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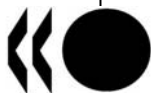
**ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY**

**SERIES ON THE SAFETY OF MANUFACTURED NANOMATERIALS
Number 13**

**REPORT OF AN OECD WORKSHOP ON EXPOSURE ASSESSMENT AND EXPOSURE
MITIGATION: MANUFACTURED NANOMATERIALS**

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**OECD Environment, Health and Safety Publications
Series on the Safety of Manufactured Nanomaterials**

No. 13

**REPORT OF AN OECD WORKSHOP ON EXPOSURE ASSESSMENT AND
EXPOSURE MITIGATION: MANUFACTURED NANOMATERIALS**

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among UNEP, ILO, FAO, WHO, UNIDO, UNITAR and OECD

Environment Directorate

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

Paris 2009

Also published in the Series of Safety of Manufactured Nanomaterials:

- No. 1, *Report of the OECD Workshop on the Safety of Manufactured Nanomaterials: Building Co-operation, Co-ordination and Communication (2006)*
- No. 2, *Current Developments/ Activities on the Safety of Manufactured Nanomaterials: Tour de table at the 1st Meeting of the Working Party on Manufactured Nanomaterials (2006)*
- No. 3, *Current Developments/ Activities on the Safety of Manufactured Nanomaterials: Tour de table at the 2nd Meeting of the Working Party on Manufactured Nanomaterials (2007)*
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- No. 8, *Preliminary Analysis of Exposure Measurement and Exposure Mitigation in Occupational Settings: Manufactured Nanomaterials (2009)*
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ABOUT THE OECD

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

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

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FOREWORD

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

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

Based on the conclusions and recommendations of the Workshop [ENV/JM/MONO(2006)19] it was recognised as essential to ensure the efficient assessment of manufactured nanomaterials so as to avoid adverse effects from the use of these materials in the short, medium and longer term. With this in mind, the OECD Council established the OECD Working Party on Manufactured Nanomaterials (WPMN) as a subsidiary body of the OECD Chemicals Committee. This programme concentrates on human health and environmental safety implications of manufactured nanomaterials (limited mainly to the chemicals sector), and aims to ensure that the approach to hazard, exposure and risk assessment is of a high, science-based, and internationally harmonised standard. This programme promotes international co-operation on the human health and environmental safety of manufactured nanomaterials, and involves the safety testing and risk assessment of manufactured nanomaterials.

This document is the report of the Workshop on Exposure Assessment and Exposure Mitigation, which was held in October 2008. It intends to provide information on the outcomes and discussions of the WPMN related to the safety of manufactured nanomaterials. The opinions expressed in this document are those of the participants to the workshop and do not necessarily reflect the official views of the Organisation or of the governments of its member countries.

The Working Party endorsed this report at its 5th Meeting on March 2009. This document is published on 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)

The Working Party on Manufactured Nanomaterials¹ 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.

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, Singapore and Thailand; and c) observers and invited experts from UNEP, WHO, ISO, BIAC², TUAC³, and environmental NGOs.

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.

The Working Party is implementing its work through eight main areas of work to further develop appropriate methods and strategies to help ensure human health and environmental safety:

- Development of a Database on Human Health and Environmental Safety (EHS) Research;
- EHS Research Strategies on Manufactured Nanomaterials;
- 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; and
- Co-operation on Exposure Measurement and Exposure Mitigation.

Each area of work 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.

This document was prepared by the WPMN steering group 8 leading the work on *Co-operation on Exposure Measurement and Exposure Mitigation*. The Working Party endorsed it at its 5th Meeting on March 2009.

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 OECD.

CO-OPERATION ON EXPOSURE MEASUREMENT AND EXPOSURE MITIGATION

In November 2007, the OECD Working Party on Manufactured Nanomaterials decided to start work on **Co-operation on Exposure Measurement and Exposure Mitigation**. A steering group lead by the US, and comprising delegates from the WPMN, was tasked with developing this work.

The operational plan outlines three phases of work: 1) exposure in occupational settings; 2) exposure to humans resulting from contact with consumer products and environmental releases of manufactured nanomaterials; and 3) exposure to environmental species resulting from environmental releases of manufactured nanomaterials including releases from consumer products containing manufactured nanomaterials.

This document is the report of the OECD Workshop on Exposure Assessment and Exposure Mitigation, which was held on 20 October 2008, in Frankfurt, Germany. This report includes a summary of the plenary presentations 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>.

OECD WORKING PARTY ON MANUFACTURED NANOMATERIALS (WPMN)
WORKSHOP ON
“EXPOSURE ASSESSMENT AND EXPOSURE MITIGATION”

Hosted in cooperation with

the Business and Industry Advisory Committee to the OECD (BIAC)
and
the German Federal Institute of Occupational Safety and Health (BAuA)

Organized by the WPMN Project on “Co-operation on Exposure Measurement and Exposure Mitigation” (SG8)

Sponsored by the German Chemical Industry Association (VCI)

Summary Notes

Welcoming Remarks

The German Chemical Industry Association (VCI) welcomed the participants and expressed its pleasure for the active participation of the workshop that underlines the importance of the issue.

Stefan Engel, BIAC, thanked the organizers, OECD and VCI. Engel expressed his hope that the workshop will contribute to consensus building concerning exposure assessment and exposure mitigation.

Peter Kearns, OECD secretariat, stressed the importance of the projects on exposure measurement and exposure mitigation and of the future co-operation from stakeholders, institutions and industry to follow-up the ambitious scope of the WPMN Steering Group 8 (SG8) leading the work on “Co-operation on Exposure Measurement and Exposure Mitigation”.

Vladimir Murashov, Chair of the OECD work on Co-operation on Exposure Measurement and Exposure Mitigation (SG8), saw the OECD playing a critical global role to rapidly develop and implement harmonized tools for data collection and data analysis at inter-government level. It noted that the work initially focused on occupational exposures since it is widely recognized that the primary area of concern for adverse human health effects with any emerging technologies is in the workplace. As knowledge base for this area is rapidly evolving, the OECD’s WPMN organized this workshop to initiate consensus building discussions and to facilitate SG8 project development. Murashov pointed out that another workshop in the US in 2009 was in preparation with focus on population exposures and exposures to the environment. Murashov gave also thanks to BIAC, OECD, VCI and BAuA for sponsoring the workshop.

Session 1: Exposure Measurement (including Analytical Methodologies and Occupational Measurement Strategies)

Latest Developments in Analytical Methodology⁴

Thomas Kuhlbusch, IUTA, Germany, gave an overview on the latest developments in analytical methodology. Kuhlbusch suggested that following up monitoring exposure does not necessarily mean to apply the appropriate dose metric. The task of exposure measurement is monitoring with differentiation between manufactured nanomaterials and ambient nanoparticles. Number and surface area, time intervals of measurement and control of background contrast are backbones of exposure metrics.

According to Kuhlbusch, exposure measurement has to focus on aerosols and airborne particles. Therefore the analysis of exposure routes is important. Although it can be observed that the nanoparticle uptake probability rises in the size range of nanoparticles with 20 – 80 nm in diameter, it has to be obeyed that the internal dose that determines biological responses is different.

The level of detection required by regulators has to be discussed; therefore it is a question of whether threshold limits (e.g., for single particles) may be helpful. Kuhlbusch followed up that whatever the political answer to that question may be, science strongly expresses the need to base limit values on hazard assessment results.

Exposure measurement should accomplish a check on personal exposure in environmental settings. Thus continuous or "online" measurement techniques have to be implemented. Discontinuous sampling for physical-chemical analysis may be the next step within the measurement protocol.

State-of-the-art for nanoparticle exposure measurement uses a combination of methods with several different types of measurement devices for various properties. It is important that measurements be conducted at distinct locations and under different nanoparticle activities when establishing continuous monitoring at workplaces.

Personal sampling measurement techniques are lacking but are being developed as basic technologies with high time resolution are available in principle. International quality assurance and quality control is very important to assure adequate performance standards.

Differentiation of particle measurement from background is a prerequisite for any monitoring activity that meets regulatory requirements for exposure control at the workplace. It has to take into account physical-chemical properties from the manufactured products. To set up standardized measurement, appropriate reference materials for different sizes and morphologies, furthermore reference procedures for handling and testing, are needed.

Kuhlbusch concluded that measurement techniques and devices are available in principle and have been tested to measure nanoparticles, and further developments are to be expected. Especially personal easy-to-use equipment for SMEs and dose relevant devices are still needed or has to be improved further.

⁴ See Annex

Nanoparticle Measurement in the Workplace for Risk Assessment⁵

Yi Jongheop, Seoul National University (SNU) Korea, reported on nanoparticle measurement. The measurements revealed a strong size and type dependency. It was observed that silver nanoparticle agglomeration could be characterized by a specific growth factor. Furthermore nanoparticle formation is subject to temporal changes. Jongheop summarized that measurements are mainly affected by humidity and agglomeration changes in dependency from the pH. Thus SMPS data must be controlled and corrected due to water vapour effect (within the size range of 10 – 40 nm particles), heating effects, and flow velocity/powder pouring effects (occurring during processing and storage).

The feasibility and reproducibility of measurement methods (on-line monitoring with SMPS systems) have been tested at the workplace determining silver particles. Polystyrene particles of 50 and 100 nm have been used as reference material.

Yi reported that the measurements have been conducted during the production process at different steps. The changes in nanoparticle size distribution have been monitored.

In the discussion, the aerosol generation from liquid suspension and the changes size range by agglomeration were debated.

Distinction of Carbonaceous Nanomaterials from Background Airborne Particular Matter⁶

Mariko Ogasawara, JNIOOSH, Japan, showed the results of measurements monitoring workplaces at different times, seasons, and exposed to different particle sizes. She concluded that background effects (such as emissions from diesel or electric pumps, ventilation, fork-lifts etc.) are inevitably part of the background burden; therefore real time monitoring is only advisable when background is low and not fluctuating. Ogasawara showed that particle background in factory housings is generally twice as large as in ambient air. Measurements sometimes are effected by by-product transfer within production processes and flaking as these processes cause variations in the physical state of the measured particle (e.g., bundled or unbundled particles, agglomerated or coagulated material). Ogasawara summed up that chemical analysis of carbon allotropes has to follow case-by-case procedures, whereas most difficulties are observed in sampling preparation procedures.

Ogasawara reported that improved measurement protocols for Multiwall Carbon Nanotubes (MWCNT) have been developed, but control measurements still have to be adopted. Different reference standard materials showed different results with dependency on shape, impurities and by-products. For Single Wall Carbon Nanotubes (SWCNT), a combination of different measurement methods has to be used.

Ogasawara concluded that in the workplace real time instruments are to be used and have to be supported by chemical analysis. The methods can only be developed case-by-case and should imply a check of background sources.

In the following discussion it was stressed that the sensitivity of the methods lies in the µg-range. Ogasawara reported that the background effects from carbonates could be separated by the high temperatures of measurement process. For analysis of carbon fibres a database that characterise effects of shape and impurities is currently under development. Generally it can be concluded that exposure assessment is a very complex matter but is going to be adapted for easier application by actual research.

⁵ See Annex

⁶ See Annex

Session 2: Determinants of Exposure in the Workplace

Relevance of Dustiness and Aerosol Dynamics for Personal Exposure⁷

Thomas Schneider, NFA, Denmark, reported that in-house methods to monitor product quality control are already in place in industry, but for exposure measurement, standardized methods still have to be developed. As dustiness is the most important amongst several major exposure determinants, the generation of the standardised microgram amounts of dust - e.g. by instruments as rotating drums or vortex shakers - is a basic prerequisite.

Testing the generation of different TiO₂-particles revealed peaks around 200 nm and 1 µm. For measurements with particles up to 600 µm a particle mobility analyser above 600 µm particle analyser should be used.

Thomas Schneider reported also that ISO has started developing tests to determine particle dustiness. He questioned if additional reference test methods are needed. To choose the correct metrics for each method applied, the activity profile of the particles has to be comparable. To determine possible hazardous effects, it has to be clarified if nanoparticles are subject of deagglomeration processes in liquid media of the lungs.

To assess particle aerodynamics, important parameters are turbulence, coagulation, surface deposition, and adsorption. For further assessment, computational simulation is a useful tool to predict real time measurements. The instruments for modelling are available in principle but need further development and adaption; more results are likely to be expected from the “Nanotransport”-project funded by the European Commission.

Schneider thought also that scenario banding is a suitable instrument to determine exposure in the workplace.

In exposure measurements it could be shown that nanoparticles attach to larger particles in the background in dependency on the particle properties and background aerosol. Field experiments revealed a limit for exposure measurements at workplace within the size range of 50 - 70 nm or within 10 – 30 nm at production sites respectively. In the discussion it was resumed that even the measurement process can influence the state of the nanoparticles.

Development of Exposure Situations in the Workplace⁸

Derk Brouwer, TNO, Netherlands reported on the development of instruments to assess exposure situations in the workplace. This is especially of importance for downstream users. Brouwer stressed that most of the currently available studies have an explorative character. A focus of scientific exploration lies with the questions of spatial and temporal variation of nanoparticle emissions at background level. Background nanoparticles make it extremely difficult to determine low nanoparticle activities with low contrast to background level. As in regular exposure situations there are only very few primary nanoparticles or aggregates but many agglomerates, nanoparticle related activities can only be observed for a limited duration. Projects that may deliver progress in the near future are the NANOSH project of the European Commission that develops modified methods to measure dermal exposure or the Dutch TNO project on developing devices for static monitoring to give an overview on nanoparticle related activities. First results show that there is no increase of nanoparticles emissions in number concentration in the size range below 100 nm whereas emissions can be observed in this size range above 100 nm.

As the measurement strategy is of great importance, Brouwer recommended conducting control measurements and using well characterised background reference (outdoor, periods of no activity etc.). A thorough data analysis has always to take into account the results of models for size distribution and should include qualitative TEM measurements for control. Furthermore he recommended to build a database (e.g., at OECD) that could be used to harmonize measurement methodology.

⁷ See Annex

⁸ See Annex

Session 3: Plenary Discussion on Session 1 and Session 2

In the following plenary discussion on Sessions 1 and 2 with Kai Savolainen and Session 1 and 2 speakers, the following questions have been discussed:

a) What are the best exposure metrics according to the state-of-the-art?

Participants came to the conclusion that only toxicology can reveal the decisive parameters for exposure measurement. The technology by itself is already in place, for example sensitive methods for measuring number concentration as a good metric to start with. The determination of the adequate time periods for exposure measurements and assessment must be clarified. Therefore a database could help to enable analysis of current exposure measurement results.

Particle formation and particle transport is considered to be a very important process. Within that process, particle scavenging may be fastest and thus lead to the conclusion that levels of measurement may be too small to be of relevance. Correlation of measurement results to a nanoparticle related activity is considered most relevant.

The NanOSH project funded by the European Commission could so far not agree on metrics. Participants stated that mass and number concentration should be measured together for a given substance surface area.

b) Which data can be reliably collected?

According to participants number size distribution should be measured and other metrics may be derived by calculation. It was mentioned that pre-charging and morphology have to be taken into account. Thus there are some good reliable basic data (particle number and particle size distribution) that need to be standardized and harmonized to allow comparison. It was felt that measurement of number concentration would be a very sensitive parameter for real workplace environments. It was agreed that reliability of measurement is affected by inability to distinguish background levels and reference material.

c) What approach could be preferred for exposure measurement?

According to participants results of exposure measurement should be used to establish measures to prevent exposure. Furthermore the OECD Sponsorship Programme should examine differentiation of manufactured nanoparticles from ambient nanoparticles. The OECD WPMN should take care to ensure close cooperation between analysis and toxicology.

d) How to qualitatively assign nanomaterials into exposure categories?

It was discussed that particle-distribution reveals information to monitor production. For assignment into exposure categories, heavy metals and quantum dots may be grouped together. Any collection of data should be the basis for further benchmarking. The participants did not discuss assignment of nanomaterials into exposure categories.

Session 4: Exposure Mitigation Measures

Efficiency of Engineering Controls

Chuck Geraci, NIOSH, USA, focussed his talk on controlling nanoparticle release from the production facility based on his report on evaluating exposure mitigation measures. To efficiently control nanoparticle exposure, an efficient capture system is needed and the physical-chemical properties of the material produced have to determine the control system applied. A distinction has to be made between open handling, liquid systems, and new materials that are produced in low annual volume scale.

The following measures to control nanoparticle exposure may, according to Geraci, be selected upon:

- Prevention through design;
- Alignment with known or anticipated health hazards;
- Other factors influencing exposure risks;
- Incomplete health hazard datasets that will prompt conservative control approaches; and
- Expect control performance to be similar to fine powder handling.

The decision on which type of control measure will be appropriate depends on the level of knowledge on exposure conditions and substance hazard. Enclosed production facility, for example, have proven good performances; alternative measures can be easily adopted (e.g., ventilated enclosure to control potential emissions).

Geraci concluded that the design of safety measures has to follow synthesis to production, and that many control strategies can be re-designed for nanomaterials manufacturing. Evaluation is needed to determine if measures match with requirements for workplace safety. Furthermore gap analysis is required.

Efficiency of Personal Protective Equipment

Frederik Schuster, CEA, France reported that the EU project “Nanosafe” started in 2002 as a global effort. The first phase is looking at advanced detection and monitoring technologies. It is directed to facilitate incremental and breakthrough innovation by new nanomaterials by providing adequate safety measures so that safe development of nanotechnologies can be ensured.

According to NanoSafe experiences, efficiency evaluation of Personal Protective Equipment (PSE) requires a whole life cycle approach. Rapid *in vitro* toxicity screening and *in silico* methods are developed within the project. Therefore batches having been used in nuclear technology are re-designed to read out and monitor personal exposure on nanoparticles.

It has been shown that HEPA filters are efficient measures to protect from nanoparticle emissions. Gloves have been tested against exposure with CNT a size range tests of 15 – 250 nm. Tests for clothes and further testing procedures for gloves are in the process of being established.

Furthermore, safe processes for nanoparticle slurring systems (e.g. within the “Saphir project” – Safe NanoManufacturing Process), surface technologies, automotive applications, and materials for building are subject of current developments including educational software for workforce.

Session 5: Risk Assessment in the Workplace

Qualitative Risk Assessment:

Paul Swuste, Delft University of Technology, spoke of public perception being derived from generalized reception of nanoparticle pathogenicity. According to Swuste, the instrument of Control Banding (CB) is designed to assist especially small and medium enterprises (SMEs) to cope with uncertainties in a risk assessment. Hazard bands are set up according to parameters of European regulation; exposure bands follow production volumes, impact, and dustiness of nanoparticles. The Control Banding instrument can be applied on chemicals, ergonomics, occupational risk prevention exercises, or nanoparticle-exposure. It is put into practice by the exposure levels “extremely likely”/“less likely”/“likely”/“probable” and the following risk levels: “very high”/“high”/“medium”/“low”. Control Banding may be limited by the uncertainty of factors and scores of probability and severity. Advantages of the instruments are its transparency and simplicity.

