nanomat

Fraunhofer IGB

Science-Industry-Symposium

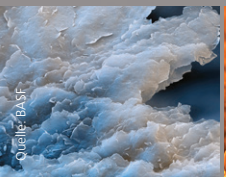
NanoVision 2015

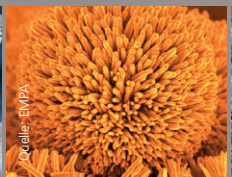
// Program

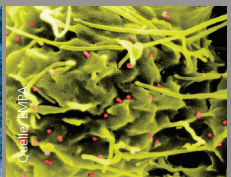
// **January 22nd – 23rd 2015**

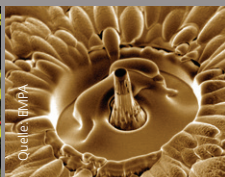
// Fraunhofer Institute for Interfacial Engineering and Biotechnology (IGB)

// Nobelstraße 12, 70569 Stuttgart, Germany









Program Overview

Thursday, January 22nd 2015

08:30 Registration, Meet & Greet

09:00 Thomas Hirth (Fraunhofer IGB), Christian Punckt (NanoMat)
Welcome Notes

09:15 Günter Tovar (Fraunhofer IGB)
Fraunhofer-Allianz Nanotechnologie & Projekthaus NanoBioMater der Universität Stuttgart

09:45 Bernhard Rieger (Merck)
Quantum rods and their application in displays

10:15 Frank Menzel (Evonik)
Nanostructured materials and their use in energy generation, storage, and saving

10:40 Elmar Rother (Evonik)
A life cycle view on nanostructured insulation materials for resource efficiency

11:00 Coffee Break

11:15 Annika Vogt (Charité Berlin)
Carrier-Based Transcutaneous Cell Targeting

11:45 Twan Lammers (RWTH Aachen)
Nanomedicine and Theranostics

12:15 Walter Mier (U Heidelberg)
The limitations of nanosized materials for medicinal applications

12:45 Posters & Lunch

14:00 Peter Wick (Empa)
The safe use of nanomaterials – only a vision?

14:30 Robert Landsiedel (BASF)
Pulmonary toxicity of nanomaterials: A critical comparison of in vitro assays with in vivo studies

15:00 Ralf Schulz (U Koblenz-Landau)
Aquatic ecotoxicology of nanomaterials

15:30 Coffee Break

16:00 Christof Asbach (IUTA)
Strategies and techniques for exposure assessment in workplaces

16:30 Carsten Möhlmann (DGUV)
Arbeitsplatzexposition und Schutzmaßnahmen

17:00 Thomas Gebel (BAuA)
A Strategy towards nanomaterial risk assessment

17:30 Break

18:00 Posters & Dinner

Friday, January 23rd 2015

08:30 Luis Cachon, Ralf Stich (Testo AG)
Diffusion charging for portable nanoparticle instrumentation

09:00 Gerfried Lindenthal (Ing. Büro Espenau), Leander Mölter (Palas GmbH)
Measurement of gas-borne nanoparticles with counting measurement methods

09:30 Coffee Break

09:45 Hanns-Rudolf Paur (KIT)
Particle characterization at the air-liquid interface

10:15 Carsten Weiss (KIT)
Toxicity profiling of inorganic nanomaterials in mammalian cells

10:45 Andrea Haase (BfR)
Proteomics approaches for hazard assessment of nanomaterials and for supporting NM classification

11:15 Coffee Break

11:30 Carolin Kranz (BASF)
Social acceptance and regulation of nanomaterials

12:00 Antje Grobe (DIALOG BASIS)
Communicating responsible innovation: From early warnings towards open innovation processes

12:30 Tovar / Punckt
Closing remarks

12:40 Lunch & Discussion

Lectures

Thursday, January 22nd 2015, 09:15

Fraunhofer-Allianz Nanotechnologie & Projekthaus NanoBioMater der Universität Stuttgart

Günter Tovar
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The Fraunhofer Institute for Interfacial Engineering and Biotechnology (IGB) offers R&D solutions in the fields of medicine, pharmacy, chemistry, the environment and energy. Its competences comprise Interfacial Engineering and Materials Science, Molecular Biotechnology, Physical Process Technology, Environmental Biotechnology and Bioprocess Engineering, as well as Tissue Engineering.

The activities of the Nanotechnology Alliance cover the whole R&D value chain and are focused on e.g. multifunctional coatings for use in the optical, automotive and electronics industry, the design of special nanoparticles as fillers (carbon nanotubes, metals, oxides etc), nanocomposites, functional materials e.g for biomedical applications and CNT-based structural materials and actuators. The alliance also treats questions regarding toxicology and operational safety when dealing with nanoparticles.

The Projekthaus NanoBioMater at the University of Stuttgart is a research structure which unites institutes of the Faculty for Energy-, Process- and Bio-Engineering and the Faculty for Chemistry in its focus on nanobiomaterials, featuring hydrogel based materials comprising nanostructured elements.

Research & development examples in nanotechnology and nanomaterials will be described for all three institutions.

Thursday, January 22nd 2015, 09:45

Quantum rods and their application in displays

Bernhard Rieger
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Thursday, January 22nd 2015, 10:15

Nanostructured materials and their use in energy generation, storage and saving

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The first scientific publications dealing with effects of nanomaterials were already published in the first half of the 20th century. Just in the 80s of the last century, nanotechnology became a new and independent research area with the newly available measurement devices as atomic force microscopy or high resolution scanning electron microscopy which made the nanoscale visible. From today's perspective, the last decade again changed the perception of nanotechnology from a purely academic science to an application-driven science.

