

Supporting information for NO(A)EL derivation based on lung clearance

6 µg Ag-NP (15 nm)
(rat, inhalation, single dose)



50 µg of Ag-NP
(rat, instillation, single dose)



(Takenaka et al., 2001)

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Repeated Dose Toxicity: Inhalation

nano-Ag: Sung et al., 90day inhalation Toxicity (Rat), 2008 and 2009

~18 nm Ag-NP in air; 0 / 0.05 / 0.13 / 0.51 mg/m³

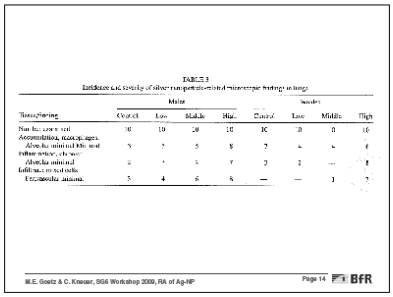
LOEL 0.05 mg/m³, silver residues ↑ at all doses

LOAEL 0.51 mg/m³, bile duct hyperplasia
Males: 0/10, 0/10, 1/10, 4/9
Females: 3/10, 2/10, 4/10, 8/10 (also single cell necrosis)

indications for chronic alveolar inflammation at the high dose
(LDH, albumin, cell numbers / infiltrates)

lung function changes at high dose
(tidal volume ↓, minute volume ↓, peak inspiratory flow ↓)

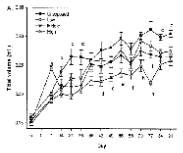
NOAEL 0.13 mg/m³
***(NOEL** < 0.05 mg/m³, based on silver accumulation, granuloma)*



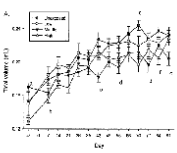
7

Lung function changes described by Sung et al. (2008)

Male



Female



Reference Value Derivation: Inhalation

medium-term and intermittent exposure

NOAEL 0.13 mg/m³ *(based on liver/lung histopathology and lung function changes)*
+ 2.5 (SF for interspecies variability)
+ 10 (SF for intraspecies variability)

proposed acceptable external exposure level
0.005 mg/m³

lower than previously derived reference values for silver dust at the working place (0.1 mg/m³)

chronic exposure

NOEL 0.0035 mg/m³ *(based on accumulation / reduced clearance)*
should be taken into account

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Choice of Dose Metrics: Inhalation

metrics (unit)	study	NOAEC	LOAEC
weight / volume (mg/m³)	90 day	0.13	0.51
surface / volume (10^8 nm²/ml)	90 day	2.4	6.6
number / volume (10^6/ml)	90 day	1.4	2.9

ratio decreases from ca. 4 to ca. 2 at the same geometric mean diameter

Particle size in product was similar to that of tested particles

-> relevance in the specific case ?

Repeated Dose Toxicity: Dermal

nano-Ag:	no data
Bulk:	no data
Ionic silver:	NOAEL 137 mg/kg bw/d, guinea pig, 56 d
Dermal absorption:	- low but uncertain - likely lower for any nano than ionic Ag
Conclusion:	ionic silver: - dermal NOAEL >> oral RfD *(0.005 mg/kg bw/d, human)* nano-Ag: - uncertainties identified for local effects -> value not derived

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Genotoxicity / Carcinogenicity

in vitro

Nano-Ag:	ROS generation, secondary genotoxicity *(e.g. Carlson, 2008)*
Ionic silver:	negative (various tests), potential clastogen (aneuploidy) *(IUCLID)*

in vivo

Nano-Ag:	negative bone marrow micronucleus test at 1000 mg/kg bw/d x 28 days *(Kim et al., 2008)* not tested at site-of-contact
Bulk:	no distant tumors, rat (fibrosarcoma at implantation site) *(IUCLID)*
Ionic silver:	no data

Conclusion: likely threshold based (ROS, chronic inflammation)

Definition of Safety Factors

according to the Technical Guidance Document on Risk Assessment of ECB:

interspecies variability	x 4 (toxicokinetics) x 2.5 (toxicodynamics) 10
intraspecies variability	x 3.2 (toxicokinetics) x 3.2 (toxicodynamics) 10

QUESTION:

Additional Uncertainty for Nanomaterial Variability = ?
(e.g. nano-to-nano)

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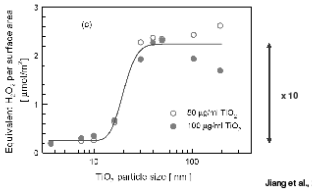
Example for nano-to-nano variability:
ROS generation by TiO_2-NP in vitro per surface area



Jiang et al., 2008

SUMMARY

- Reference values were proposed
- MoE calculation was not possible due to lack of access to exposure estimates / measurements
- Oral RfD based on ionic silver
- Inhalation RfD based on lung+liver pathology and lung function (90-d rat)
- Lower NOEL for accumulation / reduced clearance from 28-d study to be considered for chronic exposure settings
- Dermal RfD not derived
- Open points: e.g. additional assessment factors, dose metrics

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(2-3) Presentation from Netherlands

Risk Assessment Case Study
Nanoparticles under REACH
Nanosilver as a case study

Eric A.J. Bleeker
National Institute for Public Health and the Environment

OECD Workshop on Risk Assessment of Manufactured Nanomaterials in a Regulatory Context
September 16-18, 2009, Washington D.C.

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)

* Registration, Evaluation, Authorisation and restriction of CHemicals

Disclaimer

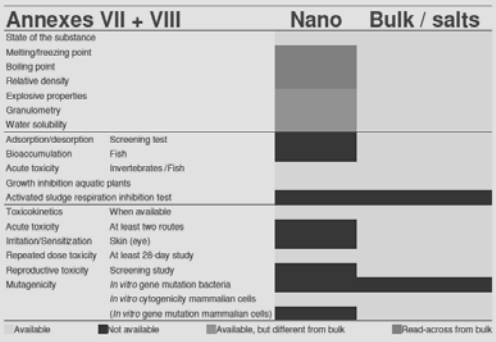
- This case study is purely a scientific exercise with the aim to generate recommendations for future guidance on how to deal with the chemical safety assessment of first generation nanomaterials under REACH
- (Nano)silver was chosen because it is rich on data which was easily available (*e.g.* Wijnhoven 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

* Wijnhoven SWP, Peijnenburg WJGM, Herberts CA, Hagens WI, Oomen AG, Heugens EHW, Roszek B, Bisschops J, Gosens I, Van de Meent D, Dekkers S, De Jong W, Van Zijverden M, Sips AJAM, Geertsma RE (2009) , Nano-silver - a review of available data and knowledge gaps in human and environmental risk assessment, Nanotoxicology 3: 109-138.