In the discussion it was pointed out that Control Banding approaches are already being applied by the US industry. It was made clear, however, that establishment of a Control Banding regime for nanoparticles needs strong international consensus as a first step towards any further possible application.

Approaches for the Definition of Threshold Limit Values for Nanomaterials

Bruno Orthen, German Federal Institute of Occupational Safety and Health (BAuA), Germany discussed important parameters of an appropriate metrics for exposure measurement. According to the BAuA threshold limit values (TLVs) for nanomaterials should become the target of more intensive debate. According to Orthen several approaches for setting TLVs for MNs can be found in literature. To date, legally binding TLVs are available only for amorphous silica (2 - 6 mg/m³). NIOSH has drafted exposure limits for TiO₂ (2005). TLVs for respirable nanomaterials might be derived from the database of corresponding micro scale particles. BSI has issued such relative benchmark levels. (the TLV relation might be estimated to be 0.066 for insoluble material derived from results by NIOSH, 0.1 for CMARs, 0.5 for soluble nanomaterials).

Intensified research on the mechanism of action of nanoparticle in the biological media is needed to derive TLVs on a sound scientific basis. BAuA has proposed to conduct at least 3 month *in vivo* toxicological studies regarding all possible workplace atmospheres with detailed characterised material. Orthen concluded that the approaches to establish TLVs are based on scientific data that take into account necessary elements of caution.

Based on a discussion in Germany Orthen estimated that for regulatory needs a risk level of 0.004 % seems to be acceptable on a long-term perspective.

In the following discussion, it was agreed, that a factor of 15 to derive TLV may be suitable as a maximum. Further discussion on appropriate factors for micro- and nanosized particles is necessary.

Session 6: Plenary Discussion on Session 4 and 5

In the following plenary discussion on Sessions 4 and 5 with Brian Fullam and Session 4 and 5 speakers, the following questions were discussed:

a) What are minimum requirements for exposure mitigation?

Geraci spoke on risk characterisation of possible exposure scenarios that may provide information to build up a library of solutions for industrial processes with requirements especially of new materials for risk mitigation to be evaluated. Evaluation of physical parameters should start with dustiness.

Participants identified the need to test gloves against fibrous particles although attention should be paid to the fact that in industrial process gloves are only needed for spill off cleanings and not as protection against permanent exposure.

b) Can “mitigation factors” be developed for engineering controls for nanomaterials?

According to the experts only a range of efficacy for engineering control parameters can be given.

c) How to qualitatively assign nanomaterials into hazard categories?

According to some experts, the factors to estimate the hazardous potentials of substances in the Control Banding regime may be an instrument used to direct nanomaterials into hazard categories. Both the advantages and disadvantages of Control Banding were discussed. The scientific background is not ready to establish the necessary control banding categories.

d) What are the relevant metrics?

Experts pointed out that in research projects, mass, number concentration and surface area are used as metrics. Besides the extension of metrics, their application needs further discussion. The measurement of size dependent sampling is already implemented but mass is still a relevant metric, if the route of exposure should be described properly.

According to the experts from academia and authorities, a factor of 50 % accuracy may be enough for regulators. As first step is to demonstrate that exposure can be controlled.

Panel Discussion

Participants: Kearns (Chair, OECD), Bönke (EU), Klein (BMAS), Ogasawaka (JNIOH), Murashov (NIOH), Friedrichs (BIAC), Wriedt (TUAC)

a) How are exposure measurement and exposure mitigation for nanomaterials in occupational settings covered in national regulations?

According to representatives of the European Commission, it can be concluded from regulatory assessment that regulatory framework covers nanomaterials including obligations for workers. For adequate risk assessment, instruments have to be ready in place. The European Commission reserves a considerable amount of resources for research in developing the knowledge base and filling knowledge gaps.

SG 8 Chair Vladimir Murashov pointed out that US Occupational Safety and Health Act (US OSHA) states that the employer is ultimately responsible for the safety of workers including nanotechnology workers. A number of existing US OSHA standards apply to nanotechnology and nanomaterials. Examples are Hazard Communication Standard, Respiratory Protection Standard, Personal Protective Equipment Standard, Hazardous Chemicals in Laboratories, Substance-specific standards. Questions remain, however, about adequacy and relevance of these standards for nanotechnology workplaces.

According to TUAC, the application of the European Chemical Agents Directive requires guidance for nanomaterials. Risk assessment is an issue for all regulatory frameworks and none exclude nanomaterials.

Boenke and Klein from the German Ministry of Employment and Social Affairs (BMAS) pointed out that the precautionary principle is related to risk management but not to risk assessment, putting the producers in charge to derive and to read across information to assess the possible risks of nanomaterials.

b) How should uncertainty/paucity of data be handled in conducting risk assessment and developing risk management programs for nanomaterials in occupational settings?

c) What is the role of qualitative risk assessment and risk management tools in ensuring occupational safety and health of nanomaterials?

Ogasawaka from the Japan National Institute for Occupational Health and Safety (JNIOSH) stated that the JNIOSH issued instructions with tentative guidance to handle nanomaterials in February 2008. Currently a committee is working to improve these instructions and is expected to release results in March 2009.

BIAC stressed that uncertainty in exactly assessing exposure does not mean miscalculating risk at workplace. Moreover the chemical industry is used to dealing with uncertainty in data and has therefore well established risk mitigation measures in place. TUAC noted, however, that there still remain difficulties for down-stream users handling manufactured nanomaterials.

According to the European Commission it will be useful to have toxicologists and scientists of physical chemical analysis exchange and pool their knowledge to develop feasible, easily applicable and cost effective methodologies. Furthermore exposure modelling is expected to give reliable guidance until exact data is available.

d) What is the role and status of health surveillance for nanomaterials in ensuring safety and health in the workplace?

Klein from BMAS reported that results from authorities with obligatory and mandatory health surveillance have not revealed any nanospecific effect. Experts added that health surveillance studies may be adapted to new medical endpoints. BIAC made clear that health surveillance is a primarily a question of hazard.

Murashov pointed out that NIOSH published some guidance on medical screening of workers potentially exposed to nanomaterials in 2007. Until NIOSH gets more information on health endpoints specific to exposures to manufactured nanomaterials, it is recommended to conduct needs assessment, take practical measures to control exposures, and to consider implementing established medical surveillance approaches. The experts did not recommend establishing nanospecific medical surveillance at this time.

e) What is the role of OECD WPMN in ensuring occupational safety and health of nanomaterials globally?

The WPMN chair of the work on Co-operation on Exposure Measurement and Exposure Mitigation (SG8) pointed out that OECD is especially effective at conducting economic evaluations, harmonizing test guidelines, exchanging information and data, and facilitating adoption of globally-harmonized voluntary and regulatory programs by governments around the world. It can also provide a mechanism for leveraging research resources by facilitating international government program co-ordination. Specifically for occupational safety and health of nanomaterials, the WPMN initiated two projects to “Provide recommendations on measurement techniques and sampling protocols for inhalational and dermal exposures in the workplace” and “Compare guidance on personal protective clothing, gloves and respirators.” Kuhlbusch wants OECD to establish a database with information on exposure.

Geraci spoke on market driven place process to derive guidance for risk assessment measures as traditional scientific paradigm for developing a new metric will not be sufficient for today’s business.

Kearns explained OECD’s role in co-ordination and exchange of information that is directed to develop globally harmonized approaches for exposure measurement and exposure mitigation. The WPMN SG8 has conducted prioritization efforts and is seeking feedback on work. The audience encouraged OECD to provide more guidance derived from its work.

Conclusions from the workshop

Measurement techniques and devices are available in principle and have been tested to measure nanoparticles. But standard measurement processes have to be agreed on that are founded on a reliable basis on reference materials and measurement calibration.

The design of safety measures has to follow the whole life cycle. Many control strategies can be re-designed for nanomaterial manufacturing.

Personal, easy-to-use equipment and dose relevant devices are still needed or have to be improved further. Standards for Personal Safety Equipment (PSE) are necessary.

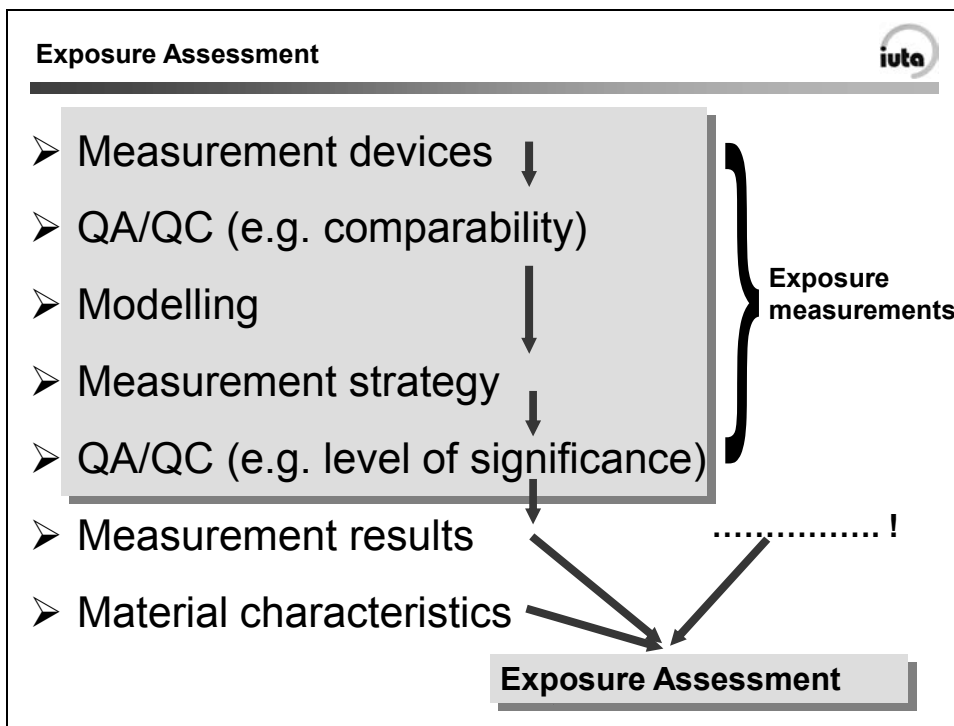
OECD should function as co-ordinator and should consider establishing a database with information on exposure measurement and exposure mitigation measures for handling nanomaterials.


ANNEX: PRESENTATIONS

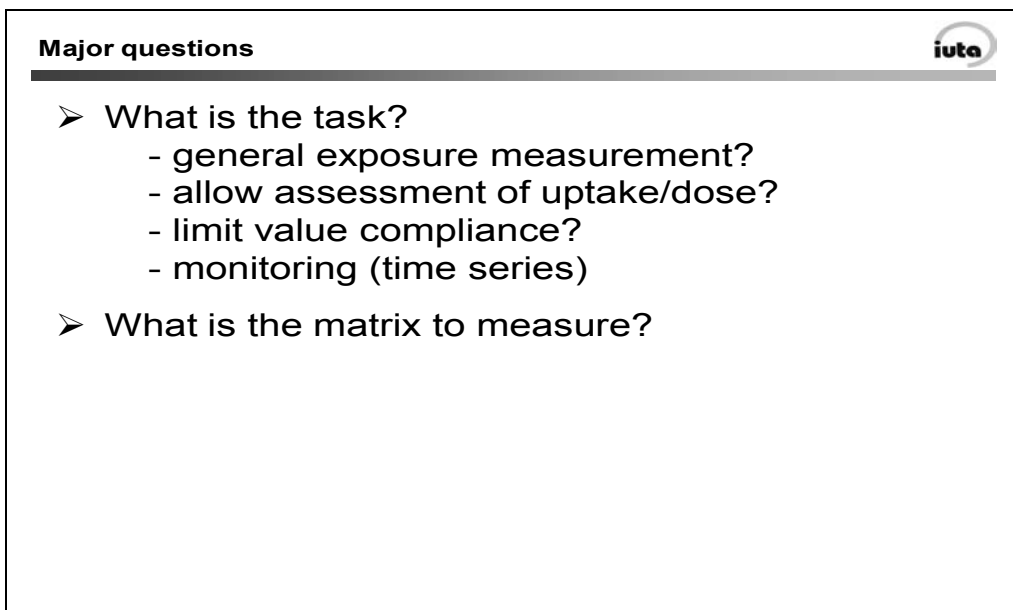
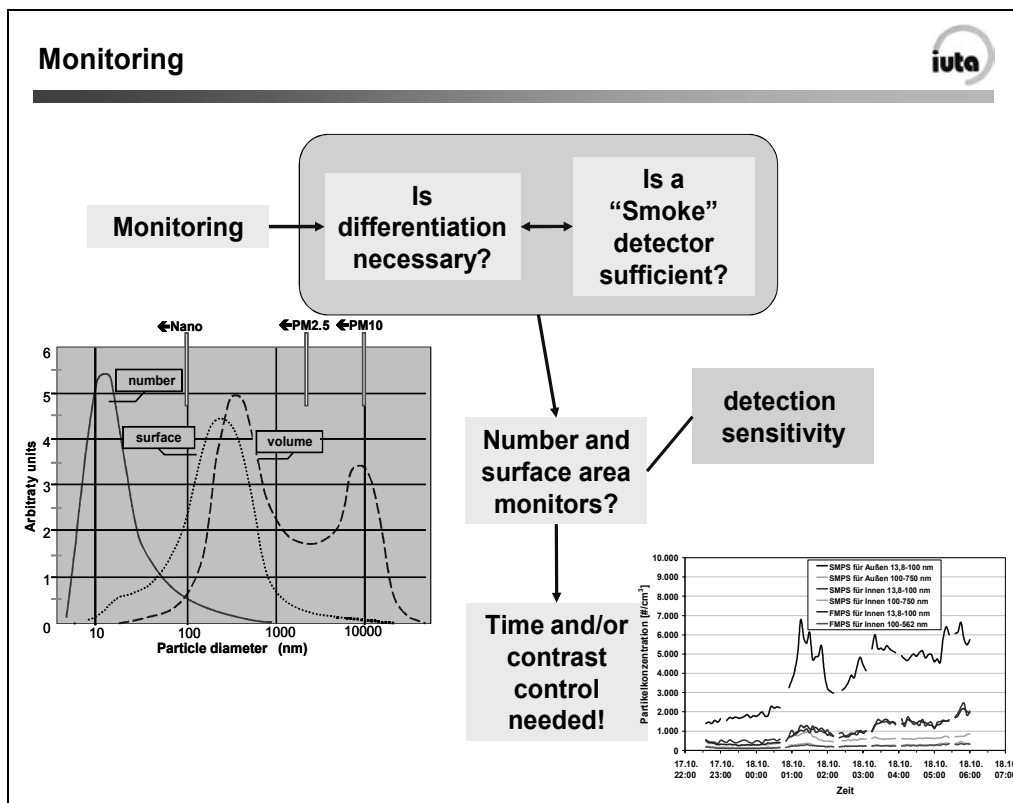
Presentation 1

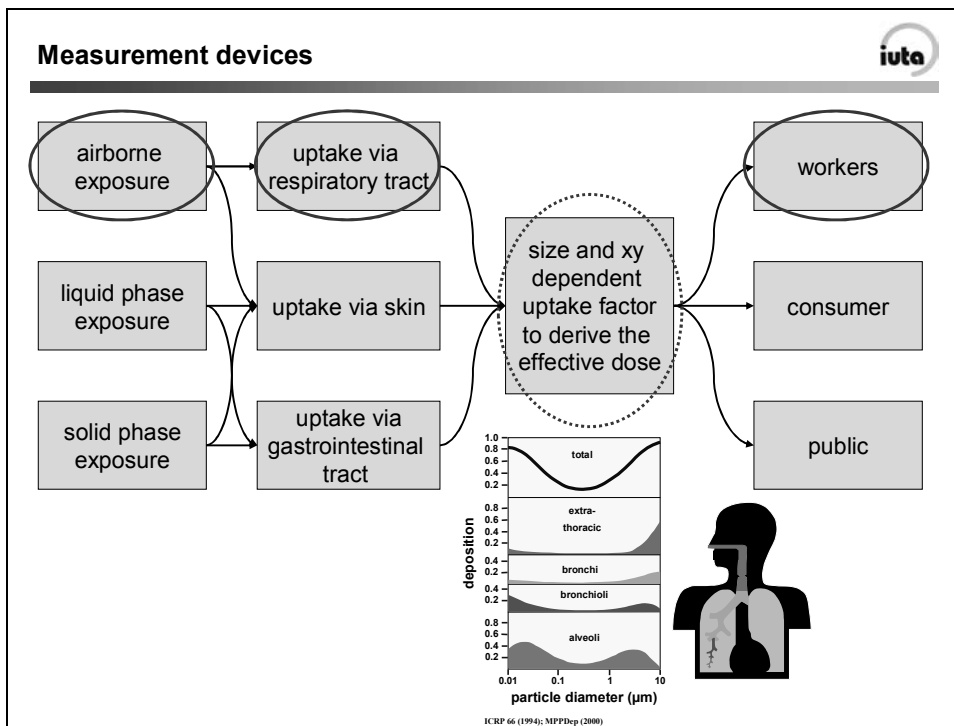
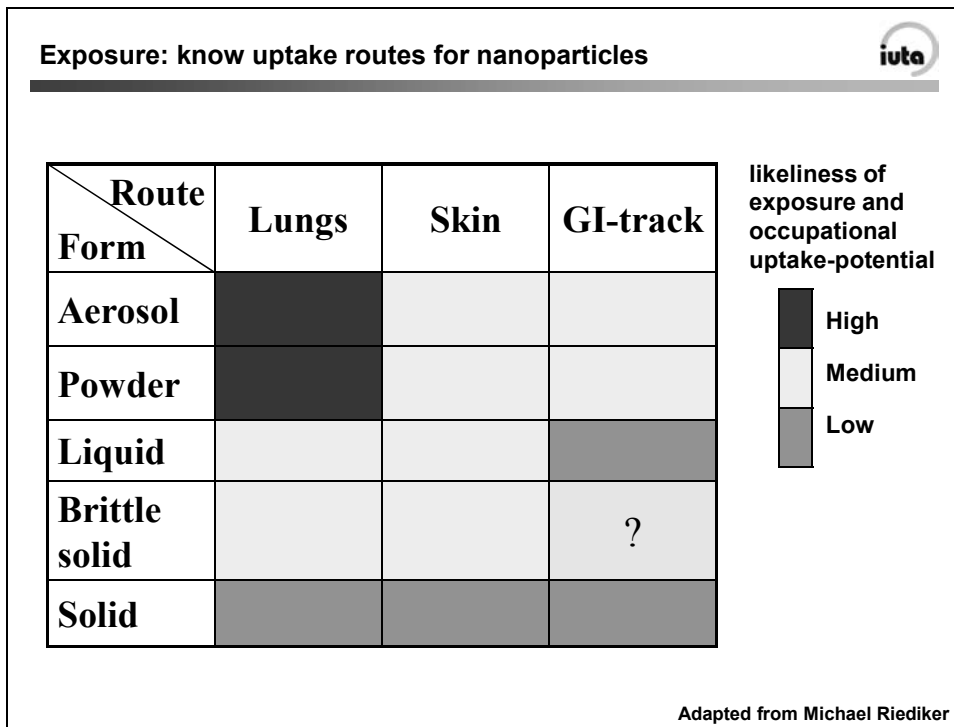
Exposure Measurements- Latest Developments in Analytical Methodology: Thomas Kuhlbusch





- Major questions** 
- What is the task?
 - monitoring (time series)
 - general exposure measurement?
 - allow assessment of uptake/dose?
 - limit value compliance?





