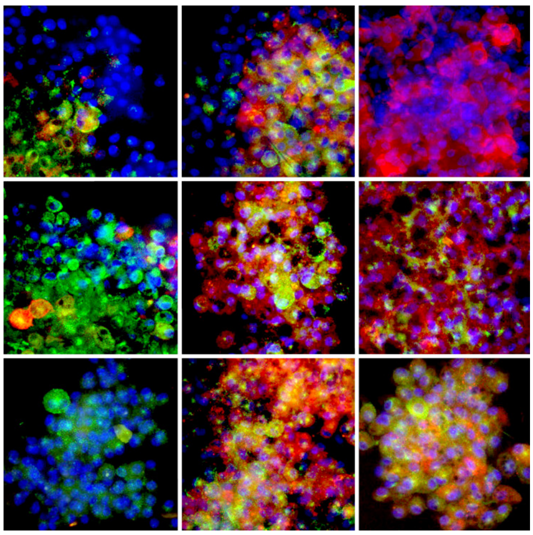
ENPRA Risk Assessment of Engineered NanoParticles

mnt



Environmental, Health and Safety Impacts of Nanoparticles

European Observatory on NanoSafety

N°5
December 2011

Environmental, Health and Safety Impacts of Nanoparticles n°5
December 2011
Edition:
Observatoire des Micro et NanoTechnologies
CEA-CNRS - UMS 2920
Minatec® - MMNT, 3 Parvis Louis Néel
38 054 Grenoble cedex 09
Tél. : +33 (0)4.38.78.20.70
Fax : +33 (0)4.38.78.24.21
E-mail : OMNT@cea.fr
http://www.omnt.fr

Publishing Director:
Stéphane Fontanell

Managing Editor:
Marie-Claire Toufektsian

Publishing Assistant:
Interligne

Printing:
PressVercors
France

N°ISSN en cours
Dépôt légal 4ème trimestre 2011

Cover Illustration:
Induction of iNOS (green) followed by arginase-1 (red) expression in 3D cultures exposed to Asbestos (top row) or 2 different types of carbon nanotubes (middle and bottom rows) as detected by immunofluorescence after 7, 10 or 14 days (from left to right). Cells were counterstained with DAPI (blue). Reprinted with permission from Particle and Fibre Toxicology 8, 17 (2011). Copyright 2011 Sanchez et al; licensee BioMed Central Ltd. To see also: "Brown Univ.: An in vitro 3D model for assessing granuloma formation by high aspect ratio nanomaterials" on page 11.

Upstream processes and devices
- Molecular Electronics
- Nanoconstruction
- Bio-inspired Nanotechnologies
- NEMS

ICT
- Organic Electronics (*)
- Materials and components for optics
- Spintronics
- Nano-electronics
- Nanocomponents

Biology & Health
- Micro & Nanosystems for biology (*)
- Micro & Nanomedicine (*)
- Environmental, Health and Safety Impacts of Nanoparticles (*)

Energy
- Batteries and fuel cells, Photovoltaïc, Thermo-electricity, Power MEMS and energy harvesting

(*) Periodic reports written in English. Other reports are written in French

Environmental, Health and Safety Impacts of Nanoparticles

N°5
December 2011

Introduction

The fifth meeting of the European Observatory on NanoSafety (EONS) took place in Paris on October 13, 2011. The present report summarises the literature analysis and the discussions developed during this event.

About the European Observatory on NanoSafety

The European Observatory on NanoSafety (EONS) is a collective initiative launched in 2009 by the Observatory for Micro&Nanotechnologies (OMNT) and the European consortium ENPRA (Risk Assessment of Engineered NanoParticles). Every 6 months, EONS meetings bring together experts in nanotechnology environmental health and safety (including OMNT experts, partners of the ENPRA project and invited key scientists) and provide them with the unique opportunity to collectively review and comment the latest research progresses of the domain. Topics addressed by the panel cover the full scope of 'NanoSafety' including detection and characterization of nanomaterials, toxicology, ecotoxicology, risk assessment and risk management as well as normative and regulatory aspects. Proceedings of the meetings are published by the OMNT

