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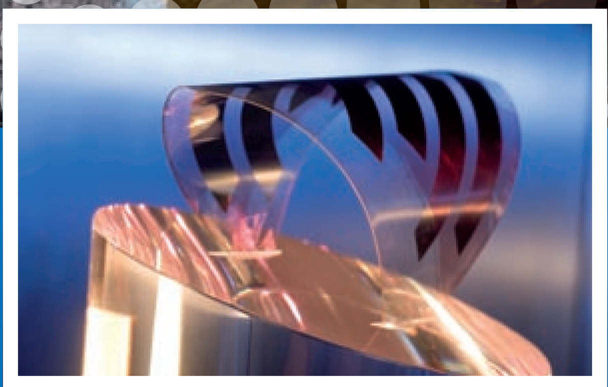

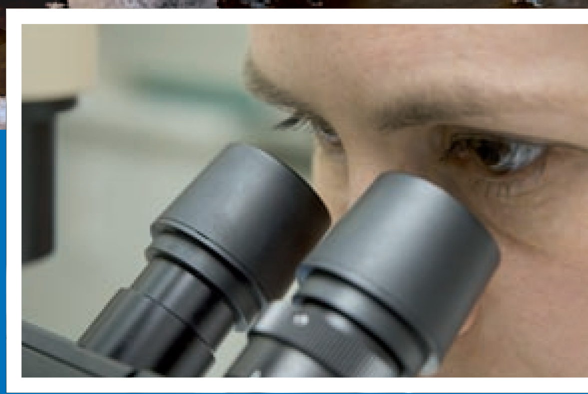

Health-related Aspects of Synthetic Nanomaterials

IMPRINT

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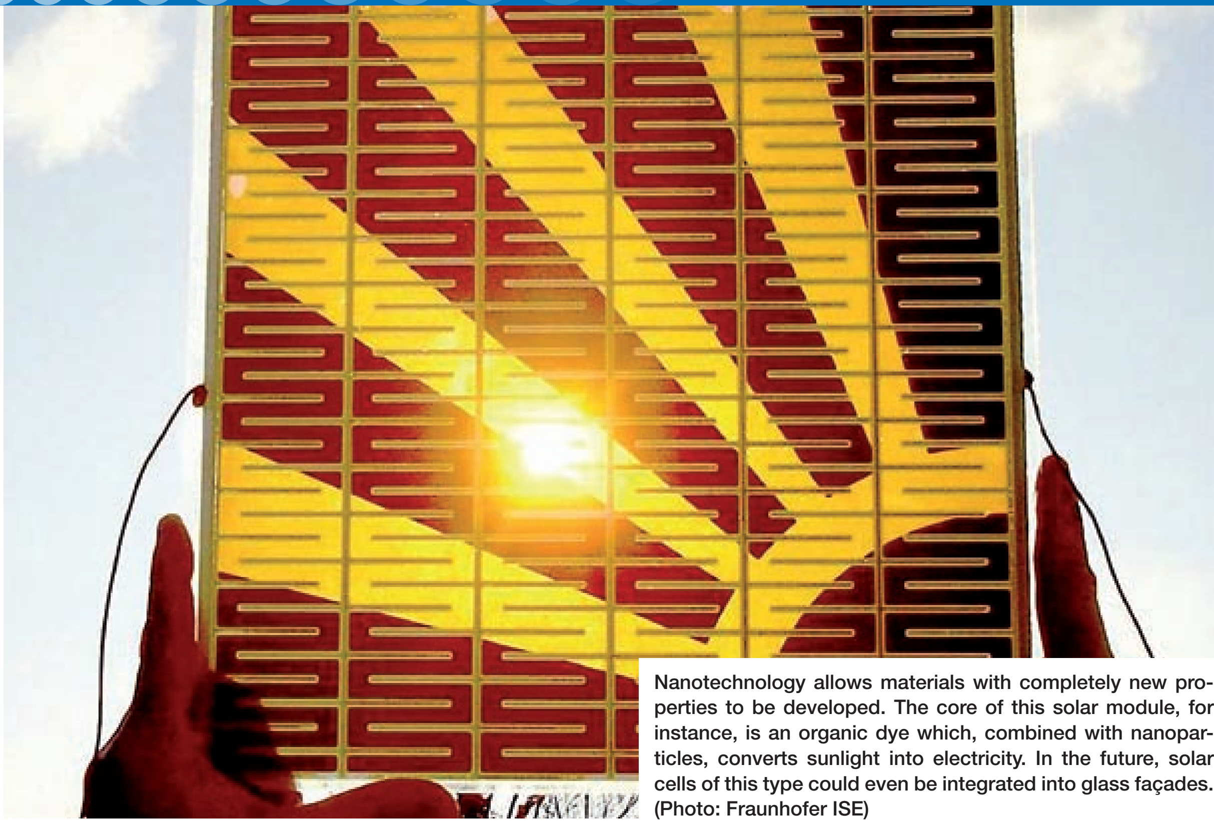


Nanotechnology allows materials with completely new properties to be developed. The core of this solar module, for instance, is an organic dye which, combined with nanoparticles, converts sunlight into electricity. In the future, solar cells of this type could even be integrated into glass façades. (Photo: Fraunhofer ISE)

Dealing with nanotechnology responsibly

Nanotechnology has become a buzz word. Over the past couple of years, nanotechnology has developed into a technology with a promising future whose importance may be compared to that of modern information technology when computers were introduced. After all, practically every branch of industry sooner or later will benefit from nanotechnology.

Nanotechnology has long been an accepted branch of science. Specialized research disciplines, such as nanooptics, nanobiotechnology, nanomedicine, nanoelectronics, and nanomaterials research, have been established. Nanomaterials can be found in many products for everyday use, from sun cream to toothpaste with a repair effect, to wall paint which repels dirt, and to new materials for medical implants. The list of new or improved products with “nano” inside is becoming longer and longer. This is no surprise, as nanomaterials have unusual properties and allow completely new applications to be found. Just think of flexible ceramics, or of paper which is heat resistant, transparent and hard as glass, but can still be folded.

Responsible use of a technology with a promise for the future, such as nanotechnology, must be taken for granted. For this reason, the NanoCare joint project in Germany deals with open questions about potential health hazards stemming from nanomaterials. NanoCare is a cooperative venture of researchers from science and industry funded to the tune of euro 5 million for a period of three years by the German Federal Ministry for Education and Research. The industrial partners contributed another euro 2.6 million.

