



ISSA Symposium
Nanotechnology
Lucerne, 4-5 Oct 2010
www.issa.int/prevention-chemistry

Abstracts

Nanotechnology – Prospects and occupational risks

New challenges for prevention

KKL Lucerne, Switzerland
4–5 October 2010



Dr. Denis Bemer, INRS, Nancy

Filtering nanoparticle aerosols

Many industrial processes require air exempt of particles. Different levels of air filtering is therefore necessary to protect personnel and some manufacturing processes. Questioning the performance of fibre filters with respect to aerosols containing particle sizes of only a few nanometres is legitimate, given the spectacular development in nanotechnologies. A study has been conducted to verify the assumption that theoretical filter efficiency is reduced, when nanoparticles are involved. At present, no efficiency reduction phenomenon due to thermal recoil has been observed for particles larger than 3 nm, irrespective of the filters and particles tested within the scope of this study.

Dr. Markus Berges, IFA, St. Augustin

Occupational exposure 2

Exposure estimation from aerosol measurements in nanotechnology industries

In the framework of the European NANOSH project, a detailed attempt was carried out to determine the aerosols at workplaces. It includes the development of a sampling strategy as the first step in combination with structured observations and registration of activity-time patterns, ventilation conditions and collection of contextual information. The measurements consisted of a full array of instruments, including mobility particle sizer, condensation particle counters, (low-pressure) cascade impactor and diffusion charger, located at workplaces. Simultaneously measurements of the background at surrounding places were carried out for reference. In addition to the online measurements, aerosols are sampled by both static devices e.g. electrical precipitators and personal air samplers, also equipped with a special designed filter including a TEM grid to enable off-line analysis for characterization and identification.

Handling of multiwall carbon nanotubes in powder form under lab scale conditions seemed not to release single tubes. During a leakage in the production of nanosized TiO₂ individual primary particles could be detected. Pouring operation of nanosized TiO₂ in paint production released particles, but no difference to operations with micrometer sized material could be observed. TEM analysis showed no evidence of single nanoparticles. Sieving, drying and pouring operations of nano sized ZnO showed particle concentrations below 100 nm, but their origin is to be checked against surrounding sources like motor emissions and other processes. Also an analysis of activity time periods against non-activity periods is taken into consideration as well as TEM analysis in order to find evidence of airborne nanoparticles.

Acknowledgment: the NANOSH project is supported by EU-FP 6 program, contract NMP4-CT-2006-032777.

Berges, M.¹, Möhlmann, C.¹, Pelzer, J.¹, Bard, D.², Mark, D.², Brouwer, D.³, Stuurman, B.³, Jankowska, E.⁴

¹IFA-Institute for Occupational Safety and Health, Sankt Augustin, Germany

²Health and Safety Laboratory, Harpur Hill, Buxton, UK

³TNO Quality of Life, Zeist, The Netherlands

⁴Central Institute for Labour Protection - National Research Institute, Warsaw, Poland

Daniel Bernard

Guide to Best Practices – Nanomaterials and SHE

Chemistry forms the basis for designing and developing nanomaterials, whose expansion is embraced by the continuous development of increasingly high-performance innovative nanomaterials offering new functional characteristics. Through its research and development, production, application and transformation activities, the chemical industry is therefore involved at every stage of nanomaterial implementation and usage.

In every circumstance, the chemical industry applies a prevention and protection policy aimed at achieving a higher level of hazard control, not only in the design of its products and processes, but also in the construction and operation of its installations.

Naturally, this policy therefore applies to the development of nanomaterials and leads to applying to them procedures that take into account both available knowledge and uncertainties concerning their dangers and risks. The industrialists involved are thus duty-bound to comply with legislative and regulatory provisions, in particular those of the French Labour Code in relation to chemical hazards, which require assessment, management and control of risks to employee health and safety.

Within the scope of undertakings embraced by “Responsible Care®” programme, the Union des Industries Chimiques has drafted a *Guide to Best Practices* in nanomaterial production and implementation to provide chemical industrialists with essential scientific, technical and regulatory information. This guide, whose first edition was published in March 2009, is destined to be updated based on expanding knowledge to enable industrialists to develop their means of prevention and protection. In particular, this document takes into account AFSSET¹ recommendations. Equivalent guides have been drafted in other European countries and bodies, such as the VCI² in Germany. The current guide concerns risk prevention and protection in the workplace. Implemented means will depend on the chemical nature and the physical chemical, toxicological and ecotoxicological properties of the nanomaterials considered as well as the exposure scenarios retained. Management of co-products, non-standardised products and waste products must also be taken into account. From production right through to the end of the life of objects incorporating them, nanomaterials will successively involve various industrial stakeholders throughout their value-adding chain (production, formulation, transformation, forming, even machining and assembly, end-of-life processing/recycling). Their entire life cycle should therefore be considered and analysed in the risk assessment process.