Occupational Exposure

IUTA & TUD:
Currently available information on nanomaterial exposure in the workplace

Reviewed by R.J. Aitken

Emerging evidence of the release of nanomaterials in particulate form into the air for a range of occupational scenarios

Risk is determined by the hazard of nanomaterials and the extent (level and duration) to which people and/or the environment, are exposed. Most of the papers in the published literature are concerned with the hazard potential of nanomaterials. This paper published by the **Institute of Energy and Environmental Technology** (**IUTA**) and the **Technische Universität Dresden** (**TUD**) is concerned with occupational exposure to nanomaterials and presents a definitive review of all of the currently available peer-reviewed literature relating to workplace studies (25 in total) and laboratory studies of particle release (21 in total).

The 25 workplace related exposure studies, summarised in Table 1, used a range of approaches but most applied a combined approach based on time series assessment and spatial analysis often with additional physico-chemical characterisation (e.g. by electron microscopy SEM/TEM). There was a focus on production tasks, rather than downstream applications and end-use. 22 of the 25 studies showed nanomaterial release of particles greater than 100 nm, while 13 indicated nanomaterial release of particles less than 100 nm.

The 21 studies of particle release by laboratory testing, included "dustiness" testing based on simulation of industrial activities such as grinding, spraying etc. Ten of the studies were on powders and applied methods based on existing dustiness tests such as the rotating drum, free fall and vortex shaker. In these studies, release was highly dependent on energy and physico-chemical properties such as size and surface coating. Two studies focussed on suspensions, where it was found that the sonication process leads to the production of droplets containing nanoparticles. The remaining nine studies assessed release from coatings through abrasion and sanding, and from composites through cutting or drilling and showed evidence of the release of nanoparticles embedded in the matrix material.

Nanomaterial	Production	Handling/Refinement	Bagging/Shipping	Processing	
				Powder or suspension	In fixed matrix
Carbon Black	1	2	2	1	
CNT, CNF Fullerenes	8	8	2	4	2
Ag	2	1		2	
TiO_2	3	3			
SiO_2	2	2	1	1	
AL_2O_3	1	1		3	2
Metals	3	2		1	
Metal oxides	4	4	1	4	
Others	1	1		1	1

Table 1: Exposure scenarios considered in the reviewed studies.

This article provides a comprehensive overview of all of the available literature regarding occupational exposure to nanomaterials. It highlights important information on the methodologies used, exposure levels and physico-chemical characteristics of the aerosols released. Almost all of the reviewed studies established evidence of nanoparticle release, mostly to agglomerates and composites.

The paper offers the best review currently available concerning occupational exposure to airborne nanomaterials. It provides the starting point for some useful meta-analysis of the available data, but there is further scope for more analysis on the data compiled. Although multiple measurement methods have been used, modalities are emerging, in particular the use of a tiered approach. Metrics, background levels, instrument performance, aspect ratio, and sensitivity are all issues which need to be considered. Almost all of the reviewed studies found evidence of release.

There is still almost no real personal exposure data in the literature and the linkage of release data to personal exposure is still missing. The reported laboratory studies provide valuable additional data but many different approaches are being used and a more uniform approach is required. These exposure studies provide a basis for toxicity studies to calibrate dose and provide useful information on nanomaterial forms (e.g. nanoparticles embedded in a matrix, agglomerates) relevant to actual exposures.

"Nanoparticle exposure at nanotechnology workplaces: A review" ; T.A.J. Kuhlbusch, C. Asbach, H. Fissan, D. Göhler, M. Stintz : ***Particle and Fibre Toxicology*** **8**(1), 22 (2011).

EONS12-11-1

Risk Assessment & Risk Management

NIOSH:
Minimising risk for occupational inhalation exposure to carbon nanotubes and carbon nanofibres

Reviewed by K. Aschberger

The US National Institute for Occupational Safety and Health (**NIOSH**) summarises in its draft "Current Intelligent Bulletin" adverse respiratory health effects following inhalation exposure and presents a recommended exposure limit (REL) for carbon nanotubes (CNT) and carbon nanofibres (CNF).

