Leibniz Research Alliance
Nanosafety

Nanoparticles can be found in everyday life and the working environment, just about everywhere. Many everyday products, technical achievements and innovations cannot do without nanotechnology. The tiny materials are, for example, contained in touchscreens, energy storage materials or in medical implants, and are used in material optimisation or medical diagnostics. Embedded in coatings, bound in liquids or loose as fine dust or powder, their unique properties stem from how small they are; measuring 1 to 100 nanometres, they are about the size of some viruses or pharmaceutical molecules.

Do nanoparticles therefore have an effect on the reactions in human cells? Which mechanisms are behind it? How should nanoparticles be designed to be safe? Which test system can be used to check this? What do experts and laypeople associate with the terms nano and nanosafety? And is there a way to save the research output in a database and make it comparable?

Under the umbrella of the Leibniz Association, six Leibniz institutes and external partners look at the topic of nanosafety from their different perspectives. Chemists, physicists, materials scientists, toxicologists, medical scientists, biologists, education researchers and database specialists bring their competence and working methods to bear collaboratively to find answers to these questions. The Leibniz Research Alliance Nanosafety provides the framework for their common efforts.

www.leibniz-nanosicherheit.de


INM
Leibniz-Institut für Neue Materialien
Neues Denken. Neue Materialien.
FORSCHEN AUF DEM CAMPUS – DAS INM
INM
DAS INM IN ZAHLEN

Prof. Dr. Eduard Arzt
Scientific director of INM and speaker of the Leibniz Research Alliance Nanosafety

Welcome

Nanotechnology has grown out of science fiction into a key technology and has arrived in our daily lives. Today, materials and structures sized one to one hundred nanometres have become ubiquitous: in surface finishes, sun screens, cosmetics, but also in mobile devices, automotives, and diagnostic and therapeutic devices. Further applications that appear on the horizon concern, for example, improved energy storage and novel adhesive systems.

As in all emerging technologies, the opportunities and risks of nanomaterials must be investigated and carefully assessed. For this purpose, INM – Leibniz Institute for New Materials has brought together the relevant Leibniz expertise and created the Leibniz Research Alliance Nanosafety. In cooperation with five partner institutions, we aim to understand, develop and explain: How do nanomaterials interact with human cells, tissues and organs? When can nanomaterials be considered safe and how can we integrate safety into the production process? How can nano-research data be usefully compared? And lastly, how does the public form an opinion about the topics nano and nanotechnology?

Such issues are being dealt with on a worldwide scale. In the Leibniz Association, we are fortunate to draw upon research methods originating from natural sciences, engineering and social sciences to identify sustainable solutions. Biologists, chemists, medical scientists, toxicologists, physicists, materials scientists, and educational researchers contribute their different viewpoints and help to get a clearer focus on nanosafety issues.

There is no better place to address these questions than in the Leibniz Association – for the best of all possible worlds.

Prof. Dr. Matthias Kleiner
President of the Leibniz Association

While the world around us appears to grow more virtual, we are constantly surrounded by different materials. Today, we are able to scale many materials down to the smallest size ranges; as small as to an individual atom – and design nanomaterials. This allows the application of well-known functionalities in new contexts; however, materials change some of their characteristics considerably when they become smaller. These changes can be useful and innovative to some extent though their use requires knowledge about their causes and effects. These innovations can result in functional applications, such as nanoparticles in cancer therapy, but they also introduce new challenges to research such as exploring toxicological properties and effects.

Nanotechnology is developing rapidly and has long since become part of daily working life, the economy and the environment, entailing relevant questions on nanosafety. A general conclusion whether nanotechnologies or nanomaterials are safe or not cannot yet be drawn. Thus, we need more and highly qualified research activities about nanosafety to ensure that scientific findings and necessary legal regulations can and will keep pace with the fast market processes.

Such research activities are brought together and undertaken by the Leibniz Research Alliance Nanosafety, addressing safety-relevant issues that are, at the same time, raised and made possible by nanomaterials and nanoproducts. The six participating Leibniz institutes do this in a reliably cooperative manner for the benefit of society, inter- and transdisciplinarily and applying high scientific standards – typically Leibniz!

Contents

Nanotechnology and Nanosafety

Nanotechnology: Key enabling technology of the 21st century

According to nano.DE-Report 2013, more than 1100 companies in Germany are involved in nanotechnology research and development and the marketing of commercial products and services. About 800 research institutions are currently active in the field of nanotechnology. The total turnover of German nanotechnology enterprises amounts to more than 15 billion euros.

The numbers demonstrate: Nanotechnology is a key enabling technology of the 21st century.

No other cross-sectional technology is developing as rapidly as nanotechnology nor has any other technology become an integral part of daily work, business and environmental activities as nanotechnology has. Many applications or products are enhanced or made possible by nanotechnology because unique properties result precisely from how small the particles are. Using nanotechnologies, materials, objects, and structures in a size range between 1-100 nanometres can be fabricated, manipulated, or analysed. The potential applications for nanotechnology are huge. They range from improved energy storage, innovative protection of metallic or ceramic material surfaces, and applications in mechanical engineering and the automotive sector to novel properties in the fields of electronics or optical media and modern medical techniques for diagnosis and therapy.

Safe nanomaterials and nanoparticles

Consumers, researchers, and employees in industry and commerce encounter nanotechnologies and nanoparticles in many places in their working environment and daily routine. Therefore the question of nanosafety is highly significant for society. Eventually, an acceptance of nanotechnology products will only be achieved if they are harmless and consumers do not assume hazards linked to such products. To this end, two things are necessary: nanomaterials have to be safe, and consumers have to be able to inform themselves in detail on these materials. Reliable studies do not indicate alarming results for nanomaterials currently in use; however a general conclusion on the question whether nanomaterials or nanotechnologies are inherently safe is still not possible. The applications, particles, and research approaches are too different and hinder the necessary comparability. Moreover, basic mechanisms have not yet been understood. Therefore, the research alliance addresses the following three essential topics.

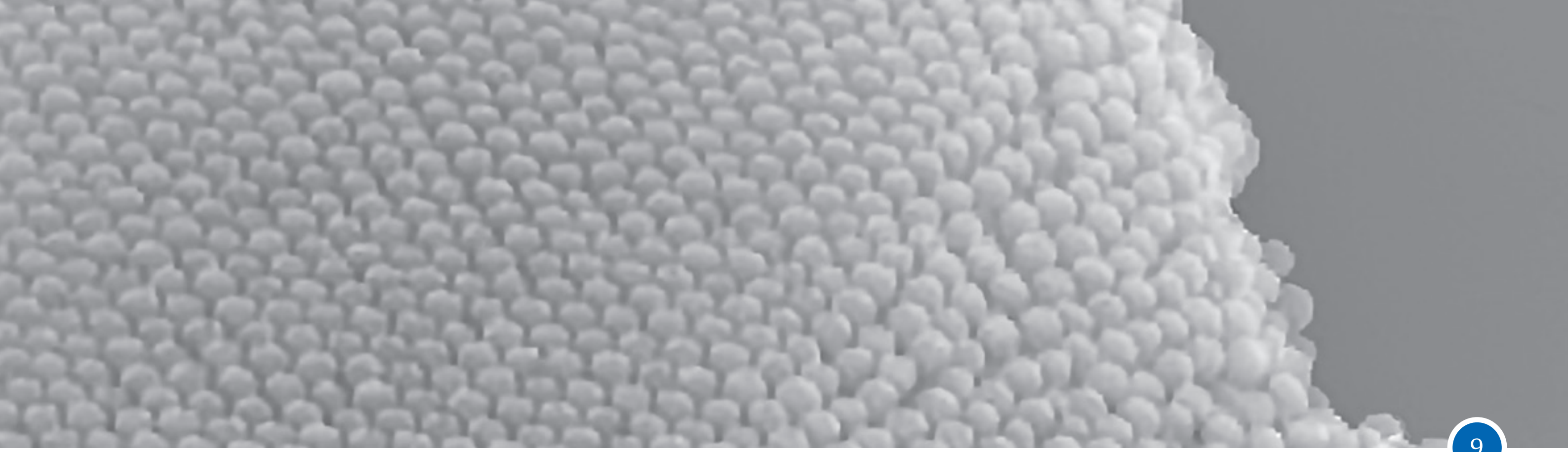
Understand basic mechanisms

Whether nanomaterials can be applied safely is dependent on various factors: first of all, their material-dependent, immediate effects on living organisms. It is important to know if nanomaterials reach living organisms and through which pathway they reach them. On the one hand, it is known that inhaled ultrafine dust can stress the lungs. On the other hand, in the light of targeted drug delivery, e.g. for tumour therapies, it is necessary that nanoparticles deliver pharmaceuticals close to the site of action within the body, i.e. close to or even into body cells.

The physical and chemical properties of nanomaterials can – but do not inherently – cause impairments of some functions of the human body. One fundamental aim of the research alliance, therefore, is to identify the interactions of nanomaterials with the human body and to elucidate the corresponding mechanisms.

