

First Evaluation on the Joint Research Strategy of German Governmental Research Institutions

"Nanotechnology - Risks related to Nanomaterials for Humans and the Environment"

(2007 - 2011)



Figure 1: Lotus effect (Photograph: BAuA/Fox).

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Brief portraits of the involved governmental research institutions¹

BAM

The BAM Federal Institute for Materials Research and Testing is a senior scientific and technical Federal Institute with responsibility to the Federal Ministry of Economics and Technology (BMWi). BAM is the successor of the Public Materials Testing Office (Staatliches Materialprüfungsamt) founded in 1871 and of the Chemical-Technical State Institute (Chemisch-Technische Reichsanstalt) set up in 1920. BAM's mission is 'safety in technology and chemistry'. BAM has its responsibilities in

- Advancement of safety in technology and chemistry
- Physical and chemical inspections of materials and plants including supply of reference methods and reference materials
- Promoting the transfer of knowledge and technology in BAM's key areas
- Collaboration in developing legal regulations like on safety standards and threshold values
- Consulting on safety aspects of materials technology for the Federal Government and industry.

Pursuing its mission as a Federal Institute for materials technology and chemical engineering, BAM ensures ongoing safety in technology and chemistry through

- Research and development
- Testing, analysis, approval and certification
- Consultation, information and advice.

BAM's key areas of activity comprise

- Analytical chemistry
- Safe handling of dangerous materials and dangerous goods
- Safe and environmentally compatible use of materials
- Safe operation of technical systems and processes
- Damage mechanisms and damage analysis.

¹ The portraits of the institutes refer to 2013. They may have changed after forming of a new government in 2014.

BAuA

Safe and healthy working conditions mean social progress and a competitive economy. The Federal Institute for Occupational Safety and Health (BAuA) conducts research and development in the field of safety and health at work, promotes the transfer of knowledge into practice, advises policymakers and performs sovereign functions - under chemical safety regulations, in product safety and with the health data archive of the uranium processing of WISMUT in the former GDR. BAuA is a governmental research institution within the purview of the Federal Ministry of Labour and Social Affairs. More than 600 people are employed at the sites in Dortmund, Berlin and Dresden and at the Chemnitz field office.

The description, evaluation and management of work-related risks from exposure to hazardous substances and biological agents are the main responsibilities of the division "Hazardous Substances and Biological Agents". Further development of the regulatory framework and practical solutions for safe handling and the legal tasks of an assessment unit under the CLP, REACH and Biocides regulation of the EU are the main missions of this division.

The division "Federal Office for Chemicals" encompasses the sovereign functions of BAuA under the German Chemicals Act, and in particular the authorisation procedure for all biocidal products marketed in Germany and the implementation of the REACH Regulation for all industrial chemicals. The division "Transfer Management" makes available an extensive stock of information on safety and health at work. Research results and practical solutions are prepared for various target groups and are available on the internet or as printed material. The Information Centre offers knowledge and information on all fields of occupational safety and health.

With the DASA Working World Exhibition the BAuA operates an internationally renowned exhibition facility. The aim is to use the modern means of exhibition presentation to enhance the visitors' awareness of health and safety and to convey to a broad public the notions of a humane world of work.

BfR

The Federal Institute for Risk Assessment (BfR), located in Berlin, is an institution of the Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) and was founded in succession to the precedent Kaiserliches Gesundheitsamt of 1876.

The tasks of the BfR are specified in its Founding Law, which was enacted as part of the restructuring and reorganisation process of consumer health protection in Germany.

In addition, BfR's work has been integrated by legislation in the execution of more than ten other laws, including the plant protection law, the genetic engineering law, the food and feed

law as well as the chemicals law. Other specific control and supervisory tasks have been designated to the Federal Ministry of Environmental Protection (Chemical Safety in the Food Chain) and the Federal Ministry of Transport (Hazardous goods transport, Waste-Water Convention). The central task of the BfR is the scientific risk assessment of food and feed as well as of substances and products. The assessment reports are used as basis information for consumer health protection decisions made by the Federal government. The institute has no control functions; however it is involved in several registration and licensing processes.

The BfR is commissioned by legislation to conduct research in areas that are correlated to its assigned tasks. To guarantee that risk assessments are carried out uninfluenced and unaffected by any political, financial or social interests, the Institute is defined in its founding law as legally independent in its assessment and research activities. Through research programmes and numerous memberships in national and international panels, the BfR secures and supports scientific state of the art knowledge in order to maintain competence and expertise in risk assessment that is independent of any individual scientific interests. Another major emphasis is the cooperation with the European Food Safety Authority (EFSA), for which the BfR is the German national contact point (EFSA-Focal-Point).

UBA

'For our Environment' is the mission statement of the Federal Environment Agency (UBA). Founded in 1974, the UBA is Germany's central federal authority on environmental matters. Its key statutory mandates are:

- to provide scientific support to the Federal Government (e.g. the Federal Ministries for Environment; Health; Research; Transport, Building and Urban Affairs);
- implementation of environmental laws (e.g. emissions trading, authorisation of chemicals, pharmaceuticals, and plant protection agents),
- protection of human health against environmental pollutants and health-related environmental monitoring
- information of the public about environmental protection.

Identifying tomorrow's problems today. The UBA sees itself as an early warning system which detects potential future adverse impacts on mankind and his environment in a timely fashion, assesses associated risks, and offers proposals for practicable solutions. To that end, experts at the Agency carry out research in in-house laboratories in addition to commissioning research projects to scientific institutions in Germany and abroad. UBA acts as partner and Germany's contact point for many international organizations, including the WHO, UNEP and OECD.

The UBA is divided into five divisions and the central division (administration). It has a total staff of around 1500, who work at 13 sites, of which seven are measuring stations of the UBA's own air monitoring network. Some 900 of UBA's total staff work in Dessau-Roßlau.

PTB

The Physikalisch-Technische Bundesanstalt (PTB) is the national metrology institute of Germany providing scientific and technical services. It is the highest technical authority under the auspices of the Federal Ministry of Economics and Technology (BMWi) and is the successor of the Physikalische Technische Reichsanstalt founded in 1887, the first metrology institute worldwide. The PTB's place of residence is in Braunschweig and Berlin. The institute consists of ten divisions and has a total of about 1900 employees (1300 permanent/ 600 temporary).

The core competence of the PTB is metrology, the science of measurement and its application. Basic research and progress in the field of metrology as a basis for other official tasks are among the statutory functions of the institute. A special focus is laid on future requirements of metrological services in order to be able to provide fundamentals needed to create the necessary infrastructure in time.

Research and Development currently takes up two thirds of all activity in the PTB and consists of the focal areas.