Major questions



- What is the task?
 - general exposure measurement?
 - allow assessment of uptake/dose?
 - limit value compliance?
 - monitoring (time series)
- What is the matrix to measure?
- What level of detection is needed?

Exposure measurement - Limit of detection




- Which limits of detection are necessary / required?

**Shall single NP,
shall 1,000-100,000 N/cm³,
shall only > 100,000 N/cm³
be detected ?**

ENP Detection	
Number (#/cm ³)	Surface (µm ² /
<1,000	< 0.01
1,000-100,000	10 – 1,000
> 100,000	> 1,000

Has to be based on hazard assessment results!


Exposure measurement – ideal 

P.J.A. Borm *et al.*, *Part. Fibre Toxicol.* 3:11, 2006

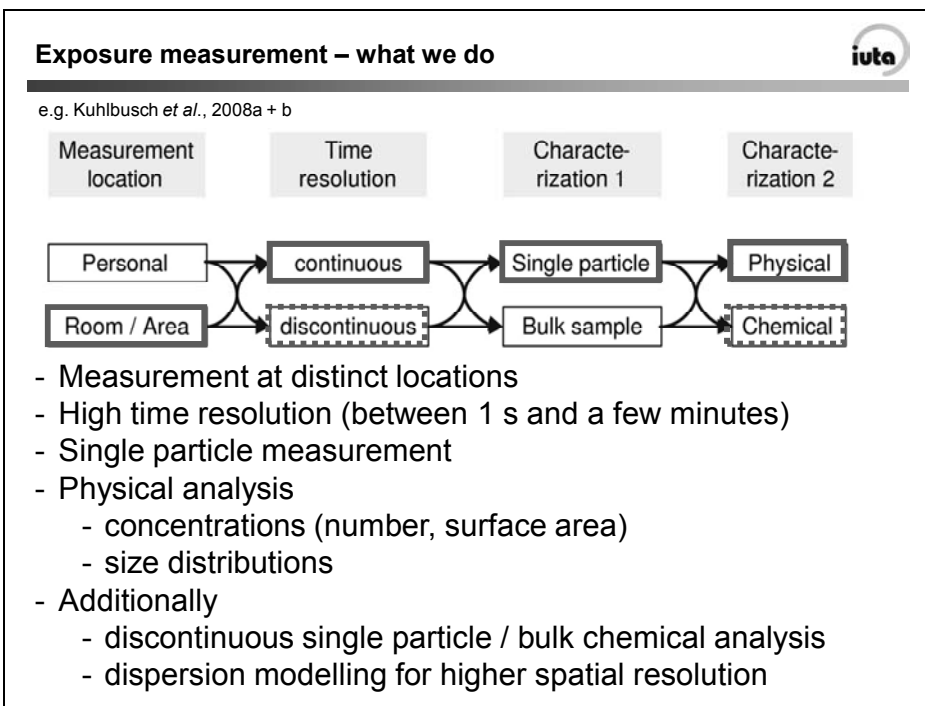
Measurement location	Time resolution	Characterization 1	Characterization 2
Personal	continuous	Single particle	Physical
Room / Area	discontinuous	Bulk sample	Chemical

Ideal:

- Personal measurement
- High time resolution (continuous measurement)
- Information on each single particle
- Physical and chemical analysis



➤ **State-of-the-art**



Measurement devices

Property	Sampling	Instrumentation Analysis	Conti.	Personal/ Portable
Number concentration		CPC / CNC	Yes	Yes
Number size distribution		SMPS, EMAP		No (Yes)
Sum of diameter ($d^{1.13}$)				
Surface area concentration*				
Surface area desorption				
Size distribution				
Hygroscopicity				
(relative) humidity morphology		ESCA	No	Yes
Mass size distribution		quadr. ELPI, chemical analysis	No	Yes
Particle reactivity	Filtration sampler	EPR	No	Yes

*: Fuchs surface area equivalence

- A variety of techniques and devices is available
- Most publications: use of CPC and SMPS systems
- Currently lack of personal / easy to use devices
- Promising developments (EU-NanoDevice) (surface area, diffusion batteries....)

Newer devices

Personal sampler

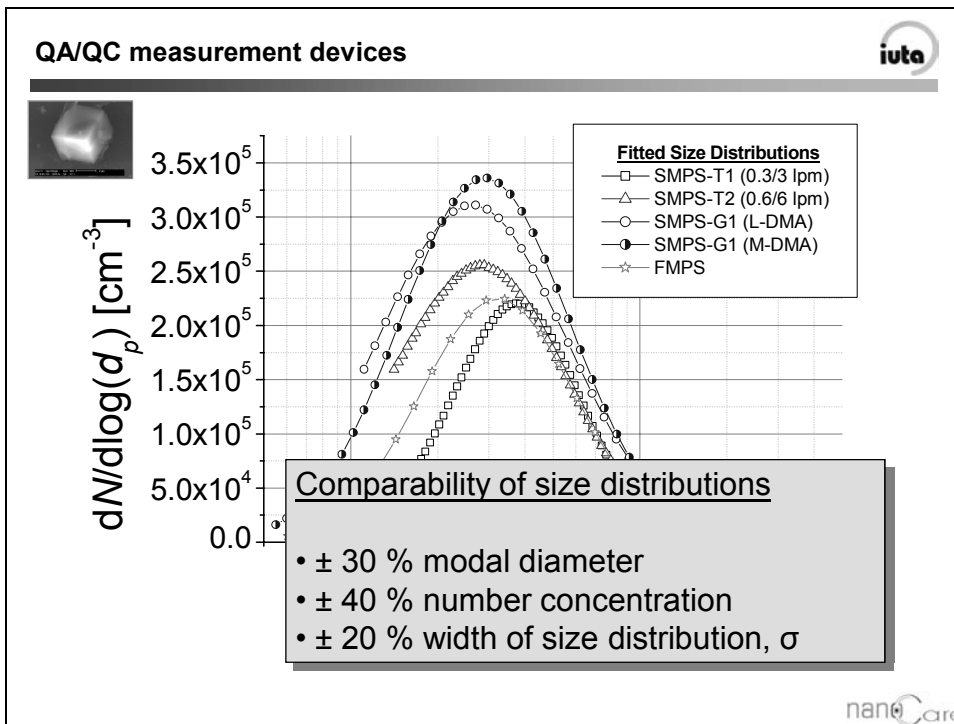
Handheld CPC and Lung deposited particle surface area monitor Aerotrak ($\mu\text{m}^2/\text{cm}^3$)

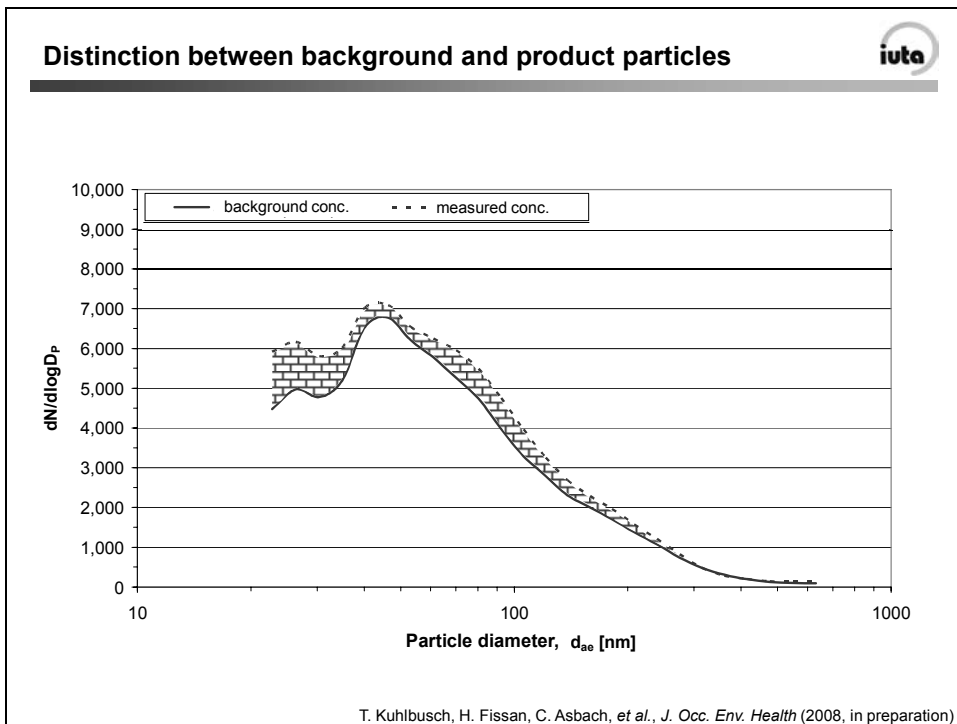
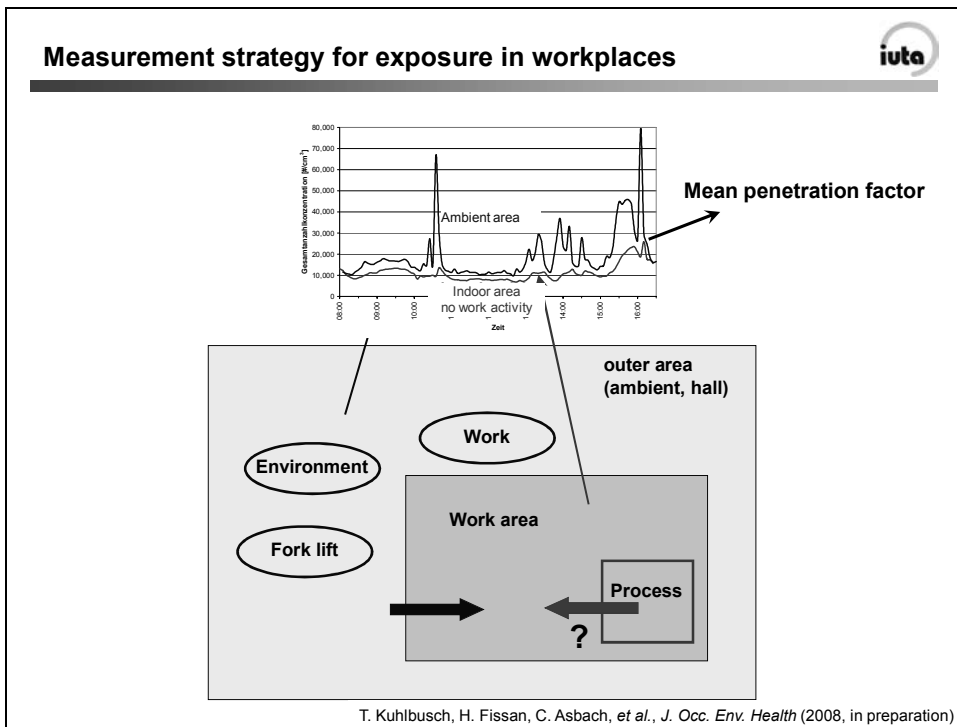
surface area monitor LQ 1-DC ($\mu\text{m}^2/\text{cm}^3$)

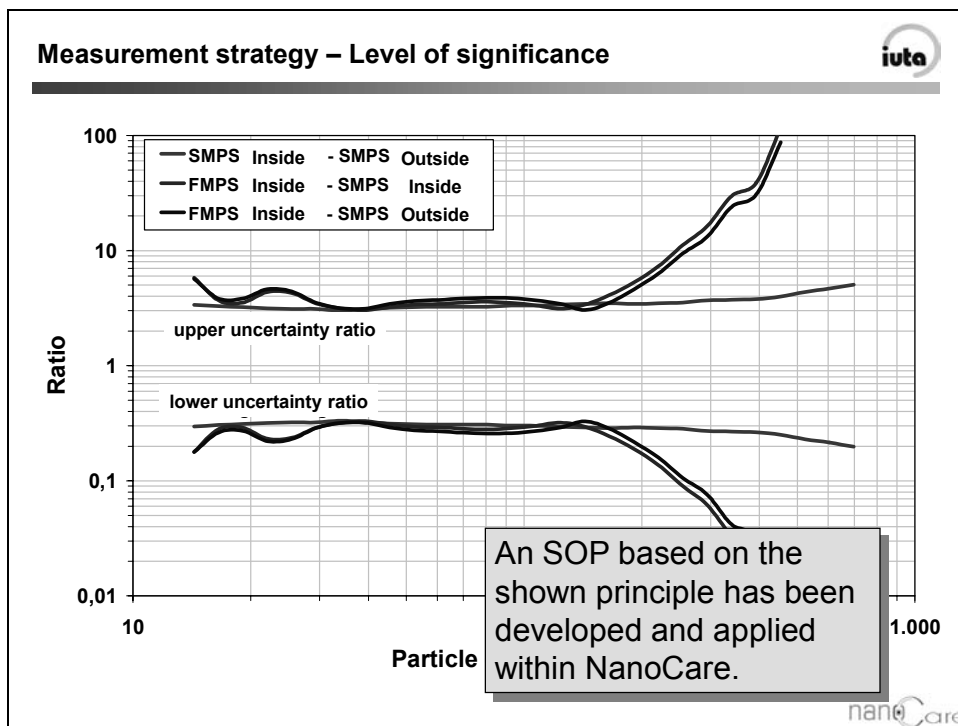
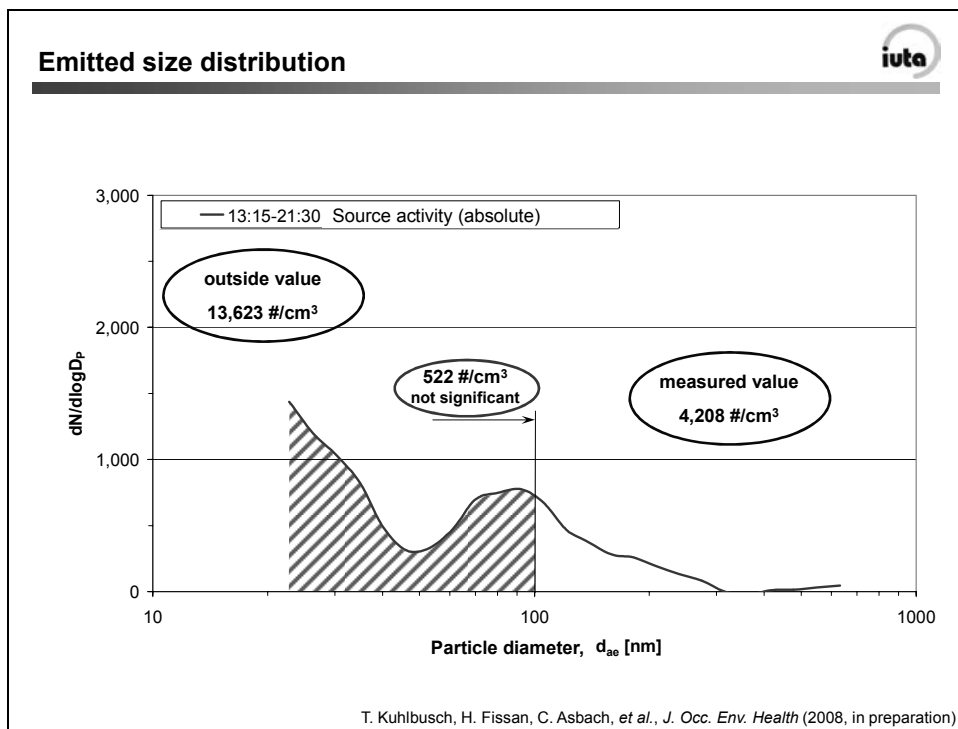
Matter-Engineering

Handheld CPC and Lung deposited particle surface area monitor Aerotrak ($\mu\text{m}^2/\text{cm}^3$)

TSI







Reference material



- Reference materials with respect to particle size calibration (primary standards)
- Reference materials are needed in all cases when no primary standards are available, e.g. in toxicological tests
- Reference materials are needed for testing and quality control of measurement devices
 - Spheres with different primary sizes
 - Spheres – agglomerates/aggregates – fibres
 - Different material properties
 - hygroscopic – hydrophilic
 - conductivity / solubility
 -
- But also reference procedures are needed on the handling of the material for QA/QC or test purposes, e.g. aerosolization

Outlook



- An array of measurement techniques and devices are available and have been tested
- Personal, easy-to-use, dose relevant devices still need to be developed or improved (Projects and commercial developments are ongoing)
- Measurement strategies have been developed and tested in the field. Applicability to a wider area should now be tested.
- Identification of NPs?
- QA/QC for devices and measurement strategies are quite crude (e.g. uncertainty range) or unknown. → need for test criteria/test facilities and refinements
- Need of investigations of exposure relevant material characteristics allowing early assessments

Presentation 2

*Distinction Between Carbonaceous Nanomaterials and Background Airborne Particulate Matter:
Mariko Ono-Ogasawara*

Distinction between Carbonaceous Nanomaterials and Background Airborne Particulate Matter