NanoCare scientists publish their findings in scientific journals and make them available to the public at large on the website **www.nanopartikel.info**. This brochure, too, explains the motivation and the objectives of NanoCare, providing an overview of some of the research findings.

nanoCare has achieved a lot

The NanoCare Consortium was established in 2005 to study more closely potential health-related effects of industrially produced nanoparticles. A knowledge base has been created by internally standardized methods and conventional biological test systems, on the basis of which the properties of nanomaterials under study can be assessed systematically and reliably.

The scientists of the NanoCare project conducted their studies on industrial nanomaterials. Employing modern techniques, they analyzed the biological effects and exposure levels at the workplace in the production of nanomaterials in order to better estimate potential risks on the basis of this knowledge.

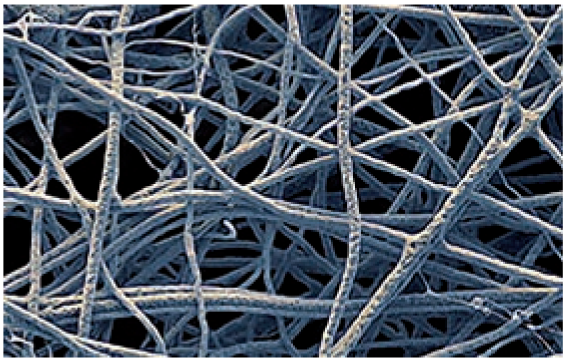
In addition, it was important to the members of the NanoCare project to communicate their findings, i.e. discuss them with stakeholders, such as politicians, journalists, representatives of churches, trade unions and other groups of society, and with the public at large. A total of five dialog events have shown that the general public so far has shown little interest, unlike the representatives of groups of society, in obtaining information about potential consequences of the use of nanomaterials. As there is an evident need for more information, the internet presence of the NanoCare project will be expanded further into a basis for an open dialog about nanotechnology in Germany.

The NanoCare staff organized several campaigns to inform the general public of their research. The nanoTruck of the German Federal Ministry for Education and Research (BMBF) was on site for the dialog with the public in Hamburg and Munich. (Photo: Harald Krug)

Standardized Test Methods

The NanoCare project has contributed to standardizing international test methods and will continue to do so. Thus, the Organization for Economic Co-operation and Development (OECD) has been supplied with important NanoCare findings to improve internationally acknowledged test strategies. Within the OECD, Germany is also responsible for implementing an extensive test program of nanostructured titanium dioxide; results obtained in the NanoCare project provide significant contributions to this activity.

In addition, the staff of NanoCare has drawn attention in several publications to some major mistakes in many earlier studies of nanoparticles which thus contributed to misinterpretations. One major purpose of the NanoCare project therefore was to standardize the methods and test procedures employed so that other research groups could use them reliably. Despite the large number of possible materials, biological systems, and biological effects, NanoCare has made considerable progress in this effort.



Nano-objects come in various shapes. The hydrogen storage nanocubes (large picture) can be used in miniaturized fuel cells. The nanofibers (small picture) developed, for instance, for clothes with integrated UV protection are one thousand times finer than a human hair. (Photos: BASF)

What is meant by "nano"?

"Nano" has become a buzz word. What does it really mean? "Nano" stems from the Greek *nanos*, i.e. dwarf. Consequently, a nanometer is a tiny fraction of a meter or, more precisely: one billionth of a meter. All particles with at least one outer dimension, i.e. length, width or height, between 1 and 100 nanometers are referred to as nano-objects in the jargon of the field. Nano-objects which are nanoscale in all three dimensions are nanoparticles. This has been laid down in a DIN CEN ISO standard effective since August 2008. The tiny size of these particles can perhaps be demonstrated best by this comparison: A nanoparticle compares to the size of a soccer ball roughly like a soccer ball compares to the size of the planet Earth.

Actually, nano is not new

Long before the specific industrial production of nanoparticles, people made and even used such tiny particles. In one of its most important steps, the development of classical photographs is based on the formation of silver nanoparticles. Slash-and-burn techniques and transport give rise to soot nanoparticles.

Nanoparticles are not exclusively manmade but also occur in nature. For instance, forest fires and the recurring fires of the savannah every year emit soot nanoparticles much like manmade combustion processes.

Important terms

Nanomaterial

Nanomaterial is a generic term frequently used to comprise, among other things, nano-objects and nanoparticles as well as their aggregates and agglomerates.

Agglomerates

Nano-objects have the pronounced tendency to agglomerate, thus forming agglomerates of micrometer or millimeter sizes, for instance in powders. These agglomerates can be disintegrated again, for instance by powerful stirring, as their component parts are bound by relatively weak forces. s

Aggregates

Aggregates, on the other hand, are combinations of nano-objects held together by strong forces, such as chemical bonds. They can no longer been disintegrated into their component parts, unless enormous energies were applied.

For easier reading, this brochure will not use the proper scientific terms, nanomaterials and nano-objects, but mostly refer to "nanoparticles".

Today we know that even old church windows contain nanotechnology: The red shade is produced by nanosize gold. (Photo: ©leiana, Fotolia.com)

Industrial-type carbon black is an old established nanomaterial. It greatly improves the properties of tires and, moreover, acts as a pigment. (Photo: Christian Kellner, Fotolia)

Nanoparticles may have exhibit a variety of shapes far from uniform. However, they always have very large surfaces in relation to their masses, and mostly consist of a relatively small number of atoms or molecules, which gives rise to so-called quantum effects. Their properties therefore clearly differ from those of a material of the same chemical composition which is not nanoscale. Gold nanoparticles, for instance, have a reddish gleam, nanoceramics are flexible like foils, all of which properties allow them to be used for completely new applications.

Nano inside

Nanomaterials are being used in many ways, from special areas in medicine to everyday products, such as skin lotions and wall paint. The classical nanomaterials long produced in large quantities include the industrial type of soot referred to as “carbon black.” Carbon black is contained in car tires, increasing their abrasion resistance, adhesion, and elasticity. Carbon black is also a common black pigment used in inks, paints, polymers, and many other compounds. Another example of nanomaterials long used in large quantities is synthetic silica or, chemically, silicon dioxide.

Nanoparticles in medicine

There are many applications of nanoparticles in medicine. As silver ions can kill bacteria, a property exploited for more than 2000 years, medical equipment and other articles of use (computer keyboards, dishwashers, even socks) are now coated with nanosilver. Nanoparticles are to be used also as tiny drug carriers, moving active agents through the body and releasing them at the target point. This reduces the risk of side effects. In tumor treatment, iron oxide nanoparticles are scoring their first successes. They are injected right into a tumor and heat up when an external magnetic field is applied. The heat generated in this way kills the tumor cells. A similar effect is exploited in the use of iron oxide nanoparticles in special adhesives which are cured quickly and effectively by microwaves without simultaneously heating the components around them.