The chemical industry is conscious of the challenges and opportunity raised by nanomaterial development. In placing on the market products that are harmless to consumers, the chemical industry possesses the necessary skills to ensure that such products are responsibly developed by guaranteeing employee health and safety, whilst controlling the risks of dissemination and environmental impact.

U.I.C. Nanotechnology Advisor

¹ Les nanomatériaux, sécurité au travail AFSSET, July 2008

² Responsible Production and Use of Nanomaterials, 11/03/2008, Verband der Chemischen Industrie/VCI, Guidance for handling and use of nanomaterials at the work place

Dr. Thomas Brock, BG RCI, Heidelberg

Prevention measures in nanomaterial R&D

Nanotechnology in the Laboratory: Safety Principles in Research and Development

Like most substances new nanomaterials are prepared in laboratories. The Development of new products starts in lab-scale. Due to the fact that the bigger part of these never make their way to the market the safety-related properties of these nanomaterials are not investigated extensively. This means that exposure control is the sensible thing to manage risks in laboratories. Actually they share this fate with most new substances.

Since free nanoobjects, at least the ones on the smaller side of the scale, show behaviour more similar to gases than to dusts, the well-established principles of exposure control in laboratories are very efficient when used appropriately. They are also effective with the more dust-like fractions. A recent study shows that it seems to be more of a problem to convince researchers in laboratories to use the appropriate practices [1].

Examples for efficient measures are:

- Risk assessment, not only for the nanomaterial (toxicity, flammability), but also including risks from starting materials or solvents, e. g. (keep exposure ALARP)
- Preparation and handling of nanomaterials in closed systems, solved or suspended in liquids or enclosed in a matrix
- Fume hoods or laminar flow benches (N. B.: HEPA-filtering is effective for nanoobjects but not for substances with a vapour pressure): Proper usage determines the effectiveness of the measure (for instance, do not block the air flow inside the fume hood with big apparatus)
- Avoidance of skin contact (hygiene, wear proper gloves, clothing and shoes – eye protection taken for granted in laboratories)
- Use of proper respiratory protection if nanoobjects can become airborne

Following prudent safety practices in the laboratory is mandatory. For more details see [2].

[1] F. Balas, M. Arruebo, J. Urrutia, J. Santamaria, Nature Nanotechnology **5**, 93 – 96 (2010)

[2] DGUV (ed.): Guidelines for Laboratories: Working Safely in Laboratories (BGI/GUV-I 850-0e), Heidelberg 2009 (see also www.guidelinesforlaboratories.de and www.laborrichtlinien.de)



Professor Vicki Colvin, Department of Chemistry, Rice University

“Nanotechnology in the Environment: Safety by Design”

Intelligent strategies for the safe design of nano-objects

Nanotechnology-enabled systems offer much promise for solving difficult environmental problems ranging from water purification to waste remediation. These solutions must not only be cost-effective and sustainable, but they must also be safe for people and the environment. Our emerging understanding of the interface between nanomaterials and biological systems gives us the critical ability to approach the latter issue early in the development of nanotechnology. This talk will discuss in some detail how the chemical and physical properties of engineered nanomaterials impact their biological effects in model systems. Three case studies, ranging from fullerenes to metal oxides, illustrate the vast diversity of nanomaterial features and biological response. The composition of a nanomaterial is the primary factor in describing acute biological effects, and among the different examples nanoparticle charge and surface coating can be of equal importance. Interestingly, the size of the inorganic material itself – such an important feature for applications development – in these three examples is secondary in defining the materials’ acute biological effect. In all cases, the biological and environmental compartments experienced by nanomaterials lead to substantial modification of their hydrodynamic size and charge. The bio-modified material that results is the central element to understand and characterize in order to detect the underlying correlations between the inorganic nanomaterial phase, composition and size with biological outcomes. These correlations form the basis for guidelines that permit researchers creating new nanoparticles to focus their energy on materials that are ‘safe by design’



Dr. Stefan Engel, BASF SE, Hazardous Chemicals Management

Definition of the Phrase Manufactured Nanomaterial and Metrological Uncertainties

Manufactured nanomaterials have a huge potential; from resolving grand societal challenges to being a practical help in everyday life.