Mariko Ono-Ogasawara

Japan
National Institute of Occupational Safety and Health

Contents

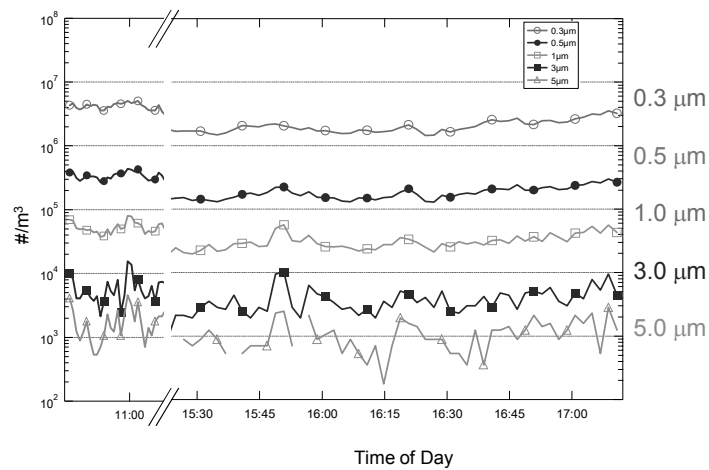
- Introduction
 - Background effect
 - Sources
 - Effects on measurement
- How to distinguish between nanomaterial and background
 - Examples MWCNT and Fullerene
- Conclusion
 - Procedure for exposure measurement

Introduction

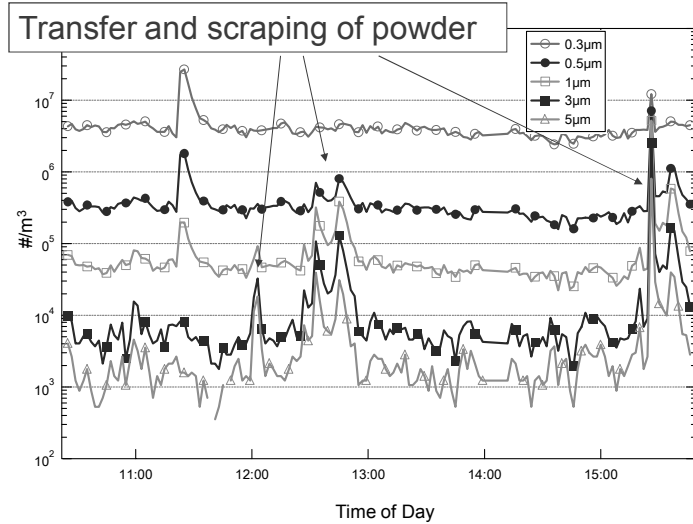
Qualitative measurement

- To find hot spot of nano-particles
 - with real-time monitoring instruments
 - OPC (Optical Particle Counter)
 - CPC (Condensation Particle Counter)
 - Available only when background concentration **low and not fluctuated**
 - Electron microscope – not quantitative

Field survey: Clean-room background measured by OPC

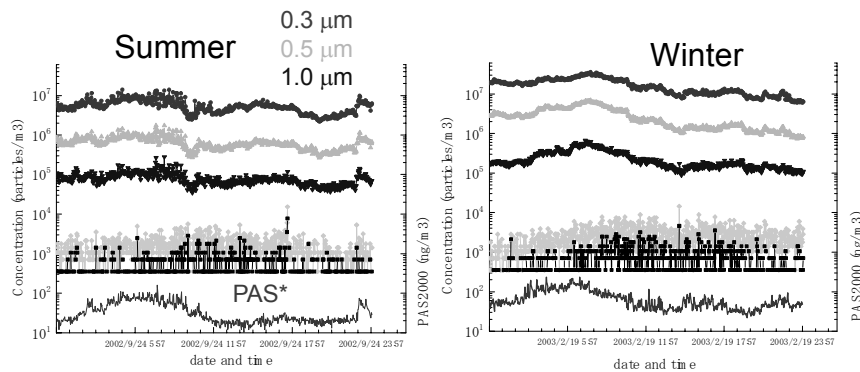


Field survey: Fullerene handling in a clean-room measured by OPC



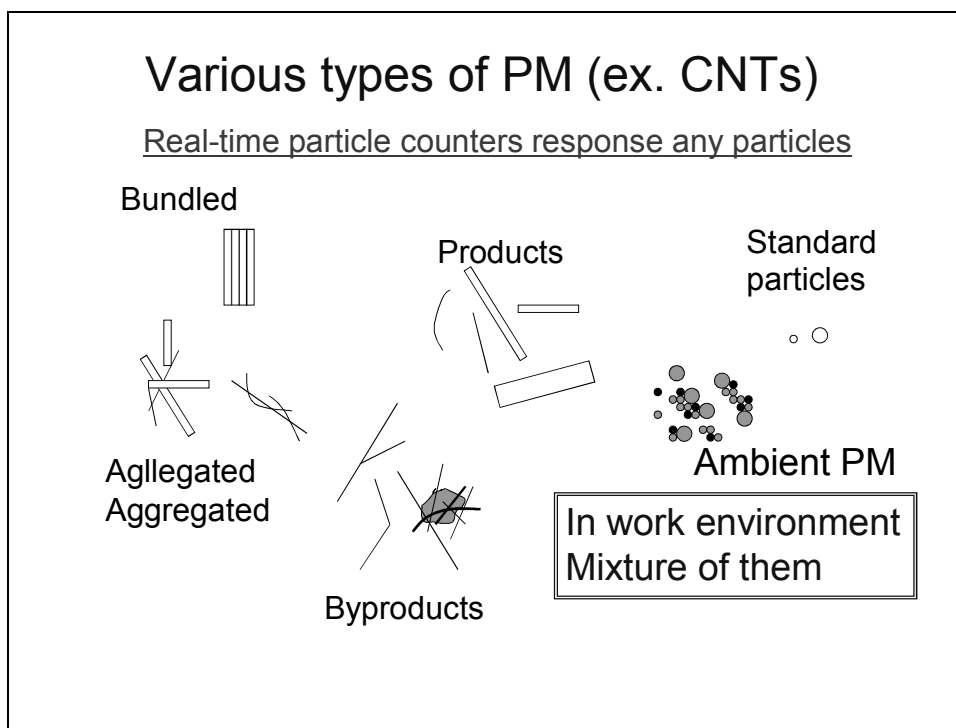
Ambient PM monitored by OPC (Heavy traffic roadside)

Usually high concentration observed at outside



Dilution ratio: ca.13

* PAS: Photoelectric Aerosol Sensor



Background sources and components of nano-size particles

Sources	Components				
	OC	EC	Metals	Others	Nanomaterials
Ambient PM	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Forklifts	<input type="radio"/>	<input type="radio"/>			
Machines	<input type="radio"/>		<input type="radio"/>		
Oil pumps	<input type="radio"/>		<input type="radio"/>		
Vacuum cleaners			<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Air conditioning	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Effects of background PM on measurement

Real-time monitoring instruments suitable only for clean environment because not able to separate objective particles from background PM

Quantitative measurement is needed

- To distinguish objective particles from background PM
- To support real-time measurement
- To determine concentration of nanomaterial
 - Chemical analysis is necessary in many cases because of background effect

Chemical analysis

- Selection of methods – case by case

Nano-materials containing metals

- ICP-MS
 - Pre-treatment is difficult

Carbonaceous materials

(Carbon nanotubes, Fullerenes)

- No appropriate methods for monitoring carbon nanotubes and fullerene

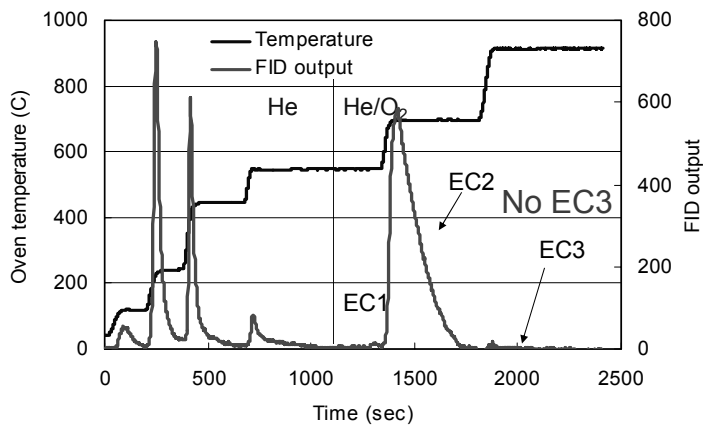
Chemical analysis of carbonaceous nanomaterials

- Semi-quantitative methods for carbonaceous nanomaterials
 - Multi-wall carbon nanotube (MWCNT)
 - Fullerene (C₆₀)

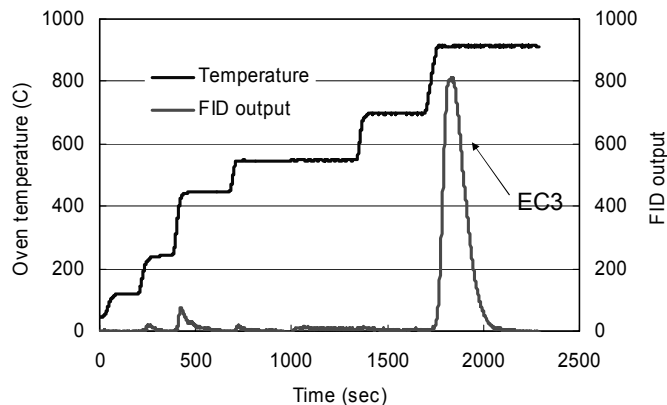
Analysis of MWCNT

- Instrument: OC/EC carbon monitor
 - Analytical protocol: modified IMPROVE
 - Final temperature - 920°C
 - EC3: Carbon evolved at 920°C
 - Index of MWCNT
- Detection limit: 0.3 µg-C for one analysis

Thermogram: PM of heavy traffic roadside

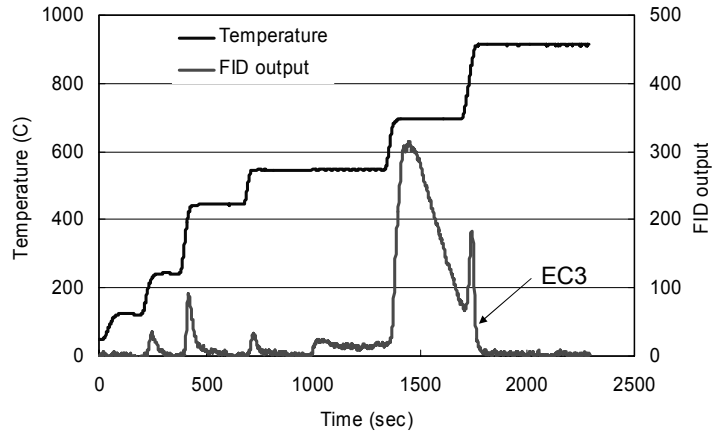


Thermogram: MWCNT (Sigma-Aldrich)



Very pure MNCNT not burned at 920°C
by Adding Fe³⁺ → Burned

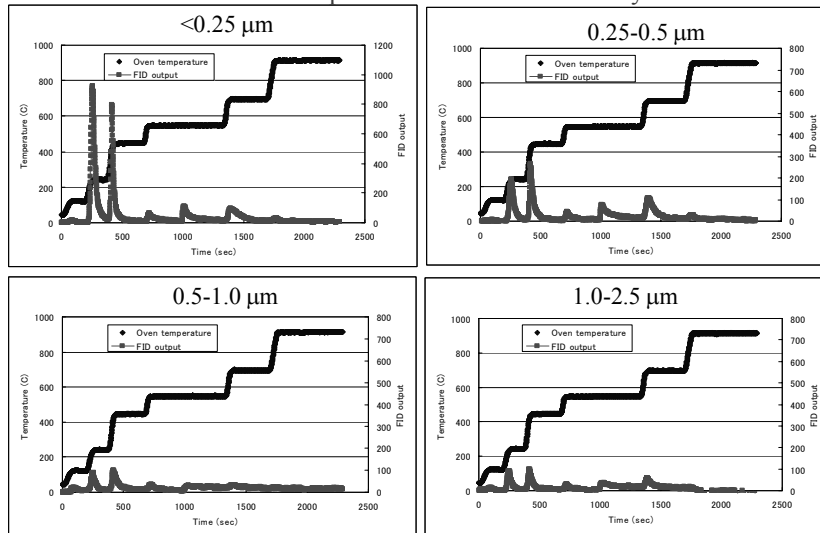
Thermogram: MWCNT(origin unknown)



Rare case: MWCNT evolved as EC2
Effect of shape and impurity?

Field survey: Outside of factory Thermograms

Smaller particles are more affected by ambient PM



Results of field survey: MWCNT production

- Data not allowed to show
- MWCNT in work environment and personal exposure monitored with EC3
- EC3 shows
 - Different size distribution for maintenance and packing work
 - Mitigation effect of engineering control observed
 - Background in factory house twice larger than outside ambient air

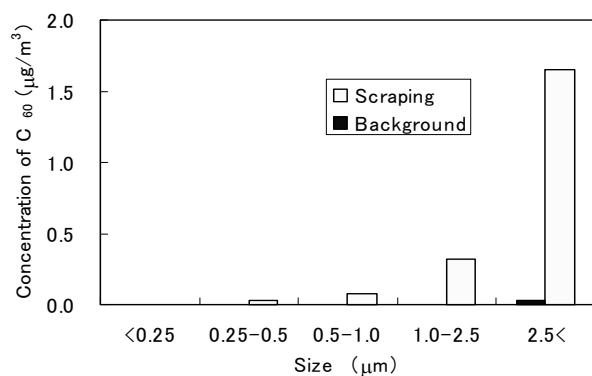
Analysis of C₆₀

- Instruments: HPLC/UV
- Using ordinary reversed phase column
- Toluene/acetonitrile eluent

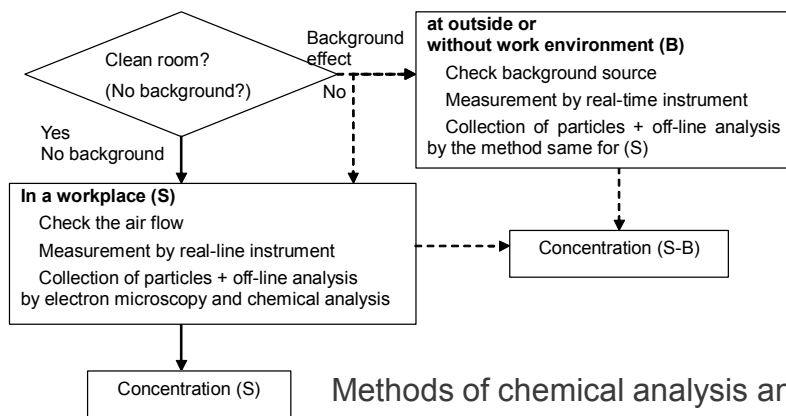
Field survey: same site as pages 4-5 HPLC analysis of Fullerene

Scraping: 0.002 mg/m³

Background (no operation): ND



Conclusion: Procedure for exposure measurement of industrial nanoparticle




Methods of chemical analysis and standard material for quantitation should be selected case by case

Presentation 3

Relevance of Dustiness and Aerosol Dynamics for Personal Exposure: Thomas Schneider


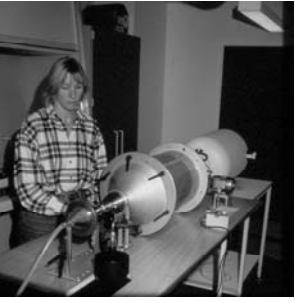
Relevance of Dustiness and Aerosol Dynamics for Personal Exposure

Thomas Schneider
The Nanotoxicology and Occupational Hygiene Group



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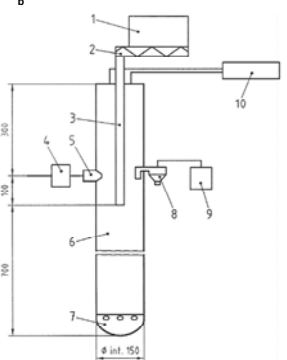
Dustiness test

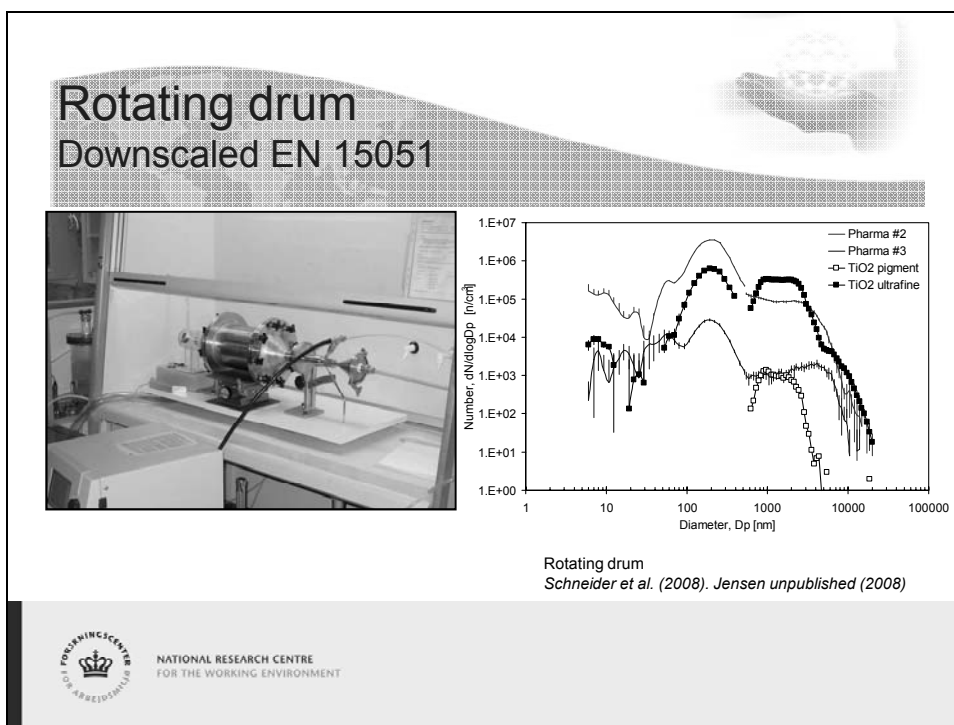
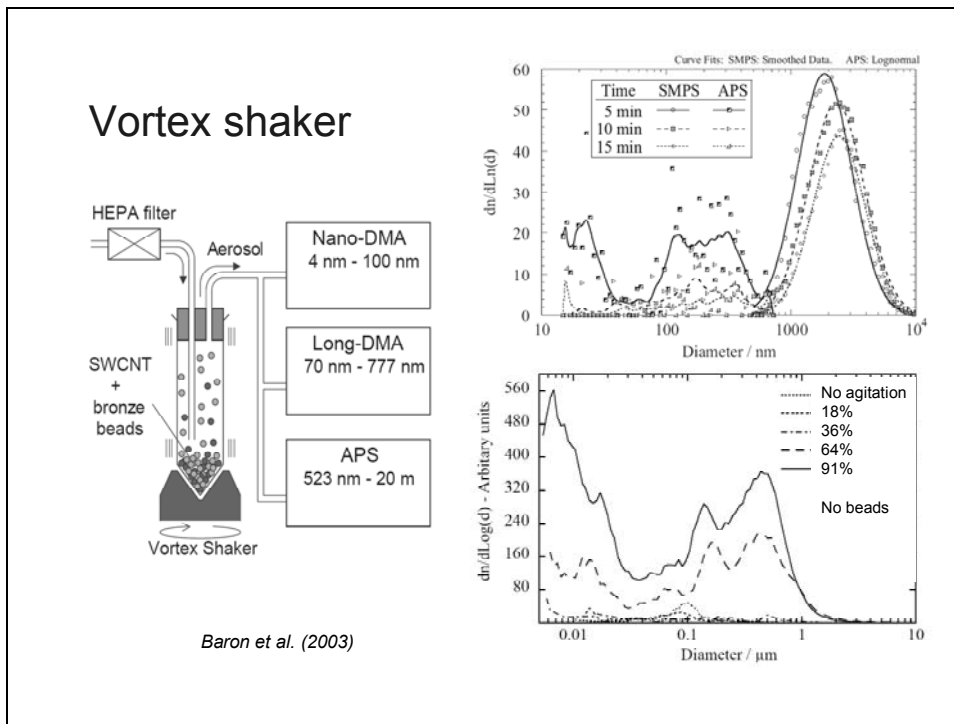