When used as fillers they reinforce silicone rubber and thicken printing inks and toothpastes. Also paper for very glossy prints contains these silicas.

Powder suspensions made of silicon dioxide, aluminium oxide and cerium oxide nanoparticles are used in the electronics industry for cleaning and polishing silicon wafers, the substrates of computer chips or solar cells.

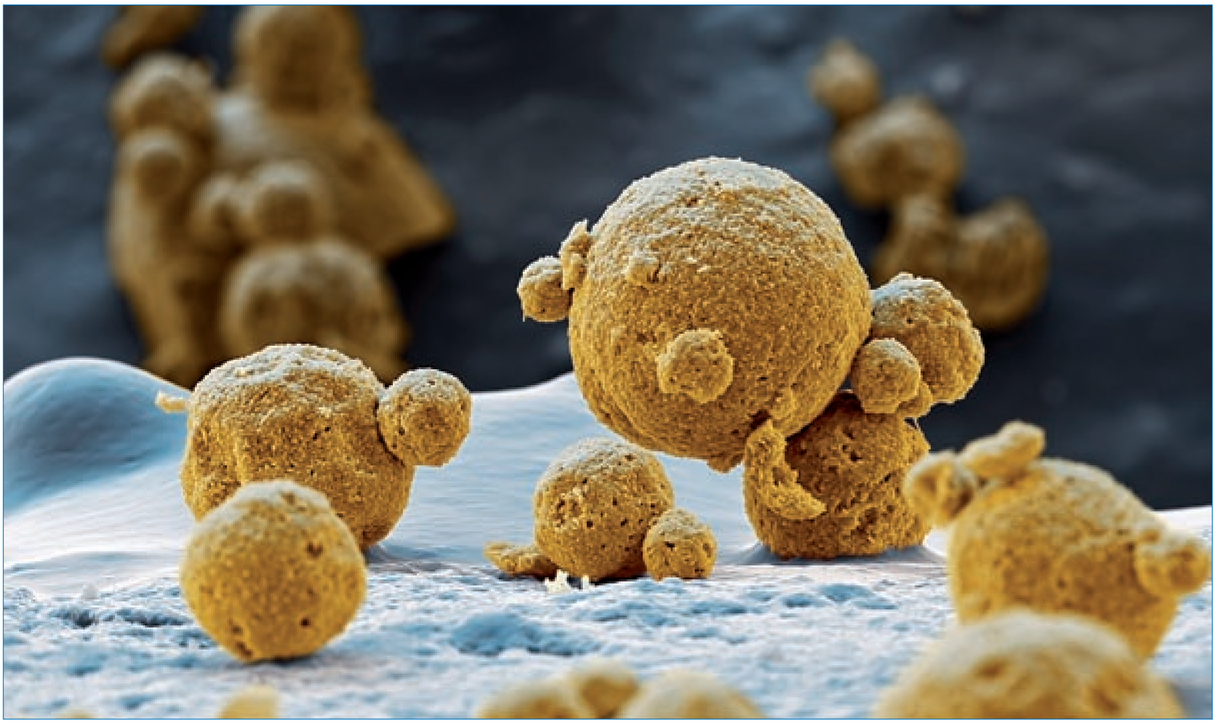
Nanoparticles of titanium dioxide and zinc oxide act as effective UV filters in sun creams and textiles protecting against the sun. Paints and dyes, also lipsticks and other cosmetic products, contain nanomaterials as pigments producing sparkling and coloring effects.

Magnetic fluids, so-called ferrofluids, contain iron oxide nanoparticles. They are used, for instance, to cool loudspeaker boxes and act as liquid sealants.

Also organic materials are being used in which inorganic nanoparticles are firmly embedded. These composites apply one of nature's basic principles. Fine structures on the order of a few nanometers, in which inorganic minerals combine with organic cement, are the reason for the extraordinary stability of bones, tooth enamel, and mother-of-pearl. When used as binders, these composites improve the quality of varnishes, paints, and plastering materials. They are also used in adhesives and for coating leather, wood, and textiles.

These examples represent only a small number of applications of modern nanotechnology. In addition, nanocatalysts help chemical industries to conserve resources; also catalytic converters used in cars require less platinum when this precious metal is present in a nanoform. Nanomaterials play an important role also in power technology, for instance in producing energy storage devices and in the development of improved solar cells.

The applications and possibilities listed here indicate that people can come into direct contact with these new materials. Consequently, nanomaterials must be examined for potential effects on health as a matter of precaution, and their possible environmental impacts must be studied. In the NanoCare project, scientists are focusing especially on aspects of health by examining possible exposures at the workplace and conducting a variety of biological tests in order to exclude, if possible, any negative influences on health.



Electron micrograph of nano- to micrometer-size metal oxide particles used to store energy in lithium ion batteries. The lithium ions are enclosed in the metal oxide. In this way, no inflammable lithium can be produced, and the batteries are safer. (Photo: BASF)

Assessing and limiting risk

A lot is known about the nanomaterials currently on the market. Nanomaterials are a special type of chemicals, thus covered by the existing legal regulations on chemicals, drugs, food, cosmetics, and detergents, and by many other rules and regulations.

The first complete applications for registration of volume products filed under the new European Chemicals Act, REACH, were for nanomaterials. Nevertheless, new nanomaterials could give rise to effects not detectable by current methods. Precisely at this point, NanoCare started developing standard procedures to study effects which could be specific to nanomaterials.

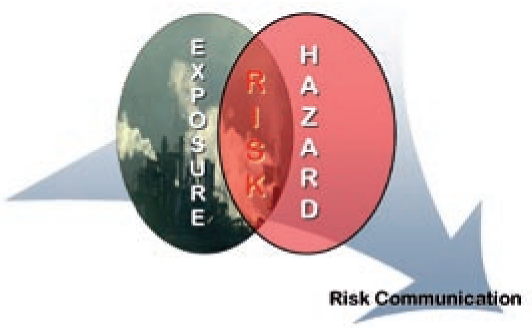
Technologies with new applications always give rise to questions of safety. Current safety research into nanomaterials therefore seeks to find answers to these questions in order to make nanomaterials even safer.