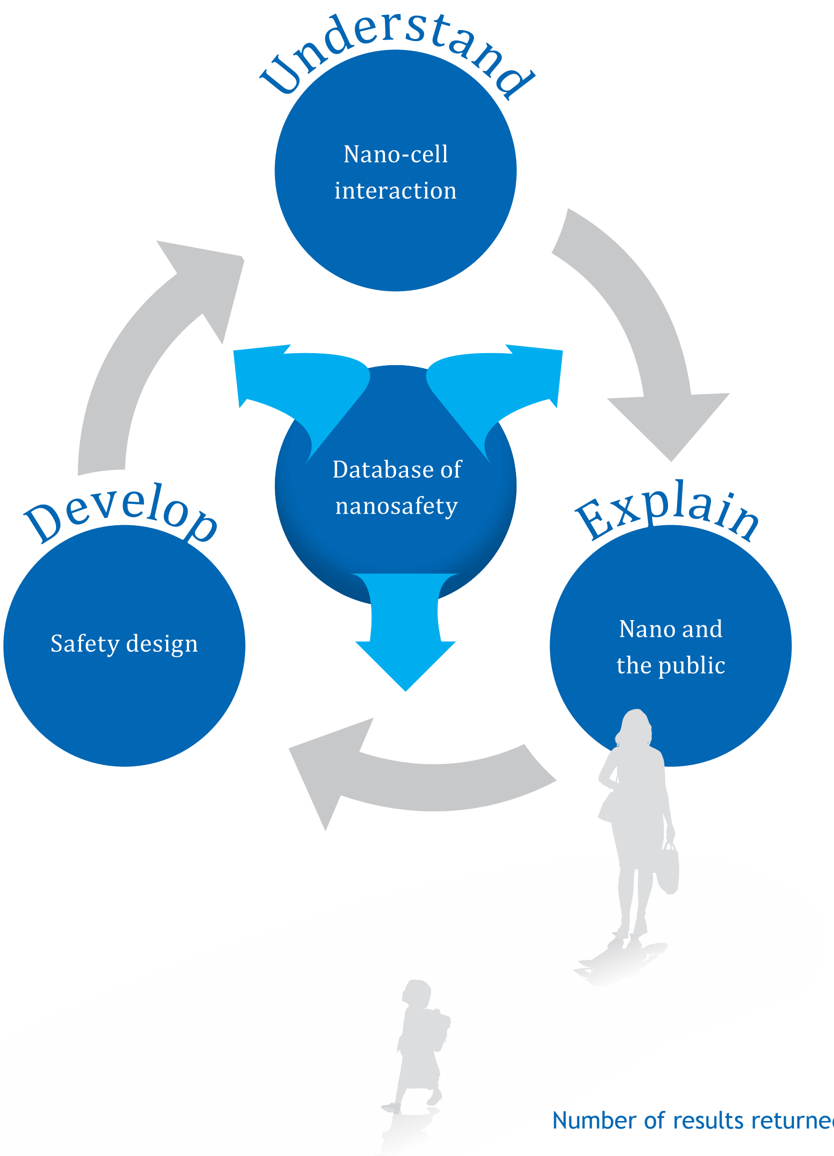
Develop safe nanomaterials

From the knowledge of interaction mechanisms between nanomaterials and biological systems, the research alliance intends to derive concepts that can be used as early as during the development phase of new nanomaterials. Our goal is to respond to current developments in industrial production and to provide test systems for industrial applications.



Explain issues and make them comparable

The research alliance also tackles the question how the public can form an opinion about nanosafety based on current developments. To answer this, the alliance investigates how professionals and laypeople exchange information and opinions on this subject through conventional and digital media. The alliance also aims to build a platform to make various research data comparable.



23.000.000

Number of results returned in a Google search for nanotechnology

Understand

Understand mechanisms

There are various paths for nanoparticles to get into the human body and reach or enter individual cells. The particles reach the lungs through inhalation, the skin through external application or the digestive tract through ingestion. The interactions and interaction mechanisms with the body cells vary according to the entry pathway because the biology and biochemistry of the lung, skin, and intestine are distinct.

Nanoparticles, too, have varying features. They are customised for each individual application. Thus, for example, the size, chemical composition, surface characteristics, form, and the degree of clustering determine the properties of the nanoparticles. This results in a great variety of nanoparticles.

When nanoparticles touch the cell surface or enter the cell, the intricate reactions of the cell meet the complexity of nanoparticles. What happens when nanoparticles make contact with cells can therefore only be understood if biochemical reactions inside the cell are set side by side with the material properties of nanoparticles.

The researchers are therefore interested in:

- Where do nanoparticles end up inside cells?
- Which mechanisms are responsible for the uptake of nanoparticles into the cell?
- Which mechanisms and reactions occur inside cells in exposure to nanoparticles?
- Which effects do these mechanisms and reactions have on the body? Can initial inflammatory reactions for example be put down to the presence of nanoparticles?
- Do nanoparticles cause cells to change the way they work?
- Can nanoparticles stimulate tumour growth or is it the opposite?
- Do nanoparticles impact the development of cells or their cell division ability?
- Do nanoparticles act on all tissues in the same way?
- Which interrelation can be identified for the uptake of nanoparticles into the human body between microscopic mechanisms and toxicological processes?

Highlight: Leibniz Doctoral Project

How Do Nanoparticles Stimulate Cell Reactions?

The behaviour of cells is controlled by external factors, initiating a chain of biochemical reactions on contact with cellular surfaces. In general, these so-called signalling cascades are activated by interactions between ligands and cell-surface receptors. This project studies how nanoparticles influence signalling cascades.

Modern nanomaterials can interact with cells of the human body in a specific way, triggering either desired or potentially harmful effects. In the Leibniz doctoral project, INM and IUF together address the question if and how nanoparticles affect cellular signalling pathways. The research is focused on the lung as nanoparticles can enter this organ via inhalation. In an *in-vitro* model, lung cells are exposed to nanoparticles that have been generated at INM. Using these nanoparticles, the scientists at IUF conduct biochemical studies on the activation of signalling pathways. At first, the signalling molecules involved are identified. In a second step, their degree of activation is measured. Additionally, the scientists at INM use microscopy techniques in order to yield data on the uptake and distribution of nanoparticles as well as signalling molecules within the cells.

Goals

- Analyse effects: How do nanoparticles influence the various steps of signalling pathways?
- Identify uptake pathways: Via which pathways are the receptor-ligand complexes and nanoparticles internalised by the cells?
- Relate nanoparticle influence and distribution: How are biochemical and structural information related to each other?

State

First experiments at IUF with lung epithelial cells indicate that nanoparticles in non-cytotoxic doses inhibit the growth of cells. Dependent on their size, silica nanoparticles reduce the activation (by phosphorylation) of the epidermal growth factor (EGF) receptor as well as of the downstream signalling proteins ERK and AKT; the smallest particles exert the strongest effect. A subsequent treatment of the cells with EGF does not restore the growth behaviour of the cells.

Fluorescence imaging at INM shows that, after contact with the EGF, nanoparticles prevent the translocation of the EGF receptor from the cell membrane into the cells. At the same time, the cells internalise the nanoparticles within minutes. First examinations of the locations of EGF and nanoparticles suggest that both are bound to each other and reside in endocytic vesicles.

Outlook

Further studies, focusing on the so-called co-localisation of both components, will contribute to a better understanding of the detailed interactions between the EGF receptor, its ligand, and nanoparticles. In the future, analyses of further receptors and their interactions with nanoparticles will be performed.

Participating Leibniz institutes

- IUF
- INM

Publications

H. Peuschel et al. (2015). Quantification of internalized silica nanoparticles via STED microscopy. BioMed Res Int.

C. Schumann et al. (2012). A correlative approach at characterizing nanoparticle mobility and interactions after cellular uptake. J Biophotonics.

K. Unfried et al. (2008). Carbon nanoparticle-induced lung epithelial cell proliferation is mediated by receptor-dependent AKT activation. Am J Physiol - Lung Cell Mol Biol.

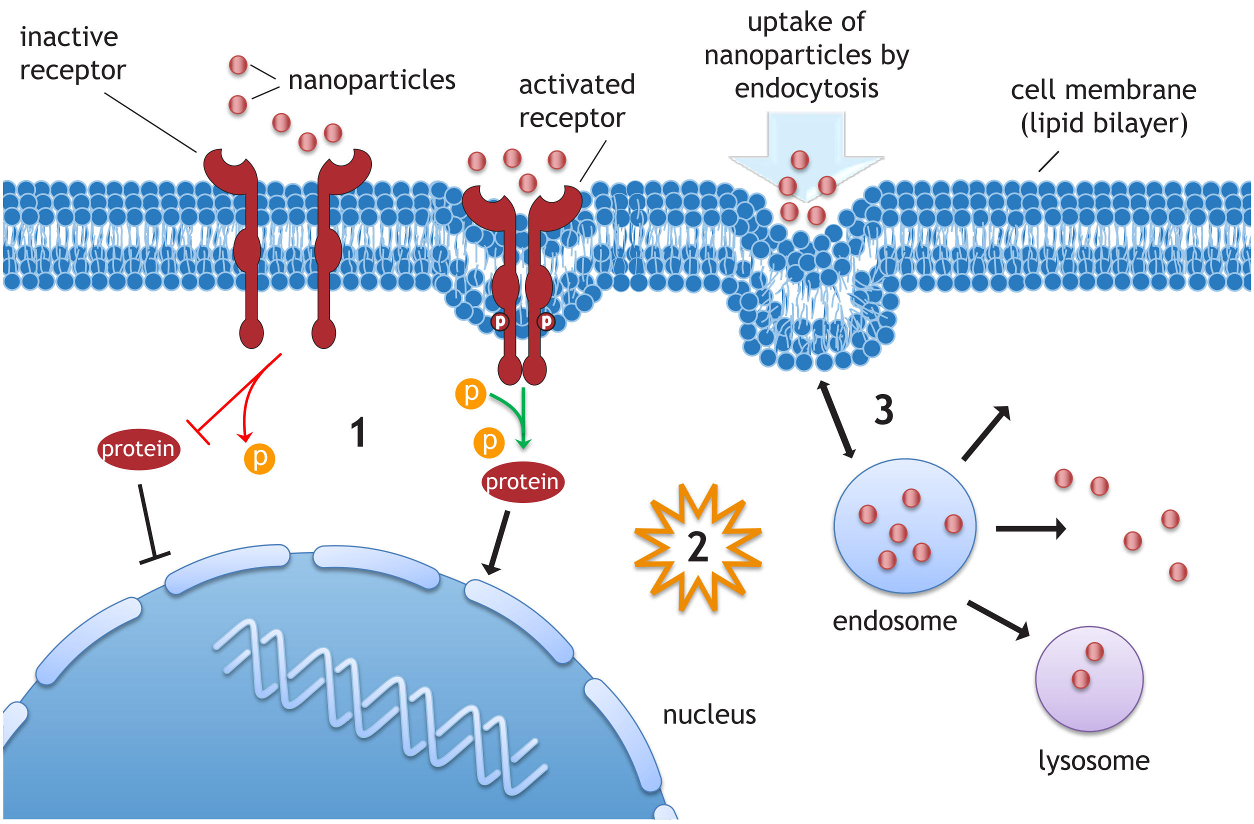
U. Sydlik et al. (2006). Ultrafine carbon particles induce apoptosis and proliferation in rat lung epithelial cells via specific signaling pathways both using EGF-R. Am J Physiol Lung Cell Mol Physiol.