A variety of nanostructured powders have been produced on industrial scale for many decades. The metal oxides made by flame hydrolysis of volatile metal precursors like silica, alumina, and titania are examples of products with a long history of more than 60 years.

Fumed silica is a prominent example for a nanostructured product manufactured in large scale. In fact, it is a family of specialty products with a broad variety of applications. The identifying feature of nanostructured materials is that their internal or surface structure is in the nanoscale, but their external dimensions are typically greater than the nanoscale range. The fumed silica aggregate is the smallest indivisible unit upon dispersion; aggregates are distributional in nature with a size range typically above 100 nm.

In the presentation important industrial applications of fumed silica will be highlighted, focusing on energy related topics such as energy generation, energy storage and energy saving.

Thursday, January 22nd 2015, 10:40

A life cycle view on nanostructured insulation materials for resource efficiency

Elmar Rother
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Globally, buildings are responsible for 40% of annual energy consumption and up to 30% of all energy-related greenhouse gas (GHG) emissions. Collectively, this sector is responsible for one-third of humanity's resource consumption (UNEP 2011). The International Energy Agency (IEA) and the OECD project that by 2050, energy demand in the building sector will increase by 60%, which is a larger projected increase than is projected for the transport sector or industrial sector (IEA & OECD, 2010).

The improvement of thermal insulation of buildings in hot as well as cold climates is a major lever for the reduction of energy consumption in buildings – reducing heating needs in winter and cooling needs in summer. The actual choice of insulating materials in a building depends on various parameters, such as legal requirements (e.g. fire protection), thermal resistance (directly connected with necessary thickness of layer for a given thermal resistance), architectural and esthetic issues as well as price. "Green" building standards require a certain level of insulation for new and renovated buildings. More and more the term "grey energy" gets common in the building sector, where "grey" stands for energies for the manufacturing and processing of the building materials, their transport and disposal. This life cycle view ideally considers all process steps, from "oil well" or quarry to final disposal of the materials, including infrastructure and electricity generation systems. Life Cycle Assessments go even further by not only analyzing energy, but assessing various environmental impacts such as global warming, acidification, smog formation, eutrophication, land use, etc. Ongoing activities in the EU try to standardize the "product environmental footprint" (PEF) with 14 impact categories (EU 2013) - where also one pilot is currently being run on building insulation.

Some results are presented about a recent LCA for insulating materials based on nanostructured silica showing life cycle related benefits.

UNEP (2011): Sustainable Building and Climate Initiative; website: http://www.unep.org/sbci/

IEA & OECD (2010): Energy Technology Perspectives 2010: Scenarios and Strategies to 2050. Paris: International Energy Agency and the Organisation for Economic Co-operation and Development.

EU (2013): 2013/179/EU: Commission Recommendation of 9 April 2013 on the use of common methods to measure and communicate the life cycle environmental performance of products and organisations

Thursday, January 22nd 2015, 11:15

Carrier-based Transcutaneous Cell Targeting

Annika Vogt
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Although overall penetration rates of nanomaterials across intact skin barrier appear to be minimal, increasing experimental evidence emerges that the skin immune system can still recognize and internalize larger molecules and nanoparticles, e.g., via natural barrier interruptions such as hair follicles, or when epidermal antigen-presenting cells are put in an activated state, which can be induced even by mild skin barrier disruption.

Using different particles types ranging from solid anorganic particles, biodegradable and non-biodegradable polymer particles, virus-like-particles and viruses, we characterized skin barrier translocation and cellular uptake as well as trafficking of migratory particle-positive cells from the skin in human skin explants and mice. The chemical composition of the carrier types and the loaded substances greatly affected particle stability, penetration depth and penetration pathway of the particles as well as the kinetics of drug release. Using high resolution imaging techniques, e.g., in vivo laser scanning confocal microscopy, scanning transmission x-ray microscopy, as well as experimental setups for magnetic cell separation and cell migration from skin explants, we identified hair follicles as important sites for a translocation of nanomaterials into the viable tissue. An increase of vaccine storage capacities in the skin, effective immune-activation, combined with the administration of antigen in particulate form which provides protection from degradation, aggregates in hair follicle openings and facilitates cellular uptake, could open new perspectives for transcutaneous immunization strategies.

Clinical proof-of-concept obtained in three clinical trials using conventional influenza vaccine which suggested that transcutaneous immunization could be especially beneficial for the induction of cellular immune responses. Following up on these results, three Phase I clinical trials using particulate candidate vaccines against HIV, based on DNA or Modified Vaccinia Ankara Virus, respectively, are ongoing to study the potential impact of topical vaccine application on pretreated skin surface on the amplification of CD8 cellular and mucosal immune responses.

Thursday, January 22nd 2015, 11:45

Nanomedicine and Theranostics

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Nanomedicines are 1-100(0) nm-sized carrier materials designed to improve drug delivery to pathological sites. By preventing (chemo-) therapeutic drugs from being excreted by the kidney and degraded by the liver, nanomedicines assist in improving the pharmacokinetics and the biodistribution of low-molecular-weight agents. Moreover, by delivering drug molecules more efficiently to pathological sites, and by attenuating their accumulation in potentially endangered healthy tissues, nanomedicines improve the therapeutic index of drugs, i.e. the balance between their efficacy and toxicity.
In the present lecture, I will introduce the basics of nanomedicine-mediated drug targeting, I will present several examples of formulations used in the clinic for treating cancer and inflammatory disorders, and I will highlight several recent preclinical advances, dealing e.g. with the targeted treatment of metastasis, and drug delivery across the blood-brain barrier. Finally, I will discuss the potential of (nano-) theranostics and image-guided drug delivery. By combining diagnostic and therapeutic agents within a single nanomedicine formulation, the biodistribution and target site accumulation of the carrier material can be visualized and quantified, and this information can be used pre-select patients, and to individualize and improve (chemo-) therapeutic treatments.