An internationally agreed, science-based definition of manufactured nanomaterials is under controversial discussion and has not yet been presented. Thus, the question what would qualify a material as being a nanomaterial has not yet been decided. Landmarks in the ongoing debate have been the terminology published by ISO's Technical Committee 229 (EN ISO TS 27687, 2008), opinions delivered by the EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR Opinion 012, 2009), the legally binding definition in the recast of the Cosmetics Regulation (1223/2009 EC) and also the proposed convention of the German Chemical Industry Association (VCI).

The question related to the outlined definition dilemma how to adequately characterize manufactured nanomaterials is not resolved accordingly. A path-breaking approach may be the OECD guidance manual (ENV/JM/MONO(2009)20), which has been established within OECD's comprehensive testing program of manufactured nanomaterials.

Basically, most of these parameters are also described in appendix R7 of the REACH Regulation. The ongoing REACH Implementation Projects on Nanomaterials are currently evaluating, if the technical guidance document may possibly have to be adjusted to specifically address nanomaterial properties.

The presentation wants to give an overview on the present definition situation of manufactured nanomaterials including their implications and will also give you an impression of the scope and limitations of available analytical methodologies.



Dr. Robert Falkner; London School of Economics and Political Science

“Regulation of nanomaterials”

Over the last decade, leading nanotechnology countries have sought to strengthen risk regulation for nanotechnologies but have experienced severe information asymmetries. The regulation of nanotechnologies is complicated by a high degree of scientific uncertainty, lack of knowledge about environmental and health risks and uncertainty regarding the commercial application of nanotechnology developments in the global economy. The presentation reviews the emerging regulatory landscape for nanotechnologies in leading industrialised countries and at the international level. In a first step, it identifies the main similarities and differences between European and US regulatory approaches and examines the potential for regulatory convergence and divergence in a transatlantic context. In a second step, it investigates the growth of international coordination and cooperation in the field of nanotechnology regulation, with a view to establishing best practices and identifying global governance gaps.



Martin Fierz, University of Applied Sciences of North-West Switzerland (FHNW),
5210 Windisch

Portable and simple instruments for measuring nanoparticles

Many of the standard instruments used for measuring airborne nanoparticles are large, heavy and expensive, require a mains connection and cannot be used by laymen. Gradually it is realized that less complicated methods are needed for workplace measurements – at least for an initial assessment of air quality –, and various manufacturers now have simpler instruments on offer. I will briefly present some of these instruments, limiting myself to those that are battery-operated and small enough to allow portable measurements. At present, these are light-scattering measuring devices, micro-aetholometers, TEOM portables as well as two instruments developed at FHNW – the electric diffusion battery and the mini-Diffusion Size Classifier (mini-DISC).



Dr. Eric Gaffet, Nanomaterials Research Group (NRG) UMR CNRS 5060

Manufacturing methods for nanomaterials/nanoparticles

Since the 1980s, multiple research studies have shown that nanostructured materials have physical chemical properties distinct from equivalent microstructured materials.

Nanomaterials in the form of powders, coatings or solid pieces, are composed of crystallites smaller than 100 nm. They contain a significant proportion of grain boundaries compared with conventional materials. The volumetric fraction and thickness of these grain boundaries can reach 20% for 10 nm crystallites and 0.7 nm respectively.

Nanostructured materials are produced by a wide range of physical, chemical and mechanical methods. In the latter case, mechanosynthesis is the most frequently used (mechanical alloying, ball milling, mechanochemistry).

The different methods of obtaining nanomaterials in powder and/or solid forms will be discussed during this symposium, and specific properties induced by this nanometric scale will be described.

Dr. André Gzásó, Austrian Academy of Sciences, Institute of Technology Assessment,
Vienna

Use of nanoparticles in product manufacturing

NanoTrust – Contributing to an informed public risk debate on nanotechnologies and possible applications

Nanotechnology is an emerging branch of research and technology development. Up to now, safety aspects have not yet been thoroughly researched enough in order to allow for conclusive assessments regarding postulated risks. At the same time, concerns about potential risks are being raised and there are first signs of a public debate. Not least against the background of the experiences in the area of biotechnology, a foresighted nanotech policy is necessary, which is based on profound and well presented analyses.

In 2005 the European Commission has adopted an action plan for Europe. In this document a “safe, integrated and responsible strategy” was proposed. The European Commission postulates that “risk assessment related to human health, the environment, consumer and workers should be responsibly integrated at all stages of the life cycle of the technology ...”. Therefore, the European Action Plan for Nanotechnology and most of the subsequent national action plans suggest co-ordinated activities mainly in two areas, i.e. (1) increasing support for research on environmental, health and safety issues of nanotechnologies and (2) scientifically based risk communication to encourage an informed public debate.