Alexander Kümper
Leibniz doctoral student, INM and IUF

Cell sketch

Nanoparticles can activate or inactivate the receptor via interaction. Stimuli are passed from the membrane towards the nucleus by signalling cascades (1), initiating cellular responses (2). Nanoparticles and receptors are internalised by the cells in endocytic vesicles (3). From there, both are either deposited in lysosomes, exported out of the cells or released into the cells.

> My doctoral project is based on the current state of the art and takes a biochemical and toxicological approach. The results are of interest for nanosafety as well as medical-pharmaceutical applications. As a doctoral student, the project offers me the unprecedented opportunity to access the scientific resources of two Leibniz institutes and benefit from their extensive know-how.



120

Airborne nanoparticles per hour that can reach the cells of the deep lung

Highlight: NanoCOLT

How Do Carbon Nanoparticles Affect Healthy and Diseased Lungs?

Carbon based nanomaterials, in particular Carbon Black, are produced worldwide in a megaton scale. Carbon Black is used in many products in the form of Carbon Black nanoparticles (CBNPs) and can enter the lung with the air we breathe. In the project, the largely unknown effects of chemically modified CBNPs on the lung are investigated, looking at healthy as well as diseased lungs.

The organ that is most likely affected by airborne nanoparticles like CBNPs is the lung. In the deep lung of human beings, the walls of the approximately 480 million alveoli are thinner than one thousandth of a millimetre (< 1 µm) in places. This enables the exchange of breathing gases with the blood, but at the same time renders the whole lung prone to damage. According to estimations, the human lung is exposed to 100 billion nanoparticles per day.

It has already been shown that pure CBNPs have marginal biological effects after short-term exposures. In contrast, it has not sufficiently been analysed whether nanoparticles with a modified surface chemistry are more or less toxic than the pure CBNPs. The investigations into the long-term effects of CBNPs on the lungs have been just as inadequate. The NanoCOLT consortium dedicates itself to these issues by application of a multi-stage test procedure (see figure).

Besides the effects on the healthy lung, NanoCOLT particularly addresses the question whether an injured or diseased lung shows an altered reaction to CBNPs, for example after being damaged by the air pollutant nitrogen dioxide or suffering from allergic bronchial asthma.

Goals

- Generate and characterise surface modified CBNPs
- Investigate the consequences arising from repeated exposures of epithelial cells of airways and lungs to modified CBNPs
- Elucidate how lung epithelial cells affected by nitrogen dioxide or during allergic bronchial asthma react to CBNPs
- Find out whether modified CBNPs boost the allergenic potential of allergens

Outlook

NanoCOLT aims at increasing the understanding of the long-term effects of inhaled CBNPs. The experiments will contribute to a better assessment of the specific hazard potential of CBNPs for patients with lung disease.

Participating Leibniz partners

- Research Center Borstel

Associated partners

- Karlsruhe Institute of Technology
- University of Lübeck
- University of Marburg
- Fraunhofer Institute for Toxicology and Experimental Medicine

Funding

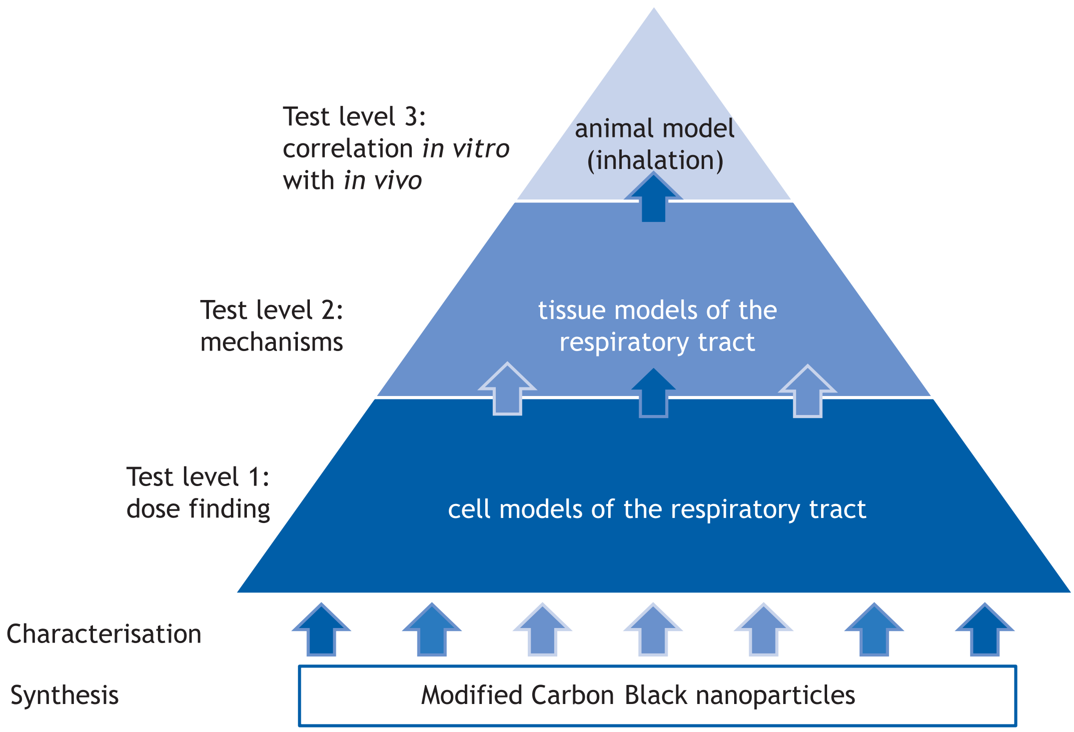
NanoCOLT: Long-term effect of modified carbon black nanoparticles on healthy and damaged lungs is funded by the Federal Ministry of Education and Research (BMBF, support code: FKZ 03X0153)

Dr. Sina Webering
Experimental Pneumology, FZ Borstel

Scheme of the multistage test procedure

NanoCOLT sets out to test the long-term effects and the effects of repeated exposures of the airways and lungs to CBNPs by use of increasingly complex test models. The materials used are modified and well-characterised CBNPs. The test systems range from basic cell and advanced tissue models *in vitro* to animal models with inhalation studies.

" An adult at rest breathes in and out around 10,000 to 15,000 litres of air per day. This enables a large amount of air pollutants, pathogens, pollen, and dust particles to enter the lung. The airways and alveoli of the lung comprising a total surface area of about 120 m^2 are highly sensitive tissues. The alveolar walls partially measure only fractions of a micrometre in thickness. We are primarily interested in the question how airways and alveoli, which in the case of existing lung diseases already exhibit histological changes, react to inhaled nanoparticles. In Germany, several million people suffer from chronic lung diseases like asthma or COPD. However, the existence of such diseases is scarcely integrated into risk assessment.



100.000.000.000

Number of particles that we inhale every day

Develop

Develop safe nanoparticles

Nanoparticles and nano-objects are incredibly diverse. They can, for example, consist of several elements, come in various sizes and forms, or be charged differently and carry different functional groups on their surfaces. According to the combination of these properties, there is a plethora of types of nanoparticles, every type having distinct properties. It is assumed that each kind has different effects on a living organism. Therefore, an effort is made to work out a system that allows at least a rough classification of not only the nanoparticle properties, but also of their interaction with living organisms. On top of that, there are several ways of entry into biological systems such as the skin, nose or mouth. Going from there, nanoparticles get to targets such as the lung or intestine, whose environmental conditions differ considerably.

For their classification, special test systems are necessary, which not only reproduce the conditions in living organisms as truthfully as possible but also allow quick and cost-effective assessments. Such test systems are intended to facilitate the correlation of specific nanoparticle properties with their impact on the system, i.e. the cellular reaction mechanisms. To this end, scientists tend to use *in-vitro* settings, which means they experiment with cultures of human or animal cells that are grown in a lab, outside the body. The aim is to discover cell reactions that can be taken as indicators of other nanoparticle-specific effects. In addition to cell cultures, researchers develop new, more complex test systems. The fruit fly *Drosophila melanogaster,* for example, is utilised to look at the reactions of the immune system.

The Leibniz Research Alliance aims to take advantage of such test systems for the development of new, modern nanomaterials. These test systems can also be made available for industry. Only if we know the properties that are responsible for the negative effects of nano-objects can we design nanomaterials that are safe from the beginning. Following this safe by design approach makes these materials safe and ensures that they remain harmless throughout the entire product lifecycle – from application to end users and disposal.

The researchers are therefore interested in:

- How can nanoparticles be classified?
- Which properties of nanoparticles are relevant for which effects and how can new nanomaterials be designed with this in mind?
- Which test systems are suitable for the categorisation of nanoparticles?
- How can the test systems be utilised in industry to make nanomaterials safe as early as in their making?

Highlight: Toxicological Assessment

How Can Nanomaterials Be Categorised?