Thursday, January 22nd 2015, 12:15

The limitations of nanosized materials for medicinal applications

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The possibility to utilize nanotechnology for drug development has caused pervasive interest and funding opportunities. The public perception of the field of nanoscale science originally referred to technologies dealing with nano-mechanics, nanomaterials, nano-optics and nanoelectronics but increasingly anticipates progress in nanomedicine. Nanoparticles used for pharmaceutical applications are normally above the renal exclusion limit (approximately 50 kDa) but small enough to pass all blood capillaries. With the components required to attain specific function, targeted nanoparticles reach a few hundred nanometers (the size of the smallest bacteria) and constitute an intermediate between large proteins, (i.e. antibodies with a hydrodynamic radius of approximately 15 nm) and microspheres (particles in the micrometer range, typically 10 to 200 microns).

At first glance nanoparticles have the potential to greatly extend the current repertoire of therapeutic applications by providing the means to transport various cargos. Unfortunately, there are serious shortcomings in the clinical application of nanoparticles. The lack of specificity of a naked nanoparticle has been approached by coupling the nanoparticles to targeting molecules such as antibodies, receptor affine peptides, folate receptor ligands or bisphosphonates on their surface. The main idea behind most nanosized drug platforms relies on their potential to encapsulate the cargo and thereby shield it while transported to the site of action and thereby prevent its action prior to arrival. Finally, the modifications required to facilitate targeting and biocompatibility, however, increase the size of the particle - detrimental for the quality of pharmaceuticals which is generally decreased with increasing size.

Thursday, January 22nd 2015, 14:00

The safe use of nanomaterials – only a vision?

Peter Wick
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Engineered nanomaterials (ENMs) with their unique and novel properties are expected to be applied in different products of our daily life. These new material properties have also raised concerns about potential adverse effects for human health and environment. The life cycle of an ENM containing product and its design determine the exposure, fate and hazard scenario. To reduce the risk of social and economic drawbacks as having had with some chemical products in the past, a mechanism for making decisions at early stage of product design to identify the most appropriate ENMs including biological or toxicological effects would be very useful. However the human and ecotoxicological risk data of these materials are rare or not conclusive. Due to the large varieties of applied nanomaterials, researchers would need years and substantial means to gather and analyze all the data necessary to perform a comprehensive risk assessment for ENMs.

In this paper the challenges of ENMs assessment will be discussed. Aside dosage, assay interference or agglomeration of nanomaterials a special emphasis will be made on material properties and their influence on the biological effects as well as the uptake and translocation across biological barrier tissue such as the placenta barrier of selected nanomaterials.

Thursday, January 22nd 2015, 14:30

Pulmonary toxicity of nanomaterials: A critical comparison of in vitro assays with in vivo studies

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Inhalation of airborne particles is the main exposure route for many nanomaterials and a short-term inhalation method for nanomaterials was developed to identify potential toxic effects as well as their potency and regression or progression after the end of the exposure . The method also provides data on organ burdens, biopersistence and clearance. Inhalation studies with more than 30 nanomaterials are available and identified pulmonary inflammation as the main effect of inhaled nanomaterials . The toxic potencies covered, however, three orders of magnitude. For the evaluation of potential long-term effects (including carcinogenicity) a chronic inhalation study is currently performed; interim results are already available .

On the one hand, possible risks of nanomaterials are related to the specific uses of specific materials. On the other hand, it will not be possible to test all nanomaterials in all uses and life-cycle stages. Hence, safety assessment will use grouping of nanomaterials and testing addressing specific data needed for the risk assessment. The ECETOC task force on nanomaterials has reviewed existing concepts on grouping and assessment of nanomaterials and is preparing a proposal for a comprehensive framework to group nanomaterials regarding their risk for human health based on intrinsic material properties, use and release, uptake and biopersistence as well as system-dependent material properties and bio-physical interactions, early biological (cellular) and (apical) toxic effects .

[1] *Ma-Hock, Lan, et al. „Development of a short-term inhalation test in the rat using nano-titanium dioxide as a model substance." Inhalation toxicology 21.2 (2009): 102-118.*

[2] *Landsiedel, Robert, et al. „Application of short-term inhalation studies to assess the inhalation toxicity of nanomaterials." Particle and fibre toxicology 11.1 (2014): 16. Ma-Hock, Lan, et al. „Comparative inhalation toxicity of multi-wall carbon nanotubes, graphene, graphite nanoplatelets and low surface carbon black." Particle and fibre toxicology 10.1 (2013): 23.*

[3] *Keller, Jana, et al. „Time course of lung retention and toxicity of inhaled particles: short-term exposure to nano-Ceria." Archives of toxicology 88.11 (2014): 2033-2059. Konduru, Nagarjun, et al. „Biokinetics and effects of barium sulfate nanoparticles." Particle and fibre toxicology 11.1 (2014): 55.*