Nanosilver case study

- Metallic silver, in nanoform 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



Classification & Labelling / Chemical Safety Assessment?

Nanosilver case study: No/insufficient information

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

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Classification & Labelling / Chemical Safety Assessment?

Nanosilver case study: No/insufficient information

- 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

8

Classification & Labelling / Chemical Safety Assessment?

Nanosilver case study: No/insufficient information

- Exposure Assessment
  - environmental exposure
    - EUSES limitations for metals (K_d 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

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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 t/y)

* Still under debate

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Further lessons learned

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

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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)

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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

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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 to which human/environment are exposed)

* Starting point for all testing is the adequately characterized nanomaterial. During testing there should be continuous monitoring and measuring of any change in the nanomaterial characteristics.

Toxicological information*

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

* Starting point for all testing is the adequately characterized nanomaterial. During testing there should be continuous monitoring and measuring of any change in the nanomaterial characteristics.

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 (K_d values)

* Starting point for all testing is the adequately characterized nanomaterial. During testing there should be continuous monitoring and measuring of any change in the nanomaterial characteristics.

Next tier

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

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Acknowledgements

Marja Pronk
Susan Wijnhoven
Evelyn Heugens
Willie Peijnenburg
Robert Luttik
Betty Hakkert

18

(2-4) Report from chair of Nano-Ag case study

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 Stropp and Dr. Jacques Ragot
Bayer Schering Pharma AG and Bayer MaterialScience AG
Germany

OECD Workshop on Risk Assessment of Manufactured Nanomaterials in a Regulatory Context
September 16-18, 2009
(slides updated)
Washington D.C.

Content

- Background of the Case Study
- Approach
- Characterization Baytubes®
- Use Pattern
- Hazard Assessment:
  - Evaluation of the literature on CNTs
  - Toxicological Test Program Baytubes®
- Exposure Assessment
- Risk Characterization and Assessment Human Health
- Eco-toxicological Test Program for Baytubes®
- Conclusions

2009-September - 2 -

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

*** www.baycareonline.com**

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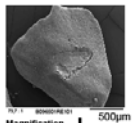
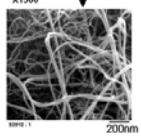
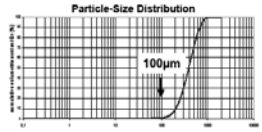
Baytubes® – Characterization

- CNTs are a large family of distinct products
- Baytubes® are Multi-Walled Carbon Nano Tubes:
  - Form large and stable agglomerates of high chemical purity
    - Purity >95%; Cobalt ca. 0.5%; D50 ca. 500µm
  - Short, thin & entangled tubes
    - Mean tube diameter ca. 11nm
    - Mean tube length in dispersion ca. 0.2-1µm
  - Display a low respirable dustiness (EN15051-B)
  - Have an low agglomerate density
    - 0.32 g/cm3 (ca. 10 times lower than Carbon Black)





Particle-Size Distribution



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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 turbine
  - Potential use in all applications where reduced weight is desired (e.g. automotive, aeronautics)
- **Production capacity?**
  - Current capacity at BMS: 60 metric tons / year

Hazard Assessment: 1. Evaluation of the literature on CNTs (1)

- **ca. 430 references are identified until now**
- **The materials tested are not identical to Baytubes®**
  - Single/Multi-Wall (SWCNT/MWCNT), Impurity profile, Diameter, Aspect ratio, Bulk density, Stability…
- **The studies (mainly in vitro) give no consistent picture:**
  - Lack of test substance characterization before and after sample preparation
  - Limited information on sample preparation and test substance formulation
  - Lack of (validated) negative and positive control groups
  - Limited number of parameters examined
  - Limited number of dose groups; no data on dose-response relationship (often only one dose tested)
  - Artificial route of exposure and bolus exposure, e.g. intratracheal instillation (recently inhalation studies start to become available)

} in vivo

Hazard Assessment: 1. Evaluation of the literature on CNTs (2)

- **Examples from the literature demonstrating the complexity:**
  - SWCNT induce indirect cytotoxicity in vitro by medium depletion (Casey et al., Tox Letters 179, 78-84, 2008)
  - Protein is absorbed to SWCNTs (Zhong et al., Carbon 47, 967-973)
  - SWCNT interact with dyes used to assess cytotoxicity

    (Casey et al., Carbon 45, 1425-1432, 2007, Davoren et al., Toxicology in vitro 21, 438-448, 2007, Pulskamp et al., Toxicology Letters 168, 58-74, 2007, Monteiro-Riviere Inman, Carbon 44, 1070-1078, 2006, and Wörle-Knirsch et al., Nano Letters 6, 1261-1268, 2006)

  - **Confounding factors need to be considered** (see e.g. Doak et al., Mutagenesis 24, 285-293, 2009 and Belyanskaya et al., Carbon 45, 2643-2648, 2007)

Hazard Assessment: 1. Evaluation of the literature on CNTs (3)

Specific Question: In vivo Toxicity of MWCNT compared to Asbestos after single i.p.* or intrascrotal application**

With „long and thick" MWCNT:

- Fiber-like response in short term assay in C57Bl/6 mouse (*7 days; Poland et al., Nature Nanotechnology (2008) 3, 7, 423 – 428)
- Mesothelioma in p53+/- heterozygous knock out mouse (*up to 180 days; Tagaki et al., J. Toxicol. Sci. (2008) 33, 1, 105-116)
- Mesothelioma in F344 rats (**up to 52 weeks; Sakamoto et al., J. Tox. Sci. 34, 65-76, 2009)

With „short, thin and tangled" MWCNT:

- No fiber effect in short term assay in C57Bl/6 mouse (*7 days; Poland et al., Nature Nanotechnology (2008) 3, 7, 423 – 428
- No carcinogenic response in long term study in Wistar rats (*2 years; Muller et al., Tox. Sci. (2009), 110, 442-448)

For further information see backup slides

Hazard Assessment: 1. Evaluation of the literature on CNTs (4)