Different to most other new technologies nanotechnologies make specific demands to public discussion. Firstly, there is a lack of clarity regarding the term itself: There is no generally accepted definition of nanotechnologies, yet, and the use of several definitions is confusing. Nanotechnologies is an enabling technology with a wealth of conceivable applications which makes a categorisation of applications vage and ambiguous. Moreover, there exists a huge variety of development stages. Last but not least nanotechnologies is genuinely interdisciplinary research. The second challenge to public discussion is the risk knowledge gap, i.e. there exists a discrepancy between knowledge on risks and the state of development of certain application. Also timeframes can have wide ranges and are normally not communicated clearly. The third and most important demand is the lack of usable structured and therefore usable information while the demand of information by public interest is increasing. As documented in the first half of 2006 by two projects, on the state of risk and accompanying research there is massive need for research and communication. Therefore the Austrian Ministry of Transport, Innovation and Technology (BMVIT) aimed to meet these needs in a national project. The project “NanoTrust” was established in October 2007 at the Institute of Technology Assessment and will be active until 2013. In the light of NanoTrust’s thematic focus on health and environmental risks as well as on societal aspects of nanotechnology, the team at the Institute of Technology Assessment is interdisciplinary (biology, physics, law, philosophy).

The heart of the research project is to continually (1) survey, analyse and summarise the state of knowledge regarding potential health and environmental risks of nanotechnology, (2) to inform the interested public about these issues by publishing its results. The main goals of NanoTrust are:

- To elaborate dossiers on specific topics of interest appearing in the public discussion on the risks of nanotechnologies;
- To organize regular workshops and conferences on special topics such as communication on nanotechnologies or on open questions of risk assessment;



- To set up a network with the core national and international actors and hence form an information platform;
- To identify important open issues of risk assessment;

All investigation, research and statement on the use of nanotechnologies and nanomaterial and the existence of certain nanoproducts have therefore to be evaluated and measured against the special conditions described above. Some research on consumer products has been carried out as part of NanoTrust and will be presented here in a categorised manner.

André Gzásó, Myrtill Simkó, Ulrich Fiedeler, Michael Nentwich

Austrian Academy of Sciences, Institute of Technology Assessment

Strohgasse 45/5, 1030 Vienna; +431 51581-6578; agazso@oeaw.ac.at

Project homepage: <http://nanotrust.ac.at>

Alexander Graff, ÖSBS, Leoben, Austria

Exposure in the workplace

In spite of the advantages which nanotechnology offers, among other things, with respect to properties of materials, caution is advisable as concerns industrial safety. With the exception of research results and epidemiological studies of health effects due to ultrafine aerosol particles, the amount of data in nanotechnology concerning the health aspects of exposure to particles < 100 nm remains inadequate.

The Austrian Centre for Combatting (Dust-Induced) Silicosis (ÖSBS) has for 60 years dealt with the measurement and assessment of powders or substances contained therein as well as of fibers in the workplace. In addition to the determination of concentrations of inhaled noxious substances occurring during work processes, there is now a new focus on sub-micron particles. Whether these are ultrafine aerosol particles (such as welding fumes, combustion particles from diesel engines etc.) or particles from manufacturing processes in nanotechnology is of no importance for the measurement of particle concentrations and the assessment of the whole range of particles. In the following, several examples of exposure measurements resulting from practical work in recent years will be presented and discussed.

Dr. Yves Guichard, *INRS, Centre de Lorraine*

***In vitro* cytotoxic and genotoxic effects of metal oxide nanoparticles**

The toxicological effects of nanoparticles (of which one dimension is less than 100 nm) could differ from those of larger particles, particularly due to the large reactive surface areas they possess. Understanding the specific toxicological character of nanometric particles would undoubtedly allow better assessment of exposure-related risks under work conditions. With this objective in mind, our research was directed towards the *in vitro* cytotoxic and genotoxic effects of metal oxide nanoparticles. In the literature, these particles exhibit strong radical activity capable of inducing various cytotoxic effects, in particular cell oxidising stress. Available data on the genotoxic effects of metal oxide nanoparticles are currently fragmentary and often contradictory. Our work focused on both the cytotoxic effects (inhibited cell growth and induced intracellular oxygen reactive species) and the genotoxic effects (formation of micronuclei and induced DNA lesions) of titanium (TiO₂) and iron oxides. Samples of manufactured nanometric and submicrometric, anatase and rutile TiO₂, Fe₂O₃ and Fe₃O₄ were tested *in vitro* on Syrian hamster embryo cells. Physical chemical properties of the samples were analysed (chemical composition and structure, size and specific area). Particle radical activity was also studied in an acellular environment. The results revealed more significant effects of cell growth inhibition for the corresponding nanometric particles (except for iron oxide Fe₃O₄). In the case of anatase and rutile TiO₂, these differences in cytotoxic effect were related to particle radical activity. Induced intracellular oxygen reactive species was also greater for TiO₂ and Fe₂O₃ nanometric particles. On the other hand, the size of these particles had no clear influence on their genotoxic effects.