Nanotoxicology keeps yielding new findings. In order to organise the multitude of novel research results systematically, IfADo has attempted to classify all the nanomaterials that have already been examined into three groups.

Consumers, producers and politics need a reliable toxicological assessment of health risks that might be initiated by nanomaterials. In this context, it is important to answer the question if the size of the materials alone can account for their potential toxicity and how the vast multitude of different nanomaterials can be categorised in a reasonable way.

Goals

Categorise nanomaterials according to

- their physicochemical properties
- their preferential uptake pathways
- their modes of action

State

According to the current literature, a nanospecific toxicity mechanism does not seem to exist. Products that contain nanomaterials are not generally hazardous. Regarding their toxicity, nanomaterials can be divided into three categories:

1. Nanomaterials that can release metal ions or interact with biological structures or whose surfaces have catalytic properties

2. Fibre-like nanomaterials that affect the lungs

3. Biopersistent, granulous nanoparticles that initiate inflammatory processes after deposition in tissue

Outlook

Authors of nanotoxicological studies can draw on the proposed categories to systematically identify the relevant sub-step of a specific cell reaction. Furthermore, the categorisation helps to perform a toxicological risk assessment by means of the data extracted from the countless studies. Novel nanoparticles are categorised using microscopy techniques (e.g. calcium imaging) that allow a detailed analysis of cellular effects, e.g. on epithelial or neuronal cells.

Funding

Advisory commission of the German Association for Toxicology

Publications

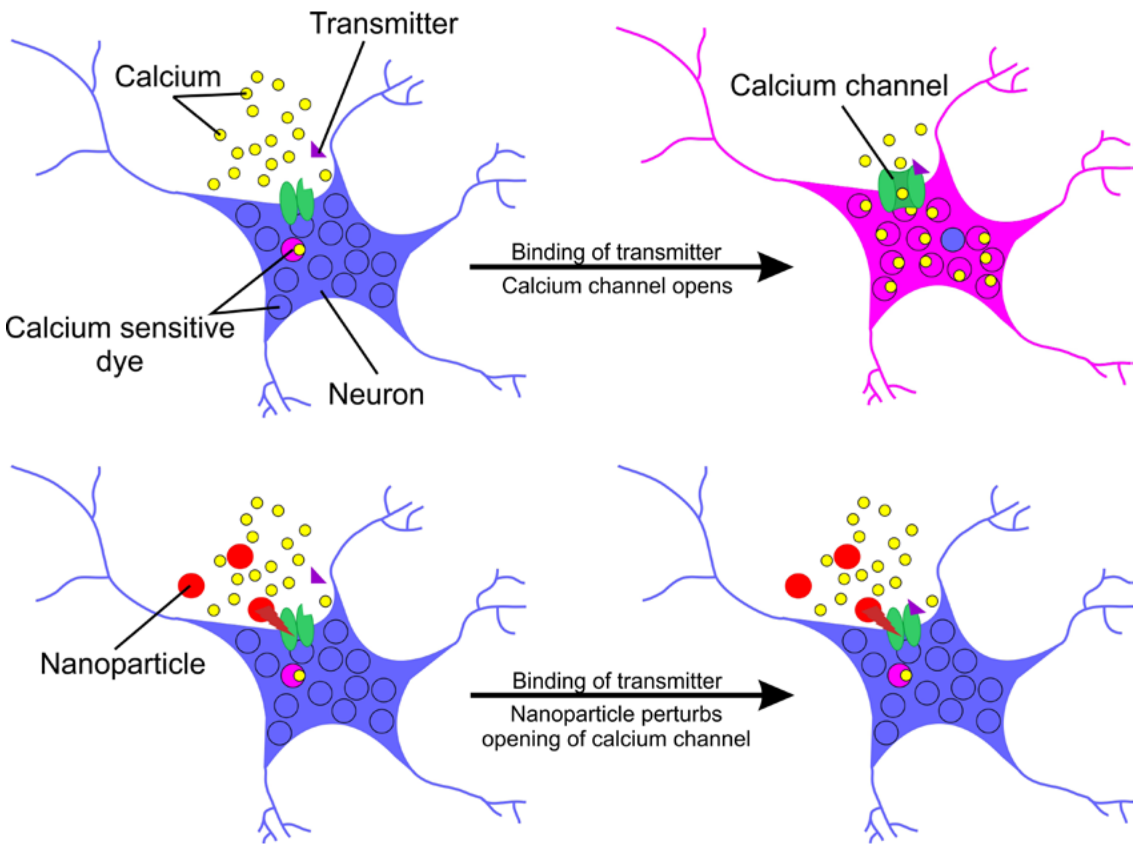
T. Gebel et al. (2014). Manufactured nanomaterials: categorization and approaches to hazard assessment. Arch Toxicol.

Dr. Julia Liebing
Research group Neurotoxicology and Chemosensation, IfADo

Calcium imaging

Changes in intracellular calcium concentrations are the basis for diverse physiological processes. Calcium imaging is able to visualise these changes, allowing for the determination of the nanoparticle impact. At first, neuronal cells are loaded with a calcium-sensitive fluorescent dye. After a messenger molecule binds to a specific receptor, calcium channels are opened. Calcium then streams into the cells and binds to the dye. Thereby the dye changes its fluorescent properties, which can be detected as colour change. Nanoparticles can influence the opening of calcium channels. How this takes place exactly is investigated at IfADo.

Nanoparticles can enter the brain via the nose, for example after inhalation. To get there, they use transporters that reside in the neuronal cells of the olfactory nerve. In the brain, nanoparticles can have negative effects, for instance, if they prevent neurons from transmitting information. In order to investigate such processes, we use so-called calcium imaging. Initially, cells are exposed to nanoparticles. Then, the neuronal cells are stimulated by messenger molecules that are naturally present in the brain. Whenever the stimulated cells respond differently in the presence of nanoparticles, this indicates that nanoparticles affect signal transmission.



over 1.000.000.000

That many neurons make a human brain

Explain

Explain issues and make them comparable

Research on nanotechnology and nanotechnological products is a topical scientific area. On the one hand, it promises to enrich everyday life, for example through improved energy generation and storage, new communication technologies or novel medical implants and therapies. On the other hand, the term nano is defined and used differently across disciplines so that the possibilities of application seem too diverse and therefore uncontrollable. As a result, nano and nanotechnology provoke anxiety and concerns about safety.

Among other things, this is due to the regular consumer getting information about nano from a variety of different sources. The number of websites dealing with nano and nanotechnology is huge, science shows on TV mediate, museums address the issue in exhibitions, and public expert lectures want to inform about nano aspects. Science fiction novels and films imagine a nano that is often disconnected from state-of-the-art science. Scientific publications and talks reflecting the results of top-notch research add up to this: from all this information, everyone – layperson or scientist – gets their own ideas and forms their own opinion. This means that the reader, listener or viewer does not only obtain factual knowledge.

Only in an ideal case is he or she given a deeper understanding of complicated and controversially discussed relations. Such an understanding can only be achieved by laypeople and scientists alike if they judge and compare the different pieces of sometimes inconsistent information. For laypeople, this is made even more difficult thanks to the specialised scientific language and methodology. Establishing the comparability of scientific results is also an issue because scientists take different approaches and use different nanomaterials to draw conclusions.

The researchers are therefore interested in:

- How do experts and laypeople take in controversial scientific information?
- How do experts and laypeople form their opinions about nano and nanosafety?
- How can scientific results in nano-related research be made comparable?
- How can such scientific data be archived to ensure long-term availability to the public and the expert community?

Highlight: Controversial Science

How Do Laypeople Understand Controversial Scientific Information on the Internet?

Nanosafety has been the subject of heated public debates. Science-related information about this issue is often vague and contradictory, which is typical of complex research topics. This project investigates how laypeople deal with controversial scientific information on the internet, how they evaluate it and how their understanding can be fostered by suitable support measures.

The internet has become a central source of information, not only when searching for simple facts. Rather, searches about complex and controversial topics, e.g. the potentials and risks of new products and technologies, are carried out on the internet too. When it comes to understanding and evaluating the enormous amounts of information about such topics, laypeople quickly reach their limits. They usually lack the domain-specific skills and background knowledge to critically assess heterogeneous kinds of information. First, online sources of information can vary enormously with regard to their quality or credibility. Second, online information is characterised by a certain amount of contradictions and vagueness, which is typical of science but can confuse laypeople.

Goals

- Identify important factors: What influences the online reception of controversial scientific information?
- Apply findings: Develop and test support measures

State

Studies at IWM have identified three factors that are important for the reception of controversial scientific information: the searchers' domain-specific background knowledge, their knowledge-related beliefs, and the strategies and competencies they have in dealing with the vast amount of online documents. These factors do not only influence the reception process but also determine how searchers interpret information when writing a short summary about their findings. The reception process can be made visible using eye-tracking and logfile analyses as well as verbal reports. The reception process is not only affected by the searchers' personal characteristics and experiences but also by the way information is presented. If, for example, information is arranged in a way that a person can easily notice contradictions between webpages, he or she will pay greater attention to information about the source and will take a more critical stance. At the same time, source-related information that is presented in a salient way on websites or search-results pages will guide the evaluation, selection and reception of certain contents.

Outlook

These findings can be used to develop measures that support internet users in dealing with contradictory online information and that encourage them to evaluate the quality of information. Such support measures can take different forms. For instance, the user-interface of information portals can be designed and structured in specific ways, or instructional materials can be developed to improve online research skills enabling searchers to identify credible information sources on the internet.

Participating Leibniz institutes

- IWM
- INM

Funding

Leibniz Association

Publications

Y. Kammerer et al. (2015). When adults without university education search the Internet for health information: The roles of Internet-specific epistemic beliefs and a source evaluation intervention. Comput Hum Behav.