Before nanomaterials are distributed commercially, they are examined for potential hazards to humans and the environment like any other new product. Existing rules and regulations apply also to nanoproducts. (Photo: Matty Symons, Fotolia)

The risk concept

Before new products come on the market, manufacturers must assess their potential risks to humans and to the environment. Of course, this also applies to nanomaterials. In that assessment, they consider both the hazard potential stemming from the properties of a material and the so-called exposure of people or nature to that material.

Whether a substance is harmful to health depends not only on its properties but, very much so, on the quantities taken up by a living being. Hence, the more we know about the properties of a substance, and the better we can detect it, for instance, at the workplace or in the environment, the better we will be able to assess potential risks and, if necessary, guard against it. This precisely is the objective scientists pursued in the NanoCare project.



Risk is defined as the product of exposure and hazard. (Picture: Harald Krug)

The dose makes the poison

Impairment of health due to chemicals, but also other substances, depends on their concentration at the site of action. As long as 500 years ago, Paracelsus recognized that "all things are poison; there is nothing without poison; only the dose makes a thing non-poisonous." Consequently, health hazards arise from the hazard potential (effect) and the possible uptake (exposure). If one of these parameters equals zero, there is no risk. This is the case, for instance, if a material cannot be released.

Nanocare findings

Particle production and characterization

The nanomaterials under study were categorized in three different groups:

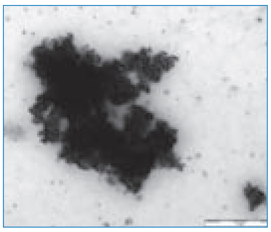
- Industrial carbon black as a nanomaterial consisting of pure carbon
- Metal oxides, including titanium dioxide, cerium dioxide, and zinc oxide
- Barium sulfate and strontium carbonate salts

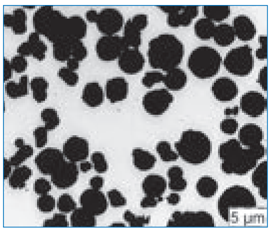
The size and size distribution as well as the degree of aggregation and agglomeration of the nanomaterials were determined to characterize material properties. In addition, the pH, electric conductivity, solids concentration and the surface potential of nanoparticles in an aqueous suspension were measured.

Essential: results must be comparable

The scientists of the NanoCare research project used for reference two nanomaterials which had been studied in great detail before: titanium dioxide and carbon black. The data generated within NanoCare about the nanomaterials studied in less detail up to that point were then compared with the findings about carbon black and titanium dioxide.

Moreover, the project partners elaborated so-called standard operating procedures (SOPs) for studies of nanomaterials which precisely describe repetitive identical approaches. These SOPs ensure that all laboratories involved treat the nanomaterials and living cells as well as other auxiliary agents used in the tests in the same way, thus arriving at comparable results. The standard operating procedures developed within the NanoCare project can be found in the internet under www.nanopartikel.info for downloading.





Electron micrographs of industrial carbon black (left) and titanium dioxide: These two substances have been well characterized and therefore served as reference materials in the NanoCare project. (Photos: NanoCare Consortium)

Equipment for nanoparticle production. Even minor differences in size or shape of particles can influence the behavior of nanoparticles in the body. (Photo: Forschungszentrum Karlsruhe GmbH)

Essentials of the NanoCare project

Particle production
Specific modification of the particles under study in terms of size, surface charge, and surface chemistry. Additional parameters are surface loading (coating) and hydrophobing.

Particle standardization and characterization
One particularly important requirement was that all partners use the same material. Only in this way is comparability of the findings ensured. For this purpose, also facilities and methods had to be standardized.

In-vitro models
Selection of suitable cells/types of cells to be studied, such as pulmonary phagocytes, epithelial cells, and co-cultures, as well as definition of applicable biomarkers for effect monitoring (determination of hazard potential).

In-vivo validation in animal models
Verification of findings in a few animal experiments, and extrapolation from in-vitro to in-vivo conditions.

Reality: assessment of exposure at the workplace
The number, agglomerate stability, and dispersion of nanoparticles at the workplace as well as adaptation and development of new methods of measurement.

Data preparation, interpretation, and knowledge base
Analysis of the data collected in NanoCare as well as of relevant findings in the specialized literature; maintenance of a knowledge base for internal and external uses.

Knowledge transfer: communication and dialog
Internal dialog and knowledge transfer to structure research findings. Dialog events and expert meetings as well as web portal, publications in the internet, and also contributions to journals.

Interactions of nanoparticles and cells

As mentioned above, all substances are toxic; only concentration makes the difference. The toxicologists of NanoCare therefore wanted to find the dose level below which no damage occurred in the test systems. Two different approaches were used: On the one hand, substances were tested in vitro, i.e. “in the glass,” in laboratory experiments on isolated cells outside a living organism. The other approach implied studies in living animals under in-vivo conditions.

In-vitro tests: cell types and biological effects

For their toxicological tests, scientists used different cell types, including cells from the top layers of the lung, skin, and intestine, but also phagocytes of the immune system and cells from the innermost layers of the lymphatic vessels and blood vessels. They studied the response of cells to nanoparticles, for instance, whether cells produced aggressive oxygen radicals or other substances indicative of stress and inflammatory responses of the cell. Does the cell die or is it able to protect itself against nanoparticles? Do nanoparticles affect genes and cell replication? Are nanoparticles deposited in the cells, or where do they dock onto the surface of cells? To clarify issues like these, NanoCare scientists standardized existing test methods and developed new ones from scratch.

The lung is considered the main portal of entry of airborne nanoparticles. Consequently, uptake by inhalation was studied in animal experiments within the NanoCare project. (Picture: Sebastian Kaulitzki, Fotolia).

In-vivo tests: animal experiment about inhalation

The uptake of nanoparticles from the air was studied in animal experiments with rats. The rats inhaled various nanoparticles in different concentrations. For comparison, the same studies were conducted with clean air. The NanoCare scientists analyzed the contents of proteins and the activity of enzymes in the pulmonary lavage fluid and in the pulmonary tissue of rats. Moreover, they studied under the microscope whether the pulmonary tissue and the respiratory tract of the animals had changed in a pathological way. Also the concentrations were determined above which nanoparticles produced effects. The findings of the in-vivo tests were compared with those of in-vitro models.

Titanium dioxide, a multitalent

Titanium dioxide will be used below to explain the different health-related aspects of the NanoCare project. Titanium dioxide, whose chemical formula is TiO_2, is the ninth most frequent mineral of the earth lithosphere. It occurs in rock and as a constituent part of other minerals. For industrial use, it is processed by specific refining techniques producing a whitish powder. Titanium dioxide is chemically stable, heat resistant, and has a high refractive index. It can be used for many things, for instance as an important white pigment for paints, varnishes, textiles, polymers, and paper. Under the label of E171 it is used as a food additive, and is also found in drugs, toothpastes, and many other products for everyday use.