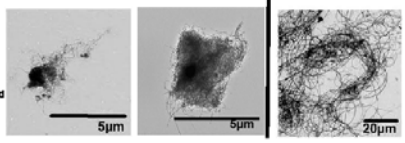
MWCNTs compared to Asbestos: differentiated picture

→ Existing fibre pathogenicity paradigm seems valid for MWCNTs

→ Case by case assessment necessary: Structure Activity Relationship seems possible, needs to be further defined

→ **Baytubes® belong to the category short, thin, tangled MWCNTs for which no "fiber-like" pathogenic behavior is expected based on the available data**

	Short/tangled MWCNTs*	Baytubes®	Long MWCNTs*
▪ Mean Diameter:	ca. 15nm	ca. 11nm	80-200nm



* Electron Microscopy: Materials tested by Poland et al. in dispersion Dispersion not fully described

Hazard Assessment: 1. 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
    - there is not yet a clear picture regarding mode(s) of action
    - inhalation studies are regarded to be 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 423,** feeding; vehicle dietary cream)
  - LD50 rat: >= 5.000 mg/kg; no signs of toxicity and no mortality
- **Acute toxicity, dermal (OECD 402**, dry test substance material and moisted wrapping)
  - LD50 rat: > 2.000 mg/kg; no local effects, no signs of toxicity and no mortality
- **Primary skin irritation (OECD 404**, moisted with water)
  - Non-irritant (rabbit): no skin effects
- **Primary eye irritation (OECD 405,** dry test substance)
  - Non-irritant (rabbit): reddened conjunctivae in 1/3 animals; reversible within 72 hours, no systemic intolerance reactions
- **Sensitization (OECD 406, modified Guinea Pig Maximization test**, vehicle petrolatum; formulated to yield a paste, warmed at 37°C; maximum achievable concentration 23.8% used for induction and challenge)
  - Negative (no skin effects in all animals)
- **Genotoxicity in vitro** (vehicle deionised water; 30 min bath sonication, 25°C, 47kHz; Shift of agglomerate size from >100 µm down to 10 µm under incubation conditions)
  - Not clastogenic in chromosome aberration test in vitro (OECD 473)*
  - Not mutagenic in AMES Test (OECD 471)*

* Wirnitzer et al., Toxicology Letters 186, 160-165, 2009

Toxicological Test Program Baytubes® : Inhalation Studies in Rats

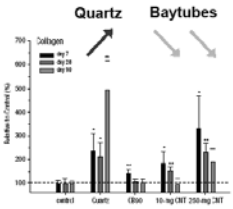
- **The inhalation toxicity test program was developed to**
  - **cover regulatory aspects (dose-response relationship for acute and repeated dose toxicity, classification)**
  - **to gain insight in the principle mode(s) of action => reference materials, extended and hypothesis driven study design**
- **Baytubes®' agglomerates are too large to be tested as-is. They need to be processed (e.g. micronization)**
  - **In the inhalation studies with Baytubes® the test substance was subject to grinding (centrifugal ball mill) to increase dustiness, however without deterioration of the typical agglomerate structure**
- **Test materials in the lung were carefully characterized**
  - **Entangled agglomerates of tubes predominate in inhalation atmosphere**
  - **Under the conditions of the studies with Baytubes® single tubes could not be identified in lung cells (cytospin)**

Toxicological Test Program: Acute Inhalation Study in Rats*

▪ Poorly Soluble Particle effects at 11 mg/m³

- **Study design (extended OECD TG 403)**
  - 1x6h exposure; 7, 28 and 90-day post-exposure observation; 11 and 241 mg/m3;
  - Baytubes®; Reference substances: Quartz and Carbon Black (CB)
- **Results: No mortality (LC50 rat: > 241 mg/m³)**
  - Conc. >=11 mg/m³ cause a poorly soluble particle effect (essentially reversible)
  - Pulmonary toxicity is related to the MWCNT structure, but not cobalt
  - Baytubes and Quartz are markedly different
  - Baytubes compared to CB is consistent with density related overloading

    => less particle mass is needed to exceed the volumetric overload limit for the inhibition of macrophage-mediated clearance (particle volume rather than surface area most critical)



* Pauluhn 2009/2010 submitted; Pauluhn, Inhalation Toxicology 21, 40-54, 2009; Pauluhn, Toxicology Letters 186SM S225, 2008

Toxicological Test Program: Subchronic Inhalation Study in Rats*

- **Based on the results of the acute inhalation toxicity study the following modes of action were proposed:**
  - First: Acute toxicity due to the putative adsorptive depletion of essential homeostatic factors involved in surfactant homeostasis
  - Second: volumetric particle overload that may trigger retention-related responses, which affect biopersistence and long-term toxicity of deposited material
- **This information was included in the study design of the 13-week inhalation study; three aspects were given particular attention:**
  - Shape and structures of the test material in exposure atmospheres and recovered from digested BAL-cells of subchronically exposed rats
  - Cumulative-dose and pulmonary inflammatory response induced by aerosolized MWCNT over a postexposure period of 6 months compared to those reported for carbon black (CB)**
  - Are differences in toxic potencies of CB and MWCNT caused by the nanotubular structure *per se* or by differences of the specific densities of agglomerates and earlier attainment of lung overload
- **Study design: according OECD TG 413, but hypothesis driven with additional parameters and recovery of up to 6 months**
  - Doses: 0 - 0.1 – 0.4 – 1.5 – 6 mg Baytubes®/m³ 6h/day; incl. bronchoalveolar lavage (BAL)

* Pauluhn 2009/2010 submitted; Pauluhn, Inhalation Toxicology 21, 40-54, 2009
** Elder et al., Tox. Sci. 88, 614-629, 2005

Toxicological Test Program: Subchronic Inhalation Study in Rats*

▪ Poorly soluble particle effect confirmed

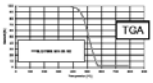
- **Results: 0.1 mg/m³ was tolerated without changes in BAL considered to be adverse. This is in line with histopathological examinations**
  - Clear effects at 1.5 and 6 mg/m3, borderline effects at 0.4 mg/m3
    - elevation of polymorphonuclear leucocytes [PMN] in BAL and soluble collagen, histopathological changes in upper and lower respiratory tract
  - The findings match those observed in studies with poorly soluble particles of low specific density
  - The inflammogenic potency of Baytubes® is associated with its low bulk density leading to **volumetric overload of macrophages**
  - The concurrence of nasal and pulmonary NO(A)ELs may suggest that the MWCNT agglomerate structure promoted **„tissue adherence"** with subsequent injury and response to injury
  - **No evidence of any toxicity outside the respiratory tract**
  - Translocation/dissolution/breakage into small tubes or fibres did not occur (cylospin)
  - **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