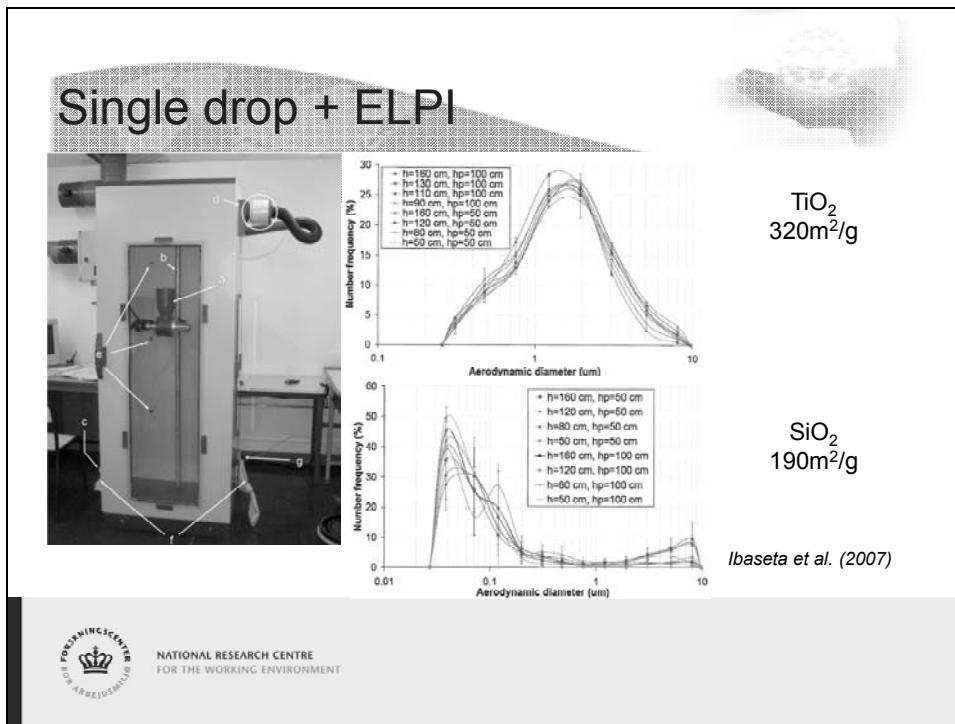
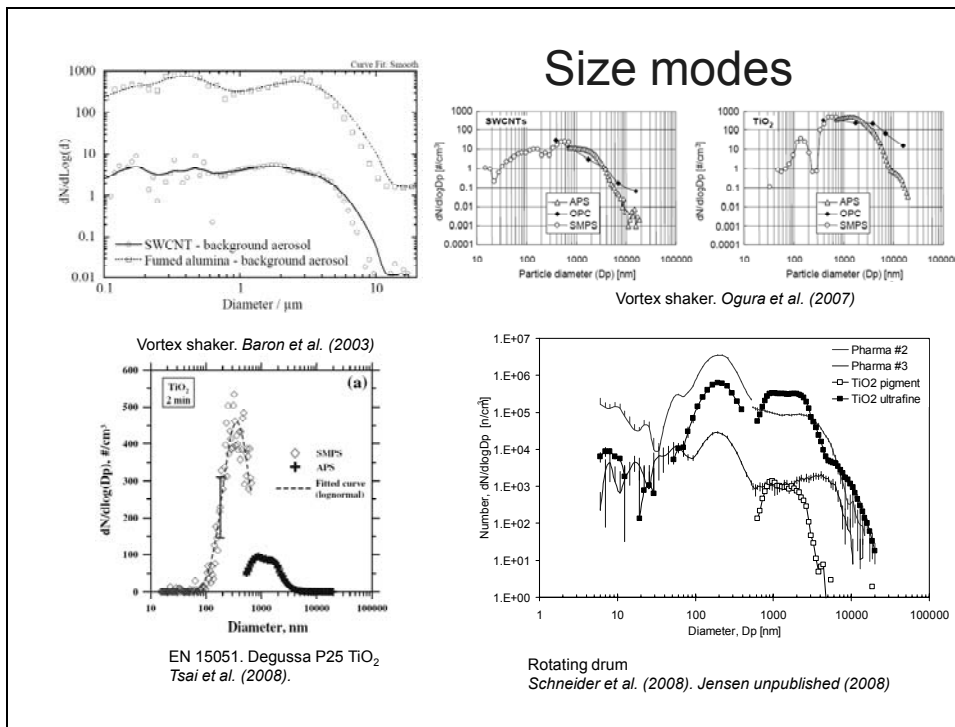
Baron et al. (2003)

Rotating drum
Continuous single drop

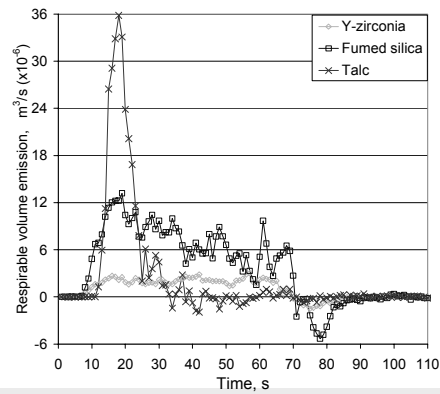
EN 15051. 2006



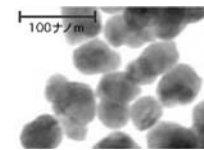
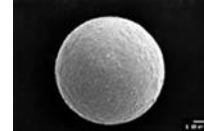




Emission rate Single drop vs rotating drum



Y-zirconia



Schneider et al. (2008)



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Additional reference test methods?


- Rotating drum: broadest range of activities and materials
- Single drop preferred by others
- EN 15051 includes both. Not equivalent
 - Some propose range of methods for better similarity with real scenarios
 - Dual single drop/rotating drum test may do
- If several reference methods, pick method giving lowest dustiness
 - Need similarity
 - Metric or
 - Activity class *Marquart et al. In prep*
- ISO: Special MNP dustiness test



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Handling MNP powders

- Generally very little surface area below 100nm
- Distinct size modes, robust GMD
 - 200-300nm (mobility diam)
 - above 1 µm (aerodynamic diam)
- Entire respirable fraction/alveolar deposition fraction
 - Differences between respirable size modes
 - Agglomerate strength/stability?
 - Biologically available surface area?
 - Modal characterization

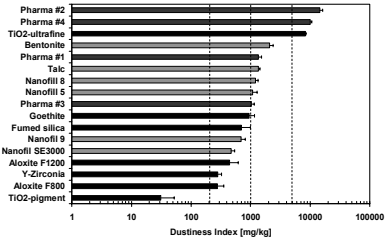


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Dustiness is one among several major exposure determinants

9 Modifying Factors (MF):

- Intrinsic emission potential (*E*)
- Activity emission potential (*H*)
- Local controls (*LC*)
- Separation (*Sep*)
- Segregation (*Seg*)
- Surface contamination (*Su*)
- Dilution (*D*)
- Personal behavior (*P*)
- RPE




Material	Dustiness Index [mg/kg]
Pharma #2	~10,000
Pharma #4	~10,000
TiO2-ultra fine	~10,000
Bentonite	~10,000
Pharma #1	~10,000
Talc	~10,000
Nanofill 8	~10,000
Nanofill 5	~10,000
Pharma #3	~10,000
Goethite	~10,000
Fumed silica	~10,000
Nanofill 9	~10,000
Nanofill SE3000	~10,000
Alloxite F1200	~10,000
Y-Zirconia	~10,000
Alloxite F500	~10,000
TiO2-pigment	~10,000

$$C_t = (C_{nf} + C_{ff}) \cdot RPE$$

$$C_{nf} = (\dots \cdot LC_{nf} \cdot P_{nf} + Su_{nf}) \cdot D_{nf}$$

$$C_{ff} = (\dots \cdot LC_{ff} \cdot Seg_{ff} + Su_{ff}) \cdot D_{ff} \cdot Sep_{ff}$$



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Source-receptor based model
Cherrie et al. (1999), Tielemans et al. (2008)

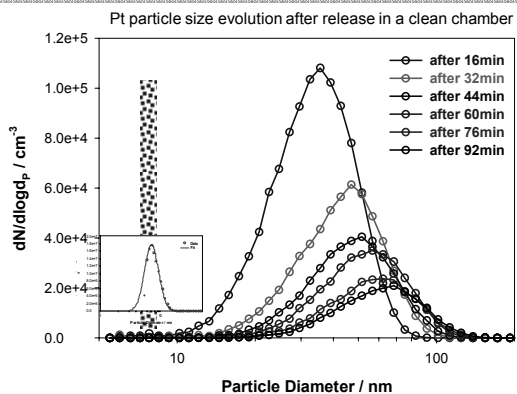
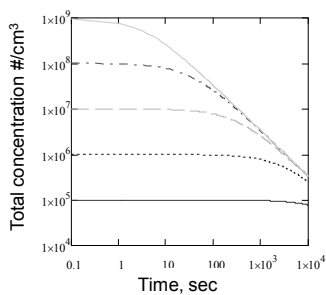
Aerodynamics

- Single (multi) compartment (box), well-mixed
 - Turbulence intensity
 - Mixing time 7-15 min in offices
 - Boundary layer
 - Coagulation
 - Surface deposition
 - Adsorption
- CFD for spatio temporal evolution



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Coagulation

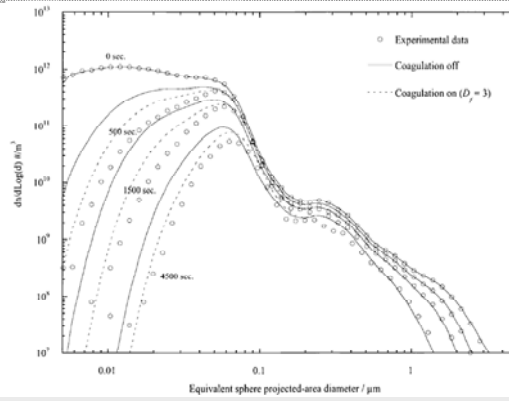


NANOTRANSPORT (2008)



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High-speed grinding



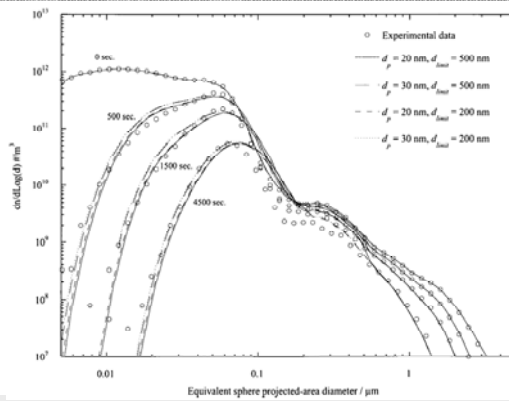
Aluminum
Stirred box
Coagulation
Surface deposition

Maynard AD, Zimmer AT (2003)



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High-speed grinding

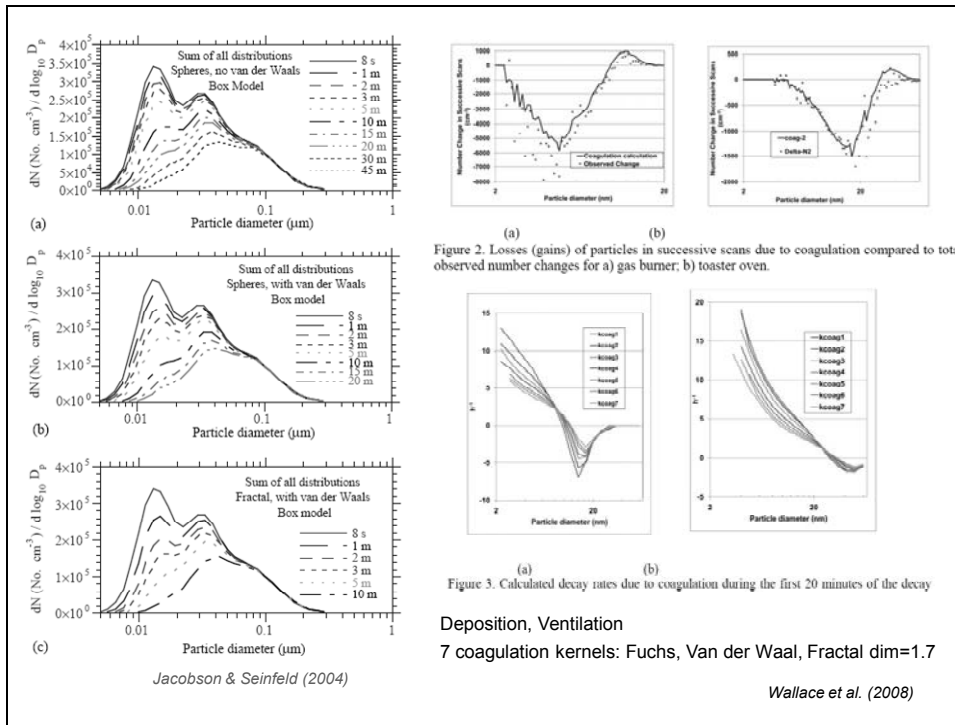


Aluminum
Stirred box
Coagulation
Surface deposition
Fractal dimension 1.7

Maynard AD, Zimmer AT (2003)



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Removal by surface deposition in competition with exhaust/ventilation

CFD

Lai and Chen (2006)

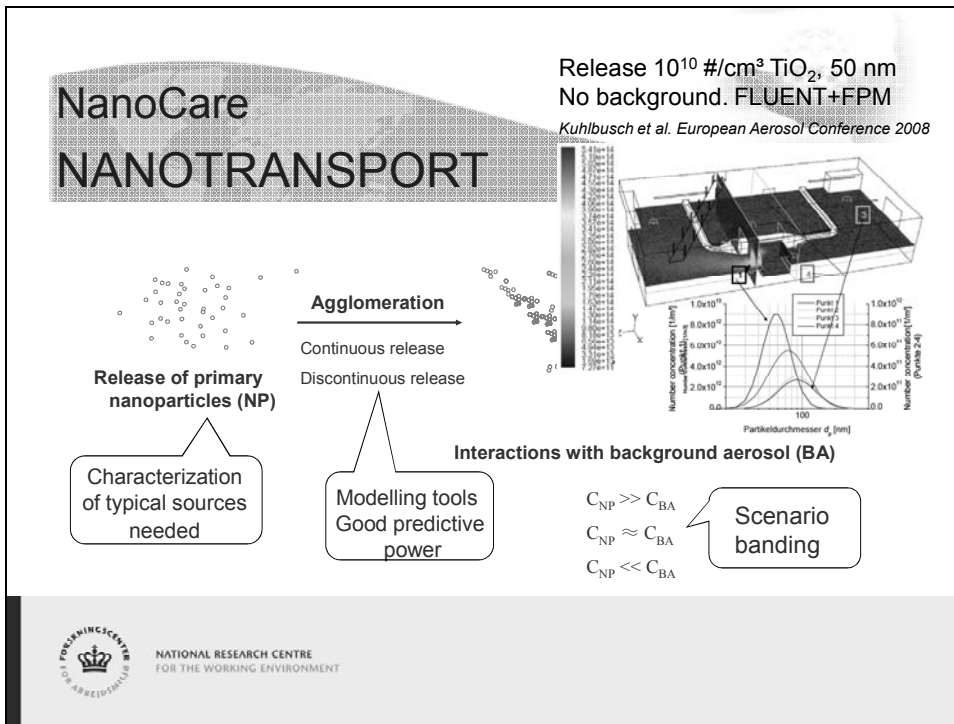
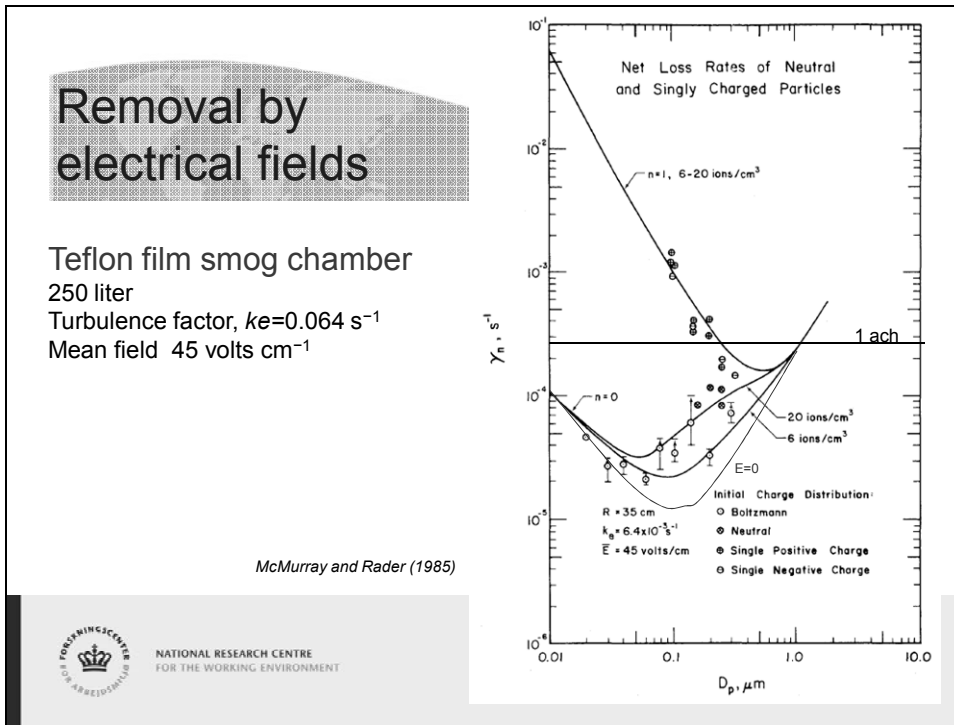
deposition fraction

particle size (μm)

→ Secondary sources
 → Resuspension if $> 1\mu\text{m}$

NANOTRANSPORT: $< 14\%$

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Worker exposure MNP production

- MNP aggregates/agglomerates and MNP attached to larger background particles
- Apportionment of MNP to these structure types determined by MNP and background aerosol
 - Concentration, size
 - Mixing intensity, residence time
- Banding of scenarios according to apportionment
 - A. High concentration at source
 - Control source
 - B. Low concentration at source
 - Concentration of attached MNP still lower
 - C.