Dr. Bertrand Honnert

Production and usage of nanomaterials (particle engineering) in France

This paper reviews a sector-based study of the production and usage of nano-objects implemented in different industrial processes. The purpose of the study was to undertake an exhaustive determination of the type of nano-objects involved, the quantities used and the employee populations potentially affected. It was deployed in three stages represented by a survey, a pilot and a supplementary phase.

The survey phase involved collecting information by means of a bibliographical study, Internet consultation and industrial site visits. It allowed us to draw up a description of the main nano-objects concerned: titanium dioxide, carbon black, amorphous silicon, alumina. Nano-objects of secondary importance in tonnage terms, such as rare and emerging earth metals, carbon nanotubes or nanoclays, were also listed. An estimated 2000 to 4000 employees are potentially exposed at different production stages.

A pilot phase was launched in control sectors, such as chemical, paint, ink, varnish and plastics industries, in order to refine this study. This involved sending a self-declaration questionnaire to all 1048 establishments making up these sectors. Based on a 47% response rate, the survey confirmed production and usage of nano-objects listed during the preliminary phase, to which iron and zinc oxides and calcium carbonate were added. Fourteen establishments foresee the use of nano-objects, mainly titanium dioxide and carbon nanotubes, in the future. Moreover, this pilot study highlighted the problems faced by user establishments in assessing nano-objects based on the data sources available to them, namely safety and technical datasheets.

Prof. Dr. Harald Krug, EMPA, St. Gallen

Toxicological approach to nano-objects, especially nanoparticles and nanofibers

"Nanotechnological products" have already found their way into the market, not only in industrial applications but also in consumer-related domains (Krug 2008). One can encounter them in places like supermarkets, gas stations or clothes shops. Quite a use is made in the medical sector and other applications are entering the markets.

In this rapid developing environment of new products and uses consumers as well as other social groups see a massive increase of possible health risks too. So one can raise the question to what extent negative effects associated with the use of new nanomaterials are socially acceptable.

To identify and calculate possible risks of nanomaterials you have to understand the specific characteristics of nanoobjects. Therefore three principles will be presented which are essential for possible biological effects of nanoobjects. These are a facilitated transport through biological barriers, a considerable increased surface-to-volume ratio and influences of the materials the nanoobject is made of. All three principles are directly related to a possible toxicity of nanoobjects and will be exemplified. The understanding of biological activities is a basic requirement for future use and acceptance of these new materials which could contribute so much to the solving of future problems.

Literature:

Krug HF (2008): Nanotechnologie - Zwerge erobern den Alltag. Chemie Ingenieur Technik 80, 1653-1660.

Krug HF und Wick P (2010) Nanotoxikologie – eine interdisziplinäre Herausforderung. Submitted to: Angewandte Chemie



Prof. Dr. Harald F. Krug

Prof. Dr. Harald Krug was born in 1952 in Edermünde-Besse and studied biology and chemistry at the University of Kassel before receiving his PhD from the University of Göttingen and going on to work for several years at the Karlsruhe Research Centre. In 1996, Krug habilitated at the University of Karlsruhe in the field of environmental toxicology. He is currently the coordinator of NanoCare, a BMBF-funded project dealing with the systematic investigation of the potential risks of nanomaterials. He has been with Empa since 2007, where he heads up the Materials-Biology Interactions department

Prof. Krug received the 2006 Award of cwi-German Ceramic Society and in 2007 the Research of Baden-Württemberg to 'alternative and supplementary methods animal experimentation



Prof. Dr. Claus-Michael Lehr, Saarland University

Nanomedicine: Delivering drugs across biological barriers with nanoparticulate carriers

The focus of our research over the past ten years has been on the biological barriers of the gastro-intestinal tract, the skin and the lungs. This presentation will highlight some of our recent results or data of work in progress in these three areas, either concerning the development of new in-vitro models or new drug carriers systems, for which the nano-size often has turned out to be advantageous.