[4] *Landsiedel, Robert, et al. „Pulmonary toxicity of nanomaterials: a critical comparison of published in vitro assays and in vivo inhalation or instillation studies." Nanomedicine 9.16 (2014): 2557-2585.*

Thursday, January 22nd 2015, 15:00

Aquatic ecotoxicology of nanomaterials

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Thursday, January 22nd 2015, 16:00

Strategies and techniques for exposure assessment in workplaces

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Inhalation of nanoparticles can lead to severe adverse health effects. Exposure hence needs to be controlled, particularly in workplaces where engineered nanoparticles are produced or handled. The assessment of exposure to nanoparticles requires a differentiation of the engineered nanomaterials from ubiquitous background particles. While a definitive online differentiation of engineered nanomaterials from other background particles is usually impossible, pragmatic tiered approaches have been proposed by a number of groups around the globe.

These approaches are all very similar and typically contain three tiers. The first tier comprises data gathering for the considered workplace to obtain information if nanomaterials may be released. If exposure to nanomaterials cannot be excluded from tier 1, the second tier comes into play, which foresees a simplified assessment of the particle concentrations in the workplace and comparison with the background concentration. These measurements are carried out with simple handheld or personal instruments. If the assessment in the second tier provides evidence that particles may be released, leading to worker exposure, tier 3 needs to be followed that foresees a detailed analysis of the workplace aerosol. In tier 3 the particle size distributions are measured in a wide size range and particle samples taken for consecutive chemical and/or morphological analysis. These measurements are conducted with very accurate state-of-the-art instrumentation. Workplace and background concentrations are measured to differentiate between background particles and those stemming from nanomaterials. Consecutive electron microscopic analysis of the sampled particles can provide clear evidence for the presence or absence of engineered nanomaterials.

The measurements in the different tiers require different types of measurement instruments. Devices used in tier 2 mostly comprise handheld condensation particle counters and portable or personal diffusion charging instruments. Devices to be used in tier 3 include electrical mobility analyzers for the measurement of particle size distributions and electrostatic, thermal, filtration or impaction samplers for the collection of particles for subsequent chemical/morphological characterization.

A harmonized approach for exposure assessment will be presented and the available measurement devices introduced.

Thursday, January 22nd 2015, 16:30

Arbeitsplatzexposition und Schutzmaßnahmen

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Eine Exposition von Arbeitnehmern während des Herstellungsprozesses von Nanomaterialien kann insbesondere an Schnittstellen zwischen geschlossenen und offenen Verfahrensschritten, wie bei der Abfüllung, bei der Probenahme, bei Reinigungs- und Wartungsarbeiten oder bei Störungen des bestimmungsgemäßen Betriebs stattfinden, denen sicherheitstechnisch besondere Aufmerksamkeit zu widmen ist. Dabei stehen die inhalative und die dermale Exposition im Vordergrund. Die Gefahrstoffverordnung [GefStoffV 2010] sieht die folgende Vorgehensweise zum Schutz der Beschäftigten vor Gefährdungen vor (s.a. http://www.baua.de/de/Publikationen/Fachbeitraege/Gd4.pdf):

1. Informationsermittlung,
2. Gefährdungsbeurteilung,
3. Festlegung der Schutzmaßnahmen (Substitution, technische, organisatorische, persönliche Schutzmaßnahmen, Prävention, Explosionsschutz),
4. Überprüfung der Wirksamkeit der Maßnahmen (messtechnische und nicht-mess technische Methoden),
5. Dokumentation: Berücksichtigt werden müssen alle Arbeitsvorgänge und Betriebs zustände inklusive Wartung, Instandsetzung, Störungen und Überwachungstätigkeiten.

Das Institut für Arbeitsschutz ermittelt seit ca. 15 Jahren die Arbeitsplatzkonzentrationen von ultrafeinen Partikeln und Nanoobjekten. Ein vorläufiger Beurteilungsmaßstab zur Durchführung von Schutzmaßnahmen findet sich auf den Internetseiten des IFA: http://www.dguv.de/dguv/ifa/Fachinfos/Nanopartikel-am-Arbeitsplatz/Beurteilung-von-Schutzmaßnahmen/index.jsp. Er gibt Anzahlkonzentrationen in Abhängigkeit der Dichte und der Größe von Nanoobjekten an, die im Mittel über den Beurteilungszeitraum (z.B. eine Schicht) nicht überschritten werden sollen.

Reichen solche organisatorischen und technischen Schutzmaßnahmen nicht aus, wird empfohlen, persönlichen Atemschutz (z. B. Atemschutz der Filterklasse P3 oder P2) zu tragen. Wenn Atemschutzmasken getragen werden, so müssen diese dicht anliegen. Dabei sind die geltenden Tragezeitbegrenzungen und Regelungen zu arbeitsmedizinischen Vorsorgeuntersuchungen beim Tragen von Atemschutz zu beachten. Der Unterweisung und dem Training der Beschäftigten kommt entscheidende Bedeutung zu.

Zum Schutz vor Hautkontakt sollte auf ausreichende mechanische Stabilität von Handschuhen und auf Schäden im Handschuhmaterial geachtet werden. Die Überlappung der Handschuhe mit weiterer Schutzkleidung sowie das richtige An- und Ausziehen spielen für die Vermeidung eines möglichen Hautkontaktes eine wichtigere Rolle als das Durchlassverhalten des Materials. Gewobene Schutzkleidungsmaterialien bieten einen schlechteren Schutz als Membranmaterialien. Zusätzlicher Chemikalienschutz kann unter Umständen nötig sein.