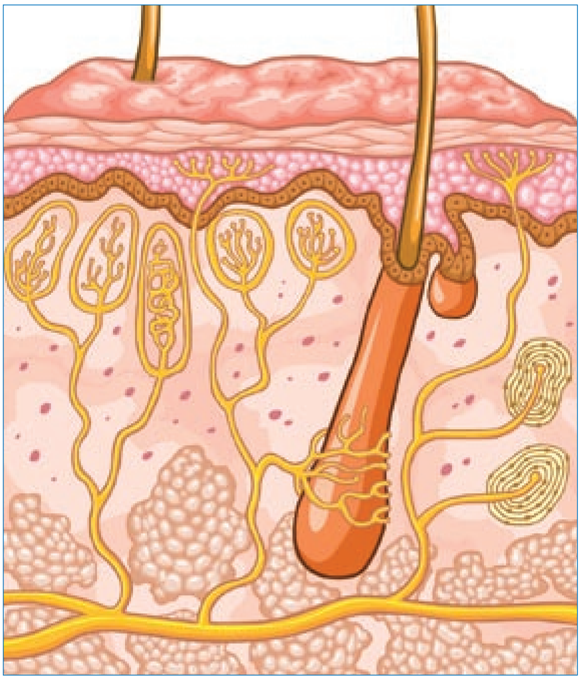
Conventional Titanium dioxide is used as a white pigment in wall paint and many other products. (Photo: Sandro Götze, Fotolia)

Nanostructured titanium dioxide, on the other hand, has physical properties completely different from those of its big brother. It is not white, but transparent. It is not used in food, but employed as an effective UV filter in sun creams, textiles, agents for timber protection, and many other products. Because of its energy absorbent properties, nanostructured titanium dioxide can also be used in solar panels. Ultrafine titanium dioxide particles are also components of self-cleaning surfaces; being miniature catalysts, they degrade organic pollutants.

Healthy skin offers good protection

As nanostructured titanium dioxide is used in many sun creams for protection against UV-radiation, this automatically raises the issue of potential side effects on the skin. Although this aspect was not among the activities of the NanoCare project, the large-scale European NANODERM project looked into this question and found out that nanoparticles are unable to penetrate healthy skin and enter the body on this pathway. More information is available from the scientists conducting that study (www.uni-leipzig.de/nanoderm/).

Nanoparticles in cosmetics are considered unproblematic as they will not enter the body through healthy skin. (Photo: Victoria Alexandrova, Fotolia)



The skin is an excellent barrier to nanoparticles. (Picture: OOZ, Fotolia)

Nanostructured titanium dioxide in body cells

Like other particles, bigger as well as smaller ones, nanostructured titanium dioxide can be taken up by cells. However, the important criterion is the part of the body contacting these particles. The most sensitive organ is the lung, but here the phagocytes of our immune system are specialized literally in "gobbling up" any foreign invaders and removing them. It has been shown that phagocytes will take up respirable particles in vitro, both bigger and very small ones. Consequently, it was possible to analyze their effects in a model.

In-vitro studies with nanostructured titanium dioxide

In-vitro studies are conducted to examine cellular reactions and elucidate action mechanisms so as to better understand potential effects in organisms. The contact of a cell with nanostructured titanium dioxide, and the uptake of particles in the cell, triggers typical cell responses. In the experiments conducted by NanoCare partners, but also in studies by other laboratories, it has become evident that nanostructured titanium dioxide

- influences cell vitality, i.e. the "health" of a cell, only at very high concentrations;
- causes inflammatory reactions of a cell. These reactions are a typical response of cells to invaders. They help fight the foreign body, prevent its spreading, or help repair damage;
- also promotes the generation of reactive oxygen compounds and radicals.

A phagocyte removing nanoparticles. (Photo: Harald Krug)

The key findings of the NanoCare studies show biological effects of nanoparticles to be a function of their structure, shape, and size. All effects observed occur exclusively at very high concentrations, i.e. concentrations not found in everyday use. Yet, these observations are important because they help to better understand the basic impact of nanoparticles on living cells.

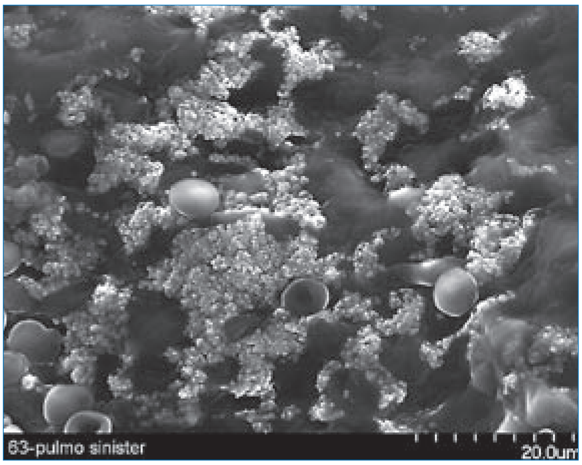
In-vivo studies: inhaled nanostructured titanium dioxide

In the debate about potential health hazards posed by nanomaterials, inhalation of dust is considered particularly critical. Consequently, inhalation studies of laboratory animals were performed alongside in-vitro tests of cell cultures. The NanoCare experiments served to investigate the biological effects, especially inflammatory reactions, after repeated uptakes of nanomaterials. The results of these experiments can be summarized as follows:

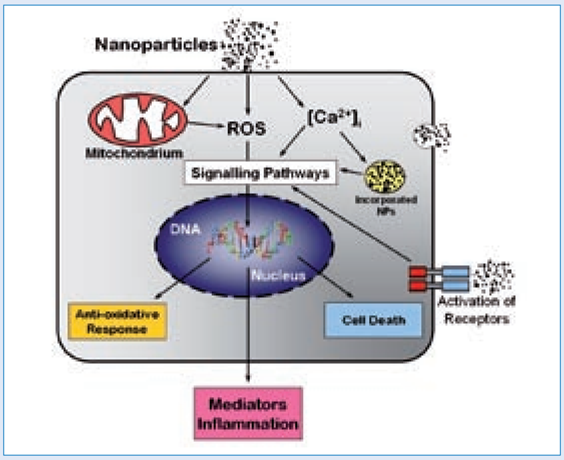
- At the low test concentrations (which would still be considered very high in real-life situations) the nanoparticles do not trigger any pathological responses in the lung.
- Higher concentrations give rise to inflammatory responses in animal experiments, which is in excellent agreement with the findings of in-vitro experiments.
- It was clearly demonstrated, assuming equal masses, that larger particles cause less pronounced responses than nanoparticles.
- The inflammatory reactions did not last long but subsided completely after a few days.