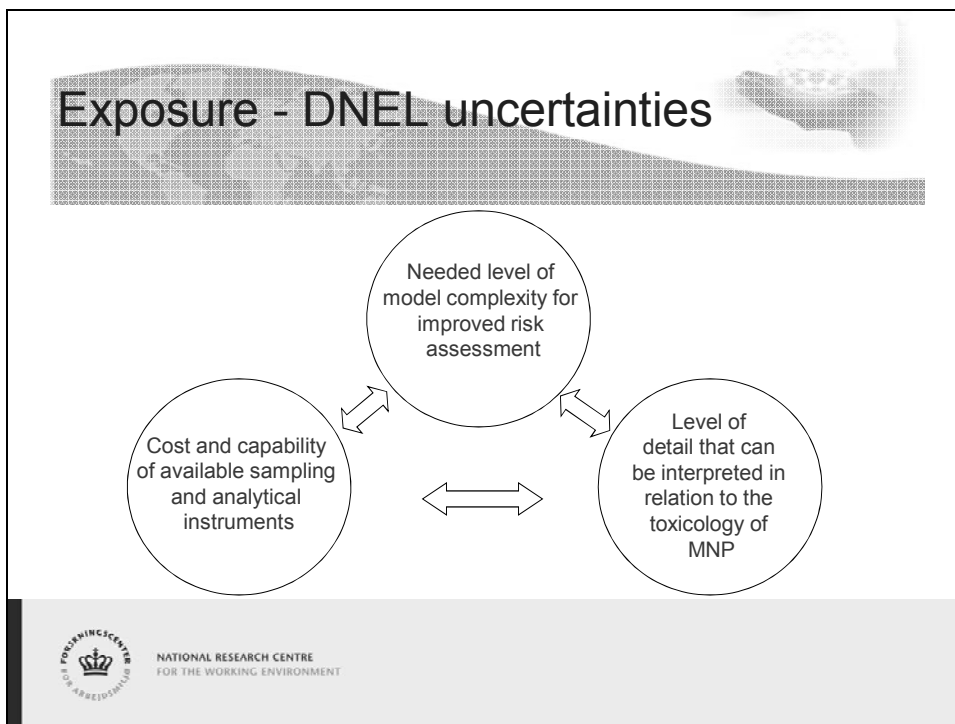
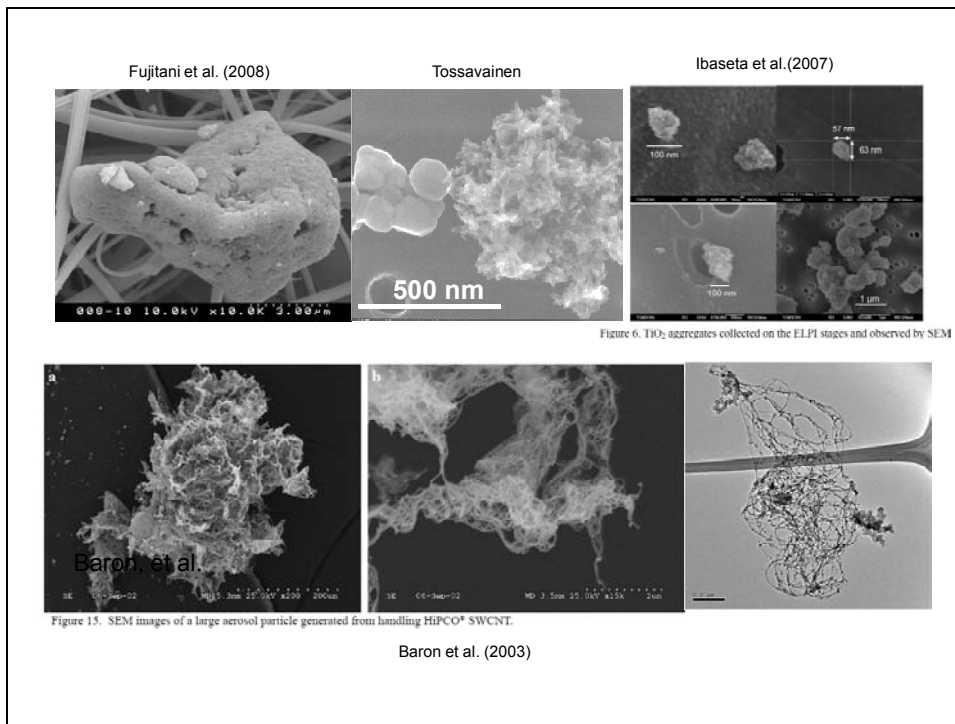
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Field equipment for non-fibrous MNP source identification

- Handling bulk MNP
 - Entire respirable fraction/alveolar deposition fraction
 - Lower diameter limit
 - 50-70 nm
 - Less sensitive to combustion background
- Production
 - Lower diameter limit 10-30 nm
 - Upper limit?

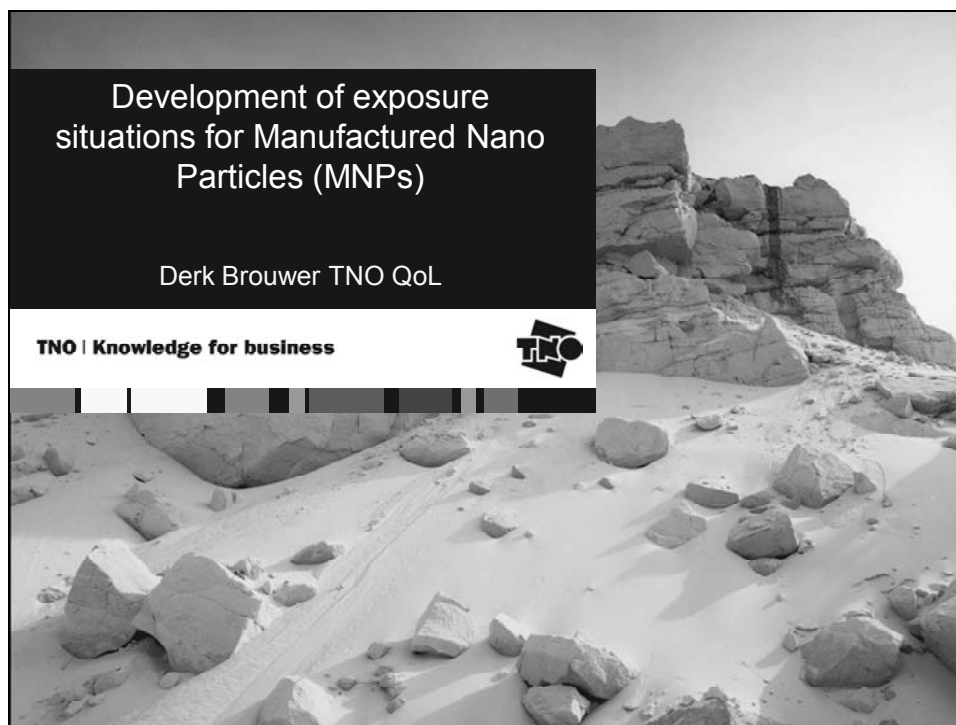


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Presentation 4

Development of Exposure Situations for Manufactured Nanoparticles (MNPs): Derk Brouwer



'Preface'

- (occupational) Exposure **situation** combines facts, assumptions, and interferences that define a discrete situation where potential exposure may occur (ISEA/IPCS; Zartarian et al 2004)

≠

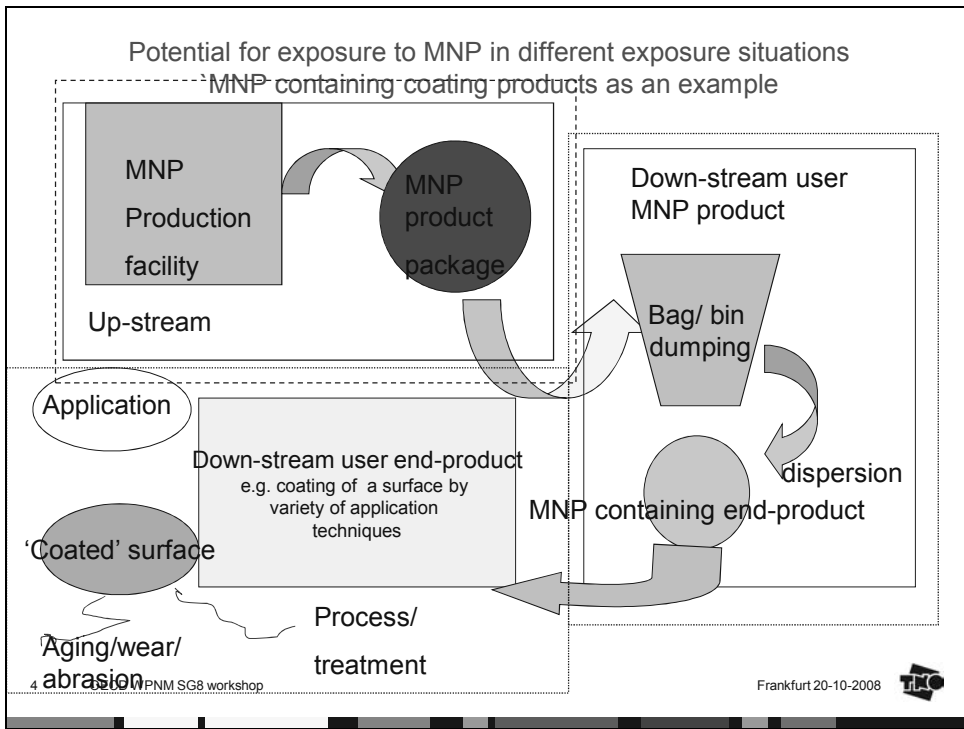
- (occupational) Exposure **scenario** REACH , describes the operation conditions and risk management measures for safe use



Contents

- What has been done with respect to workplace studies
 - Published and ongoing studies
 - Observations/ preliminary conclusions
- What could/ should be done to achieve
 - estimates of (personal) exposure from workplace air monitoring results
 - Development of exposure situations

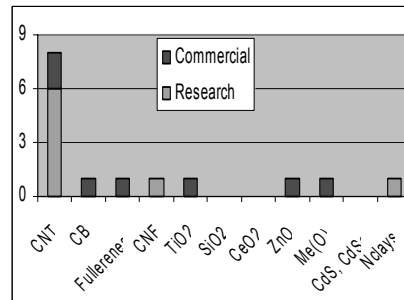
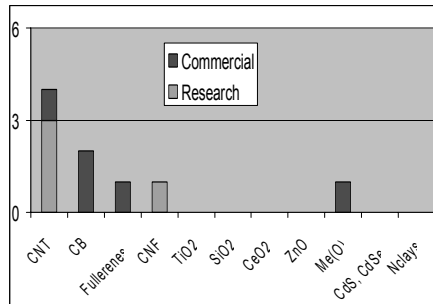
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(indication of) Numbers of exposure studies ⁽¹⁰⁻⁰⁸⁾
 Production of MNPs (research- commercial scale)

Peer reviewed (published+ in press)

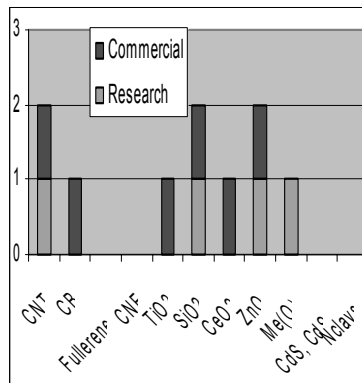
Published + NANOSH
 (NMP4-CT-2006-032777)



Kuhlbusch et al 2004, 2006; Maynard et al, 2004; Methner et al., 2007, 2008
 Han et al, 2008; Yeganeh et al, 2008; Tasai et al, 2008, Bello et al, 2008
 Bello et al, in press; Demou et al, 2008



(indication of) Numbers of exposure studies ⁽¹⁰⁻⁰⁸⁾
 Down-stream use of MNPs (research- commercial scale)




Studies release of MNPs from
 MNP-containing (end)products

- Abrasion nano-coated surfaces (VDL-Germany)
- Sanding nano-coated surfaces (Koponen et al, NRCWE-Denmark)
- Cutting CNT composites (Bello et al in press)




Workplace 'exposure' studies

- Studies have research/ explorative character
- Focus on emission of particles/ inhalation exposure
 - nano-scale 'conventional' substances and 1° generation MNP
- Rather similar approach
 - Instrumentation
 - Strategy

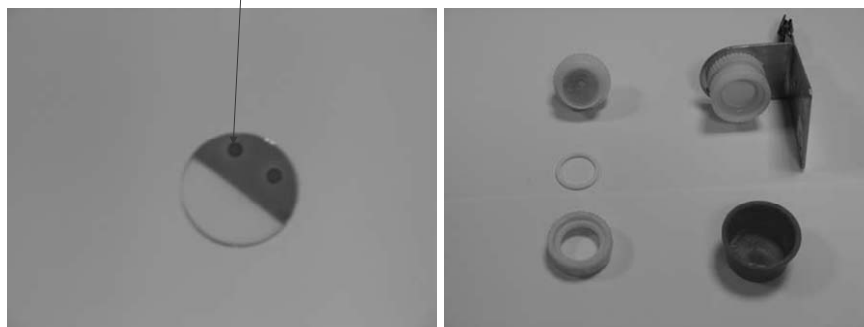
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Instrumentation

On-line	Size distribution	SMPS (ELPI)	APS
	Number concentration	SMPS ELPI	CPC
	Mass concentration	TEOM DUSTTRAK	
	<i>Surface concentration</i>	<i>LQ1-DC</i>	<i>NSAM</i>
Off-line	Sampling	TEM grid (precipitator)	Filter (PAS) Impactor
	Analysis (size/shape)	TEM	SEM
	Analysis (elemental)	EDS/EDX	Carbon detection

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Assembly TEM grids / polycarbonate filter / pre-coated gold filter for Personal Air Sampling NANOSH /Tsai et al 2008

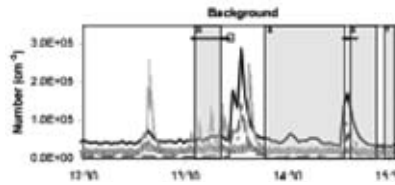


Observations/ preliminary conclusions

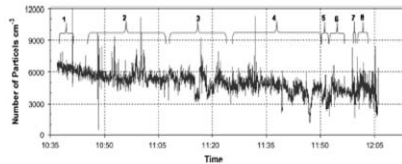
- Substantial spatial and temporal variation of (non-MNP?) 'background' levels
- Outdoor conditions (industrial area/ traffic) and intrusion/ infiltration
- Low 'contrast' concentration levels 'activity'/ handling periods and periods with no/hardly any activity
- Increased particle number concentration: mode particle size distribution > 100 nm (200-300nm) ; increase < 100 nm often associated with combustion and electrical tools
- Characterization; Strong indications for 1) very few primary NPs, 2) many agglomerates, 3) some aggregates
- In general: limited duration of MNP-related activities \approx exposure duration
- Indications for weak/ hardly any correlation mass/number/surface area



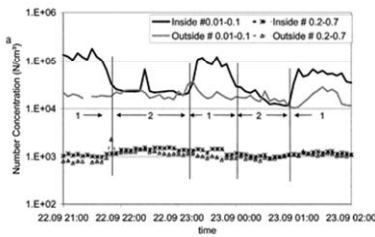
Examples of time/activity- concentration profiles



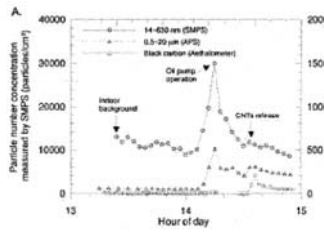
Yeganeh et al., 2008



Bello et al., 2008



Kuhlbusch et al., 2004



Han et al., 2008



Explorative assessment of dermal exposure Modification of DREAM



Exploring the feasibility to use a structured observational method to assess dermal exposure to engineered nanoparticles (ENPs)



Materials

DREAM is an observational method to evaluate dermal exposure based on mass transport processes/routes and determinants of exposure as identified by the conceptual model of dermal exposure (Figure 1). It consists of an inventory and an evaluation part (Wendel-de-Joude et al., 2003). The inventory part comprises a hierarchically structured questionnaire with six modules: company, department, agent, job, task and exposure. Information is obtained by observations and interviews. To explore the feasibility of applications of the DREAM approach to ENP exposure scenarios, only the task and exposure modules were used in the questionnaire (Table 1).

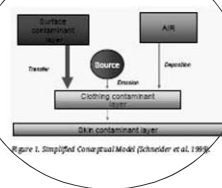


Figure 1. Simplified Conceptual Model (Schneider et al., 1999)

titanium dioxide of iron hydroxyhydride (suspension). All scenarios indicated that dermal exposure was possible or likely to occur, however resulting from different routes e.g. direct contact, deposition, or transfer (Table 2).

Table 1. Feasibility of Method of dermal exposure by route.

Exposure	Collection	Deposition	Transfer
Preparation liquid	+	-	-
Deposited powder	-	-	-
Washing after powder (used)	-	+	+
Washing after wash (ENP)	+	+	+
Generation of Al powder	+	+	+
Respirating	+	+	+

+ occurrence likely, + occurrence possible, - occurrence unlikely

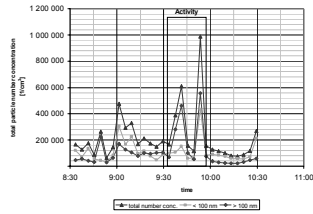
Conclusion

It showed to be both feasible and useful to assess dermal exposure to ENPs using the modified DREAM questionnaires. Therefore, assessment of dermal exposure will be included in the main exposure studies of the NANOSH project.

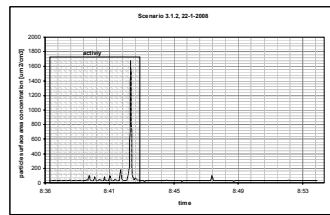
References



How to get from time/activity- concentration profiles to estimates of exposure?