Inflammatory bowel diseases, such as Morbus Crohn or Colitis Ulcerosa, are painful for the patient and moreover difficult to treat due to the increased mucus production and the occurrence of diarrhea. We could demonstrate that the anti-inflammatory drug rolipram, when delivered by nanoparticles made of biodegradable PLGA, led to a prolonged alleviation of colitis syndromes in rats and a reduction of central nervous side effects, compared to the same dose of the drug administered as an aqueous solution [1, 2].

With respect to skin drug delivery, there is an interesting new hypothesis that nanoparticles may penetrate along hair shafts and to thus accumulate in hair follicles [3]. However, applying PLGA nanoparticles loaded with flufenamic acid, were mostly seen in the intercellular clefts between the keratinocytes [4]. The observed enhancement of epidermal penetration may instead be explained by an acidic microclimate around the hydrolyzing polymer particles, leading to a reduced dissociation and higher lipophilicity/better penetration of flufenamic acid [5]. This data points out that, besides of their small size, the chemical composition of such nanomaterials remains evenly important.

Due to their large surface area and excellent blood supply, the lungs are an attractive alternative route for drug delivery, both for local as well as for systemic action. By escaping mucociliary or macrophage clearance, inhaled nanopharmaceuticals could perhaps be used as platform for pulmonary sustained release delivery systems. Finally, nanoplexes formed between biodegradable polymeric carriers and DNA/RNA-based drugs can be used to facilitate cellular transfection [6]. We are currently using this approach for the delivery of telomerase inhibiting antisense oligonucleotides to lung cancer cells [7,8].

References:

- [1] Lamprecht A, et al., Size-dependent bioadhesion of micro- and nanoparticulate carriers to the inflamed colonic mucosa, *Pharm. Res.* 18:788-793(2001).
- [2] Lamprecht A. et al., Biodegradable nanoparticles for in treatment of inflammatory bowel disease. *J.Pharm.Exp.Therap.* 299:775-781(2001).
- [3] Lademann J. et al., Nanoparticles - An efficient carrier for drug delivery into the hair follicles. *Europ. J. Pharm. Biopharm.* 66:159-164(2007).
- [4] Stracke F. et al., Multiphoton microscopy of dermal penetration of nanoparticle-borne drugs. *J.Invest.Dermatol.*, 126:2224-2233(2006).
- [5] Luengo J. et al., Influence of nanoencapsulation on human skin transport of flufenamic acid. *Skin Pharmacol. Physiol.* 19:90-197(2006).



- [6] Ravi Kumar MNV et al., Preparation and characterization of cationic PLGA nanospheres as DNA carriers. *Biomaterials* 25:1771-1777(2004).
- [7] Nafee N et al., Chitosan-coated PLGA nanoparticles for DNA/RNA delivery: *Nanomedicine: Nanotechnology, Biology, and Medicine*, 3:173-183(2007).
- [8] Tätz S et al., Influence of chitosan content on the delivery efficiency of cationic chitosan/PLGA nanoparticles, *Eur.J.Pharm.Biopharm.* 72: 358–369 (2009)

Dr. Myriam RICAUD, INRS Paris

Risk assessment and prevention in the workplace: background, issues and prospects

Colossal budgets and almost unbounded hope vested in nanoparticle and nanomaterial production and usage in many business sectors have already led to multiple industrial applications, showing that occupational exposure to nanoparticles is effectively real. Given the many unknowns associated with these new chemicals, their potential health effects and the problems encountered in characterising occupational exposure to them, quantitative risk assessment would seem difficult to implement under most working conditions. A precautionary approach should therefore be adopted and procedures specific to preventing these risks should be set up in all occupational environments, in which nanomaterials are implemented (companies, research laboratories, universities, etc.) and throughout the product life cycle. These safe working practices, which will need to evolve as stable information is published on the adverse effects of nanoparticles, are intended to prevent, or at least reduce to a minimum, occupational exposures to these materials. Collective and process-integrated protection must always be favoured: working in a vacuum, automating processes, enclosing equipment, collecting pollutants, filtering workplace air, etc. Regular monitoring of working conditions and worker exposure must also be ensured.



PD Dr. Michael Riediker, Institute for Work and Health / Lausanne, CH

“Nanos“: what applications and what perspectives?

Nanotechnology allows for the creation of very small structures in the size of a few nanometers. The properties of such nanostructured materials are often very different from normal material made of the same substance, which allow for novel products in all domains of our daily life. New properties, however, also mean that there is a potential for new negative effects. Thus, while some augurs predicted a new industrial revolution, others feared the end of the world to be near.