First recommended exposure limit for carbon nanotubes

NIOSH derived Benchmark dose (BMD) and the 95% lower confidence limit estimates (BMDL) from available animal subchronic inhalation studies with CNT, supported by short term studies and studies applying intratracheal instillation and pharyngeal aspiration. These values were extrapolated to humans by accounting for species differences in alveolar lung surface area and, as well, extrapolated to estimated working life time exposure concentrations (8 h TWA, 40 h/w, 50 w/y, 45 y). The resulted 95% lower confidence limit of the benchmark concentrations of 0.2 – 2 µg/m^3 (for deposited and retained lung doses respectively) are associated with a 10% excess risk of developing early-stage pulmonary effects.

These levels are lower than the upper limit of quantification (LOQ) of the currently recommended analytical method for measuring airborne CNT (NIOSH 4050), which is 7 µg/m^3 elemental carbon. NIOSH therefore recommends this value as REL (recommended exposure value) for an 8-hr TWA (time weighted average) respirable mass airborne concentration. According to NIOSH, this REL allows to lower the risk, however it does not ensure an appropriate protection of the worker's health; therefore all efforts should be made to reduce airborne concentrations as low as possible below this REL.

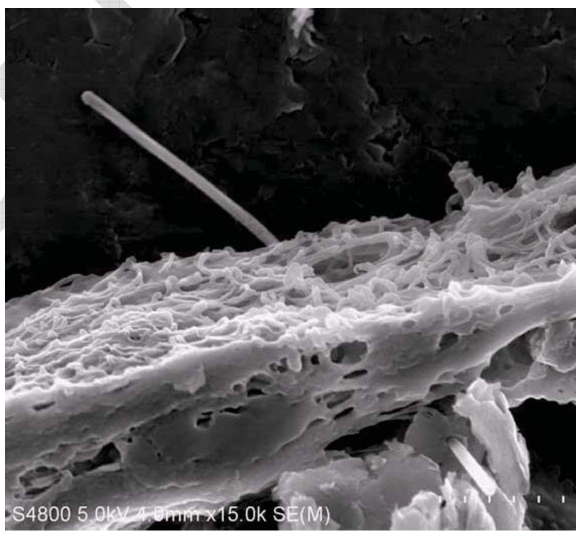


Figure 10: A field emission scanning electron micrograph of a multi-walled carbon nanotubes (MWCNT) penetrating the pleura of the lung.
Image courtesy of Robert Mercer, and Diane Schwegler-Berry, NIOSH.

The document also compares the REL with other available occupational exposure levels or equivalent reference values (2.5 – 50 µg/m^3 for 8 h TWA). NIOSH discusses that the approaches leading to higher reference values assume a first-order clearance and may overestimate the clearance of poorly-soluble and non-spherical particles and therefore under-predict the lung burden in human lungs.

All current reference values are expressed in mass/volume, which may not be the best predictor of certain lung diseases. Additionally, a mass based sampling method might not be sufficiently sensitive to detect low mass concentrations of CNTs. Therefore research is needed to determine the most sensitive dose metrics.

Finally the bulletin gives recommendations to minimise the risk of developing respiratory diseases for workers through exposure control measures and implementation of an occupational health surveillance programme.

This REL represents the first "official" work place reference level for CNT and CNF.

It is based on a practical and realistic approach and can reasonably be monitored. The REL is much lower than OELs for graphite or carbon black (2.5 – 5 mg/m^3) which are sometimes also used for CNTs in materials safety data sheets. However it still includes uncertainties with regard to a risk for humans of developing lung diseases and, therefore, efforts should be made to reduce airborne concentrations even below this level. The recommendations given are useful, but not specific for CNTs and CNF as many of them should in principle represent good working hygiene practices generally applicable to other particulate or fibrous materials.