Weitere Empfehlungen zum Schutz der Sicherheit und Gesundheit der Beschäftigten am Arbeitsplatz bei Tätigkeiten mit Stoffen bzw. Gemischen oder Erzeugnissen, die aus hergestellten Nanomaterialien bestehen bzw. solche enthalten, sind in der Bekanntmachung 527 des Ausschusses für Gefahrstoffe enthalten (http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/Bekanntmachung-527.html).

Thursday, January 22nd 2015, 17:00

A Strategy towards Nanomaterial Risk Assessment

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Intensive efforts have been taken in investigating toxicology and safety aspects of nanotechnology in recent years. It is time that paradigms on still existing major knowledge gaps need to be challenged. A question that repeatedly was emphasized was that nanoparticles may harbour a specific toxicity due to their size. At present there is no evidence of 'nano-specific' mechanisms of action; no step-change in hazard was observed so far for particles below 100 nm in one dimension. Moreover, there is no evidence so far that fundamentally different biokinetics of nanoparticles would trigger a novel nanotoxicity. However, data are sparse whether nanoparticles may accumulate to an extent high enough to cause chronic adverse effects.

To facilitate hazard assessment, nanomaterials may be categorized into three basic categories according to route of exposure and mode of action, respectively. One category 2 focuses on rigid biopersistent respirable fibrous nanomaterials with a specific geometry and high aspect ratio (so-called "WHO fibres"). For these fibres, hazard assessment can be based on the experiences with asbestos. Another category focuses on respirable granular biodurable particles (GBP) which, after inhalation, may cause inflammation and secondary mutagenicity that may finally lead to lung cancer. After intravenous, oral or dermal exposure, nanoscaled GBPs investigated apparently did not show 'nano-specific' effects so far. Hazard assessment of GBPs may be based on the knowledge available for granular particles. The third category comprises nanomaterials for which toxicity is mediated by the specific chemical properties of its components, such as released ions or functional groups on the surface. Nanomaterials belonging to this category have to be evaluated on a case-by-case basis, depending on their chemical identity. The proposed categorization system may facilitate future hazard assessments as a first step in the course of risk assessment.

Friday, January 23rd 2015, 08:30

Diffusion charging for portable nanoparticle instrumentation

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The European Union and other countries throughout the world will continue to integrate particle counting into their emission standards, especially since the World Health Organization reclassified diesel engine exhaust as 'carcinogenic to humans'. Last September, according to this strategy, the European Commission has proposed particle counting for several categories of internal combustion engines for non-road mobile machinery. Moreover, the Commission is working on the approach for the technical assessment of PEMS for particle number emitted by light-duty vehicles under real world conditions. In Switzerland the periodic control of the construction machinery on field is mandatory since January 2013. As result, the oncoming test procedures for different vehicles categories may include on-road measurements and periodic control of particle emissions requesting suitable technology as an extension of the Particle Measurement Program (PMP).

With an eye on real driving measurements of nanoparticles proposed in forthcoming European Emission Standards and periodic control on the field, Testo AG has unveiled novel portable instrumentation for solid nanoparticle counting and classification. This innovative instrumentation based on Diffusion Size Classifier technology measures number concentration and average diameter in a wide range under real world conditions.

In order to measure only the solid particle fraction, it is necessary to condition the sample thermally to eliminate the volatile fraction. The new instrumentation features a separate sample at the source (tailpipe, CVS tunnel or stack) and conditioning of the exhaust probe according to the Post-Dilution Thermo-Conditioning principle, which is fully PMP compliant. The portable equipment is completed with a Diffusion Size Classifier sensor. Since its measuring principle uses electrical charging to count particles, it not only enhances the quality of the global measurement under real world conditions, but also the cost of acquisition and costs per test are significantly lower.

Friday, January 23rd 2015, 09:00

Measurement of gas-borne nanoparticles with counting measurement methods

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Almost a third of Europe's city dwellers is exposed to excessive concentrations of airborne particulate matter (PM), one of the most important pollutants in terms of harm to human health as it penetrates sensitive parts of the respiratory system. Nanoparticles in particular are not really recorded with these PM methods. But especially these nanoparticles are very hazardous to health as they are absorbed directly into the alveoli.

Aerosols are a mixture of gas and particles whose dispersed phase is liquid or solid. With optical aerosol spectrometers, the particle size distribution and particle concentration is measured in the size range of 120 nm up to 100 µm by light scattering principle. Nanoparticles are defined as gas-borne particles whose length, width and height is between 1nm up to 120 nm.

Particles with a diameter of 120 nm and larger can be measured reliably of aerosol spectrometers. Particles in the nanometer range can reliably be determined with specific nano-measuring devices. For determination of concentration, a condensation particle counter and aerosol spectrometers are used. For the determination of the particle size, a differential electrical mobility classifier, type DEMC (Differential Electrical Mobility Classifier) is used. The functioning of the nano-measuring devices is explained and the corresponding results are presented in this lecture.

Friday, January 23rd 2015, 09:45

Particle characterization at the air-liquid interface

Hanns-Rudolf Paur, Sonja Mülhopt
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Engineered nanoparticles (NPs) when released into the atmosphere due to mechanical or thermal stress, may interact in complex pathways with biological materials. As the human lung is an efficient filter for inhaled particles the assessment of the toxicity of airborne NPs is an important task.