1. Fundamentals of Metrology: To this belong the realisation, maintenance and dissemination of the SI units (SI = Système International d'unités, global system of units for physical quantities such as second, metre, kilogram etc.). In this core theme the percentage of research is especially high and covers essential areas of modern natural and engineering sciences.
2. Metrology for economy: For an export oriented national economy, a highly developed infrastructure and availability of metrological knowledge of the highest standard are indispensable requirements. Through the technical development of standards, reference measurement methods and approved measurement processes, the PTB creates fundamentals for accurate and reliable measurements and tests in industry and trade and provides the necessary transfer of knowledge.
3. Metrology for society: In a wider range of public life a particular interest in correct and reliable measurements exists, covered by legal metrology. In collaboration with the federal verification authorities, the PTB arranges for accurate and reliable measurements in official and commercial use, which ultimately also serve consumer protection. A focal point in this area is the type approval or type examination of measurement devices in the

context of national or European legislations.

4. International affairs: The task of the PTB is to contribute to an internationally harmonised system of metrology and with that decrease non-tariff trade barriers. Collaboration with other national metrology institutes, essential cooperation in international bodies and technical-economical collaboration with developing and emerging nations contribute to this purpose. Through its involvement in standardisation, quality and testing committees including accreditation and certification, the PTB serves the export oriented German industry.

Preamble

This document presents a first review of over 80 projects on safety research in the field of nanotechnology that the participating governmental research institutions carried out themselves or awarded to external institutions on the basis of the joint research strategy of the Federal Institute for Occupational Safety and Health (BAuA), the Federal Institute for Risk Assessment (BfR) and the Federal Environment Agency (UBA) from 2007. In addition, core themes and issues are derived for the future direction of the federal government's safety research. The Physikalisch-Technische Bundesanstalt (PTB) and the Federal Institute for Materials Research and Testing (BAM) have since joined. Other governmental research institutions are to be included in a further step.²

In the last five years, governmental research on the safety of nanomaterials concentrated in relation to individual cases on material characterisation, effects analysis, exposure of man and the environment and questions on risk assessment, risk management and risk communication. It has been possible to close numerous gaps in knowledge; a series of findings has already flowed into national and international papers and debates on the opportunities and risks of nanotechnology.

Determining and assessing risks for humans and the environment based on the special characteristics of nanomaterials is usually more complex than for other chemical substances. Not only must scientific research be intensified, but the social dialogue has to be retained, in order to be able to use the opportunities offered by nanotechnology responsibly, and to keep pace with the increasing speed of the introduction of nanotechnological products and processes. The mandate of the precautionary protection of man and the environment can only be fulfilled through intensified efforts by government and industry on the safety of nanotechnology.

- A particular challenge facing governmental research is to identify and evaluate risks for humans and the environment during technological progress, in order in this way to prepare the foundations for decisions by the federal government. To this end it is necessary, building on existing individual findings, to find approaches for grouping the variety of nanomaterials, in order to derive generalisable statements on possible risks for employees, consumers and the environment, and to base risk management on this concept in a timely manner. This can only be done by means of continuous research, which must begin at an early stage of the innovation.

² See the brief portraits for the self-concept of the governmental research institutions named here.

- The coherent integration of the safety aspects of nanomaterials into existing legal provisions on chemical and product safety, occupational safety and health, environmental and consumer protection, will continue to remain an important task in the coming years.
- In addition, the governmental research institutions see further priorities in research on promoting both safe and sustainable use of the potentials of nanotechnology for solving global challenges. For the purposes of achieving the strategic targets shown in the federal government's nanotechnology action plan 2015, the governmental research institutions want to make their contribution in the future as well.

For capacity reasons it was not possible to include the findings of safety research by individual federal states, statutory accident insurances and other research institutions in Germany, and specific issues on the safety of medicines and medical devices. This review therefore does not claim to be a comprehensive representation of the state of nanosafety research in Germany.

The original document has an annex with information on all projects performed under the common research strategy. The annex is not part of this English translation. Detailed information on the individual projects can be retrieved through the OECD database³ on nanosafety research, the German federal government's research catalogue⁴ and the websites of the involved institutions.

In the following text, the definition of nanomaterial is based on the EU definition⁵ but without taking account of the incidentally produced materials shown in the definition.

³ <http://webnet.oecd.org/NanoMaterials/>

⁴ <http://foerderportal.bund.de/foekat/isp/SucheAction.do?actionMode=searchmask> (in German).

⁵ Recommendation of the European Commission 2011/696/EU:

'Nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm.

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1 Introduction

In the research agendas of leading industrial nations, nanotechnology has been given a key role as one of the most promising technology areas with potentials for innovation in nearly all industrial fields of application. At the same time, too little is still known about the effects of this rapidly growing future technology on man and the environment. For this reason, at the end of 2007 the Federal Institute for Occupational Safety and Health (BAuA), the Federal Institute for Risk Assessment (BfR) and the Federal Environment Agency (UBA) initiated a joint research strategy entitled "Nanotechnology: health and environmental risks of nanoparticles".⁶ This accompanies the development of nanotechnology and, for the purposes of estimating the consequences of technology, has as its aim the identification and evaluation of possible health and environmental risks of nanomaterials in an early innovation stage through joint action, and the development of strategies for risk management. In addition, it should contribute to identifying and closing the most important gaps in knowledge regarding industrial safety and consumer and environmental protection.

On the basis of the joint research strategy the participating governmental research institutions launched over 80 research projects, which were either carried out in-house by the institutions' own scientists or awarded to external qualified research institutions. This report intends a first review of the findings of the projects and to place them in the context of the current discussion on the safety of nanomaterials for man and the environment. The key questions here are: what is the status of safety research today, and what further requirement for research and development is looming in the short and the medium term? This review focuses on the necessity to advance the development of standards and recommendations for action and to support government actions. Through the integration of the governmental research institutions into the international activities of the OECD and into national and international joint projects it is possible to employ the limited resources for research on safety aspects of nanotechnology optimally.

The variety of nanomaterials is a great challenge for the evaluation of possible risks for humans and the environment, because nanomaterials with identical chemical compositions can differ not only in size and form, but also in the way the individual nanoparticles are connected to one another. In addition, there are deliberate surface treatments of the particles with other substances that also complicate any risk characterisation. For this reason, an analysis of the complex interconnections between the structure of a nanomaterial and possible effects was the focus of the research activities initiated in recent years and was accompanied by the de-

velopment of new test strategies. Successes were achieved in the characterisation of nanomaterials, the determination of particle loads and the clarification of mechanisms of action. The further development of test procedures opened up the possibility of material-related risk assessments, from which it was possible to derive initial approaches for the classification of nanomaterials depending on hazard characteristics. However, further efforts will be necessary to extend this classification to the expected variety of future nanomaterials, and then to evaluate these on the basis of suitable materials characteristics and recognised structure-activity relationships with regard to their risks for humans and the environment. The aim is to avoid part of the complex, material-specific individual studies and in spite of this to generate reliable statements for the safety of employees, consumers and the environment. To achieve international acceptance of such evaluation approaches they have to be subjected as well to a rigorous review (validation).