"Occupational Exposure to Carbon Nanotubes and Nanofibers" ; NIOSH Current Intelligence Bulletin (http://www.cdc.gov/niosh/docket/review/docket161a/pdfs/carbonNanotubeCIB_PublicReviewOfDraft.pdf).

EONS12-11-9

NIOSH : Safe handling of fine and ultra-fine Titanium dioxide: an important update from NIOSH

Reviewed by D. Bloch

In March 2011, following a first draft issued in 2005, US National Institute for Occupational Safety and Health (**NIOSH**) published its final report on occupational exposure to fine and ultra-fine Titanium Dioxide (TiO_2) and provided recommendations for occupational exposure limits (REL).

New recommendations for TiO_2 exposure limits

This report summarises all available data on respiratory effects of TiO_2, encompassing epidemiological, in vitro and in vivo studies and providing some important statements and recommendations. Due to inconclusive results of epidemiological studies (inadequate statistical power with regard to the low carcinogenic potency of TiO_2), conclusions are mostly supported by inhalation animal studies. Some of the most important outputs of the document can summarised as follows:

1) TiO_2 and other poorly soluble, low-toxicity particles of fine or ultra-fine size can induce pulmonary effects such as persistent inflammation and lung tumor and the report highlights the fact that the dose response relationship of these effects is more consistent when the dose is expressed in terms of particle surface area (Figure 11). In others words, those effects are probably better correlated to the particle surface area than to their mass or crystal structure. For example, chronic and sub-chronic inhalation studies show no difference in pulmonary inflammation or lung tumor responses with fine and ultrafine particles of TiO_2 of different crystal structure (anatase vs. rutile) when the dose is expressed as particle surface area, suggesting than surface area could be the most appropriate dose metric for assessing occupational inhalation exposures.

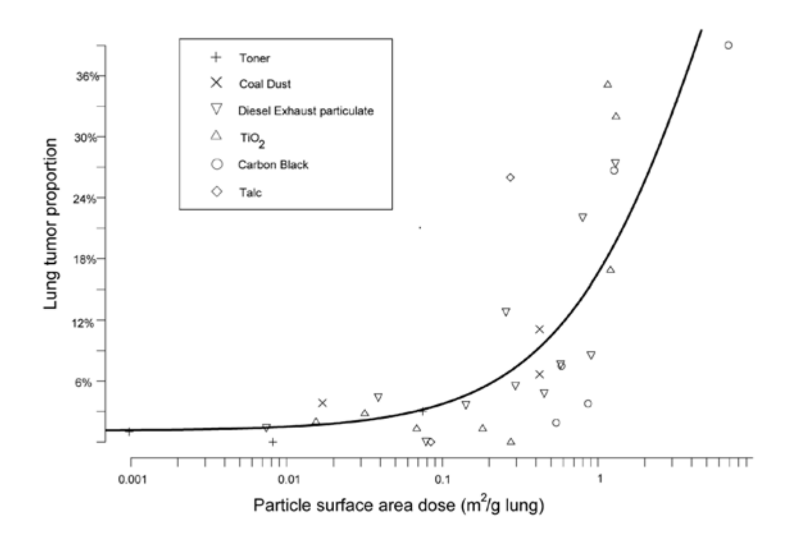


Figure 11: Relationship between particle surface area dose in the lungs of rats after chronic inhalation to various types of particles and tumor proportion.
Reprinted with permission from NIOSH Current Intelligence Bulletin N° 63.

2) Regarding fine TiO_2, only one inhalation study demonstrates the development of lung tumors at a concentration of 250 mg/m^3, whereas no such effect can be observed for concentrations of 10 or 50 mg/m^3. As concentrations above 100 mg/m^3 are generally not considered acceptable in inhalation studies, and considering that concentration of 250 mg/m^3 is probably not relevant with regard to workers exposure, NIOSH concludes that data are currently insufficient to classify fine TiO_2 as an occupational carcinogen.

3) Conversely, animal studies with ultrafine TiO_2 provide evidence that TiO_2 is not a direct-acting carcinogenic agent but acts through a secondary inflammation induced genotoxicity mechanism that is not specific to TiO_2 and might be related mostly to particle size and surface area. Thus, NIOSH considers ultra fine TiO_2 as a potential occupational carcinogen.