 * Pauluhn 2009/2010 submitted; Pauluhn, Inhalation Toxicology 21, 40-54, 2009

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

▪ End of Life

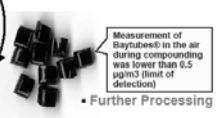
e.g. Proper disposal; Baytubes undergo complete combustion > 600°C



▪ Production

e.g. Closed System, Automated filling, Exhaust gases incinerated

Produkt Lebens -zyklus



▪ Use Phase

e.g. Nanoparticles embedded in a matrix have a negligible exposure potential

▪ Further Processing

e.g. Proper use to ensure safe handling, use of engineering controls, use of personal protection measures (MSDS)

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 inhalation
    - Effects consistent with "Poorly Soluble Particle"-like mode of action (PSP effect)
    - Findings suggest that a volumetric overload rather than specific structural features is causative for the effects observed after inhalation
    - No evidence of extrapulmonary toxicity after inhalation
  - Sub-chronic inhalation data will be used to set an OEL (0 - 0.1 – 0.4 – 1.5 – 6 mg/m3)
- **Exposure: no unreasonable exposure along the life-cycle (additive in polymers)**
  - For further processing typical exposure to Baytubes® during compounding was lower than 0.5 µg/m³ (< 0.0005 mg/m3; limit of detection)

=> Based on all data available presently, Baytubes® is safe for its current intended use

Eco-toxicological Test Program for Baytubes®

- **Ecotoxicity test results for Baytubes®**
  - Acute bacterial toxicity (OECD 209)
    - EC50 > 10.000 mg/l (activated sludge)
  - Acute toxicity to fish (OECD 203)
    - LC50 > 100 mg/l (Brachydanio rerio (zebra fish); 96 h)
  - Acute toxicity for daphnia (OECD 202)
    - EC50 > 100 mg/l (Daphnia magna (Water flea); 48 h)
  - Acute toxicity for algae (OECD 201)
    - EC50 134 mg/l (Desmodesmus subspicatus (Green algae); 72 h)
- **Exposure assessment in the environment**
  - For the applications envisaged (Baytubes embedded in polymer matrix) the exposure's potential through abrasion can be considered as negligible[1]
  - Further research on Baytubes is ongoing (e.g. Project CarboSafe within the inno.CNT alliance[2])
  - First estimations[3] support low Predicted Environmental Concentrations

=> All standard studies performed so far with Baytubes show no relevant adverse effect at realistic exposure level (GLP studies according to OECD Guidelines).

1 TRACER project sponsored by German Federal Ministry of Education and Research (BMBF), publication in preparation
2 CarboSafe project sponsored by German Federal Ministry of Education and Research (BMBF), www.inno-cnt.de
3 Müller, Nowack (2008) Environ. Sci. Technol. 42, 4447–4453

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 BronchioAlveolar Lavage (BAL)[1] 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 Party of Manufactured Nanomaterials[2]

1 BAuA, BfR, UBA (2007) Nanotechnology: Health and environmental risks of nanomaterials – Research Strategy – http://www.baua.de/nn_47716/de/Themen-von-A-Z/Gefahrstoffe/Nanotechnologie/pdf/Research-strategy.pdf?
2: Working Party on Manufactured Nanomaterials (2009) Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials. Document No. 15, OECD 2009; ENV/JM/MONO(2009)21

Thank you

for

your attention

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Backup slides

2009-September - - 21 -

Hazard Assessment: 1. Evaluation of the literature on CNTs

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

- **Tagaki et al.[2]: study in mice inadequate**
  - Non standard animal model (p53+/- heterozygous knock out mouse) of unknown relevance in the context of fibre toxicity
    - no historical experience with the test system; no information if the test system is able to differentiate between fibre toxicity and particle or solid state effects
      - very high sensitivity even for unspecific "solid state carcinogenicity" (shown by Tazawa et al., Carcinogenesis 28, 191-198, 2007)
  - Extremely high single dose (3 mg/mouse => very strong local reaction, e.g. peritonitis);
  - References: crocidolite and fullerene
  - "Long and thick" MWCNT tested
    - Induction of mesothelioma
- **Poland et al.[1]: short-term study in mice (7 days)**
  - Historical experience available with the test system; Single dose 50 µg/mouse;
  - References: short and long fibre amosite, carbon black
  - 2 different types of MWCNTs tested
    - Fiber-like pathogenic behavior for "long, thick" CNTs"
    - No fiber effect for "short, thin, tangled" CNTs

1 Poland et al., Nature Nanotechnology (2008) 3, 7, 423 – 428; 2 Tagaki et al., J. Toxicol. Sci. (2008) 33, 1, 105-116

2009-September - - 22 -

Hazard Assessment: 1. Evaluation of the literature on CNTs

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

- **Muller et al.[3]: long-term study in Wistar rats**
  - Historical experience available with the test system;
    - Two single high doses: 2 and 20 mg/rat;
    - Observation period 2 years
  - Reference: crocidolite
  - "Short, thin and tangled" MWCNTs tested
    - No carcinogenic response
- **Sakamoto et al.[4]: long term study in F344 rats**
  - Intrascrotal injection; Non standard animal model
  - no historical experience with the test system
    - High single dose (3 mg/kg bw);
    - Observation period 52 weeks
  - Reference: crocidolite
  - "Long and thick" MWCNT tested (same test substance as Tagaki et al.)
    - Induction of Mesothelioma (but no response in the positive control group)

3 Muller et al., Tox. Sci. (2009), 110, 442-448; 4 Sakamoto et al., J. Tox. Sci. 34, 65-76, 2009

2009-September - - 23 -

(3-2) Presentation from US NIOSH

Risk Assessment Case Study: Carbon Nanotubes

Eileen D. Kuempel, Ph.D.
National Institute for Occupational Safety & Health
Cincinnati, Ohio

OECD Workshop on Risk Assessment of Manufactured Nanomaterials in a Regulatory Context
September 16-18, 2009
Washington D.C.

The findings and conclusions in this presentation have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy.