It can be clearly seen that the rapidly advancing development of innovative materials requires continuous risk and accompanying research. The still too large gap between technology development and safety research has to be closed in order to be able to use new materials for sustainable products for the good of consumers. The already existing possibilities of early safe design of products and production methods (safety by design) still remain infrequently used. In order for them to be used more often in research and development, safety-specific requirements for products and processes will have to be imparted more intensively to research institutions and companies involved in micro- and nanotechnology and developed further jointly with them. However, government monitoring and enforcement authorities also have to be put swiftly in a position in which they can keep pace with the rapid progress in material and products development.

Through their activities, governmental research institutions contribute scientifically grounded and practice-oriented bridge-building between material innovation and safety for man and the environment. These include, for example:

1. developing suitable measuring techniques and methods for risk determination and enforcement of statutory requirements,
2. developing reference materials for measuring loads and for examining the harmful effects on man and the environment,
3. validating and harmonising test and evaluation strategies in a European and international context in order to make experimental results comparable,
4. developing low-cost screening tests for adverse effects for man and the environment in

⁶ <http://www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/Nanotechnology/Nanotechnology.html>

an early stage of material innovation,

5. approaches for a categorization of nanomaterials that clearly reduce the number of costly individual tests, in particular in animal experiments,
6. reliable information on currently manufactured and used nanomaterials as the basis for appropriate government action,
7. approaches for an unambiguous regulatory designation of individual nanomaterials, e.g. for appropriate hazard labelling in accordance with the EU CLP Regulation,
8. scientific findings on the risks for humans and the environment in the life cycle of consumer-oriented products from nanotechnology,
9. safe working methods for material innovations for which reliable statements on the risks for humans and the environment are not yet available.

In the sense of sustainable development, nanotechnology can only be successful if the opportunities related to nanomaterials are shown, but at the same time possible risks are identified and strategies for minimising them are developed. For this purpose a balance between innovation and safety research should be aimed for. EU chemicals and products law regards at first producers and importers as responsible for the safety of their products. Only with larger production volumes is a distribution of the burden between industry and government provided for, e.g. in the chemicals regulation REACH. As defined in the precautionary principle, the government has to ensure that the development of new technologies or materials is not associated with risks that lead to stress for the environment or health and thus stipulate corresponding specifications for monitoring and checks. In addition, the government can contribute through continuous safety research to avoiding bad investments in unsafe developments, strengthening confidence in nanotechnology and continuing to promote Germany as an innovational location as defined in the federal government's high-tech strategy. Precondition for the sustainable design of nanotechnology is therefore suitable facilities for the governmental research institutions, which can be regarded as an important investment in the future.

1.1 Challenges for safety research

One of the central tasks of the federal government's governmental research is identifying and evaluating risks for humans and the environment at an early stage. These activities, described by the German Council of Science and Humanities (Wissenschaftsrat) as preliminary research, are intended to enable governmental research institutions to make substantiated scientific advice available for politics and practice in good time. The procedure for the early detection of risks is based on the columns "Exposure" and "Effect" with which a risk of nano-

materials for man and the environment can be characterised from a scientific aspect (fig. 2).

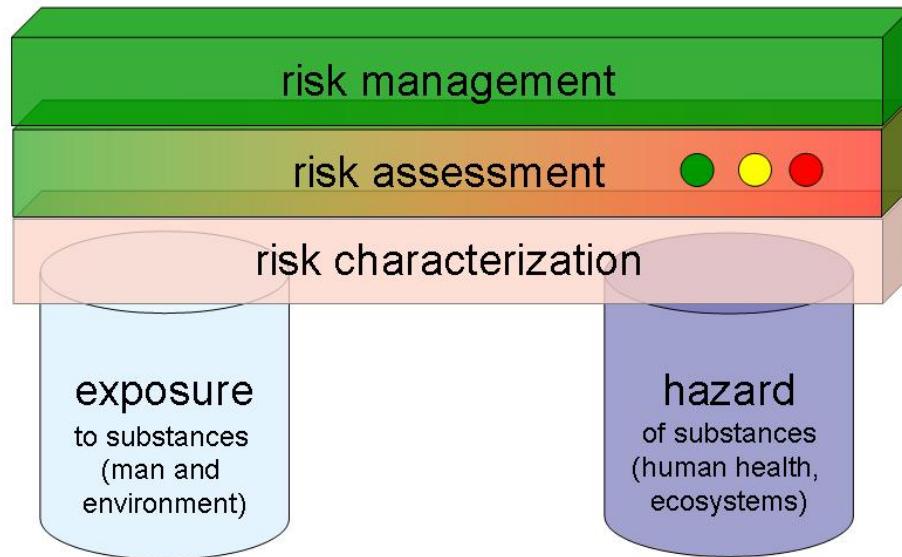


Fig. 2: Exposure and effect as columns for risk-oriented governance (figure: BAuA).

In 2007 the joint research strategy defined the requirements for a risk-oriented evaluation of nanomaterials taking account of the foundations under chemicals law. In this process, because of the nanoscale, there are a series of material properties that are significant for the evaluation of the hazard potential. Interaction with biological systems and bioavailability are influenced decisively not only by the chemical composition, but also by particle size and shape, surface (charge, reactivity and modifications), as well as by agglomeration behaviour. The synthesis technology that is selected also has an effect on the possible hazard potential of nanomaterials.

One of the greatest challenges facing the acquisition of scientifically credible toxicological and ecotoxicological data is a reliable physical and chemical characterisation of nanomaterials. The difficulties start as early as a comparison of different material batches as dry substance, and increase with the analysis of their behaviour in various milieus (atmosphere, culture medium, body fluids, bodies of water). Therefore, to clarify effects, the mechanisms on which they are based and to estimate a hazard potential for man and the environment, the properties of the respective nanomaterials must be determined under application conditions, and test systems and study design adapted taking into consideration the different absorption routes (e.g. inhaling, skin contact, swallowing). Along with the special requirements for the

experimental framework conditions, from the aspect of regulations adaption and standardisation of test systems and test methods are absolutely essential for generating toxicological and ecotoxicological findings. This includes the development and use of suitable reference materials characterised by minor variability and a narrow size distribution.

In order to be able to estimate possible effects, it has to be clarified how far the various nanomaterials can be absorbed by the organism, and how they are distributed and degraded in the organism and excreted. In addition, the processes they can trigger there have to be clarified, as well as the form in which the absorbed nanomaterials and their agglomerates remain in the body, and for how long. Decisive questions are raised regarding the release and retention of nanomaterials in the environment. What is necessary are informative qualitative and quantitative distribution studies under various application conditions that are supported by suitable procedures for characterisation "on site". Knowledge acquired in this way must be included in order to clarify whether established test methods, data requirements prescribed by law in the respective regulating areas, and the assumptions and extrapolation factors currently recognised in risk assessment, lead to reliable evaluations for nanomaterials as well.