?



Estimate of exposure (per person/shift)	
MNP (fumed silica) Confirmed by TEM analysis	Cumulative MNP surface area(µm ² /cm ³)
	± 530 (± 2.8%)

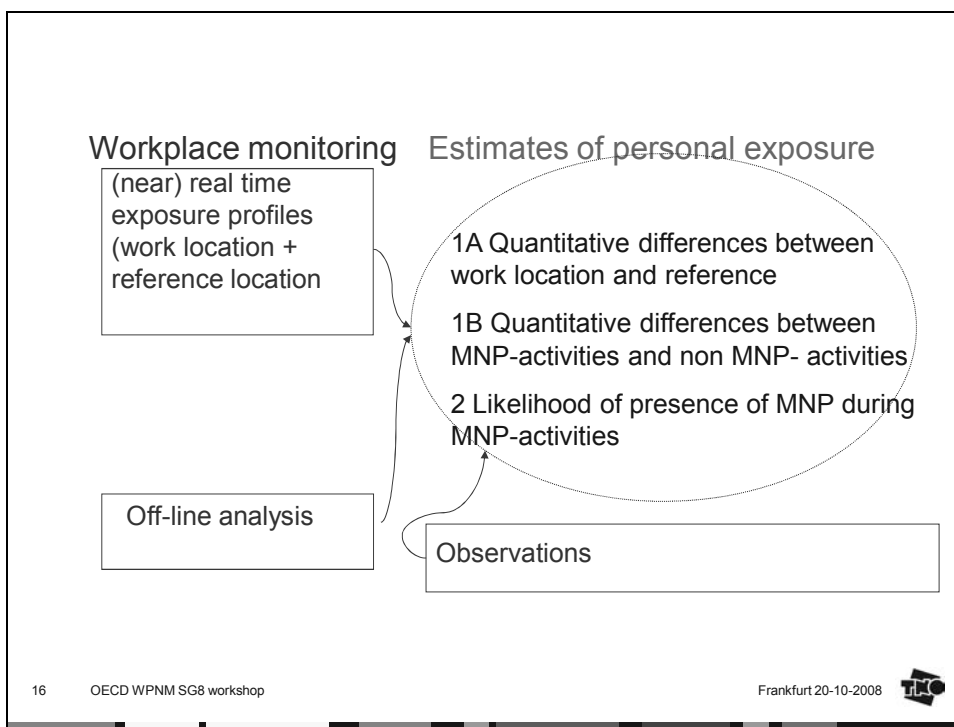
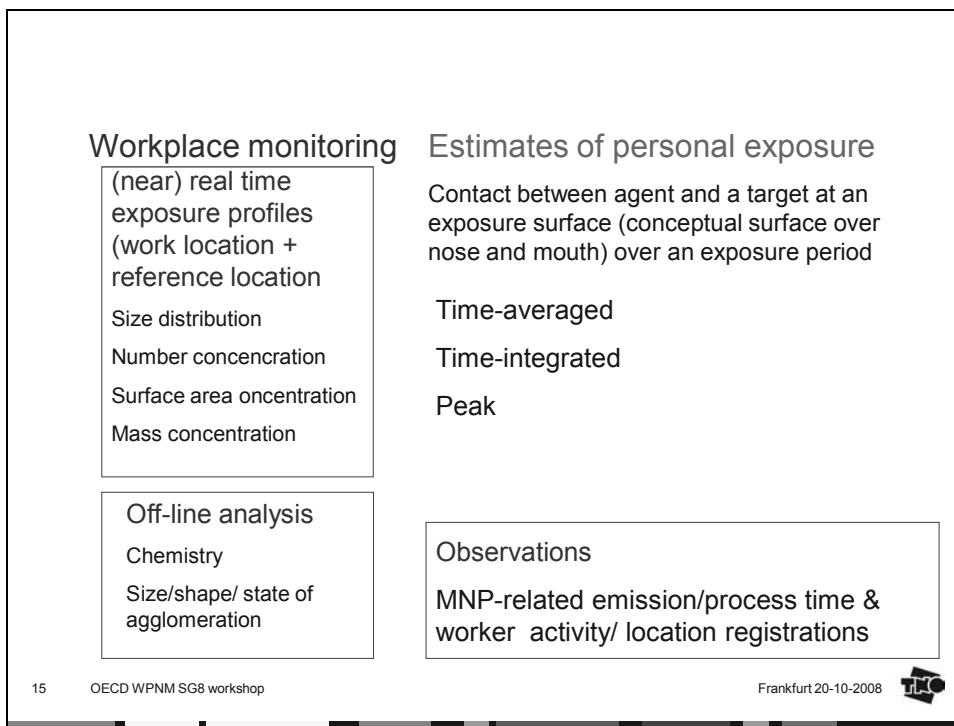


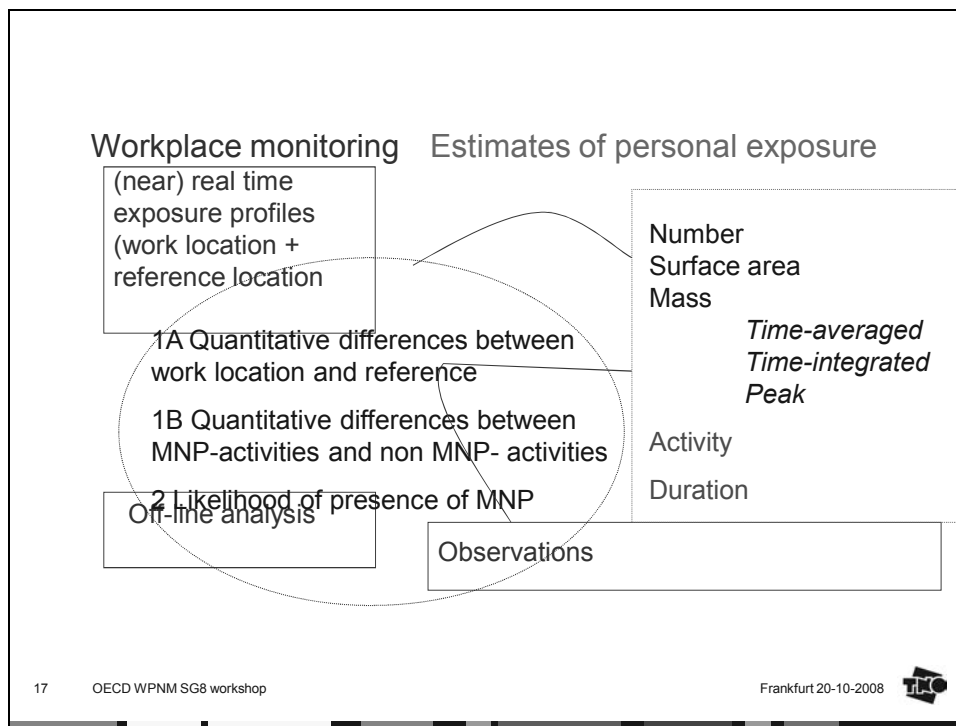
Workplace monitoring Estimates of personal exposure

Static monitoring

Mobile worker



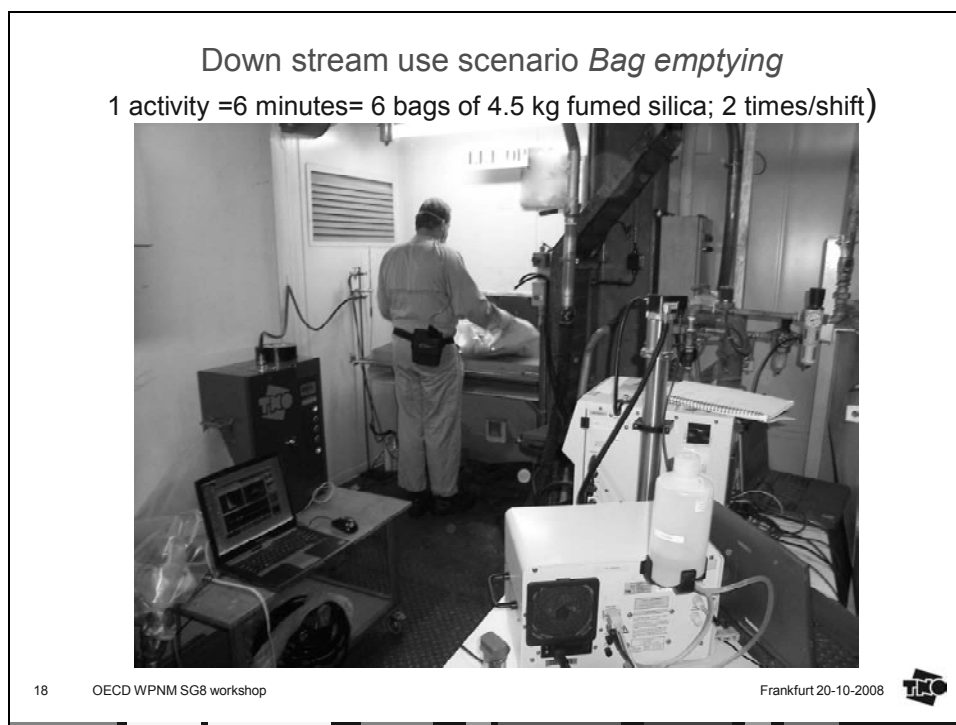




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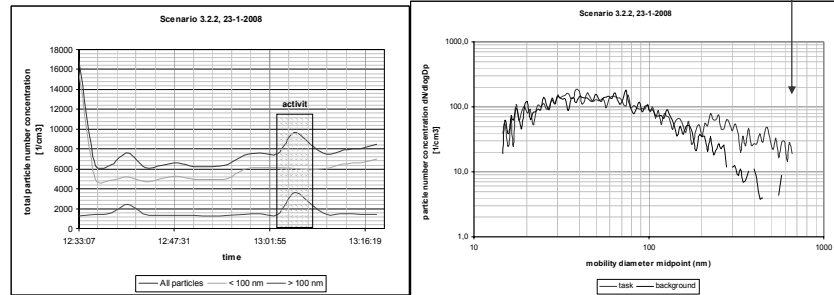
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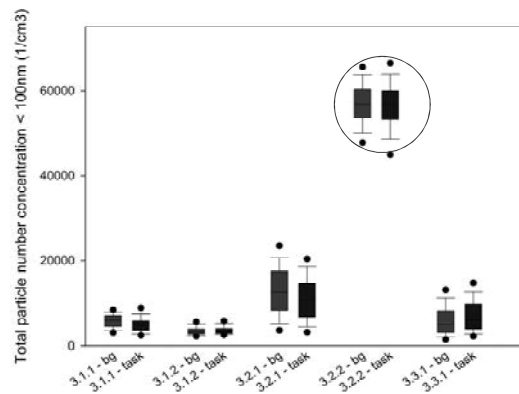
Example Particle number concentration time-plot/ size distribution

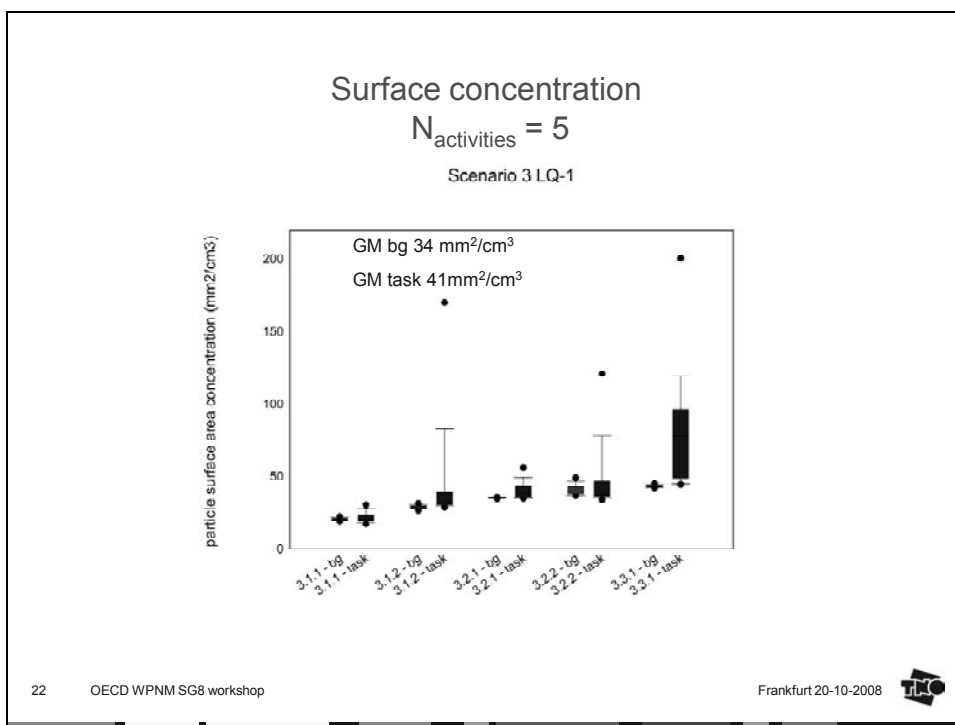
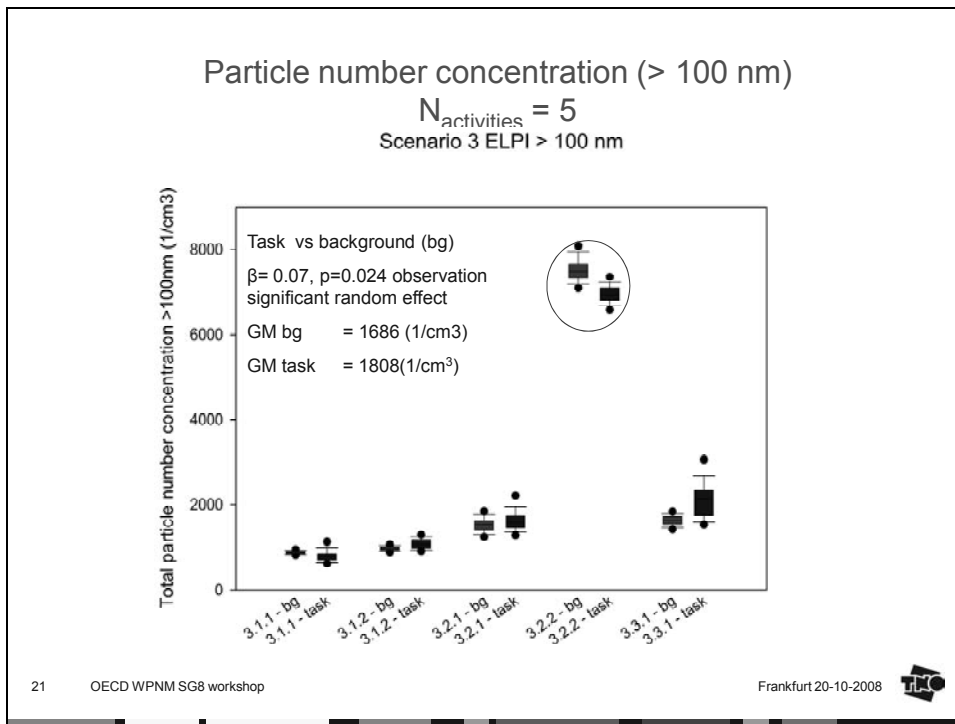


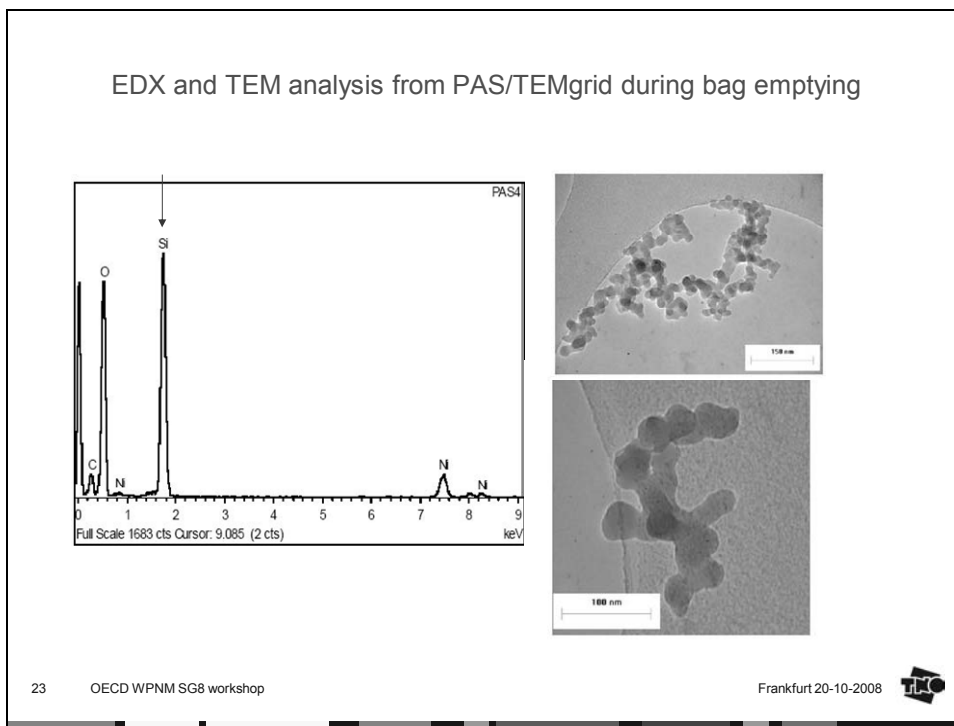
Particle number concentration (< 100 nm)

$N_{activities} = 5$

Scenario 3 ELPI < 100 nm







Example of possible interpretation of measurement results

Bag emptying		MNP (fumed silica) Confirmed by TEM analysis		
	Measurement		Estimate of exposure (per person/shift)	
	Average ($\mu\text{m}^2/\text{cm}^3$)	Duration (min)	Cumulative Total surface area($\mu\text{m}^2/\text{cm}^3$)	Cumulative MNP surface area($\mu\text{m}^2/\text{cm}^3$)
Activity	41	12	± 482 ($\pm 3.4 \%$)	± 84 ($\pm 0.6 \%$)
Non-activity	34	408	± 13900	-----

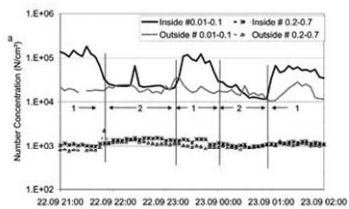
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Preliminary decision logic (NANOSH)

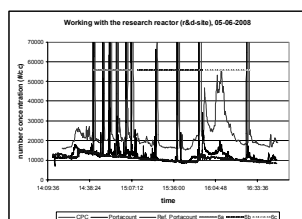
- STRATEGY
 - Repeated measurements are needed
 - Data should enable comparison MNP-related activity vs non-activity and/ or vs 'reference background'
- ANALYSIS
- REPORT



Illustration of 'reference' background/outdoors



Kuhlbusch et al., 2006



Brouwer et al. in preparation

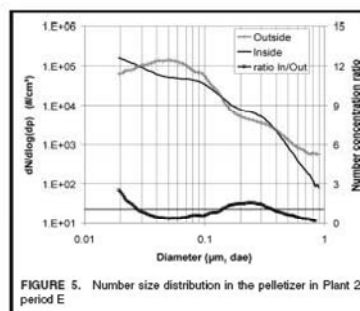



FIGURE 5. Number size distribution in the pelletizer in Plant 2 period E

Kuhlbusch et al., 2006




Preliminary decision logic
(NANOSH)

- STRATEGY
- ANALYSIS
 - Statistical differences should be determine by appropriate methods, e.g. by mixed model regression models, t-tests?
 - Peak or 95-percentile value activity should be lower than 95%-ile non-activity or reference background.
 - Mode(s) of size distribution and results (S)TEM analysis (size/shape/morphology) and EDX (elements) should be used to determine likelihood of presence of MNPs
- REPORT

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Preliminary decision logic
(NANOSH)

- STRATEGY
- ANALYSIS
- REPORT
 - As much as possible 'raw' data to enable all kind of calculations for different exposure metric (e.g. number, surface) and exposure measure e.g. average, cumulative, peak)
 - Simple 'data base' to enable meta-analysis

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Building data bases to develop exposure situations `Harmonisation = KEY

- Description of scenario
 - Production- Down stream Use/ Application-Use MNP products
 - Scale
 - MNP types
 - Task/ activity (e.g. Advanced Reach Tool)
 - Control or RM measures (e.g ART/ Fransman et al 2008 AOH)



REACH

TNO | Knowledge for business

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Development of an advanced exposure assessment tool: Advanced REACH Tool (ART)

The REACH process requires a Tiered exposure assessment to effectively cope with the broad range of Exposure Scenarios. Currently, a higher Tier model generating realistic exposure estimates is missing. A new advanced exposure assessment tool is under development.