At this point, it needs to be stated that the NanoCare experiments examined only the effects of high concentrations over a relatively short period of time. Chronic, i.e. lifelong, treatment with low concentrations still needs to be tested.

Also, the potential distribution of titanium dioxide particles from the lung into other parts of the body was investigated. For this purpose, the titanium content of the lung, liver, kidney, spleen, brain, and the lymph nodes of the mediastinum and in the region between the pulmonary lobes was measured. Other than in the lung, titanium was found only in the lymph nodes of the mediastinum. This transport into the lymph nodes is an element of pulmonary defense also observed with bigger respirable particles. No titanium was measured in the other organs.



Nanomaterial (bright) deposited in the lung after inhalation of titanium dioxide dust.
(Photo: BASF)



This is the mode of action of titanium dioxide nanoparticles on body cells: When exposed to a high load of nanoparticles, the cell generates aggressive oxygen compounds (so-called reactive oxygen species, ROS). Moreover, the influx of calcium ions (Ca2+) into the cell is increased. This initiates various signal pathways in the cell which, in the worst case, culminate in cell death. However, biochemical substances (inflammation mediators) enable the cell to start inflammatory reactions which remove the pathogenic substances or limit the damage.

(Picture modified after HF Krug et al., 2006)

Experiments conducted in a model reactor to assess flow conditions in the production of nanomaterials. (Photo: Bayer MaterialScience)

Nanoparticle releases in nanomaterials production

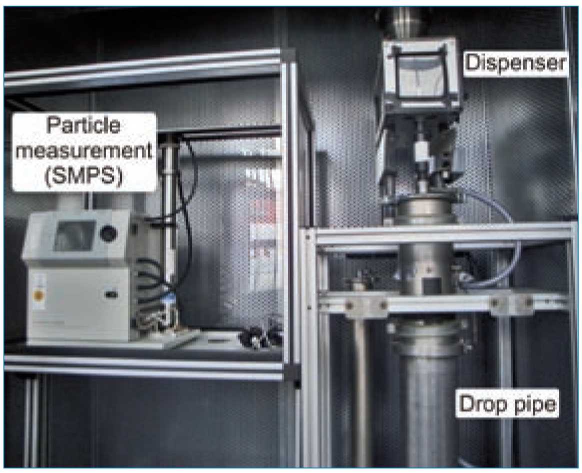
Another key area in the NanoCare project were studies of exposure at the workplace in the production and processing of nanomaterials. The scientists took into account also the distribution in air of the nanoparticles studied and any possible changes of these particles. This part of the project was subdivided into four points:

- Dustiness testing and agglomerate stability.
- Computer modeling of particle dispersion upon accidental release.
- Development of measurement techniques and methodologies.
- Measurement of nanoparticle concentrations at the workplace.

Dustiness testing and agglomerate stability

During production, the highly concentrated nanoparticles combine into larger aggregates and agglomerates as early as in the closed reactor. Further processing could subject these agglomerates to forces breaking them up again into smaller fragments or even into the original particles. As small particles can penetrate deeper into the lung than large ones, agglomerate stability plays an important role in risk assessment and for the point of deposition in the lung.

NanoCare scientists employed two different methods when studying the stability of aggregates and agglomerates: On the one hand, they fed powder on a vibrating bar into a drop tube through which clean air was blown in a countercurrent flow. This setup simulates the forces, in this case, the low shear forces, e.g. occurring when powders are poured into another vessel. The number and size distribution of particles were measured in the countercurrent flow. In a second approach, nanomaterials were subjected to high shear forces. For this purpose, the powder was first mixed with air and then forced through an orifice. This experiment simulates e.g. the



Setup for studies of agglomerate stability of nano-objects: The powder examined is fed into the down tube via the dosing system. (Photo: IGF) case of nanoparticles being released from a pressure vessel through a leakage.

Eight materials in a total of nineteen variations were studied in the drop tube. In eight of the material variants under study the number of nanoparticles increased clearly. On the whole, eleven variants showed larger agglomerates disintegrating into smaller fragments. Another striking finding was that different materials showed different intensities of dust generation. Concentrations in air were between 1000 and several million nanoparticles per cubic centimeter. For comparison: Buildings normally contain roughly 10,000 nanoparticles per cubic centimeter of room air; in the vicinity of very busy roads, these levels can rise to 100,000 nanoparticles per cubic centimeter. When forced through the nozzle, agglomerate disintegration also depended strongly on the nanomaterial used. While some materials passed the nozzle almost unchanged, others disintegrated into smaller fragments more and more as the pressure increased. These relatively new ways of determining patterns of dust generation of nanomaterials can provide important information for risk analysis, especially at the workplace.

Computer modeling of particle dispersion upon accidental release

Point measurements of particles at the workplace tell relatively little about how fast and where particles spread in a room. For instance, what happens in case of a leak when nanoparticles are released from a vessel by accident? In order to predict this situation, scientists studied particle flow in a computerized setup. Such computer models take into account various conditions, such as air circulation in a room – are the doors open or closed? -, the temperature of the air-particle mix (aerosol) released, and the size distribution of the particles released, which changes as a function of particle concentration in the air due to agglomeration. These simulations help to predict and limit exposures at the workplace.

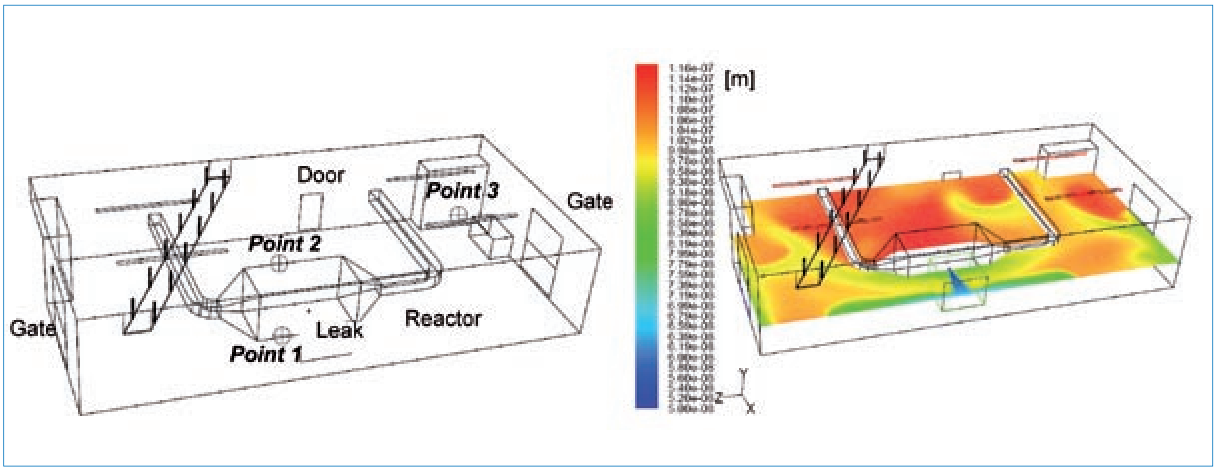
The computer model supplies data for any point in a room. For instance, it computes exposure at 1.50 meter height, the respiration height of persons standing. Computer simulation has shown also that a temperature change of the aerosol released greatly influences the propagation of particles in a room, sometimes even favoring it and thus clearly increasing the exposure of workers.