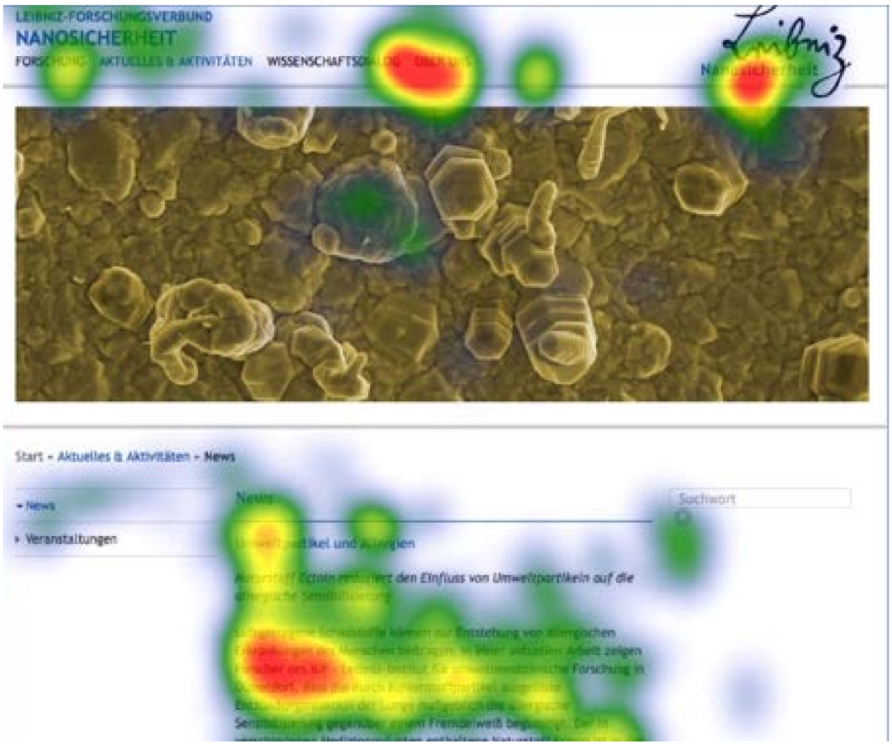
Y. Kammerer, P. Gerjets (2014). Quellenbewertungen und Quellenverweise beim Lesen und Zusammenfassen wissenschaftsbezogener Informationen aus multiplen Webseiten. Unterrichtswissenschaft.

Dr. Yvonne Kammerer
Multimodal Interaction Lab, IWM

Heat map

The figure below shows a so-called heat map of the website of the Research Alliance Nanosafety. It summarises the reception behaviour of a user based on his or her eye movements. Areas that have been intensively fixated are coloured in red, e.g. the salient About Us heading of the site (in the top centre).

" If laypeople encounter contradictory information about complex science-related topics during their online search, they are often not able to evaluate the correctness of a piece of information based on content knowledge, unlike experts. They can, however, try to judge the credibility of contents by taking source information into account. They can, for example, try to find out something about the expertise or interests of the author. Such information is often located in the About Us section of a website. Part of our research is, therefore, to investigate the factors that determine whether and to which extent laypeople look up such About Us sections during the reception of online information and how they interpret it.



250

That many images are recorded per second and eye by the eye tracker

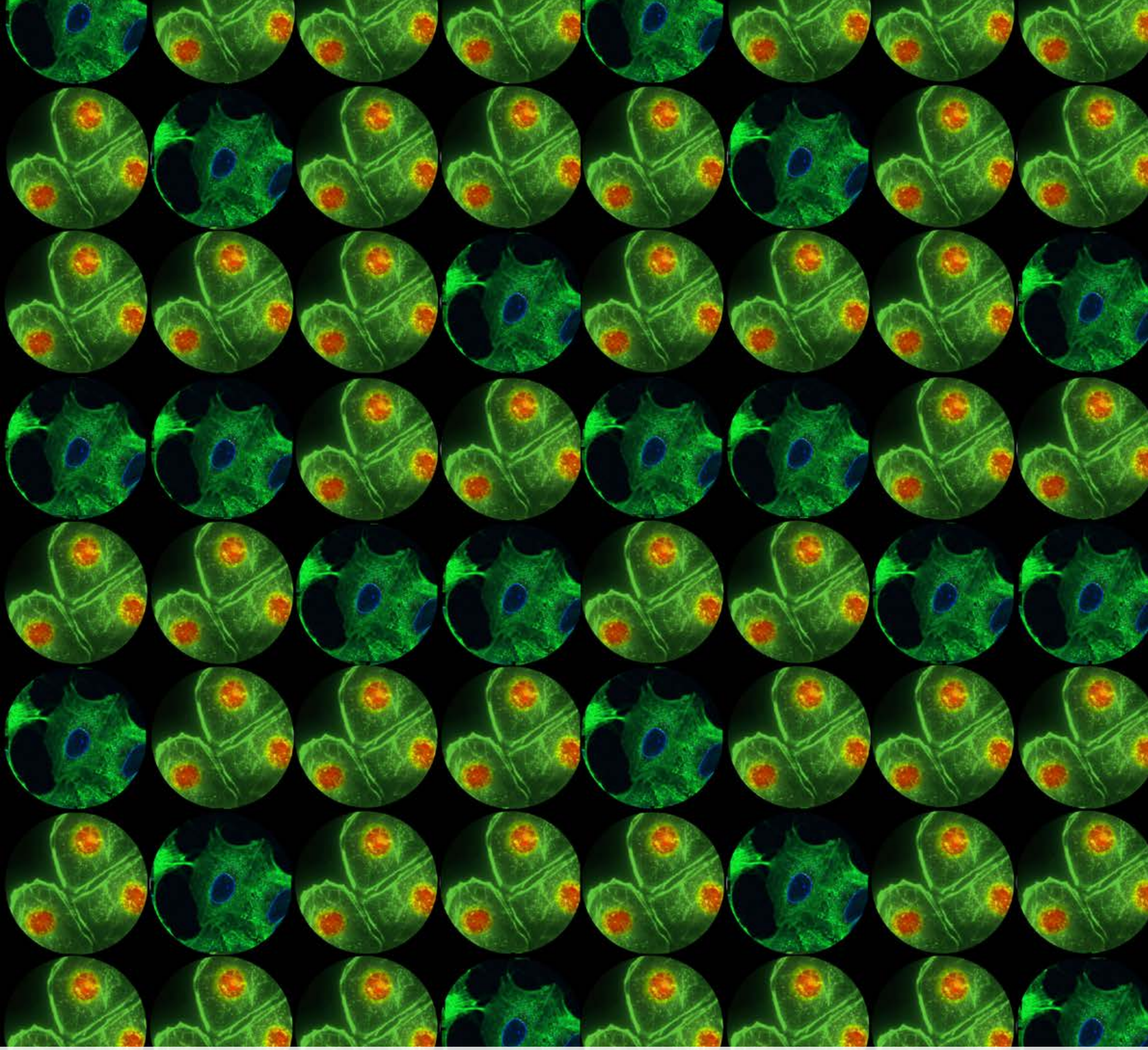
Research Facilities

STED Microscopy at INM

The STED microscope (Stimulated Emission Depletion) at INM can achieve a resolution of about 50 nanometres, which is astonishing for a light microscopy technique. It can take true-to-life images of tiny details in the size of nanoparticles, like the appearance and composition of cellular structures or protein clusters.

STED microscopy is a special technique of fluorescence microscopy. It allows the visualisation of selected cellular molecules and structures or nanoparticles by tagging these structures with fluorescent molecules prior to imaging. These dyes can be excited to glow by light. Thus, several structures in or on cells can be labelled with different colours and imaged simultaneously. In order to achieve the exceptional resolution, STED microscopy uses a trick: The microscope scans the region of interest point by point. At each point, one laser photoexcites the present dye molecules in the centre while a second laser switches off the fluorescence in the outer region. What remains is a signal with a sharply defined centre and at a resolution in the double-digit nanometre range.

For studies into nano-cell interactions, STED microscopy is a valuable tool as it also allows scientists to analyse dynamic processes within living cells. In addition, the technique enables an easy generation of three-dimensional coloured images similar to tomography. Therefore, STED microscopy is just right for the realistic visualisation of how nanoparticles bind to cell surfaces or are transported within cells.



High-Content Screening at IUF

Interactions between nanomaterials and cells can provoke characteristic reactions that might pose a risk to human health. Besides direct cell damage, nanoparticles can switch on signalling pathways that are involved in the initiation of inflammatory responses, cell division or programmed cell death. These toxicological end points could in the past be assigned to characteristic intracellular signalling pathways in different cell types of exposed interface organs, such as the lung.

A so-called high-content imaging system allows such cellular reactions to be detected using fluorescence microscopy. Based on a fluorescence microscope, the system is able to analyse a large number of samples for specific signalling proteins. It captures microscopy images that are subsequently evaluated electronically by means of standardised programs.

The information about the amount, activation status and accumulation of specific signalling proteins at a certain cellular location gives insight into the toxic potential of nanomaterials.

The relevance of such high-content screening data for the toxicity of nanomaterials is further determined by the researchers at IUF using toxicological examination methods. Besides biochemical techniques, IUF utilises *in-vivo* models to confirm the correlation between signal transduction events and toxicity. Combining *in-vitro* high-content screening with *in-vivo* studies aiming at the elucidation of responsible mechanisms reduces toxicity studies in animals to a minimum. In individual cases, IUF uses its expertise in human *in-vivo* studies to verify the relevance of the findings for human beings.

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FIZ Karlsruhe - Leibniz Institute for Information Infrastructure

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FIZ Karlsruhe — Leibniz Institute for Information Infrastructure is one of the largest organisations in the Leibniz Association and also a member of the German Mittelstand. As an organisation with a public mandate, FIZ Karlsruhe pride themselves on their neutrality and reliability. They also boast the professionalism of a service provider that has been successfully competing in international markets for many decades. Some 340 employees work at three locations in Germany and at one location in the US. Our headquarters is in Karlsruhe.