The time of these extreme hopes and fears is over. Nanotechnology is already becoming part of our daily life. Most modern computers contain nano-circuits and nanomaterial are being used for medical applications, self-cleaning textiles, ultra-stable bike-frames, better sunscreens and cleaning agents. The initial hype is over – now comes reality, which means considerable work for scientists, engineers, and policy makers, who need to ensure that nanotechnology produces a maximum of benefit at a minimum of social, environmental, economic and health cost.

The communication between stakeholders about paths to a healthy future with nanomaterials started a few years ago. At this point, there is an agreement that we need common metrics, standardized approaches for hazard identification and simple, easy and fast risk assessment tools to promote good work practices and to ensure that safety and health considerations are included in the earliest phases of material and product development. Scientists only recently started investigating nano-specific hazards and exposures. Until this research creates a good understanding of “nano-risks”, precautionary measures need to be taken. Work on this has already started and also the framework provided by the European REACH-regulation will be helpful to ensure that the goal of a healthy future with nanomaterials can be reached.

Dr. Klaus Günter Steinhäuser, Federal Environment Agency, Dessau-Roßlau

OECD Working Party on Manufactured Nanomaterials: International Rules for Nanosafety

In 2006 OECD established the Working Party on Manufactured Nanomaterials (WPMN) aiming at development of internationally agreed and appropriate methods and strategies to help identify and ensure human health and environmental safety. This decision was based upon the uncertainty in all industrial countries how to ensure safety facing the rapid development of nanotechnology. Data emerged indicating that materials in nanoscale behave differently with regard to toxicity and environmental fate. At the beginning six steering groups were set up which were devoted to different issues of nanosafety with the aim to develop publicly available materials (see: www.oecd.org/env/nanosafety). In the meantime eight steering groups work on the following themes:

- OECD Database on Manufactured Nanomaterials to Inform and Analyse EHS Research Activities (SG 1/2)
- Safety Testing on a Representative Set of Manufactured Nanomaterials (SG3)
- Manufactured Nanomaterials and Test Guidelines (SG 4)
- Co-operation on Voluntary Schemes and regulatory Programmes (SG 5)
- Co-operation on Risk Assessment (SG 6)
- The role of Alternative Methods in Nanotoxicology (SG 7)
- Exposure Measurement and Exposure Mitigation (SG 8)
- Co-operation on the Environmentally Sustainable Use of Manufactured Nanomaterials (SG 9).

Core of the activities of WPMN is the safety testing of currently 13 important and widely used nanomaterials (SG 3). Several member countries build sponsoring consortia financing jointly the experimental determination of more than fifty endpoints with regard to physical-chemical properties, toxicity, ecotoxicity and environmental fate. These efforts aim to generate sets of valid test results, develop hazard profiles and at the same time demonstrate which test guidelines for chemicals can be applied, should be modified or newly developed. This exercise is necessary because current data on nanomaterials are often contradictory and difficult to interpret.

WPMN regards nanomaterials not only as potential risk for human health and environment. To this end SG 9 was recently established, which shall investigate the potential benefits for health and environment of selected nano applications and determine the relationship between risks and benefits applying lifecycle considerations.



PD Dr. Michael Stintz, University of Dresden

Determining physical and chemical reactivity

Manufactured nanomaterials (MNM) are particles, substance, or materials that have been engineered to have one or more internal or external dimensions in the nanoscale. For many MNM, the industrial producers have already developed methods and protocols for the characterization. Most often, these methods impose well defined conditions or state of the material during the measurement, such as a high vacuum for the common types of electron microscopy. These methods also often allow already the identification of the MNM, as required for trade or regulatory purposes.

But identification of the 'fingerprint-type' does not cover the full physico-chemical characterization required to understand and predict the effect of MNM on the application-specific properties of the end-products.

An improved understanding of the MNM effects on health, safety or environment requires consideration of additional measurands, like composition, surface chemical composition, particle size/size distribution, agglomeration state/aggregation, shape, surface area, surface charge, solubility and dispersibility.

Additionally measurement is necessary under the conditions or the state of the material, which is typical for their application, including the surrounding medium – gaseous, liquid or solid matrix.

Experimental methods and results of nanoparticle release measurement from composite materials and from powders as well as standardization needs are discussed exemplarily.