Background

- ***Objective:*** Evaluate the toxicology data, methods, and uncertainties in assessing hazard and risk of occupational exposure to 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 workplace exposure data, and examples of risk assessment methods and issues

2

1

NIOSH Role

- NIOSH is authorized to develop recommended occupational safety and health standards (OSH Act of 1970)
  - Conducts toxicological research, risk assessment, exposure assessment, and health surveillance
  - Develops criteria for recommended standards
  - Forwards recommendations to OSHA

3

Substance Description & Uses

- SWCNT: Single-walled carbon nanotubes
  - ~1 nm diameter (single rolled graphite sheet)
- MWCNT: Multiple-walled carbon nanotubes
  - 2-100 nm diameter (multiple graphite sheets)
- SWCNT or MWCNT
  - Length: ~1 to 10's of micrometers
  - Dispersed or agglomerated
  - Purified or Unpurified (metal catalysts & reaction by-products)
- CNF: Carbon nanofiber (may include CNTs)
- Uses:
  - Many and growing (e.g., composites, electronics, energy)
  - Production volumes are increasing

4

2

CNT Occupational Exposure Data

Material & Process	Concentration ($\mu g/m^3$)*	Reference
SWCNT – production facility	10 - 53	Maynard et al. 2004
MWCNT – research laboratory – before & after controls	37- 434 ND - 39	Han et al. 2008
CNF composite – weighing, mixing, cutting	64 - 1,094	Methner et al. 2007
MWCNT composite – wet cutting dry cutting	54 2,110 - 8,380	Bello et al. 2009

ND = not-detected

* Most are short-term (~15-30 min) samples of total carbon

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Potential Nano-specific Components of Risk Assessment of CNTs

- *Dose metric:* Size & structure may influence dose-response relationship compared to other materials
  - e.g., Same chemical composition but different potency
  - Fiber counting methods may not detect CNTs
- *Lung deposition and disposition:* Particle characteristics, including heterogenous structures & low density, may alter deposition, clearance, and retention
- *Bioavailability:* Nano-size & structure may influence bio-distribution in tissues, cells, organelles
- *Response:* Nano-characteristics may affect mechanisms

7

CNT Hazard and Risk Assessment: Some Possible Methods with Available Data

- Qualitative approaches: *Use in Control Banding*
  - Analogy (comparable chemical & physical properties)
  - Comparative toxicity to other chemicals
  - Relative ranking or grouping
- Quantitative Risk Assessment (QRA): *Develop Exposure Limits*
  - NOAEL or LOAEL with uncertainty factors
  - Benchmark dose and exposure-attributable risk estimates

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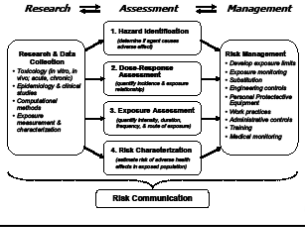
"Classic" Risk Assessment Paradigm [adapted from NRC 1983]



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4

National Research Council (USA):
Re-evaluation of the 1983 Risk Assessment Framework as Practiced

- Responded to EPA charge to recommend improved risk analysis
- Retained the four steps of risk assessment
- Recommended improving the utility of risk assessment, including determining:

"What options are there to reduce the hazards or exposures, & how can risk assessment be used to evaluate the merits of the various options?"

Dec 2008

9

5

Hazard Data Examples - Rodent Studies of SWCNT

Response	Dose & Duration*	Species & Exposure Route*	Reference
Pulmonary inflammation Granulomas	0.1 or 0.5 mg (7 & 90 d pe)	Mouse (B6C3F$_1$, male); IT	Lam et al. 2004
Cell proliferation – lung epithelial cells	2 mg/kg	Rat (F344, female); PA	Mangum et al. 2006
Pulmonary fibrosis (early onset & persistent)	5, 10, 20, 40 µg (1, 3, 7, 28 & 60 d pe)	Mouse (C57BL/6, female); PA; inhalation (whole body)	Shvedova et al. 2005, 2008;
K-ras oncogene mutations in lung tissue	5 mg/m^3 (5 hr/d, 4 d); 1, 7, & 28 d pe		
Cardiovascular – oxidative stress & plaque formation	10, 40 µg (7, 28 & 60 d pe)	Mouse (C57BL/6, male); PA	Li et al. 2007

*IT: intratracheal instillation; PA: pharyngeal aspiration; pe: post-exposure

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6

(1) Comparative Toxicity Method

- Evaluate dose associated with an adverse effect for CNT and other material(s) with existing risk assessment or occupational exposure limit (OEL)
- Apply a potency factor to estimate equivalent risk at OEL for CNT

Notes:
- Assumes same mechanism and relative potency over time
- Risk levels among OELs may vary or be unknown
- OELs may be feasibility-based

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Hazard Data Examples: Rodent Studies of MWCNT

Response	Dose & Duration*	Species & exposure route*	Reference
Granulomatous inflammation Lipoproteinosis	0.1, 0.5, 2.5 mg/m^3 (6 hr/d, 5 d/wk, for 13 wk)	Rat (Wistar, male); inhalation (head & nose)	Ma-Hock et al 2009
Pulmonary fibrosis	0.5, 2, 5 mg (28 & 60 d pe)	Rat (Sprague-Dawley, Wistar, female);IT	Muller et al 2005, 2008
Bronchiolitis obliterans Peribronchial fibrosis	12.5 mg (3 month pe)	Guinea pig (three-color, male); IT	Grubek-Jaworska et al. 2006
Immune suppression of T and NK cells	0.3, 1, 5 mg/m^3 (6 hr/d, for 7 or 14 d)	Mouse (C57BL/6, male); Inhalation (whole body)	Mitchell et al. 2007 ["MWCNT"?]
Mesothelioma	3 mg (25 wk pe)	Mouse (p53(+/-, m)	Takagi et al. 2008
No mesothelioma	2, 20 mg (2 yr pe)	Rat (Wistar, m)	Muller et al. 2008
Inflammation, by length	50 µg (1, 7 d pe)	Mouse (C57B1/6, f) all IP	Poland et al. 2008

*IT: intratracheal instillation; PA: pharyngeal aspiration; IP: intraperitoneal injection; pe: post-exposure

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Toxicity of CNT and Other Materials – Pulmonary Fibrosis in Rodents

Comparison	Approximate potency factor*	Reference
SWCNT / SiO_2	2.5	Shvedova et al. 2005
SWCNT / uf carbon black	2.5	Shvedova et al. 2005
MWCNT / uf carbon black	1.5	Muller et al. 2005
MWCNT / chrysotile asbestos	1.0	Muller et al. 2005

*Same dose and duration within each comparison:
- Shvedova: 40 µg per mouse, 28 d (SWCNT & ufCB) or 60d (SWCNT & SiO_2)
- Muller: 2 mg per rat, 60 days post IT.