We understand information infrastructure to mean all content, technology, methods, processes, and associated services needed to generate, share and preserve knowledge. With the digitisation of the sciences, the importance of information infrastructure as an enabler of research has grown immensely.

With our activities, we are making crucial contributions to improving the information infrastructure available to researchers: We provide valuable information to researchers both in academia and the private sector. To this end, we curate and index a large volume of patent and research data from various sources and we develop and operate various innovative services and e-research solutions, e.g. for confidential data management. We provide guidance to our customers, helping them to use our services both capably and efficiently. Our highest priority is the quality of our services. Accordingly, we are engaged in various projects to keep our services at the cutting edge. This includes research into new techniques for text mining and semantic analysis.

Role in the Leibniz Research Alliance

Within the alliance, FIZ Karlsruhe is primarily concerned with the management of research data.

Management of research data

With the rapidly expanding digitisation of research across all disciplines, novel solutions are needed for managing scientific data. The generation, storage, evaluation, analysis and visualisation of research data requires effective tools, processes and systems. It is their combination in e-research environments that allows for useful data management and makes the promises of e-research tangible for science.

eSciDoc is a digital repository platform offered by FIZ Karlsruhe for data management in virtual research environments.

We place emphasis on joint research projects and collaborations with other institutions, universities and commercial partners.

Publications

S. Rehme, M. Schwantner (2014). Text mining for ontology construction Data Anal, Mach Learn Knowl Discovery.

M. Razum et al. (2014). RADAR — Ein Forschungsdaten-Repositorium als Dienstleistung für die Wissenschaft. ZfBB online - Zeitschrift für Bibliothekswesen und Bibliographie.

A. Brahaj et al. (2012). Ontological formalization of scientific experiments based on core scientific metadata model. Lect Notes Comput Sci.

M. Razum (2012). Systeme und Systemarchitekturen für das Datenmanagement. Handbuch Forschungsdatenmanagement.

M. Razum et al. (2010). Research data management in the lab. 5th Int Conf Open Repos.

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FZ Borstel - Leibniz-Center for Medicine and Biosciences

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The Research Center Borstel (FZB), founded in 1947 as a research institute for tuberculosis, has become the lung research centre of the Leibniz Association. It follows its scientific and socio-political mission by conducting disease-oriented research, training and supporting young scientists and laboratory technicians, as well as providing medical care in the field of pneumology. The foundation Research Center Borstel operates research laboratories, a clinic incorporating an ambulatory healthcare center and a pathological department, as well as the National Reference Center for Mycobacteria. Altogether, FZ Borstel counts more than 500 employees.

FZ Borstel is focused on asthma and allergies, COPD as well as tuberculosis and other infectious inflammatory diseases of the lung. The overarching aim of the basically interdisciplinary research activities is to determine the causes and mechanisms of chronic inflammatory diseases of the lung in order to deduce new innovative concepts of their diagnosis, prevention and therapy.

Role in the Leibniz Research Alliance

Within the alliance, FZB is concerned with the investigation into the interaction of inhaled nanomaterials with cells of the respiratory tract.

Involved research groups

The **Priority Area Asthma & Allergy** is currently engaged in projects about nanosafety with five scientists. The projects focus on tracing the molecular mechanisms underlying the interaction of cells and tissues of the respiratory tract with synthetic nanoparticles. Involved research groups are:

Experimental Pneumology: Which long-term effects are caused by the exposure of lung epithelial cells to nanoparticles? Which effects on an existing respiratory disease are possible?

Innate Immunity: How do nanoparticles affect antigen-presenting (dendritic) lung cells? What are the implications for pre-existing respiratory diseases such as allergic bronchial asthma?

Invertebrate Models: How do the molecular signalling pathways work in airway epithelial cells, triggered by nanoparticles and potentially leading to responses of the innate immune system?

External cooperation

- Laboratory for Pulmonary Cell Biology, University of Marburg, Prof. B. Müller
- Fraunhofer Institute for Toxicology and Experimental Medicine, Prof. A. Braun, Dr. T. Hansen
- Institute for Anatomy, University of Lübeck, Prof. P. König
- Karlsruhe Institute for Technology, Prof. H. Bockhorn

Publications

L. P. Lunding et al. (2015). Poly(inosinic-cytidylic) acid-triggered exacerbation of experimental asthma depends on IL-17A produced by NK Cells. J Immunol.

L. P. Lunding et al. (2015). IL-37 requires IL-18Ra and SIGIRR/IL-1R8 to diminish allergic airway inflammation in mice. Allergy.

C. Vock et al. (2015). Distal airways are protected from goblet cell metaplasia by diminished expression of IL-13 signaling components. Clin Exp Allergy.

M. Clauss et al. (2011). Lung endothelial monocyte-activating protein 2 is a mediator of cigarette smoke-induced emphysema in mice. J Clin Invest.

C. Seifart et al. (2011). All-trans retinoic acid results in irregular repair of septa and fails to inhibit proinflammatory macrophages. Eur Respir J.

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IfADo - Leibniz Research Centre for Working Environment and Human Factors

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The Leibniz Research Centre for Working Environment and Human Factors (IfADo) investigates the demands, potentials and risks of modern work life from various perspectives – ranging from the individual cell to the entire workplace. As a result, we conduct multidisciplinary research with the overarching goal to provide benefit and welfare to the working individual and society.

Research at IfADo is divided into four fields: Ergonomics, Immunology, Psychology & Neurosciences and Toxicology. In these scientific departments, several research groups work on topics relevant to current working environments. The Toxicology group of IfADo primarily deals with the mechanisms behind the toxicity of chemical substances to the liver and the neural system and develops innovative and sensitive *in-vitro* systems. Methods from systems biology (e.g. transcription analyses) and various microscopy techniques enabling complex image analyses (e.g. calcium imaging of dissociated central and peripheral neurons) form the basis of their research. After the required validation studies with well-known model substances, these sensitive and specific *in-vitro* techniques can also be used for the analysis of new substances and materials.

The applied work of the Toxicology groups is closely linked to the regulation of harmful substances and the assessment of toxicological risks. In this respect, IfADo assumes important tasks in providing scientific advice to policymakers.

Role in the Leibniz Research Alliance

IfADo expands the range of the research alliance Nanosafety to neurotoxicity of nanomaterials and provides the project partners with systems biological methods. Within the alliance, IfADo is primarily concerned with the interaction of nanomaterials or relevant metal ions with membranous receptors of neurons (e.g. nicotinic acetylcholine receptors; nAChR).

Involved research groups

The research groups Systems Toxicology, Neurotoxicology & Chemosensation as well as the junior research group Liver Toxicology also study how nanoparticles act on the structures and functions of neurons and liver cells. These cells are secondary targets of nanomaterials, which makes the research of IfADo's Toxicology department complementary to the experiments of the members of the research alliance; they focus on the primary targets such as lung cells. The additional knowledge thus generated contributes to a better grounded evaluation of nanoparticle-induced health-damaging effects. Central topics:

- Analysing metal-coated nanoparticles and nanoparticles in welding fumes
- Studying effects of nanoparticles on the activity-dependent dynamics of neuritic structures in cell lines and primary neuron cultures
- Conducting further *in-vitro* studies to determine the cellular response by means of cell-based arrays (cytotoxicity, cytoarchitecture, regeneration processes etc.) and other techniques such as OMICs techniques (also for other partners of the LRA Nanosafety)

Currently, seven employees are engaged in the activities of the research alliance.

Publications

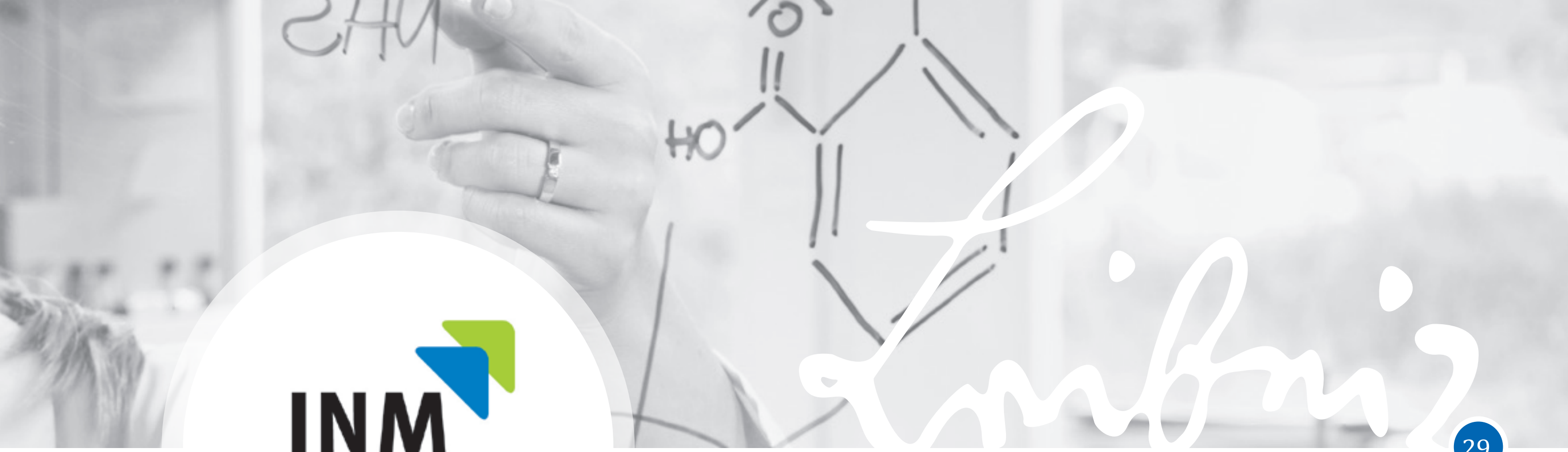
A. Bal-Price et al. (2015). Putative adverse outcome pathways relevant to neurotoxicity. Crit Rev Toxicol.