Dr. Christoph Studer, Federal Office of Public Health, Berne, Switzerland

Action Plan for Synthetic Nanomaterials

The nanotechnologies and the selective use of nanomaterials are fields of research and development which are increasingly important for the economy. With all the possibilities offered by nanomaterials it is also important to study the risk for humans and the environment, to scrutinize the existing regulations and, if necessary, to adjust them accordingly. The Federal Council recognised this and, on 9 April 2008, with its Action Plan for Synthetic Nanomaterials, adopted a working programme illustrating what will have to be done in the years to come to pave the way for safe use of nanomaterials:

- In this context, it will be essential to elaborate the required regulatory framework and the instruments to be applied for ensuring the responsible manufacture, use and disposal of synthetic nanomaterials.
- Research on potential risks for humans and the environment when manipulating nanomaterials will have to be strengthened and the necessary internationally harmonized testing methods worked out.
- The public dialogue on the prospects and the risks of nanotechnology has to be promoted.
- Industry and research institutions are to be brought to enhance their co-operation in the development and launching of sustainable nanotechnology applications.

As concerns the “regulatory framework”, the key element elaborated is the prevention scheme for synthetic nanomaterials. The prevention scheme is an assessment procedure based on the presently available knowledge and allowing an initial evaluation of health and environmental risks linked to nanoproducts. It covers the entire product lifecycle and helps to establish whether preventive measures of protection or additional analyses have to be performed.



Dr. Eva Valic, AUVA

Toxicological effects of nanoparticles – pathways of absorption, elimination and mode of action

By means of enormous reductions in size and manipulation of material down to the atomic, molecular and macromolecular scales, nanoparticles are produced which may have totally different properties compared to their materials of origin. This offers spectacular possibilities for considerably improving the efficiency of all kinds of products. The development of nanotechnology, also termed “nanorevolution”, is called a new industrial revolution. The manufacture and use of nanoparticles/nanomaterials are expanding rapidly and represent a challenge to industrial safety.

What, however, is seen as a desirable effect on one side, may produce undesirable side effects in the human body. Some properties of nanoparticles are particularly preoccupying, e.g. very high reactivity, the capacity for penetrating bodily and cellular barriers and their insolubility (biopersistence).

As things stand, the specific toxicological data available for risk assessment are insufficient, as there is just a small number of studies on individual particles, the times of exposure with respect to potential chronic effects are very short or the pathways of administration in animal experiments do not correspond to the real conditions in the workplace.

Thorsten Weidl, TÜV SÜD Industrie Service GmbH, München

Identification of hazards and assessment of risks and safety measures when handling nanomaterials particularly nanoparticles

Current discussions about nanotechnology often include risks associated with this technology. Usually the focus of the risks discussed centers on consumers. The risks in the production of nanomaterials, where the materials are often handled in an unprocessed state, generally are more pronounced though, since a protective matrix, inhibiting direct contact, is lacking.

There are some general guidelines available covering the handling of nanomaterials (eg. "VCI-Leitfaden zur Arbeitssicherheit" or some action plans) but precise information about the necessary safety measures to be taken when processing a specific nanomaterial are not covered by these guidelines. To get these information all operations in production have to be examined individually, processed nanomaterials are linked to potential paths for uptake and these paths assessed risk-wise to the extent allowed by the current knowledge about nanomaterials. Based on these results specific prevention measures ensuring occupational health can be taken.

Such a risk management system was introduced at Bühler AG in 2007. This risk management system, developed by TÜV SÜD Industrie Service GmbH (Munich) and Innovationsgesellschaft mbH (St. Gallen), was integrated in the existing quality management system (ISO 9001). By regularly checking compliance with the specified criteria the established safety-level is permanently assured.

Dr. Olivier Witschger, INRS

Airborne nanoparticle exposures: current methods and requirements

Workers and researchers involved in the manufacturing and handling of nanoparticles and nanomaterials are likely exposed by inhalation, but published information on exposures in the workplace is still sparse. The main reason of this sparseness is that measuring exposure to nanoaerosols is not an easy task. It differs in significant ways from traditional aerosols, for which established measurement procedures and techniques exist. Although guidance for assessing nanoaerosol exposure has recently been proposed by published documents like ISO TR/27628 (2006) and ISO TR/12885 (2008), there is still insufficient scientific evidence to decide on which particle size range and health-relevant exposure parameters of nanoaerosol should be measured – size selective number, surface, mass concentration or something else – to characterize exposure, or which are the most appropriate instruments or methods to use. Here, the current state-of-art and applicable measurement techniques and solutions to characterize exposure to nanoaerosol will be discussed through data obtained during field measurement campaigns, and the measurement requirements for the future considered.