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(2) Uncertainty Factor Method

- Determine no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) from animal study
- Calculate human equivalent concentration (assumes equal toxicity at equivalent dose)
- Apply uncertainty factors, e.g., 10 each, as applicable:
  - Animal to human extrapolation
  - LOAEL vs. NOAEL
  - Subchronic to chronic effect
  - Human inter-individual variability
  - Other?

Note: Assumes threshold; not risk-based

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Comparative Toxicity and OELs

How useful is this approach?

Example comparison to NIOSH RELs:

- *Crystalline silica:* 50 µg/m^3 (respirable)
  - Limit of quantitation (LOQ) of analytical method
  - Estimated excess risk at REL: >10 cases per 1,000 workers of silicosis or lung cancer [Rice et al. 2001; Park et al. 2002]
- *Asbestos:* 0.1 fiber (>5 µm in length) / cc
  - CNT is much thinner, not well-detected by PCM
- *Carbon black:* 3.5 mg/m^3 (PAH 0.1 mg/m^3)
  - Does not account for nanoparticle size effects

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Example: Deriving Human-equivalent Dose

- e.g., LOAEL for granulomatous inflammation in rats after 13-week inhalation exposure to MWCNT [Ma-Hock et al. 2009]
- *Dose (rat) (mg)* =
  Concentration (mg/m^3) x Air inhaled (rat)(m^3/d) x
  Alveolar deposition fraction x Hours exposed per day x
  Days exposed
  = 0.1 mg/m^3 x 0.38 m^3/d x 0.1 x 6/24 x 65 d
  = 0.058 mg
- *Human-equivalent lung dose*
  Dose (human) (mg) =
  Dose (rat) x Alveolar surface area (m^2) (Human/Rat)
  = 0.058 mg x (102/0.4)
  = 14.8 mg

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Example: Deriving Human-equivalent Dose *(contd).*

- *Human working lifetime equivalent concentration* =
  Dose(human) (mg) /
  [Air inhaled (human)(m^3/workday) x
  Deposition fraction x workday/yr x years]
  = 14.8 mg /
  [9.6 m^3/d x 0.1 x 250 d/yr x 45 yr]
  = 0.0014 mg/m^3 [assumes same deposition fraction as rats]

or,

~1 µg/m^3 as 8-hr time weighed average (TWA) concentration
... before applying uncertainty factors of 10-10^4 !

Note: Assuming equal lung deposition fraction in rat & human, and no lung clearance

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(3) Benchmark Dose Method

- Model dose-response relationship to determine the dose (BMD) associated with a specified level of response (e.g., 10%)
  - BMD: Benchmark dose - maximum likelihood estimate
  - BMDL: Lower 95% confidence limit of the BMD
- Use BMD(L) as point of departure (POD) to estimate risk (e.g., <0.1%)
- Extrapolate BMD(L) to humans
  - by accounting for species-specific differences in morphology, physiology, & metabolism (as applicable)
- Evaluate human exposures to characterize risk

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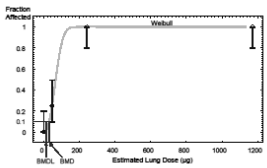
Example of Benchmark Dose Modeling

Granulomatous Inflammation after 13-wk Inhalation in Wistar Rats
[Ma-Hock et al 2009]



Excess risk 10% BMD(L): 31 (13) µg per rat lung

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Example: Extrapolating Rat BMD(L) to Humans

- Granulomatous inflammation [Ma-Hock et al. 2009]
  - *10% BMD(L): 31 (13) µg in rat lung*
- Human-equivalent lung burden to rat BMD(L)
  - Dose (human) =
    Dose(rat) x Alveolar surface area (Human/Rat)
    = 7.9 (3.3) mg in human lungs
- Now, estimate the workplace airborne concentration that would result in this lung burden...

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Example: Extrapolating Rat BMD(L) to Humans *(contd.)*

- Human working-lifetime equivalent concentration
  - *e.g.*, Multiple-path particle deposition model (MPPD) [CIIT 2002]
  - Particle characteristics reported in Ma-Hock et al. 2009
  - Assume lung deposition and clearance follow spherical particle behavior
  - Assume reference worker breathing rates & patterns
  - 8-hour TWA, 45 years:
    12 (5) µg/m^3 – but thia is at 10% excess risk level !
- Issues
  - How does CNT lung deposition & clearance compare to spherical particles
  - What is acceptable risk level for early adverse lung effects?

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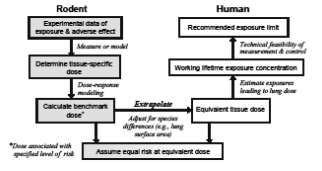
Quantitative Risk Assessment Methods to Develop Recommended Exposure Limits for Inhaled Particles



[Based on: Kuempel et al. Inhal Toxicol 19:717–724, 2008]

22

11

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 genotoxicity & cancer
- Examine relationship between short- & long-term dose-response, e.g., early effect on pathway to frank disease
- Evaluate human-equivalent lung responses to those observed in animal studies
- Compare CNTs exposures in animal studies and workplace, qualitatively & quantitatively

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CNT Risk Management – Data & Information Needs