4) Extrapolating results from animal inhalation studies to estimate the human work life time exposure (applying appropriate factors), NIOSH recommends occupational exposure limits of 2.4 mg/m^3 for fine TiO_2 and 0.3 mg/m^3 for ultrafine TiO_2, as time weighted average (TWA) concentrations for a 40–hour work week, levels that, during a working life time, are estimated to reduce risks of lung cancer to below 1/1000.

5) NIOSH proposes a rationale for a tiered approach for assessing workers' airborne exposure and interpreting the results with regard to the REL respectively for fine and ultrafine particle (Figure 12). This assessment is based on mass concentration measurements using filter collections of airborne particles, which may be considered as inconsistent regarding statements on surface area metric. However, an interesting point is the following rationale: if the mass concentration is below 0.3 mg/ m^3 (REL for ultra-fine particles, which is the most stringent REL), then no further action is needed. If the mass concentration is above 0.3 mg/m^3, it is then necessary to determine the percentage of fine and ultrafine particles respectively by appropriate electron microscopy techniques and to adjust mass concentrations accordingly. This step allows to assess whether exposure to the NIOSH REL for fine, ultrafine or combined fine and ultrafine TiO_2 has been exceeded (Figure 12).

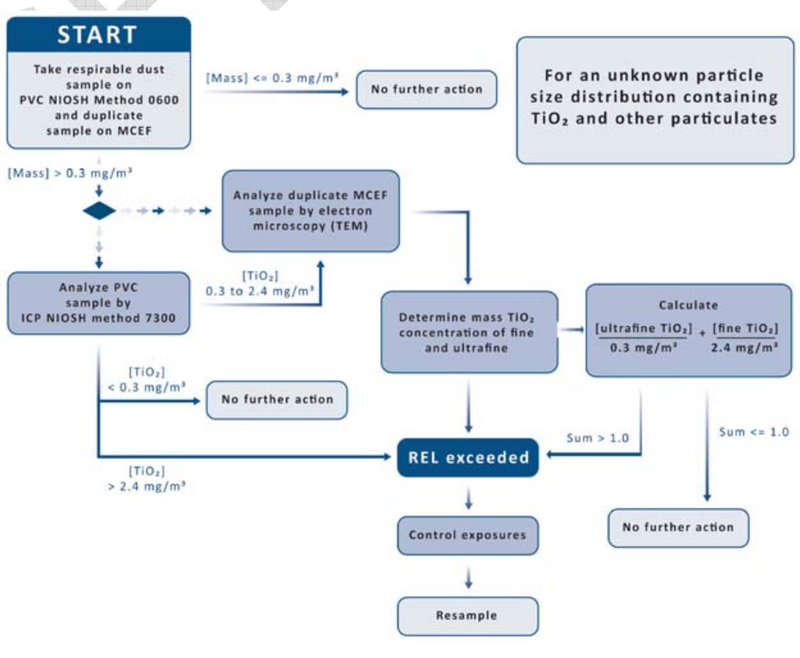


Figure 12: NIOSH tiered approach for assessing worker's exposure to TiO_2. Sample collections of respirable dusts are simultaneously performed on PVC (polyvynil chloride) and MCEF (mixed cellulose ester) filters; if concentration is above 0.3 mg/m^3, additional characterization is required; samples are analyzed both by ICP (inductively coupled plasma spectrometry) and by TEM (transmission electron microscopy) in order to allow assessment of particle size and fine and ultrafine mass concentrations and further adjustment of mass concentrations for appropriate comparison to REL.
Reprinted with permission from NIOSH Current Intelligence Bulletin N° 63.

This report provides first specific hazard classification and occupational exposure limits for fine and ultrafine particles of the same material TiO_2. The rationale for stating that ultrafine TiO_2 is an occupational carcinogenic agent while fine TiO_2 is not may seem inconsistent with regards to conventional chemical hazard classification strategies. In this respect, this report should be considered as a very pragmatic and practical document for managing TiO_2 occupational risk, and sufficiently conservative according to the current state of knowledge on TiO_2 toxicity.