Previous studies have investigated the effects of NPs on human lung cells under submerged conditions with suspensions, which make the dose determination difficult and obscure the NP's effect due to artefacts due to interaction with the culture medium, which may alter the particle size and reactivity. These difficulties can be avoided by exposing cells at the air-liquid interface to aerosols, which allow the exact determination of the applied particle size and a reproducible deposition, to determine the NP dose.

Here we report on the development and characterisation of the Karlsruhe Exposure System, which is capable of exposing 18 biological samples and controls to airborne NP simultaneously. The state of art in dosimetry for this application is discussed and compared to realistic conditions. Typical applications of the system for the biological characterisation of complex aerosols are presented.

Friday, January 23rd 2015, 10:15

Toxicity profiling of inorganic nanomaterials in mammalian cells

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Although the technological and economic benefits of engineered nanomaterials (ENMs) are obvious, concerns have been raised about adverse effects if such material is inhaled, ingested, applied to the skin or even released into the environment. Besides the physicochemical characterization of pristine ENMs also the interaction of proteins with ENMs, the so-called protein corona, becomes more and more important to understand potential adverse health effects (1, 2).

Here we investigated metal oxide nanoparticles (NPs) as those are produced in large scale and are therefore included in the OECD list of manufactured nanomaterials for future safety assessments (3,4). As the lung is the primary portal of entry for airborne NPs we exposed human lung alveolar epithelial cells A549 and murine RAW264.7 macrophages to various NPs in the presence or absence of fetal calf serum (FCS). Surprisingly, in medium without FCS amorphous SiO_2-NPs were the most cytotoxic NPs and induced a significant pro-inflammatory response in both cell types. Thus, the protein corona bound to the surface of SiO_2-NPs suppresses their biological effects, an issue which needs to be more carefully considered for in vitro – in vivo extrapolations. Further assays were developed to monitor cellular toxicity by high-content and high-throughput microscopy, which are superior to conventional toxicity assays as they monitor more accurately adverse effects even at the single cell level.

Finally, lung epithelial cells were exposed to aerosols at the air-liquid interphase (ALI) as cellular responses to NPs under submerged culture conditions might differ from those observed at physiological settings at the ALI (5). Surprisingly, cells exposed at the ALI were less sensitive to silica NPs as evidenced by reduced cytotoxicity and inflammatory responses. Hence, more studies are warranted to decipher whether cells at the ALI are in general less vulnerable to NPs or specific NPs show different activities dependent on the exposure method.

(1) *Gebel T., Foth H., Damm G., Freyberger A., Gundert-Remy U., Kramer P.-J., Lilienblum W., Roehl C., Schupp T., Weiss C., Wollin K.M. and Hengstler J.G. (2014). Manufactured nanomaterials: grouping and approaches to risk evaluation. (Review), Arch Toxicol, 88 (12), 2191-2211.*

(2) *Lynch I., Weiss C. and Valsami-Jones E. (2014). A strategy for grouping of nanomaterials based on key physico-chemical descriptors as a basis for safer-by-design NMs. NanoToday, 9 (3), 266-270.*

(3) *Panas A., Marquardt C., Nalcaci O., Bockhorn H., Baumann W., Paur H.R., Mülhopt S., Diabaté S. and Weiss C. (2013). Screening of metal-oxide nanoparticles for toxicity, anti-oxidative and inflammatory potential in lung epithelial cells and macrophages. Nanotoxicology, 7(3):274-93.*

(4) *Ruh H., Kühl B., Brenner-Weiss G., Hopf C., Diabaté S. and Weiss C. (2012). Identification of serum proteins bound to industrial nanomaterials. Toxicology Letters, 208(1):41-50.*

(5) *Panas A., Comouth A., Saathoff H., Leisner T., Al-Rawi M., Simon M., Seemann G., Dössel O., Mülhopt S., Paur H. R., Weiss C. and Diabaté S. (2014). Silica nanoparticles are less toxic to human lung cells when deposited at the air-liquid interface compared to conventional submerged exposure. Beilstein J. Nanotechnol., 5:1590-1602.*

Friday, January 23rd 2015, 10:45

Proteomics approaches for hazard assessment of nanomaterials and for supporting NM classification

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Oxidative stress is considered to be a major paradigm to explain NP toxicity. Here we focused on protein carbonylation as a consequence of oxidative stress for a set of 25 different nanoparticles, used as either plane ("pristine") materials or with different surface coatings. In parallel several in vitro and in vivo toxicity endpoints have been analyzed.

We used well characterized NP of 10 nm (ZrO_2), 15 nm (SiO_2) and 50 or 200 nm (Ag), furnished either with acidic, basic or polymeric functionalities. In addition TiO_2(NM-103,-104,-105), ZnO (NM-110, -111), CNT (NM-400, -401, -402), SiO_2 (NM-200, -203, Ag (NM-300K) $BaSO_4$ (NM-220) and AlOOH were analyzed. In a screening approach we studied time- and dose-dependent carbonylation of all NP in NRK-52E cells via 1D immunoblots. Data were correlated with cytotoxicity (WST-8, LDH assay), ROS formation (DCFDA assay) and surface reactivity (ESR spectroscopy). We applied a 2D-MALDI-MS/MS proteomics approach to identify the modified proteins. For selected NP we also analyzed lung tissues homogenates after intratracheal instillation into rat lungs. In parallel we used proteomics approaches to characterize the NP protein corona in serum as well as in purified native surfactant from pig lungs.