To handle the variety of nanomaterials appropriately it is also absolutely essential to identify joint criteria for toxicological and ecotoxicological assessment. One challenge for risk assessment consists in developing comprehensive concepts and transferable criteria that allow categorization of different forms of nanomaterials. In addition, it is necessary to develop further screening processes and strategies for the toxicological and ecotoxicological initial assessment that reduce the complexity of testing at an early stage of the development of a material and offer a reliable starting point for a tiered testing strategy in the further life of the substance.

For risk assessment, along with the estimate of the hazard potential, determination of the exposure situation for man and the environment, in other words, their exposure to nanomaterials, is necessary. For this purpose, suitable measuring methods, e.g. with portable sampling appliances in the breathing zones of employees, but also standardised nanomaterials for calibration purposes are required. In addition, the release of nanomaterials from products throughout the whole lifetime plays a part in possible exposure for man and the environment. Processing, aging, weathering and abrasion processes have to be characterised and assessed with regard to exposure and effect. The wide range of activities on safety research is accompanied by a variety of committee and dialogue activities on a national and international level. One particular challenge consists in defining the specific requirements for the risk assessment of nanomaterials, and optimising and harmonising them gradually in order to integrate them in existing statutory and subordinate regulations.

Dialogue processes can actively shape the social discourse on the acceptance, opportunities and risks of nanotechnology. This possibility was used intensively by governmental research institutions in the past few years and accompanied by social science projects on risk perception and risk communication. This discussion process, and research into innovative nanomaterials that save energy and resources and are safe, are equally important for the long-term development of nanotechnology in Germany.

2 Review of research projects conducted from 2007 to 2011

Up to the end of 2011, the participating governmental research institutions started a total of 85 research projects on the basis of the joint research strategy, 36 projects of which were successfully completed by that date. Along with projects carried out independently by the participating institutions, these included contract awards and allowances to external researchers and the increasing participation in government-funded joint projects in Germany and the EU. The most important information on the projects is available in the OECD Database on Research on Safety of Manufactured Nanomaterials and from the websites of the involved governmental research institutions. The following chapters concentrate on the conclusions drawn from the research activities.

2.1 Material characterisation

Particle size, form and specific surface of a nanomaterial were identified as important criteria for the characterisation of chemical substances and mixtures with nanoscale properties. These are able to influence the chemical bonding characteristics in the interior of a particle and on its surface. In addition, interaction processes with surrounding media can vary greatly, depending on the particle size. The significance of materials science methods and analytical expertise is correspondingly great for an understanding of such processes and interrelations. In the past five years therefore, the participating governmental research institutions have committed themselves to a series of research projects that are occupied with selected problems of the characterisation of nanomaterials.

2.1.1 Measuring technology foundations (metrology)

The comparability of methods of measurement is of fundamental importance. It can be achieved if a measurand can be calibrated directly or indirectly – i.e. via calibrated intermediate steps – with a measurement standard that realises the measurand. In the field of the physical-morphological characterisation of nanomaterials, for example, when measuring particle sizes, there are still many gaps to be filled in this process, which is referred to as metrological traceability. For example, in some cases considerable systematic deviations were found on the application of different methods of measuring size to reference materials with a uniform nanoscale with regard to their particle size. An analysis of the definition of the measurand and the measurement uncertainty specific to the method made it possible to improve understanding of the causes of such deviations in the framework of the research strategy.

Precondition for such comparison measurements on particle size distribution is the availability of reference materials with reliably known, i.e. previously calibrated, particle size distribu-

tion. Up to now, such reference particles have only been commercially available for very few material and size classes. Developing and certifying further materials is expensive and time-consuming. The governmental research institutions are taking part in the development and characterisation of such reference materials. Numerous relevant materials have been synthesised and characterised with regard to their size uniformity and stability over time in inter-laboratory tests with the inclusion of international partners.

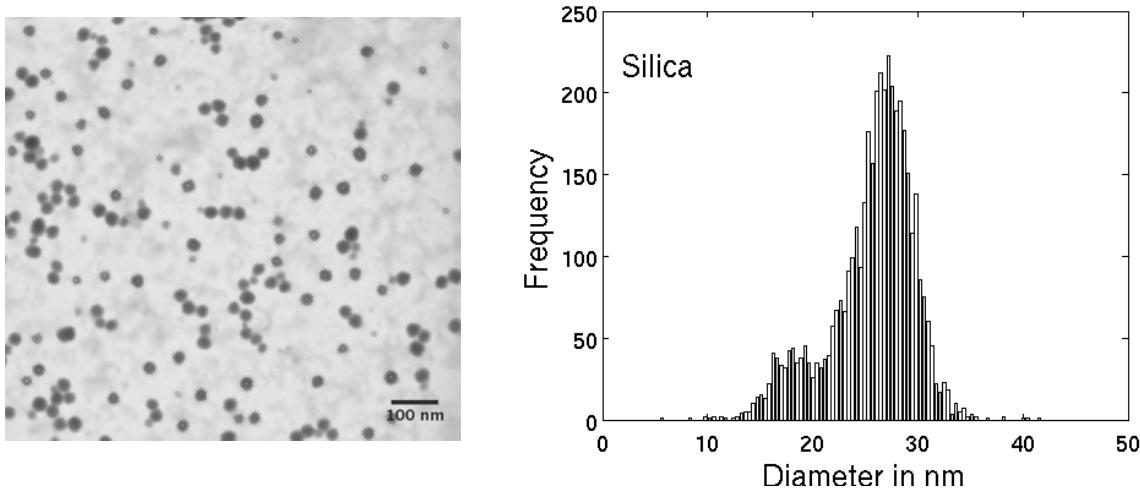


Figure 3: SEM image in transmission from a test specimen of nanoscale silicon oxide particles (left) and the results of a histogram analysis of the diameter distribution of 4400 particles (right), average diameter: $25.2 \text{ nm} \pm 1.1 \text{ nm}$ (photograph: PTB).

Industrially manufactured materials usually display wide particle size distributions. Studies with multimodal, broad particle size distributions have demonstrated the limits of the applicability of established methods such as dynamic light scattering (DLS) and triggered the development of new multistage analysis methods in which the particles are first of all fractionated into different size classes in an upstream process before sizes are measured.

Increased attention was continued to be paid to the technical aspects of sample preparation before analysing or testing nanomaterials. The causes of preparative artefacts, e.g. through disregarded coating through media components, use of surfactants, unintentional agglomerate breakup or size fractionating, have to be understood better. This still remains a great challenge because of the complex processes in biologically relevant test media. BAM and PTB have sufficient characterisation facilities that enabled a systematic study, e.g. of solubility and agglomeration processes, as well as the development of reproducible preparative methods. Among other things, questions on the stability over time of the isolation of suspended nanomaterials in liquid media were examined. Methods for the transfer of nanoparticle suspensions into dry preparations for the characterisation of selected gold, silicon dioxide and polystyrene particle types were successfully applied.

Various high-resolution microscopic measuring methods were developed further for the iden-

tification and chemical characterisation of nanomaterials that enabled different nanomaterials to be detected specifically and with high sensitivity.