Development of measurement techniques and methodologies

Measuring nanoparticles at the workplace is not an easy matter. The equipment used should reliably detect even the smallest particles. In addition, nanoparticles possibly released from a process must be distinguishable from those present in the ambient air before.

The NanoCare experts used different measurement tools. To ensure comparability of the data obtained in this way, they first ran systematic reference measurements. For this purpose, each piece of equipment was simultaneously challenged with aerosols of common salt and from particle agglomerations produced by diesel engines.

The measuring gear showed agreement in particle size determination. However, the total concentrations measured differed by up to 30%.



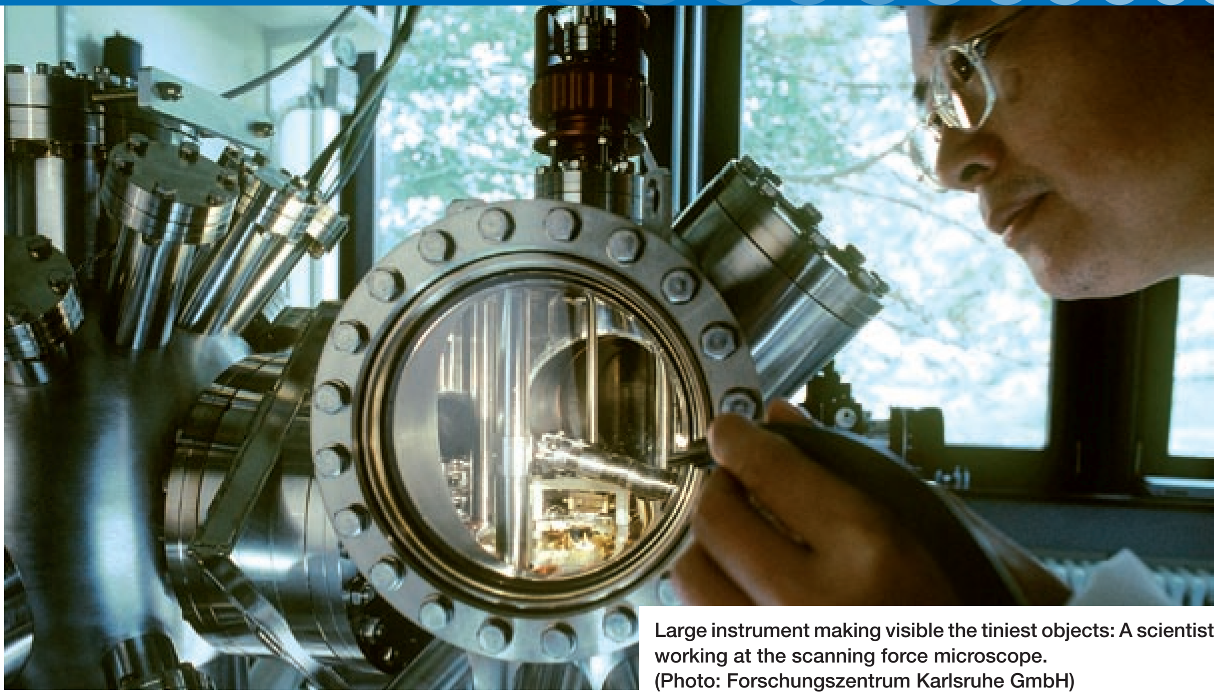
Computer modeling for a case of nanoparticles escaping from a leakage in the course of production. The colors indicate the mean particle diameter at a height of 1.50 m. Blue stands for small particles, red for larger, agglomerated particles. (Picture: IUTA, Duisburg)

On this basis, measurement strategies were elaborated for the assessment of particles released accidentally at workplaces in industry. First of all, the number of particles reaching a workplace in a manufacturing hall from the outside must be known. The background level can be determined by preparatory measurements inside and outside of the hall to ascertain the fraction of particles in the outside air entering the interior; while measurements are being conducted inside, nanoparticle production must stop. While exposure at the workplace is being measured, the outside air is measured at the same time, and the background concentration is estimated in this way. This background level is then used as a reference. Only when measured values at the workplace clearly exceed the background level, this is indicative of a leak or some other problem. However, all disturbing factors, such as fork lift trucks moving in the hall or work with welding gear, must be taken into account. Using experience from these studies, NanoCare scientists developed a measurement strategy which is now available for standardized assessment of nanoparticles at the workplace.

Measuring Exposure at the Workplace

The measurement strategy developed in NanoCare was employed at a total of eleven workplaces at four industrial locations manufacturing, packaging, and processing nanomaterials. None of those workplaces exhibited a significant increase in concentration of nanoparticles or small aggregates and agglomerates, respectively (below 400 nanometers). It is therefore safe to say that the industrial locations examined show now significant exposure to nanoparticles arising from production.

Particle measurement at an industrial workplace. (Photo: Evonik)



Large instrument making visible the tiniest objects: A scientist working at the scanning force microscope.
(Photo: Forschungszentrum Karlsruhe GmbH)

Conclusion of the project

The NanoCare project has achieved important results: Measurement strategies were developed to determine particle burdens arising from the production of nanomaterials, and were tested at real workplaces in industry. No exposure to nanomaterials of the workforce was detected. Other factors studied were the stability of agglomerates under relevant conditions and the ability of powders to release dust. Both are important parameters in risk analysis. Standard instructions were formulated to improve future comparability of the findings of toxicological studies. Like other important information, these instructions are published in the Internet freely accessible to anybody.