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

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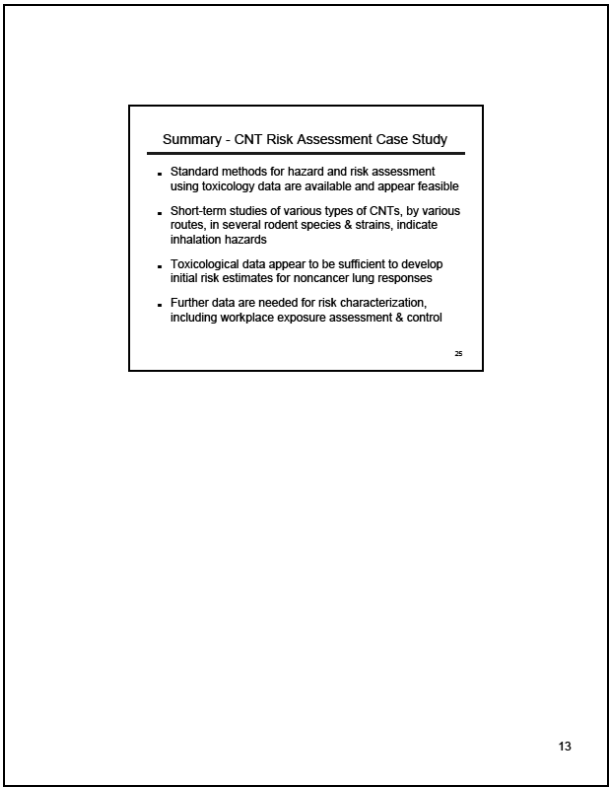
Summary - CNT Risk Assessment Case Study
Standard methods for hazard and risk assessment using toxicology data are available and appear feasible
Short-term studies of various types of CNTs, by various routes, in several rodent species & strains, indicate inhalation hazards
Toxicological data appear to be sufficient to develop initial risk estimates for noncancer lung responses
Further data are needed for risk characterization, including workplace exposure assessment & control
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(3-3) Presentation from Japan NIOSH

Risk Assessment Case Study
(MW)CNT

Mariko Ogasawara
Japan NIOSH
Japan National Institute of Occupational Safety and Health

OECD Workshop
on Risk Assessment of Manufactured Nanomaterials in a Regulatory Context
September 16-18, 2009
Washington D.C.

Background(1)

- This case study is about a topic relating to Japanese regulatory system, especially exposure assessment.
- Ministry of Health, Labour and Welfare(MHLW) issued "Notification on Precautionary Measures for Prevention of Exposure etc. to Nanomaterials (NMs)" on March 31, 2009. (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.

2

Background(2)

- Ordinary risk assessment system for occupational setting in Japan.
- If hazard evaluation is established and the administrative control level (ACL) is set, the workplace environment is classified into three categories by comparing ACL with environmental concentration.
  Control methods is determined according to the Class.
  (No personal exposure measurement required)
  Assessment is directly connected to control.
- If ACL is not set, self management activity is encouraged.
  - Present status: No ACL for NM

3

Outline

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

4

Statistical risk evaluation in Japanese administrative method

- ◆E_{A1} and E_{A2} are calculated from the data measured at multi-points in a unit work area.
- ◆$\log E_{A1} = \log M + 1.645 \log \sigma$
  E_{A1}: 95% value of concentration distribution
  M: geometrical mean, σ: geometrical standard deviation
- ◆$\log E_{A2} = \log M + 1.151 \log^2 \sigma$
  E_{A2}: equivalent to arithmetic mean

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?

5

Statistical risk evaluation in Japanese administrative method

Risk class of workplace

		Area		
		$E_{A1}<E$	$E_{A1}\leq E\leq E_{A2}$	$E<E_{A2}$
Source	$E_{source}<E$	Class 1	Class 2	Class 3
	$E\leq E_{source}\leq 1.5E$	Class 2	Class 2	Class 3
	$1.5E<E_{source}$	Class 3	Class 3	Class 3

E: the administrative control value
ex) $E_{A1}<E$ and $E_{source}<E$: 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

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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
- Manufactures usually have information about what kind of substances are present.

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CNT case study
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
    1-2 t/week/numbers of company

  Problem: CNTs of width>100nm NM?

CNT case study
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

9

CNT case study
Occupational Exposure to MWCNT

Potential exposure level

Process		Exposure	
		CNT	Others
Synthesis	Closed, Automated	Low	
Maintenance	Manual	High	Soot, PAHs, Metals, Vapors, nano-PM*
Packing/ Weighing	Manual	Medium	
	Closed, Automated	Low	Ambient PM
w/o work		ND - very low	
Outside		ND	

* Nanoparticles generated from condensation of vapors

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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

11

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)

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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.
  - Mass can be calculated from on-line data of number concentration.(Evans, et al, 2008, Heitbrink, et al, 2007)
    - Not suitable for personal exposure measurement
    - Effects from background PM and shape of PM
  - Surface area can be calculated from above data.

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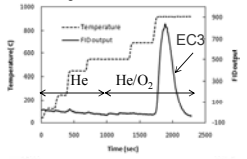
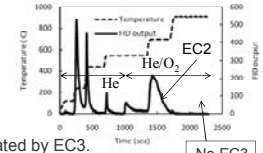
Examples of Carbon analysis

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



Ambient PM
from roadside with heavy traffic
Method: IMPROVE (final 920℃)



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.

No EC3

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.

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(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				
Assessment Problem Formulation	Exposure - Public, Occupational & Environmental	Hazard - Human Health	Ecological toxicity and Fate	Determining Risk and Linkage between Assessment and Management
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.	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 exposure.	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 hazards to humans.	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 hazards to organisms or environmental fate.	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.
Are there quantitative challenges specific to nanomaterials that should be considered at this stage of analysis?	Are there quantitative challenges specific to nanomaterials that should be considered at this stage of analysis? For example, what are the appropriate metrics for reporting exposure.	Are there quantitative challenges specific to nanomaterials that should be considered at this stage of analysis? For example, what are the appropriate metrics for reporting results of effects testing.	Are there quantitative 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).	Are there quantitative challenges specific to nanomaterials that should be considered at this stage of analysis? For example, what are the appropriate metrics for calculating and reporting risk.
What concepts from the case studies should be captured for this stage of analysis?	What concepts from the case studies should be captured for this stage of analysis?	What concepts from the case studies should be captured for this stage of analysis?	What concepts from the case studies should be captured for this stage of analysis?	Risk is Hazard x exposure; is there anything unique to nano that will affect risk management or require new risk assessment policies?
How can information from bulk materials or other nanomaterials provide insight into the assessment?	How can information from bulk materials or other nanomaterials provide insight into the assessment?	How can information from bulk materials or other nanomaterials provide insight into the assessment?	How can information from bulk materials or other nanomaterials provide insight into the assessment?	How can information from bulk materials or other nanomaterials provide insight into the assessment?
How to we define persistence and bioaccumulation in the context of nanomaterials?			How to we define persistence and bioaccumulation in the context of nanomaterials?	How to we define persistence and bioaccumulation in the context of nanomaterials?
Session B - Resolving Uncertainties				
Assessment Problem Formulation	Exposure - Public, Occupational & Environmental	Hazard - Human Health	Ecological toxicity?	Determining Risk and Linkage between Assessment and Management
Can exposure pathways typically be eliminated or emphasized as part of the problem formulation	Generally speaking should we employ the same predictive techniques used for examining exposure to chemicals	Have other end points been identified which should be considered over and above those used for chemicals?	Have other end points been identified which should be considered over and above those used for chemicals?	Can risk management be used to compensate for a lack of data, or uncertainty?
what uncertainties are relevant to nano risk assessment?	what uncertainties are relevant to nano risk assessment?	what uncertainties are relevant to nano risk assessment?	what uncertainties are relevant to nano risk assessment?	what uncertainties are relevant to nano risk assessment?
how can research resolve outstanding risk assessment methodogy issues?	how can research resolve outstanding risk assessment methodogy issues?	how can research resolve outstanding risk assessment methodogy issues?	how can research resolve outstanding risk assessment methodogy issues?	how can research resolve outstanding risk assessment methodogy issues?