2.1.2 Research on structure-activity principles

Research carried out in recent years has shown that central aspects of the action of a nano-scale material that are not grounded in its particle design are caused essentially by its surface chemical structure. Chemical surface groups are responsible for surface reactivity, material solubility, radical activity and adsorption processes. BAM and PTB initiated the development of new identification and quantifying processes for functional groups on nanoscale materials. The examination of aging processes also required an adaptation of the methodology.

In addition, the coating condition of nanoscale particles, and questions on the adhesive strength of the coating on the particles, play an important part in the clarification of the identity of the material and in toxicological or ecotoxicological assessment, among other things on the derivation of structure-activity relationships. It was possible to show the fundamental usability of coupled methods through the further development of small-angle X-ray scattering (SAXS), which is able to detect core-shell structures, and its direct linking to particle size fractionating processes.

2.2 Exposure of Humans and the Environment

The question whether exposure of man and the environment occurs in the life cycle of nanomaterials, and to what extent, was of high priority for the research strategy in all three safety areas (employees, consumers and environment). Existing measuring methods and estimate models had to be tested, adapted where necessary, or even newly developed, to determine the type, level and duration of exposure, and of the mobility of nanomaterials in the environment. In this way, foundations were created for model exposure surveys in laboratory experiments and field investigations and important empirical values were acquired for individual nanomaterials.

2.2.1 Workplace

The question of possible exposure at the workplace is raised for all synthetically manufactured and used nanomaterials. In this case, hazards resulting from inhaling released nanomaterials are in the foreground (inhalative exposure). Based on the current state of knowledge, the absorption route silicon through skin contact (dermal exposure) is of subordinate importance. The existing technology for recording and measuring fine and ultrafine particles through classifying and counting proved to be fundamentally suitable. Clear improvements were achieved in the personal recording of exposure in the direct breathing zone of employ-

ees through the development of appropriate measuring appliances. This is of decisive importance for the assessment of exposure, because particle-shaped background exposure, e.g. diesel engine emissions, welding and cigarette smoke, affect the exposure situation significantly on work with nanomaterials.



Figure 4: Handling nanomaterials in a glovebox as an example of an enclosed system at the workplace (photograph: BAuA/Völkner).

A morphological characterisation of the collected nanomaterials in the form of individual particles and of agglomerates and aggregates with the help of imaging processes, such as scanning electron microscopy, is essential for the differentiated assessment of the exposure situation at the workplace. It was not possible to ascertain a clear increase in the particle numbers concentration with the present metrological facilities on appropriate work with nanomaterials in enclosed systems and in the laboratory fume hood. In spite of this, nanostructured materials in the form of particle agglomerates can be released, as filter and resting dust samples showed. The knowledge that was acquired has flowed into a recommendation for a tiered process on the exposure assessment of work with nanomaterials under the aegis of the German Chemical Industry Association.⁷ The dusting behaviour of nanomaterials can be characterised independently of sampling at workplaces with a newly developed test stand (BAuA shaker).

⁷ <https://www.vci.de/Downloads/Tiered-Approach.pdf>

2.2.2 Consumer

With consumer health protection, the focus is on the safety of food and feedstuffs, as well as of consumer-oriented products with nanomaterials, in particular textiles, washing powders and detergents. Absorption through inhaling, skin contact and through the gastro-intestinal system is significant for estimating exposure. The focus of the research activities was on the development and adaptation of suitable sensitive methods for detecting nanoscale components. Because of the complex matrices of food, food contact materials and consumer-oriented products, wide-ranging development work with regard to the test methods was necessary first of all (cf. 2.3.1), so that reliable data for the estimation of the actual release of nanomaterials could be acquired. Specific and systematic detection requires a tiered approach, and thus the employment of coupled detection methods. Possible transfer from food contact materials is determined using the example of nanosilver and nanoclays.

2.2.3 Environment

In leaching experiments on a laboratory scale using selected titanium dioxide nanomaterials as examples it was possible to demonstrate that these nanomaterials display only slight mobility in different soil columns. In a further laboratory experiment on the simulation of a sewage treatment plant it was demonstrated that the titanium dioxide nanomaterial that was examined is retained in the model sewage sludge to a great extent (96-97 %). With these examinations not only were test results obtained for individual nanomaterials, but the fundamental suitability of the applied OECD test guidelines 312 and 303A for testing nanomaterials was documented. Another OECD test guideline for measuring the adsorbed and non-adsorbed shares of the test substance in soils (No 106) proved to be unsuitable for testing nanomaterials. Because the behaviour of nanomaterials in the environment is influenced by a variety of parameters, at the present moment statements that are capable of generalisation are not possible. Also the adaption and development of measuring methods for routine, sensitive detection of nanomaterials in different environmental compartments and in organisms are still in the very early stages. For example, although there are measuring methods for the compartment "air" for counting and size categorization of nanoscale particles, these cannot usually differentiate between synthetically manufactured nanomaterials and particles from other sources. The further morphological and chemical characterisation of individual particles that is necessary for this is in fact possible, but is still too expensive and elaborate for routine use. Unsatisfactory information on products with nanomaterials that are used makes it difficult to make quantitative statements on a possible input of nanomaterials into the environment, as a project on estimating the input into the environment of silver nanoparticles from biocidal products shows.

2.2.4 Life cycle considerations

For the safe design of nanotechnology and its products it is of decisive importance to be able to make reliable statements on exposure sources and routes over the complete life cycle. Knowledge of a possible release of nanomaterials from products and waste is particularly important for the safety of the environment, employees and consumers, because provisions of chemical law governing information (labelling, safety data sheet) take effect here to a limited extent only, if at all. Risk assessments can only be carried out and exposure scenarios described with reliable, where possible quantitative exposure data – preferably in the run-up to a broad market launch. Emissions of nanoscale particles from textiles with silver nanoparticles were examined, and from façade paints with nanoscale titanium dioxide, from vehicle tyres with carbon black and from diesel fuels with nanoscale cerium oxide. The highest probability of release exists for cerium oxide of this kind. However, quantifying exposure was not possible because of a lack of measuring methods in the environmental area. At present, examinations are taking place on the release of carbon nanotubes and fibres during the processing and disposal of nanofibre-reinforced materials.