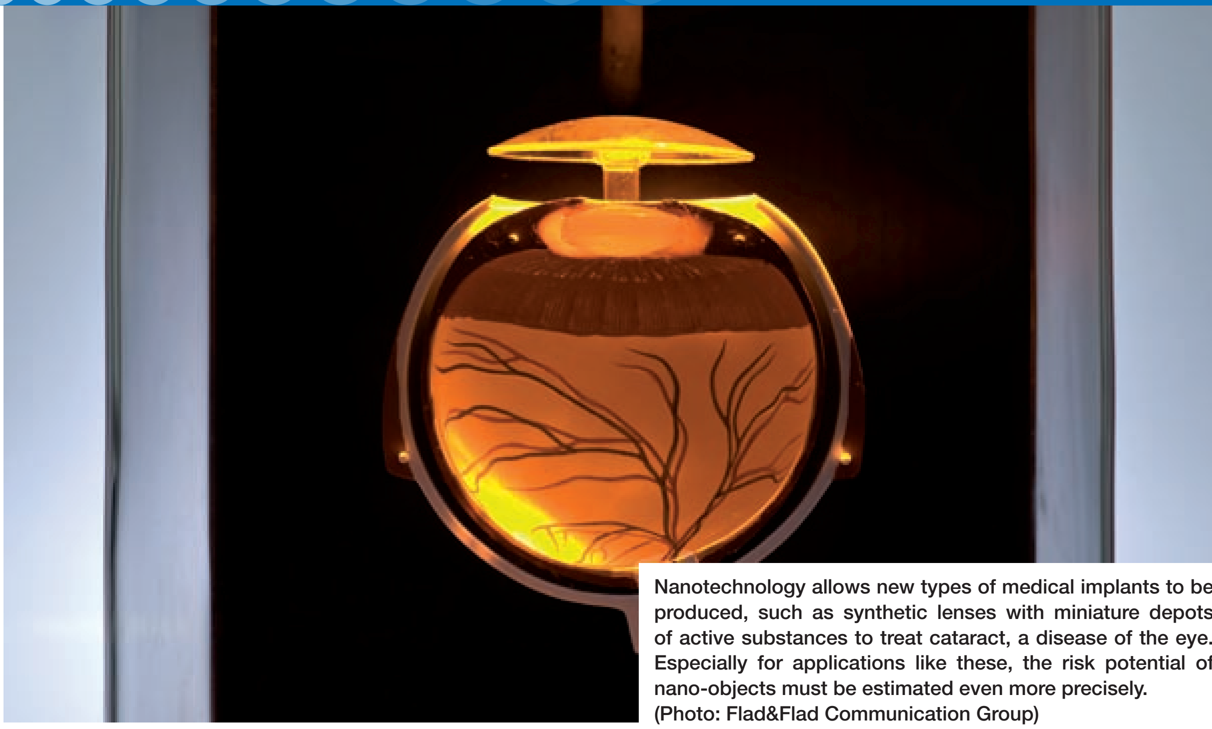
A total of eleven different nanomaterials were studied toxicologically in greater detail within the NanoCare project. For nearly all materials it was possible to define threshold levels below which no effects were detected. This is the precondition for defining limits. Penetration of cellular barriers, such as the air-blood barrier in the lung, was not found by the methods used in NanoCare. However, it must be said that the particles studied were taken up by all types of cells in the in-vitro experiment. The nanomaterials studied under in-vivo conditions, however, were found only in phagocytes of the lung, whose natural duty it is to absorb foreign matter and remove it from the lung. When present in high doses, materials caused inflammation, which is a typical response to foreign particles and is not specific to nanoparticles. The animals recovered after some time.

Some of the nanomaterials tested exhibited different biological effects. The action of "nano" therefore cannot be assessed in a generalized way, but depends on the nanomaterial in question, for instance, the materials composition, size, and structure.

Five dialog events were organized with politicians, journalists, representatives of the churches, trade unions, and other groups of society as well as members of the public about the chances and risks of nanotechnology. For all those seeking more information, www.nanopartikel.info contains detailed data: That website, too, is a result of NanoCare. A knowledge bank is made available in the Internet which is updated continuously and contains important information about the health aspects of nanomaterials.

New methods of measurement established

Methods were established in the NanoCare project which can be used to measure the biological effect of nanomaterials. Moreover, strategies were developed to measure nanomaterials at the workplace. In this way, another important basis has been laid for safe and responsible development of nanotechnology.



Nanotechnology allows new types of medical implants to be produced, such as synthetic lenses with miniature depots of active substances to treat cataract, a disease of the eye. Especially for applications like these, the risk potential of nano-objects must be estimated even more precisely. (Photo: Flad&Flad Communication Group)

Follow-on projects launched

The NanoCare project developed applications and methods of measurement for careful, sustainable handling of nanomaterials; the data were presented generally understandable to the public at various events. This had been the definition of the job scientists had to perform within the NanoCare project. Society needs such information to better assess a new technology and its benefit.

One thing is obvious: No innovation, no progress is without risk. However, consumers must know these risks in order to assess and decide whether to accept them because they are outweighed by the benefits. This is also true of nanotechnology. High risks do not necessarily mean rejection. In many areas of daily life, consumers accept high risks of a technology, provided they see a major benefit in so doing. The best example is motor traffic. Whenever we drive a car we run the risk of a fatal injury in a traffic accident.

The German Federal Ministry for Education and Research (BMBF) funded the NanoCare project, thus laying the ground for a project which has assumed model character in Europe. For the first time, scientists have elaborated, on a large scale, reproducible findings about the biological effects of nanomaterials.

This is a major scientific achievement. And yet, knowledge and lack of knowledge often exist side by side. This also applies to the complex problems of nanotechnology. The more we know, the more we can guess what we do not know. If we accept that and, at the same time, untiringly search for more new answers, this is a way of responsibly handling new technologies, such as nanotechnology. The further course is obvious: The Federal Ministry for Education and Research, even before the end of the NanoCare project, decided to launch two other funding programs devoted to the environment (NanoNature) and health (this funding measure is also called NanoCare), which will be started still in 2009. Germany thus plays a pioneering role internationally in research into the risks of nanotechnology. Future research projects should take into account studies of uptake, distribution, and excretion of nanomaterials, and interaction with cellular components in order to gain more knowledge for risk assessment of these materials.

More Information in the Internet

The scientists of NanoCare and its follow-on projects invite you to have a look at the **www.nanopartikel.info** webpage. You will learn about more research findings in nanotechnology explained in plain language.

The NanoCare-consortium

BASF The Chemical Company

Bayer MaterialScience

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