Introduction

Under REACH, Exposure Scenarios need to be developed, which describe the use of a dangerous substance under relevant Operational Conditions and Risk Management Measures. The Chemical Safety Report must document that the levels of exposure in these Exposure Scenarios are safe, in the likely absence of good quality comprehensive exposure data for many substances (especially for downstream users) exposure assessment tools are required. Currently, a higher Tier model generating realistic exposure estimates is missing. A new advanced exposure assessment tool is under development.

Outline of presentation

Table. Nine mutually independent modifying factors.

Model component	Modifying factor
Source	Activity emission potential
	Substance emission potential
Transmission	Localized control
	Separation
	Segregation
	Water treatment
	Dispersion
	Surface contamination / fugitive emission
Receptor	Respiratory protection



Building data bases to develop exposure situations `Harmonisation = KEY

- Description of scenario
- Measurements
 - Instrumentation
 - Strategy
- Analysis of data
 - Agreed decision logic
 - Sound statistical approaches
- Reporting
 - Agreed format



Simple spreadsheet formatted data base

The image displays three screenshots of spreadsheets used for data collection. The top-left screenshot shows a table with columns for 'Measurement', 'Activity', 'GM', 'GDD', 'peak', 'Mode', 'GM', 'GDD', 'peak', 'Mode', 'GM', 'GDD'. The top-right screenshot shows a similar table with columns for 'Measurement', 'Activity', 'GM', 'GDD', 'peak', 'Mode', 'GM', 'GDD'. The bottom screenshot shows a table with columns for 'General information of the room/building', 'Height', 'Length', 'Width', 'Volume', 'Mechanical ventilation (specifications/measurements)', 'Fresh air supply', 'Air exhaust to outside', 'Filter type', 'Recirculation rate', 'Mechanical recirculation (specifications/measurements)', 'Recirculated air supply', 'Air exhaust to be recirculated', 'Filter type', 'Recirculation rate'.



Acknowledgment

- TNO QoL: Birgit Stuurman, Tim Meijster, Marieke Op de Weegh
- NANOSH WP2/ Exposure Assessment
 - BGIA: Johannes Welter, Carsten Möhlmann, Markus Berges
 - HSL: Delphine Bard, Dave Mark
 - CIOP: Elzbieta Jankowska



Presentation 5

Control Banding Nanotool- A Qualitative Risk Assessment Method: Paul Swuste

**Control banding nanotool,
a qualitative risk assessment method**

Paul Swuste
Safety Science Group, Delft University of Technology, NL

Dave Zalk and Sam Paik
Lawrence Livermore National Laboratory, CA, USA

'it might be hazardous at the bottom'

size, reactivity, barrier crossing

health hazards:

Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study (Poland et al., 2008)

public perception:

Prey (Crichton, 2002)

Manufactured nanomaterials

uncertainties

- exposure scenarios
- levels of exposure
- population at risk
- deposition – clearance
- structure – effect

Xavier Miserachs El Born 1962



Origin of control banding

Pharmaceutical industry, toxicological uncertainties (1970 - 1980)

UK COSHH Essentials (Annals, 1998)

Control banding workshops (Annals, 2003; Zalk & Nelson, 2008)

Control banding, a qualitative risk assessment method

hazard bands:

EU risk phrases

exposure scenarios (bands):

volume, dustiness, volatility

control levels:

engineering principles

Control Banding applications

chemicals (WHO, ILO, IOHA, Jones et al., 2004)

ergonomics (Zalk, 2001)

occupational risk prevention strategies (Swuste, 2007)

nanoparticles exposure (Paik et al., 2008)

Control banding manufactured nanomaterials

A. D. Maynard

		Exposure Index					Exposure Index • 'Dustiness' • Amount Used
		A	B	C	D	E	
Impact Index	A						Impact Index • Bulk hazard • Surface Area • Surface Activity • Shape • Size
	B						
	C						
	D						
	E						

Control Approach			
General Ventilation		Containment	
Engineering Control		Specialist Advice	

Control banding nanotool				
	extremely unlikely (0-25)	less likely (26-50)	likely (51-75)	probable (76-100)
very high (76-100)	RL 3	RL 3	RL 4	RL 4
high (51-75)	RL 2	RL 2	RL 3	RL 4
medium (26-50)	RL 1	RL 1	RL 2	RL 3
low (0-25)	RL 1	RL 1	RL 1	RL 2

Severity score (0 – 100)	
• physical properties	0 - 10
• toxicological properties	0 - 7.5
• toxicological properties parent materials	0 - 5
Probability score (0 – 100)	
• amount used	6.25 - 25
• dustiness	7.5 - 30
• exposed population	5 - 15
• frequency and duration of operation	0 - 15
unknown ≡ 75% of highest score	

Severity score (1)

• surface chemistry	high:	10
	medium:	5
	low:	0
	unknown:	7.5
• particle size	tubular, fibrous:	10
	anisotropic:	5
	compact or spherical:	0
	unknown:	7.5
• particle diameter	1 – 10 nm:	10
	11 - 40 nm:	5
	< 41 – 100 nm:	0
	unknown:	7.5
• solubility	insoluble:	10
	soluble:	5
	unknown:	7.5

Severity score (2)

• carcinogenicity	}	yes:	7.5
• reproductive toxicity		no:	0
• mutagenicity		unknown:	5.625
• dermal toxicity			
• toxicity parent material		0 – 1 μgm^{-3} :	10
		2 – 10 μgm^{-3} :	5
		< 41 - 100 μgm^{-3} :	2.5
		> 100 μgm^{-3} :	0
		unknown:	7.5
• carcinogenicity parent material	}	yes:	5
• reproductive toxicity parent material		no:	0
• mutagenicity parent material		unknown:	3.75
• dermal toxicity parent material			

Probability score (1)

• estimated amount during operation	> 100 mg:	25
	11 – 100 mg:	12.5
	0 – 10 mg:	6.25
	unknown:	18.75
• dustiness/mistiness	high:	30
	medium:	15
	low:	7.5
	unknown:	22.5
• number of employees	> 15:	15
	11 – 15:	10
	6 – 10:	5
	unknown:	11.25

Probability score (2)

• frequency of operation	daily:	15
	weekly:	10
	monthly:	5
	less than monthly:	0
	unknown:	11.25
• duration of operation	> 4 hr:	15
	1 – 4 hr:	10
	30 -60 min:	5
	< 30 min:	0
	unknown:	11.25

Control banding nanotool

	extremely unlikely (0-25)	less likely (26-50)	likely (51-75)	probable (76-100)
very high (76-100)	RL 3	RL 3	RL 4	RL 4
high (51-75)	RL 2	RL 2	RL 3	RL 4
medium (26-50)	RL 1	RL 1	RL 2	RL 3
low (0-25)	RL 1	RL 1	RL 1	RL 2

Discussion

risk management \equiv managing scenarios

limitations

- factors and scores of probability and severity
- no design changes

advantages

- transparent, logical, and simple tool
- support for decision making under uncertainties

Presentation 6

Approaches for the Definition of Threshold Limit Values for Nanomaterials: Bruno Orthen

**Approaches for the Definition of Threshold
Limit Values for Nanomaterials**

- A) Appropriate Metrics of Exposure**
- B) Current Status and Applicability**

Dr. Bruno Orthen, 4.3

Federal Institute for Occupational Safety and Health, Germany



Overview

Part A: Appropriate Metrics of Exposure

- Established and discussed dose metrics
- Comparison of mass, volume, diameter, surface and particle number
- Proposal for the selection of dose metrics

Part B: Current Status and Applicability

- TLVs for dusts and fibres
- TLV-approaches and risk estimates for MN
- Proposal for the TLV-derivation of MN

Approaches for the Definition of Threshold Limit Values for Nanomaterials

Part A Appropriate Metrics of Exposure

3

Dr. B. Orthen, BAuA, 20.10.08

baua:

TLV dose metrics

Established TLV dose metrics for solid substances:

- Mass of granular particles
- Number concentration of high aspect fibres

Further established relevant characteristics for solids:

- Water solubility
- Particle size distribution (total vs respiratory dust)
- Crystallinity (quartz vs other forms of silicon dioxide)
- Basic morphology (fibres)
- etc.

CAS/EINECS-Nr. alone does not define all relevant characteristics (e. g. particles size)

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Dr. B. Orthen, BAuA, 20.10.08

baua:

Characteristics possibly relevant for MN toxicity

Water solubility	Particle size distribution	Agglomeration/aggregation
Surface area	Porosity	Photocatalytic activity
Pour density	Surface chemistry	Zeta potential
Redox potential	Basic morphology	Radical formation potential
Dustiness	Crystalline phase	TEM picture

etc. (source: OECD*)

- Determination of relevance for toxicity assessment needed
- Quantifying standardised methods for determination needed

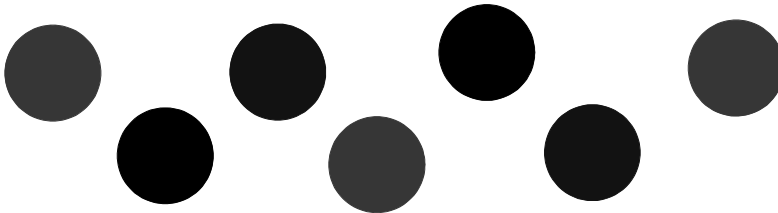
* List of Manufactured Nanomaterials and List of Endpoints for Phase One of the OECD Testing Programme; ENV/JM/MONO(2008)13/REV. www.oecd.org/document/53/0,3343,en_2649_37015404_37760309_1_1_1_1_00.html

5 b a u a :

Volume

Volume:

- Hypothesis: particle burden/volume responsible for toxicity of particles of same size with no specific toxicity
- Consequence: limited influence on a mass based system (density of average material ranging from 1.5 to 6 mg/m³), fine tuning

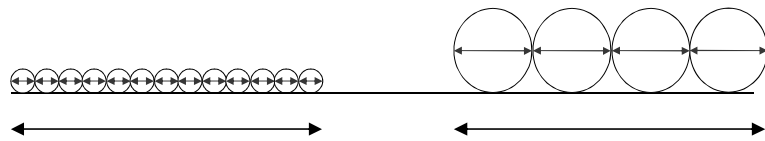


6 b a u a :

Diameter

Diameter:

- Hypothesis: Covering of biological epithelia important for toxicity
- Consequence: moderate increase of toxicity by scaling down particles related to mass



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Dr. B. Orthen, BAuA, 20.10.08

b a u a :

Surface

Surface:

- Hypothesis: Surface reactivity responsible for toxicity
- Consequence: High increase of toxicity by scaling down particles related to mass

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Dr. B. Orthen, BAuA, 20.10.08

b a u a :

Number concentration

Number concentration:

- Hypothesis: Particles are equivalent independent of size etc.
- Consequence: Very high increase of toxicity by scaling down particles related to mass

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Dr. B. Orthen, BAuA, 20.10.08

Comparison of dose metrics in relation to mass

Mass	diameter	Relation of surfaces (related to 2 µm)	Relation of particle numbers (related to 2 µm)
1	2 µm	1	1
1	200 nm	10	1.000
1	20 nm	100	1.000.000
1	2 nm	1.000	1.000.000.000

Surface: Strong increase of toxicity by scaling down particles
 Number concentration: Very strong increase of toxicity by scaling down particles

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Dr. B. Orthen, BAuA, 20.10.08

Proposal for the selection of dose metrics

Granular particles

- Measurement of mass per m^3 , if possible
- Determination of MN characteristics (surface area, primary and secondary particle size, density, solubility, surface characterisation etc...)

Fibres

- Additional measurement of high aspect fibres (fibre per m^3)

Approaches for the Definition of Threshold Limit Values for Nanomaterials

Part B Current Status and Applicability

TLVs for dusts and fibres (1)

- TLVs represent an established instrument of risk management
- TLVs for poorly soluble dusts and fibers were set in many countries

TLVs for poorly soluble dusts/fibres with specific toxicity*

- Quartz: 0.075 – 0.3 mg/m³
- Silver (metal): 0.01 – 0.1 mg/m³
- Asbestos: 0.01 – 2 fibres/cm³

* GESTIS – International TLVs for chemical substances; www.dguv.de/bgia/de/gestis/limit_values/index.jsp

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baa:

TLVs for dusts and fibres (2)

Generic TLVs: dusts with no specific toxicity

- Inhalable dust/total dust : 4 to 15 mg/m³
- Respirable fraction (fine dust, lung) : 1.5 to 10 mg/m³
e. g. for titanium dioxide, graphite, iron oxide

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Dr. B. Orthen, BAuA, 20.10.08

baa:

Threshold limit values for MN

Currently available data from toxicology indicate

- Qualitative and quantitative differences in toxicity compared to microsized particles
- Differences among MN
- The lungs are a joint target organ of poorly soluble nano- and microsized particles

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Dr. B. Orthen, BAuA, 20.10.08



Does a TLV intended for microsized particles cover MN from a legal perspective?

- From a legal perspective in most cases, yes
- So, TLVs originally intended for microscale particles are currently also binding for MN (with few exemptions)
- These TLVs for microscale particles appear in the SDS for MN
- Legally binding TLVs specifically for MN are very rare (Amorphous silica: 2 to 6 mg/m³)

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Approaches for setting a TLV for MN (1)

Draft exposure limits from NIOSH (USA, 2005) for titanium dioxide:

- Nanoscale titanium dioxide: 0.1 mg/m³
- Microscale titanium dioxide: 1.5 mg/m³
- Potency factor 15 between nanoparticles and microparticles based on long-term in vivo studies
- Reduction of risk of lung cancer below 1 in 1000
- Surface determines toxicity potential

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Approaches for setting a TLV for MN (2)

Benchmark levels (BL) from BSI (UK, 2007) for four classes of nanomaterials

Nano-BL

- fibrous MN (high aspect ratio): 0.01 fibres/cm³

Nano-BL in relation to established TLVs

- Insoluble MN: 0.066 of TLV (NIOSH relation of 15)
- CMAR MN: 0.1 of TLV
- Soluble MN: 0.5 of TLV

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Risk estimates for nanomaterials

Kuempel et al. 2006:

- Nanoscale TiO₂ and carbon black
- 0.1 % excess risk of lung cancer at 0.07 to 0.3 mg/m³

Roller and Pott 2006:

- Poorly soluble particles with no specific toxicity
- For a chronic exposure of 0.3 mg/m³

mean diameter	excess risk of lung cancer
1800 to 4000 nm	0.1 %
90 to 200 nm	0.2 %
10 to 30 nm	0.5 %

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Differences in TLV-approaches

- Methods to derive TLV (qualitative or quantitative rationale)
- Differing policies concerning acceptable or tolerable risks (e. g. 0.1 %, 0.01 %, 0.001 % excess cancer risk)
- Assumptions to cross datagaps for extrapolation of animal data to occupational exposure conditions of humans
 - Species: rats to humans
 - Duration: long term exposure
 - Mechanism of tumour formation: threshold, non-threshold, something in-between
 - High to low dose extrapolation

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How to select assumptions ?

Assumptions are needed to cross datagaps

- Best guess estimate / central tendency
- Estimates consider worst cases / to err on the side of caution

Does the precautionary principle help us selecting assumptions ?*

“The precautionary principle, which is essentially used by decision-makers in the management of risk, should not be confused with the element of caution that scientists apply in their assessment of scientific data.”

* Communication from the commission on the precautionary principle, http://ec.europa.eu/dgs/health_consumer/library/pub/pub07_en.pdf

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Proposal for TLV-derivation for granular MN (1)

Basic toxicological study for TLV:

- Phys.-chem. characterisation/product specification (surface area, primary and secondary particle size, density, surface characterisation etc...)
- Perform study with the marketed MN (at least 3 months duration in vivo)
- Simulate possible workplace atmosphere (inhalation vs instillation)
- Measurement of mass, if possible

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Proposal for TLV-derivation for granular MN (2)

Applicability of TLV

- TLV is only for the tested specific MN
- For a clearly defined product mass is an appropriate dose metric

Extrapolation of TLV to other MN

- Explore the extension of applicability by considering phys.-chem. properties

For fibres a similar approach is possible

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Thank you very much

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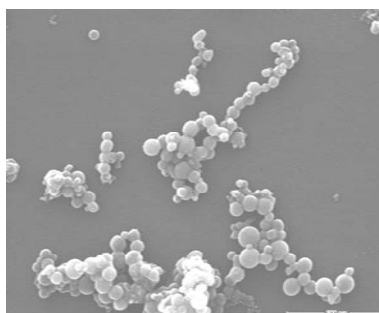


Bild: BAuA, Piltzko

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