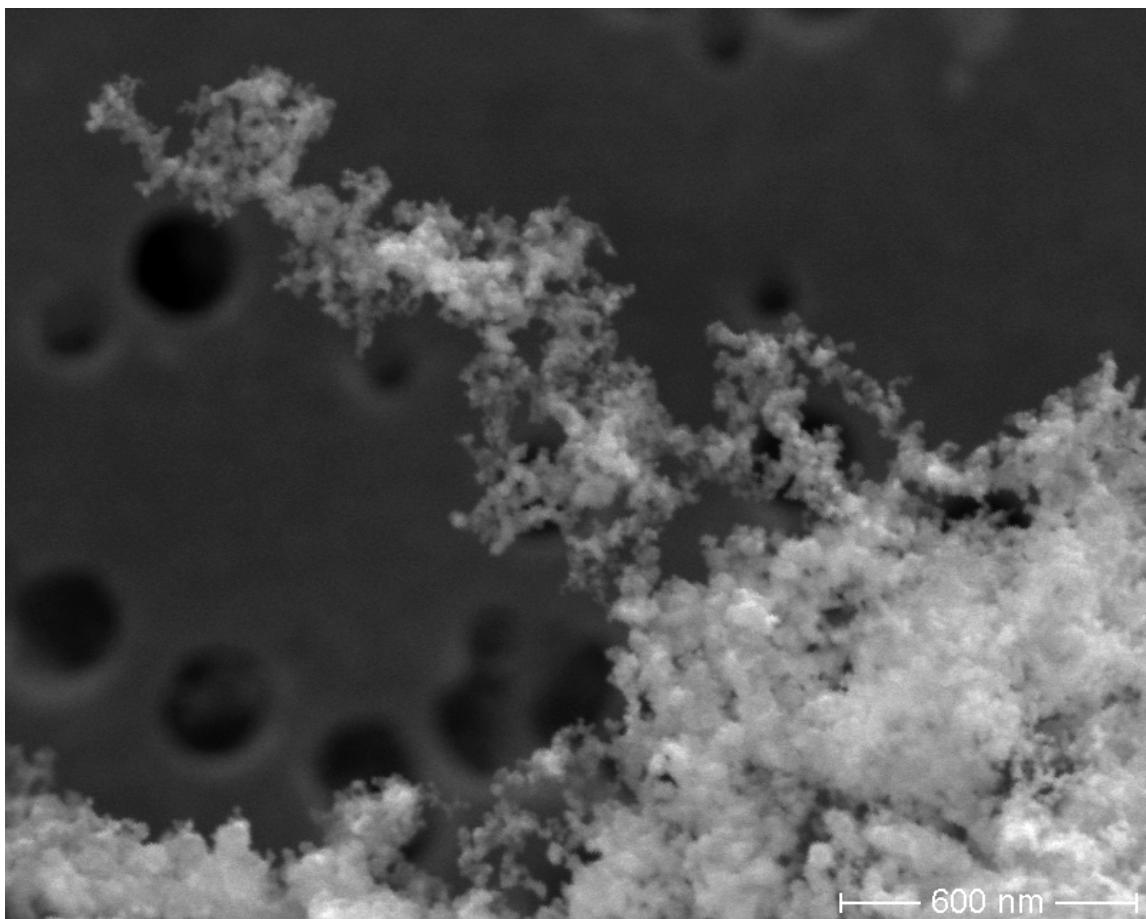


Figure 5: Nanoscaled titanium dioxide at the workplace (photograph: BAuA).

2.3 Health hazard potential

Changed toxicological properties, and thus particular health hazards, may be connected with the particular physical-chemical properties of nanomaterials. For example, the small size of nanoscale primary particles may be the cause of them being absorbed better in the organism and distributed in the body more easily than non-nanoscale forms, or differently to them. It is also assumed that nanomaterials could be particularly toxic because of their special reactivity. Specific modifications of the surface change the properties of materials and can also have an unfavourable effect on bioavailability and toxicity.

2.3.1 Test methods

Along with the various absorption routes, the choice of test methods depends above all on the type of the materials that are used. The test methods must therefore include a reliable characterisation of the nanomaterials. Quantifying is a great challenge in biological materials in particular. At present, a document that is important and wide-ranging for the regulatory context is being drawn up in the framework of the OECD WPMN process with guidelines for preparing specimens and dosimetry of nanoform test materials.

Because of the expected variety of material innovations it is necessary to have fast and low-cost methods available for the assessment of health risks through nanomaterials that at least detect significant hazard potentials in an early development stage. Not least for reasons of animal welfare, suitable in vitro methods are very attractive for estimating possible toxic effects. Cellular in vitro systems can, among other things, provide information on the mechanism of the absorption and distribution of nanomaterials in cells, as well as on genotoxicity and phototoxicity. Cell-free in vitro studies provide information on interaction with biomolecules, such as proteins, lipids and nucleic acids.

Because in vitro methods were usually developed for solutes, they have to be adapted first of all for nanomaterials, which are usually difficult to disperse finely, in order to predict the effects with sufficient sensitivity and specificity. The dosage should be determined in each test system on a cell basis.

In recent years, great progress has been made in the development of reference materials and in improving imaging verification procedures (e.g. Laser-SNMS and ToF-SIMS). Nanomaterials can be visualised in the cell and cellular changes can be verified. On the whole, various application possibilities for in vitro methods are in the offing, but further development work on harmonisation and standardisation has still to be carried out. However, it has also become clear that in vivo examinations are usually still indispensable for a scientifically reliable investigation of the hazardous properties of nanomaterials, e.g. for the purposes of categorization pursuant to the CLP Directive, or to derive limit values.

For this reason, in a series of joint projects comparative in vivo and in vitro examinations are being carried out under standardised conditions in order to obtain a comprehensive picture of possible effects on health.

2.3.2 Toxicological findings

The health hazard potential of selected commercial nanomaterials is being examined in the OECD WPMN Sponsorship Programme by means of a broad range of toxicological endpoints. The German governmental research institutions are the lead managers for the preparation of individual scientific dossiers (e.g. for titanium dioxide) and are involved in collecting and assessing toxicological data for all relevant materials. It is known from earlier in vivo studies that some first generation nanomaterials that have already been marketed for some time cause inflammation and tumours in the lungs after being inhaled. These effects are particularly marked with rigid biopersistent fibres. Similar effects can be observed with granular nanoscale materials. With selected materials, e.g. heavily agglomerated titanium dioxide, examinations showed only a slightly higher potency of the nanoscale in comparison with the analogous microscale form. Damage to the DNA in the area of the lungs was observed in the tumorigenic dosage range.

The agglomerate size and possible release of nanoparticles from agglomerates can influence the distribution of nanoparticles and the efficacy profile in the organism. A toxicokinetic study with TiO₂ nanomaterials showed that after being inhaled smaller agglomerates not only remain in the lungs as the primary target organ, but can also reach other internal organs to a slight extent. However, the pro rate distribution over the internal organs and the speed of excretion has to be examined further. In various in vivo and in vitro test systems selected nanomaterials did not display any relevant disintegration into individual free nanoparticles.

Toxicokinetic studies after inhalation of carbon nanotubes (CNTs) and after oral absorption of silver-nanomaterials were also started. In addition, in the latter study the extent of the toxic effect in dependence on the surface properties is being tested.

The PaFtox database was developed in a pilot project and offers the possibility of evaluating the existing literature on particle toxicology systematically and in a structured way. At present, 131 inhalation studies and instillation studies of rodents (study duration > 28 days) have been recorded in PaFtox.