Twelve out of 25 NP induced protein carbonylation in NRK-52E cells. The degree of protein carbonylation correlated well with overall in vitro toxicity. The 2D approach revealed a complex and distinct pattern of carbonyls. Modified proteins were identified as proteins of cytoskeleton, HSP, or proteins of major cellular pathways (i.e. glycolysis). Carbonyl modifications occurred also in lung tissue homogenates, indicating the relevance of in vitro findings. Analysis of poteomics data with hierachical cluster analysis and principal component analysis revealed differential results for the NM with respect to induced carbonyl patterns.

Taken together, analysis of protein carbonylation appears useful to describe toxic effects of NP and to better understand underlying molecular mechanisms of toxicity. Furthermore, proteomics data can support NM classification.

Friday, January 23rd 2015, 11:30

Social acceptance and regulation of nanomaterials

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For BASF, Nanotechnology is a key enabling technology we use to design new materials for our customers. We have already brought a number of nanotechnology-enabled products on the markets and expect more products in the future. To best use the potential of nanotechnology, we need safe products and a societal and political framework that enables nanotechnology innovations. Therefore already at a very early stage of the technology development, BASF has started its safety research for nanomaterials. Since 2004 we have performed more than 150 toxicology and eco-toxicology studies. To be transparent and to promote a political and societal debate we are publishing the results of our safety research in peer-reviewed journals. Moreover, BASF hosts its "Dialogforum Nano", in which we meet regularly with representatives of environmental groups, consumer organizations, sustainability think tanks and trade unions to discuss political and societal issues in the context of nanotechnology.

Regulators in the European Union and some Member States have already implemented a big number of nano-specific regulations, even though to-date no nano-specific toxicity has been identified. France for example has introduced an annual notification scheme for nanomaterials and articles containing nanomaterials. And more regulation is under discussion such as a moratorium for the approval of nano-scale ingredients in food. The regulation is justified as precautionary measure. In the presentation, an overview over BASF's nanotechnology activities with the specific focus on communication is given. In addition, the regulatory framework is shown as well as regulation under discussion. Finally the "Innovation Principle" as a concept to better balance precaution and promotion is presented. Just recently 22 CEOs of large innovation driven companies in the EU across all sectors have send a letter to the President of the European Commission Jean-Claude Juncker and asked for the "Innovation Principle" to promote the urgently needed innovation in Europe.

Friday, January 23rd 2015, 12:00

Communicating responsible innovation: From early warnings towards open innovation processes

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When the societal debates on genetically modified organisms are compared with those on nanotechnologies, many improvements can be observed. Early dialogues between public authorities, scientists, industry, trade unions and environmental and consumer organisations have increased the level of awareness for critical questions such as occupational health, environmental impacts along the life cycle and consumer safety.

These partly controversial debates have been and are still used as early warning systems. Industry has subsequently reacted with measures for avoiding workplace exposure, information and communication strategies along the value chain have been improved massively and public authorities have closely accompanied the development of new materials and technologies. The precautionary principle inspired a lot of new technical approaches and materials, following the "Safety-by-design" idea. The nanotechnology debate could thus be seen as a success story as we move towards responsible innovation made in Europe.

In Germany, the German Federal Government's NanoKommission, the Nano Dialogue of the Chemical Industry or the Dialogforum Nano of BASF count as drivers for an open debate. Additionally, internet-based information platforms such as DaNa2.0 of the German Federal Ministry for Education and Research or the platform www.nano-sicherheit.de from the Hessian Ministry of Economy – aiming to support small and medium sized companies – exemplify how information provision may support the process of responsible innovation. Recent activities in our dialogue landscape show developments towards open innovation processes between societal peer groups, consumers, research and development and industry. The NanoDiode project, an FP7 financed research initiative develops new formats of innovative dialogue across Europe for supporting responsible innovation and research. The aim is to listen to societal needs, to be inspired and to reflect on ethical, legal and environmental aspects in a very early stage of thinking.

Posters

1. *NanoMat – Innovation through Collaboration*

   Frank Schramm, Christian Punckt, Jasmin Aghassi
   NanoMat, Karlsruher Institut für Technologie

2. *NanoDiode – Developing innovative outreach and dialogue on responsible nanotechnologies in EU civil society*

   Pieter van Broekhuizen, Antje Grobe, Andrej Porovic, Daan Schuurbiers, Andreas Falk
   DIALOG BASIS

3. *Nanoparticle-induced oxidative stress alters phopho-tyrosine patterns in mammalian cells: Results of an SH2 profiling approach*

   Marc D. Driessen[1], Rainer Ossig[2], Jürgen Schnekenburger[2], Antje Vennemann[3], Martin Wiemann[3], Andreas Luch[1], Peter Nollau[4] and Andrea Haase[1]
   [1]German Federal Institute for Risk Assessment (BfR),
   [2]Biomedical Technology Center, Westfälische Wilhelms-Universität,
   [3]IBE R&D gGmbH,
   [4]Forschungsinstitut Kinderkrebszentrum Hamburg, University

4. *Characterizing EPR-mediated passive tumor targeting using contrast-enhanced functional ultrasound imaging*

   Benjamin Theek, Felix Gremse, Sijumon Kunjachan, Robert Pola, Gert Storm, Fabian Kiessling, Twan Lammers
   Experimental Molecuar Imaging, Uniklinik RWTH Aachen

5. *In vivo and ex vivo micro-CT imaging of tumor angiogenesis*

   Josef Ehling, Felix Gremse, Benjamin Theek, Fabian Kiessling, Twan Lammers
   Experimental Molecuar Imaging, Uniklinik RWTH Aachen