V. Hausherr et al. (2014). Impairment of glutamate signaling in mouse central nervous system neurons in vitro by triorthocresyl phosphate at noncytotoxic concentrations. Toxicol Sci.

J. Sisnaiske et al. (2014). Acrylamide alters neurotransmitter induced calcium responses in murine ESC-derived and primary neurons. Neurotoxicology.

I. Kern et al. (2013). Embryonic stem cell-based screen for small molecules: cluster analysis reveals four response patterns in developing neural cells. Curr Medicinal Chem.

C. van Thriel et al. (2012). Translating neurobehavioural endpoints of developmental neurotoxicity tests into in vitro assays and readouts. Neurotoxicology.



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INM - Leibniz Institute for New Materials

www.leibniz-inm.de

INM is focused on the research and development of materials – for today, tomorrow and the future. Chemists, physicists, biologists, materials and engineering scientists shape the work at INM. From molecule to pilot production, they follow the recurring questions: Which material properties are new, how can they be investigated and how can they be used in the future?

INM – Leibniz Institute for New Materials, situated in Saarbrücken/Germany, is an internationally leading centre for materials research. It is a scientific partner to national and international institutes and a provider of research and development for companies throughout the world. INM is an institute of the Scientific Association Gottfried Wilhelm Leibniz and employs around 220 collaborators. Its main research fields are Nanocomposite Technology, Interface Materials, and Biointerfaces.

Role in the Leibniz Research Alliance

INM coordinates the Research Alliance Nanosafety with Dr. Annette Kraegeloh as the coordinator and Prof. Eduard Arzt as the speaker of the alliance. Within the alliance, INM is largely concerned with material development and material properties as well as with microscopic imaging of interactions between nanoparticles and cells.

Involved research groups

The program division **Nano Cell Interactions** at INM explores the interaction between human cells and synthetic nanoparticles. Structure studies in particular contribute to determining the interaction mechanisms of nano-objects. The results enable the prediction of nanoparticle-induced effects and the development of new safe nanomaterials. Central topics:

- Producing, modifying, functionalising and characterising nanoparticles
- Producing, modifying, functionalising and characterising nanoparticles
- Conducting *in-vitro* studies to determine the cellular response by means of cell-based arrays and other techniques

Apart from the group **Nano Cell Interactions**, other research groups of INM deal with this research field:

- **Structure Formation:** How do nanoparticles assemble and how can this be used to develop novel materials?
- **Optical Materials:** Which security features can be manufactured with nanomaterials?
- **Innovative Electron Microscopy:** Which paths do nanoparticles take to get into the cell and where do they travel inside?

At the moment, eleven employees are engaged in the Research Alliance Nanosafety.

External cooperation

- Pharmaceutical Biology, Saarland University, Prof. A. K. Kiemer
- Saarland University Medical Center, Radiology, Prof. A. Bücker
  Experimental Surgery, Prof. M. Menger

Publications

H. Peuschel et al. (2015). Quantification of internalized silica nanoparticles via STED microscopy. BioMed Res Int.

M. Kucki et al. (2014). Interference of silica nanoparticles with traditional Limulus Amebocyte Lysate gel clot assay. Innate Immun.

T. Müller et al. (2012). STED microscopy and its applications: new insights into cellular processes on the nanoscale. ChemPhysChem.

S. Schübbe et al. (2012). Size-dependent localization and quantitative evaluation of the intracellular migration of silica nanoparticles in Caco-2 cells. Chem Mater.

C. Schumann et al. (2012). A correlative approach at characterizing nanoparticle mobility and interactions after cellular uptake. J Biophotonics.

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IUF - Leibniz Research Institute for Environmental Medicine

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The research mission of IUF is the prevention of environmentally-induced damage to human health. We achieve this by elucidating causal mechanisms in the effects of environmental toxicants of global relevance (including particles, chemicals and radiation). The IUF focuses on environmentally-induced aging, adverse immune reactions and neurotoxicity.

IUF has long-standing extensive expertise in particle and nanotoxicology. Building on this, a cross-institutional integrated research project has been initiated, bringing together expertise in cell biology, immunology, dermatology and ageing research, in order to study the impact of nanoparticles on human health.

Role in the Leibniz Research Alliance

Within the Research Alliance Nanosafety, IUF shares its expertise in mechanistic studies of particle-cell interactions. Besides *in-vitro* cell culture systems, transgenic *in-vivo* models including modern approaches with the nematode *C. elegans* are used. In addition, findings are compared with observations in human subjects. Together with the alliance partners, safety-related molecular mechanisms are identified. Based on its methodological diversity, IUF can contribute to the risk assessment of nanomaterials as well as the design of safe nanomaterials.

Involved research groups

- **Dr. Roel Schins**

(particles, inflammation and genome integrity):
The research group carries out studies on the molecular mechanisms of health-damaging effects caused by environmental particles. How do particle-induced inflammatory processes work? Do the particles influence the cell genome?

- **Prof. Dr. Anna von Mikecz**

(environmental noxae and cell nucleus):
The research group investigates the effects of pollutants on the structure and function of the nucleus. How do nanoparticles influence the protein balance in the nucleus, neurodegeneration and ageing processes? How can such processes be prevented?

- **Dr. Klaus Unfried**

(environmentally-induced skin and lung ageing):
The team investigates adverse effects of inhalable nanomaterials on lung epithelial cells *in vitro* and *in vivo*. Can nanoparticles trigger ageing processes and how does this work? How can particle-induced health effects be averted on the molecular level?

In total, 20 employees are currently engaged in projects of the Research Alliance.

External cooperation

- IUTA, Institute of Energy and Environmental Technology e.V., Duisburg, Germany
- RIVM, National Institute for Public Health and the Environment, Bilthoven, Netherlands
- Adolphe Merkle Institute, Fribourg, Switzerland

Publications

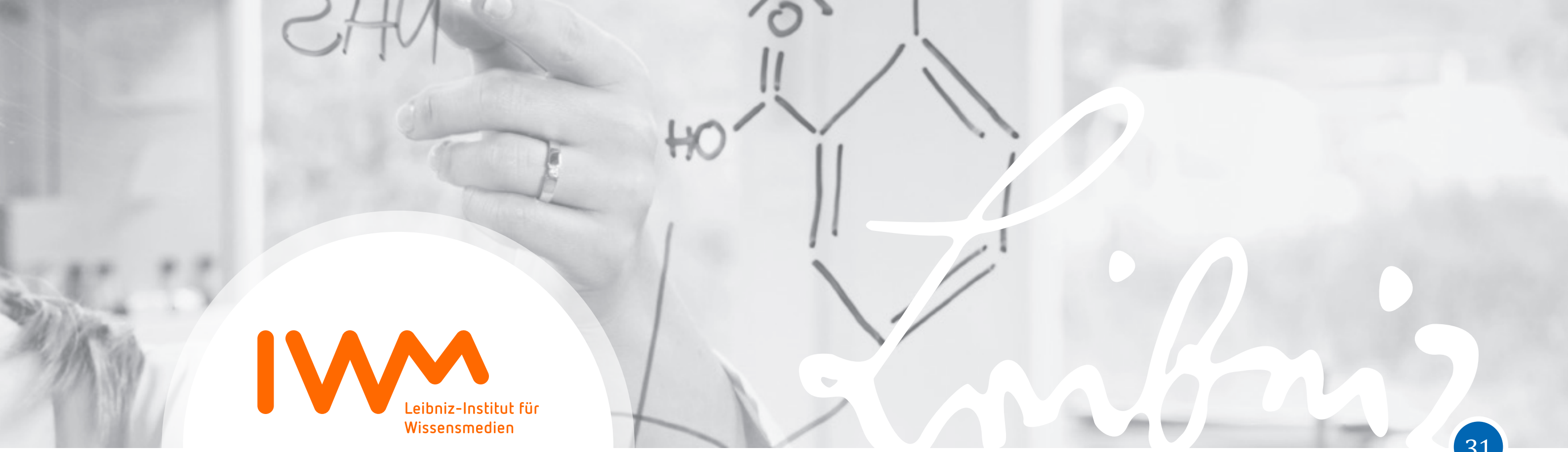
M. Kroker et al. (2015). Preventing carbon NP-induced lung inflammation reduces antigen-specific sensitization and subsequent allergic reactions in a mouse model. Part Fibre Toxicol.

A. Scharf et al. (2015). Anti-amyloid compounds protect from silica nanoparticle-induced neurotoxicity in the nematode C. elegans. Nanotoxicology.

D. Van Berlo et al. (2014). Investigation of the effects of short-term inhalation of carbon nanoparticles on brains and lungs of C57BL/6J and p47phox-/- mice. Neurotoxicology.

N. Büchner et al. (2012). Unhealthy diet and ultrafine carbon black particles induce senescence and disease associated phenotypic changes. Exp Gerontol.

K. Gerloff et al. (2013). Influence of simulated gastro-intestinal conditions on particle-induced cytotoxicity and interleukin-8 regulation in differentiated and undifferentiated Caco-2 cells. Nanotoxicology.



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IWM - Leibniz-Institut für Wissensmedien

www.iwm-tuebingen.de

The Leibniz-Institut für Wissensmedien (IWM) in Tübingen investigates knowledge acquisition and exchange with digital media. These topics are not only explored in typical settings for learning such as schools or universities, but also in museums or the workplace. We are interested in the social, cognitive and technical conditions of how digital media can support knowledge processes.

Research at the IWM is divided into two research sections. The focus of the research section *Individual use of knowledge media* is on individual learners' knowledge-related processes when using digital information. The research section *Social use of knowledge media* investigates the potential and risks of using digital communication and cooperation media for collaborative knowledge work and knowledge acquisition.