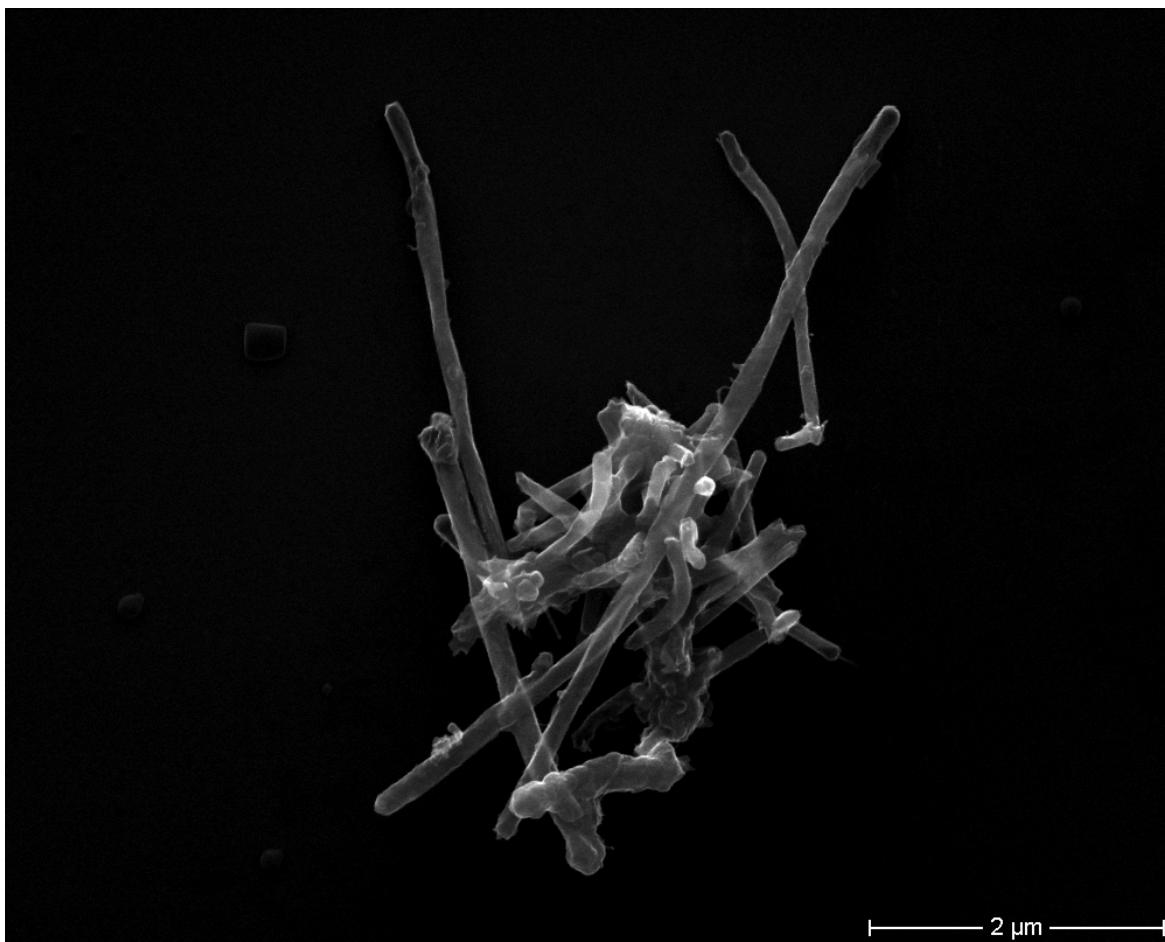


Figure 6: Rigid carbon nanotubes (photograph: BAuA/Fox).

2.4 Potential environmental hazards

Due to the new functionalities of nanomaterials, caused by their small size, in case of exposure to the environment there is a risk of an undesirable effect on the various ecosystems. In recent years, the number of scientific studies on recording the effects of nanomaterials on the environment has radically increased, whereby most studies are concerned with ecotoxic effects on organisms in water ecosystems. Studies on the ecotoxicology of nanomaterials in soil ecosystems are still very rare.

2.4.1 Test methods

In the framework of a whole series of national and international activities, among others, the OECD Working Party on Manufactured Nanomaterial (WPMN), it is being examined at present how far previous standard test methods will have to be adapted for the ecotoxicological examination of particulate nanomaterials with different sizes, shapes and chemical compositions. This comprises above all suspension preparation and characterisation, the type of application of the test substance into the test systems, the selection and frequency of the accompanying analytics, the selection and incubation conditions of the test organisms and the

stipulation of the examination parameters (alternative endpoints). The additional requirements for the test methods also have to be realisable for routine examinations, reference materials must be available. Preliminary findings from current projects show that the standardised test guidelines are applicable in principle to examinations of nanomaterials, but, in a given case, adaptions are necessary in order to guarantee comparability of the findings.

2.4.2 Ecotoxicological findings

Comprehensive dossiers with data on the ecotoxic effect of various nanomaterials in different environmental compartments can be expected from the OECD WPMN research. These data are collected largely with standard test methods (adapted where applicable) and with rigorously characterised test materials.

Comprehensive data records are found above all on the ecotoxicity of nanomaterials for aquatic microorganisms and aquatic invertebrates. Only a few years ago data were mostly only available on the acute effect, but since then also studies on the ecotoxic long-term effect of nanomaterials have been carried out. Carrying out long-term studies is methodologically difficult, because the exposure conditions must be kept constant and recorded over a long period of time. Difficulties are also encountered with the examination of the ecotoxic effects of nanomaterials on soil and sediment organisms. A suitable form of application has to be selected here; in addition, in contrast to aquatic tests it is practically impossible to determine the exact condition of the nanomaterial in the test system.

At present, only a case-by-case assessment of ecotoxicological findings is possible. Knowledge of the common critical properties would be necessary for the categorization of various nanomaterials with regard to their ecotoxic effect. Surface functionalisations of nanomaterials can strengthen or impede agglomeration, and in doing this change bioavailability and ecotoxicity. Projects running at present include ecotoxicological examinations of various nanomaterials relevant to the market (above all nanotitanium dioxide, nanosilver, nanogold). The compartments under observation are water, soil and sediment. Along with short-term tests, long term examinations are being carried out as well. In addition, current research is concentrating on examinations of nanomaterials that are matrix-bound and found in stabilisers, and on observing complex scenarios, such as occurrence in combination with environmental pollutants.

2.5 Risk assessment, management and communication

Given suitable criteria on risk assessment, comprehensive science-based risk characterisation enables recommendations for action to be derived with which risks can be eliminated or limited. In addition, risk communication is an important component of the work of the participating governmental research institutions. The process of the assessment and its findings are edited and displayed transparently and specifically for the target groups.