Finally, the report emphasizes the need for further research in the fields of i) pulmonary, cellular and sub-cellular TiO_2 toxicology, ii) workplace exposure characterization, iii) epidemiological studies, and iv) assessment of the effectiveness of control measures.

"Occupational Exposure to Titanium Dioxide" ; ***NIOSH Current Intelligence Bulletin*** N°63.

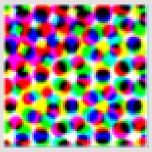
EONS12-11-10

Companies, organisations & experts quoted in this report

List of experts involved in Environmental, Health and Safety Impacts of Nanoparticles

Rob AITKEN	IOM Edinburgh, United Kingdom	ENPRA
Pascal ANDUJAR	CHI Créteil, France	OMNT
Karin ASCHBERGER	JRC Ispra, Italy	ENPRA
Mélanie AUFFAN	CNRS, Univ. Paul Cézanne, France	OMNT
Armelle BAEZA	Univ. Paris 7, France	OMNT - ENPRA
Daniel BLOCH	CEA Grenoble, France	OMNT
Sonja BOLAND	Univ. Paris 7, France	ENPRA
Jean - Yves BOTTERO	CNRS – Univ. Paul Cézanne, France	OMNT
Sybille van den BRULE	Univ. Louvain, Belgium	ENPRA
Enrico BURELLO	JRC Ispra, Italy	ENPRA
Flemming CASSEE	RIVM, The Netherlands	ENPRA
Emmanuel FLAHAUT	CNRS – Univ. Paul Sabatier, France	OMNT
Laetitia GONZALEZ	Vrije Univ. Brussel, Belgium	ENPRA
Stefania GOTTARDO	Univ. Venice, Italy	ENPRA
Peter HOET	Univ. Leuven, Belgium	ENPRA
Marie - Claude JAURAND	INSERM, France	OMNT
Wim de JONG	RIVM, The Netherlands	ENPRA
Micheline KIRSCH-VOLDERS	Vrije Univ. Brussel, Belgium	ENPRA
Jennifer McLEISH	Univ. Edinburgh, United Kingdom	ENPRA
Stéphanie LACOUR	CNRS, France	OMNT
Sophie LANONE	INSERM, France	OMNT
Ghislaine LACROIX	INERIS, France	OMNT
Dominique LISON	Univ. Louvain, Belgium	ENPRA
Steffen LOFT	Univ. Copenhagen, Denmark	ENPRA
Katrien LUYTS	Univ. Leuven, Belgium	ENPRA
Antonio MARCOMINI	Univ. Venice, Italy	ENPRA
Fabrice PETITOT	IRNS, France	OMNT
Craig POLAND	IOM Edinburgh, United Kingdom	ENPRA
Jérome ROSE	CNRS, Univ. Paul Cézanne, France	OMNT
Bryony ROSS	IOM Edinburgh, United Kingdom	ENPRA
Roel SCHINS	IUF Düsseldorf, Germany	ENPRA
Antoine THILL	CEA Saclay, France	OMNT
Lang TRAN	IOM Edinburgh, United Kingdom	ENPRA
Rob VANDEBRIEL	RIVM, The Netherlands	ENPRA

ENPRA Partners



IOM (UK)
Napier Univ. (UK)
Univ. Edinburgh (UK)
Univ. Diderot Paris 7 (FR)
CEA (FR)
Univ. Catholique de Louvain (BE)
Katholieke Univ. Leuven (BE)
Vrije Univ. Brussel (BE)
HMGU (GE)
IUF (GE)
Univ. Copenhagen (DK)
NRCWE (DK)
Univ. Venezia (IT)
JRC (pan-EU)
RIVM (NL)

Forthcoming workshop of the Observatory

OBSERVATOIRE DES
MICRO ET NANOTECHNOLOGIES
Unité Mixte de Service CEA-CNRS n°2920