(1) Assessment Problem Formulation

Assessment Problem Formulation

Chair: Richard Canady
Rapporteur: Iseult Lynch

Session A – Addressing Current Risk Assessments

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

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 dose 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

	Large particles	Nanomaterial
size	500 nm– 10 micron	100 nm 이하
respirable	Respirable + inhalable	respirable
sampling	personal > area	Personal < area
sampling equipment	cyclone, impactor, filter	DMAS, CPC, OPC, APS, ELPI, filter
sampling metric	mass, number (fiber)	number (particle, tube) mass, surface area (?)
Background concentration	Usually not measured	measured
size distribution measurement	not usually analyzed	analyzed
TEM/SEM	not usually analyzed except asbestos analysis	often performed
process episode	not usually checked	checked and recorded
Emission source identification	easy	not easy to identified

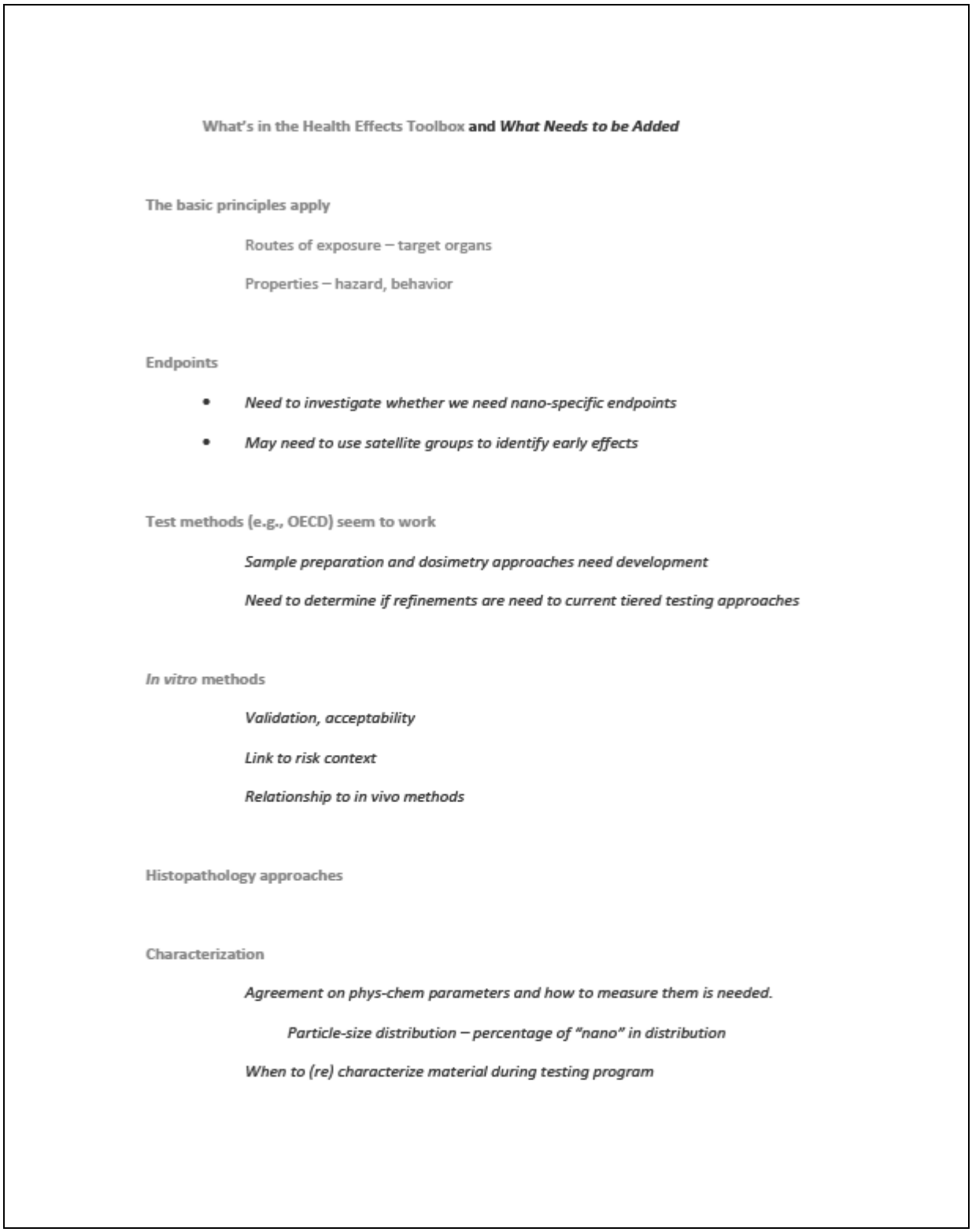
6.

- 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



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

QSARS

Phys property – biological property relationships

Epidemiology approaches

Ability to use existing data

Tracking materials

Disease- v. exposure-driven approaches

Biopersistence

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 SG6 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. Unlikely 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 quantitative 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 forms. 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 mycorhizal 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.
5. Mechanisms of bioaccumulation and determination of methods for predicting bioaccumulation.
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 RM/RMM's w/o a comprehensive RA
    - important consideration today…"Public Perception"
- Ion/Radical Dissolution and/or Translocation important considerations in RA → differing/unique RM/RMM's

Answer 2

- Acknowledged need for metric to support ID of RM/RMM's
  - Avoid different metrics if possible
  - Concordance from RA to RM/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 RM/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 for Tox, and may be important for P, B awa "clearance"
- Effects of course may be different, which can lead to differing RM/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/RMM's.

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

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