Role in the Leibniz Research Alliance

Within the research alliance, IWM is mainly concerned with the public reception of the potentials and risks of nanotechnology through digital media (e.g. internet-based information). The institute contributes its expertise in the fields of knowledge acquisition and knowledge exchange through digital media in the interest of supporting laypersons with strategies of information evaluation when using digital media to get informed about nanotechnology.

Involved research groups

The **Multimodal Interaction lab** studies the cognitive processes taking place when reading and evaluating different internet sources about complex and controversial science-related topics. Methods like eye tracking and log-file analyses are used to explore in detail how multiple internet documents of diverse origin and quality are processed. Insights gained from these analyses can be used to develop suitable measures to support users in their information search.

The **Multiple Representations lab** deals with the question how and under which conditions multimedia presentation formats can enhance the understanding of complex scientific content. An important topic is, for instance, how static and dynamic visualisations can facilitate text comprehension. An important aim of the group is to test how findings gained from basic research on knowledge acquisition through multimedia can be applied in more practical contexts.

The **Social Processes lab** investigates emotional processes in health-related web searches. An important research topic is under which conditions information about health risks evoke feelings of threat, which in turn influence the subsequent search, selection and processing of health-related information. Another important research question is how information about threatening topics can be presented in such a way that readers do not engage in an emotionally biased processing of this information.

External cooperation

- Leibniz ScienceCampus with the University of Tübingen: "Informational Environments"

Publications

H. Greving et al. (2015). Counter-regulating on the Internet: Threat elicits preferential processing of positive information. J Exp Psychol: Appl.

Y. Kammerer, P. Gerjets (2014). The role of search result position and source trustworthiness in the selection of Web search results when using a list or a grid interface. Int J Hum Comput Interact.

A. Eitel et al. (2013). How a picture facilitates the process of learning from text: Evidence for scaffolding. Learning and Instruction.

Y. Kammerer, P. Gerjets (2012). Effects of search interface and internet-specific epistemic beliefs on source evaluations during web search for medical information: An eye-tracking study. Behav Inf Technol.

Granted Projects

BMBF

FZB — NanoCOLT — Long term effects of modified carbon black NPs on healthy and damaged lungs, nanoCare, 2015-2017

INM — NanoKon — Systematic evaluation of health effects of nanoscale contrast agents, nanoCare, 2010-2013

FZB — CarbonBlack — Prediction of the human-toxicological effect of synthetic carbon black nanoparticles, nanoCare, 2010-2013

Federal Ministry of Education and Research

DFG

IUF — Identification of molecular mechanisms of carbon nanoparticle-induced senescence and aging *ex vivo* and *in vivo*, 2015-2018

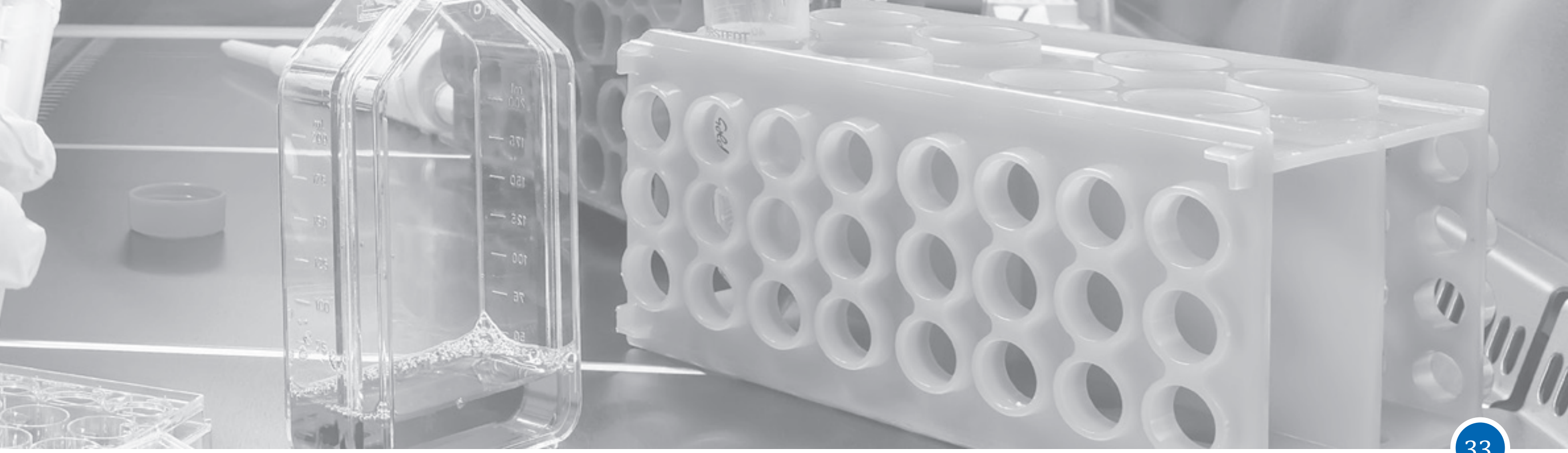
FZB — PARENTRY — How particles enter the body: investigating particle-barrier interactions in the digestive tract, SPP1313, 2008-2013

DFG

BMWi

INM — Morpheus — Multiparametric platform for the safety assessment of NPs, ZIM, 2015-2018

Federal Ministry for Economic Affairs and Energy



EU

INM	NanoReg II – Development and implementation of grouping and safe-by-design approaches within regulatory frameworks, Horizon 2020, 2015-2018
IUF	NanoMILE – Engineered nanomaterial mechanisms of interactions with living systems and the environment: a universal framework for safe nanotechnology, FP7, 2013-2017
IUF	SETNanoMetro – Shape-engineered TiO_2 NPs for metrology of functional properties: setting design rules from material synthesis to nanostructured devices, FP7, 2013-2017
IUF	nanOxiMet – Assessment of the use of particle reactivity metrics as an indicator for pathogenic properties and predictor of potential toxicological hazard, FP7, 2013-2016

Leibniz Association

INM, IUF	Leibniz doctoral project – Identification of cellular responses relevant for the safety assessment of modern nanomaterials, institutional funding in the context of the Research Alliance Nanosafety, since 2013
FZB, University of Lübeck	Priority program Biomedical engineering: Imaging disease processes, institutional funding, 2009-2015

The Leibniz Association provides funding to the Leibniz Research Alliance Nanosafety during the period 2013-2020.

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Glossary

AKT
Signalling protein, involved in signal transmission pathways, protein kinase B

Allergen
Substance that can initiate an allergic reaction

Bronchial asthma
Respiratory distress due to constriction of the airways (bronchia), caused by inflammation

Calcium imaging
Imaging techniques that depict intracellular calcium concentrations

Co-localisation
Relative position of two or more structures inside or on cells

COPD
Chronic obstructive pulmonary disease. Permanent pulmonary disease involving a limited lung function

Cytotoxic
Cell damaging

Endocytic vesicle
Early intracellular vesicle, formed by invagination of the cell membrane (cell envelope)

Endosome
Greek endo = inside, soma = body; membrane-bound vesicle inside of cells

Epidermal Growth Factor (EGF)
Signalling molecule that stimulates cell growth

Epithelial cells
Cells that cover inner and outer body surfaces (skin, lungs, gastro-intestinal tract)

ERK
Signalling protein, extracellular signal regulated kinase, MAP kinase (Mitogen Activated Protein kinase)

in vitro
Latin: in a glass; biochemical reaction that takes place outside of living organisms, a) in cultivated living cells or b) outside of cells in a test tube

in vivo
Latin: in the living, in the living organism

Ligand
Substance that binds to a macromolecular target molecule, e.g. a receptor

Log file
A file that records the actions performed with computer software

Lysosome
Greek lysis = solution and soma = body; membrane-bound digestive vesicle within cells

Nano
Greek nanos = dwarf; one part in a billion

Nanomaterial
Material, powder or liquid that contains nano-objects, e.g. nanoparticles

Nanotechnology
Methods serving the preparation, manipulation or measurement of nano-structures

Nanotoxicology
Scientific field targeting the effects of nanomaterials on living organisms and the environment

Phosphorylation
Attachment of a phosphate group to a protein with regulatory function

Receptor
Membrane-bound signalling protein that can bind a specific ligand and initiate signalling processes

Transport protein
Membrane-bound protein that mediates the transport of substances/molecules across biological membranes

1.000.000 nanometres

The space between two millimetre marks on a ruler fits

Research Alliances in the Leibniz Association

The Leibniz Association connects 88 independent research institutions that range in focus from the natural, engineering and environmental sciences via economics, spatial and social sciences to the humanities. Leibniz institutes address issues of social, economic and ecological relevance. They conduct knowledge-driven and applied basic research, maintain scientific infrastructure and provide research-based services. The Leibniz Association identifies focus areas for knowledge transfer to policy-makers, academia, business and the public. Leibniz institutions collaborate intensively with universities – in the form of Leibniz ScienceCampi (thematic partnerships between university and non-university research institutes), for example – as well as with industry and other partners at home and abroad. They are subject to an independent evaluation procedure that is unparalleled in its transparency. Due to the importance of the institutions for the country as a whole, they are funded jointly by the Federation and the Länder, employing some 18,100 individuals, including 9,200 researchers. The entire budget of all the institutes is approximately 1.6 billion euros.

Leibniz institutions form collaborative research alliances, which use inter- and transdisciplinary approaches to address current scientific and socially-relevant issues. The Leibniz institutions combine their resources and expertise in a range of topics such as energy, education, health, social research, biodiversity and nanosafety. The research alliances are open for collaboration with universities, other non-university research institutions and infrastructure facilities as well as research groups abroad.

www.leibniz-gemeinschaft.de

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