6. *In vivo nanotoxicity testing using the zebrafish embryo assay*

   Susanne Golombek, Larissa Rizzo, Wilhelm Jahnen-Dechen, Fabian Kiessling, Twan Lammers
   Experimental Molecuar Imaging, Uniklinik RWTH Aachen

7. *MR imaging of USPIO nanoparticle-labeled and tissue-engineered vascular grafts*

Marianne Mertens, Jakob Wehner, Felix Gremse, Lisanne Rongen, Philipp Schuster, Valentine Gesche, Sabine Koch, Frederik Wolf, Stefan Jockenhoevel, Fabian Kiessling, Twan Lammers
Experimental Molecuar Imaging, Uniklinik RWTH Aachen

8. *Multimodal imaging of metastasis targeting using liposomal nanomedicines*

Larissa Rizzo, Sanjay Tiwari, Claus Glueer, Gert Storm, Fabian Kiessling, Twan Lammers
Experimental Molecuar Imaging, Uniklinik RWTH Aachen

9. *Measurement of gas-borne nanoparticles*

Leander Mölter, Maximilian Weiß, Sven Schütz
Palas GmbH

10. *Grouping of Nanomaterials by Health, Safety and Environmental Characteristics*

C. Schumacher, J. Pelzer, C. Möhlmann
Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung

11. *Workplace exposure – Characterization of ultrafine aerosols/ anoaerosols – Determination of number concentration using condensation particle counters*

C. Möhlmann[1], D. Dahmann[2], V. Neumann[2], C. Monz[2], C. Asbach[3], H. Kaminski[3], A.M. Todea[3]
[1]Institut für Arbeitsschutz (IFA) der DGUV,
[2]Institute for the Research on Hazardous Substances (IGF),
[3]Institute of Energy and Environmental Technology (IUTA)

12. *The Karlsruhe Exposure System for assessment of lung toxicity of airborne submicron particles*

Sonja Mülhopt[1], Christian Schlager[1], Silvia Deabaté[2], Tobias Krebs[3], Hanns-Rudolf Paur[1]
[1]Institut für Technische Chemie, Karlsruher Institut für Technologie
[2]Institut für Toxikologie und Genetik, Karlsruher Institut für Technologie
[3]Vitrocell Systems GmbH

13. *Aging of nanoparticles modifies the toxicity for aquatic life*

Frank Seitz[1], Simon Lüderwald[1], Ricki R. Rosenfeldt[1], Ralf Schulz[1], Mirco Bundschuh[2]
[1]Institute for Environmental Science, University of Koblenz-Landau
[2]Department of Aquatic Sciences and Assessment, Swedish University of Agricultural Sciences, Uppsala, Sweden

14. *Do titanium dioxide nanoparticles reduce heavy metal toxicity?*

Frank Seitz[1], Simon Lüderwald[1], Ricki R. Rosenfeldt[1], Ralf Schulz[1], Mirco Bundschuh[2]
[1]Institute for Environmental Science, University of Koblenz-Landau
[2]Department of Aquatic Sciences and Assessment, Swedish University of Agricultural Sciences, Uppsala, Sweden

15. *Das Projekthaus NanoBioMater*

G. Tovar, C. Wege, A. Southan, D. Rothenstein, F. Geiger, S. Eiben, T. Hirth und S. Laschat
Projekthaus NanoBioMater, Universität Stuttgart

16. *Prerequisites for functionalized hybrid hydrogels: $CaCO_3$ mineralizing peptides and tobacco mosaic virus-PEG hydrogels*

D. Rothenstein, F. Geiger, A.Southan and S.Eiben
Projekthaus NanoBioMater, Universität Stuttgart

17. *Investigation of Polymer-Based Nanoparticles as Nanocarriers for Transdermal and Dermal Drug Delivery*

Fiorenza Rancan[1], Janna Frombach[1], Serap Dogan[1], Mazdak Asadian-Birjand[2], Emmanuel Fleige[2], Christina Graf[3], Marcelo Calderón[2], Rainer Haag[2], Ulrike Blume-Peytavi[1], Annika Vogt[1]
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[2]Institut für Chemie und Biochemie, Freie Universität Berlin
[3]Physikalische Chemie und Theoretische Chemie, Institut für Chemie und Biochemie, Freie Universität Berlin

18. *Nanocarrier Penetration and Drug Release Properties in the Hair Follicle Environment*

Fiorenza Rancan[1], Sabrina Hadam[1], Zahra Afraz[1], Bertrand Bellier[2], Ralf Wagner[3], Juergen Lademann[4], Bernard Verrier[5], Christina Graf[6], Eckhart Ruehl[6], Ulrike Blume-Peytavi[1], Behazine Combadiere[7], Annika Vogt[1,7]
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[7]CiMi, UPMC University Paris, Sorbonne Universités, INSERM U1135, France

19. *Developing in vitro and in vivo high throughput screening platforms for hazard prediction of manufactured nanomaterials*

Katrin Volkmann[1], Iris Hansjosten[1], Juliane Rapp[1], Iseult Lynch[2], Eugenia Valsami Jones[2], Silvia Diabaté[1], Carsten Weiss[1]
[1]Institute of Toxicology and Genetics, Karlsruhe Institute of Technology
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20. *Assessing the suitability of the FADU assay for genotoxicity testing of engineered nanomaterials*

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