2.5.1 Risk assessment

European chemical law (REACH) obliges all producers and importers to register all chemical substances that they bring on the market with a production volume of over 1 tonne/year. Information on the hazard potential and on the risks for employees, consumers and the environment that are linked to use in the life cycle should be established and assessed. The findings are the foundation for the obligatory communication of framework conditions for safe use (exposure scenarios) along the value-added chain. The specifications of the EU's Chemicals Directive REACH are supplemented by regulations specific to product groups and protective goals, which in their totality also regulate the necessity of transmitting risk relevant data to governments and the generation of additional information (test obligations). Research by governmental research institutions in the field of risk assessment, which is financed with public funds, also has to be classified in this context. Here it is above all a matter of creating reliable objective foundations for risk-related regulations in chemicals and product law, as well as for recommendations on protection of the environment, occupational health and safety and consumer protection.

Release behaviour, exposure, absorption, internal dosage and mobility, as well as (eco-) toxicological findings from in vitro and in vivo examinations, are of fundamental importance for a risk assessment of chemical substances. For the risk assessment of nanomaterials this means that the (eco-) toxicological mechanisms of action must be described and there must be information on dose-activity relationships. In addition, it has to be clarified whether, and under what preconditions, data collected from a limited number of animals (or in specific cell cultures) can be transferred to the population with the help of assumptions and extrapolation factors established for chemicals. Furthermore, relevant chemical-physical characteristics (e.g. dimension, coating, bioavailability) and data from exposure investigations or scenarios flow into the assessment. The description of existing gaps in the data and uncertainties is also part of the risk assessment. This means that new findings from the areas of characterisation of the materials,

Exposure assessment, further development of test methods and the (eco-) toxic effect flow continuously into the assessment of the risks, or enable an improved assessment that is

more efficient through the categorization approaches.

From the aspect of occupational health and safety dermal and inhalative exposure above all are significant for a characterisation of the risks. Hazard assessments are carried out here using the Hazardous Substances Regulations. For the protection of consumer health, dermal, oral and inhalative exposure through cosmetics, foodstuffs, food contact materials and articles and commodities is decisive in the framework of the respective statutory regulations. With regard to environment-related health protection the quality of indoor air, and thus inhalative exposure, must be considered in particular. Depending on the type of use of nanomaterials, exposure of the environment media water, soil, sediment and air is possible, and the waste disposal path must be tested. In spite of the different rules and exposure routes synergies arise in risk assessments in the sectors of occupational safety, environmental and consumer protection. In the meantime, along with work on assessment-relevant issues within the OECD, further national and European joint projects focussing on risk assessment of selected nanomaterials were initiated.

2.5.2 Risk management

For governmental research there are two levels that have to be taken into account with regard to questions of risk management. One level is government action (governance), which comprises in the narrow sense the further development of chemical law regulations, but also of other legal regulations that are relevant in a European and national framework for occupational health and safety, environmental and consumer protection. In addition, however, the integration of questions on the safety of nanomaterials in wide-ranging government programmes and campaigns (high-tech strategy, sustainable development, etc.) plays an important part.

The second level is the improvement of risk management through concrete recommendations on the safe design of products with nanoscale components and on their safe handling throughout the complete life cycle, from production to disposal. This is always a matter for producers or importers, but management authorities must monitor the appropriate measures on the basis of the EU's precautionary principle. In technology-oriented research institutions and start-up companies in particular there is often a lack of the necessary expertise for target-oriented, effective and economic risk management, so that support in the form of practical guidelines is required.

Most regulators by now are of the opinion that existing codes form a good framework for regulating nanomaterials, but that, in spite of this, adaptations taking account of the peculiarities of nanomaterials are required. Already in 2006 the UBA identified existing regulatory gaps through an expert's report and demonstrated scope for drafting in order to integrate specifications for nanomaterials in environmental legislation. The report describes a gradual regula-

tive procedure for accompanying novel technologies taking account of deficient knowledge with regard to risks for humans and the environment.

The foundation for appropriate government action is sufficient knowledge of the current spread of nanomaterials. A comprehensive survey of research institutions and companies that produce and use nanomaterials in Germany should be used to discover what the current spectrum of nanomaterials looks like, the workplaces that are affected and the contamination to which employees may be exposed. Various options for action for regulating nanomaterials under REACH are being analysed in a research project for the positioning of higher federal authorities in the context of current consultations in the EU on the adaptation of the REACH Regulation to reflect the requirements of nanomaterials, based on an analysis of the current definition of the material. A practical guideline for occupational health and safety is being developed and validated in field studies. It is intended to form the basis for the safety consultations for start-up companies through the BAuA as was planned in the framework of the federal government's 'Nanotechnology Action Plan 2015'.

2.5.3 Risk communication and risk perception

Along with innovation research and safety research, social-scientific accompanying research on the perception of risks and the implementation of dialogue processes (cf. 2.5.4) forms a third column of activities in nanotechnology. This is intended to bring together current trends regarding the perception of positive and negative effects of nanotechnology on the environment and health and to assess them with aim of shaping and developing communication with or between experts, producers, lobbyists, politicians and consumers. There are findings from a series of case studies, representative surveys and media analyses that enable a differentiated picture of the perception of nanotechnology to be derived and relevant influencing variables to be described.

An analysis of reporting in the media between 2000 and 2007 shows that the debate on nano-technology in German print media was not very controversial. Seventy per cent of articles emphasised the positive aspects of nanotechnological products and processes. The focus is on applications in medicine and in information and communication technology.

The positive reporting is reflected in consumers' perception of nanotechnology, which was ascertained for the first time in the framework of a population survey in 2007. It was shown here that consumers expect relief in everyday life through the use of nanomaterials in cleaning and impregnating sprays and in function textiles. On the whole, two thirds looked forward to benefits from nanotechnology rather than risks, but they do not accept nanotechnology equally in all areas of application and also demanded that research is carried out into possible risks. It was seen that the use of nanomaterials in foodstuffs was viewed sceptically. As the conclusion of an international conference held in the framework of NanoLINEN, coopera-

tion between India and European countries, it was recognised that nanotechnology can also offer solutions to the current problems of man in developing countries. However, at the same time there was a demand that a knowledge and technology transfer from developed industrial nations to emerging economies at an early stage should be aimed for, in order to guarantee the development of common standards for safe products and applications.

Follow-up surveys are intended to show whether and how media reporting and public perception have changed in recent years in an international comparison as well.

2.5.4 Social discourse on nanotechnology

In the framework of the federal government's first 'Nanotechnology Action Plan',⁸ among other things there was a reference to the necessity of a broad social dialogue, in order to establish a clear, honest and enlightened picture of the opportunities and risks of nanotechnology in society. The 2007 research strategy also regarded public discourse and transparency in dealing with nanotechnology as a fundamental component for coping with sustainable technology development and promoting acceptance among the public.

The following is an example of the federal government's various dialogue activities: as a stakeholder dialogue, the so-called NanoDialog supports as a central, national dialogue platform the exchange of opinion between social stakeholder groups and thus enables early integration of all relevant players in the debate on nanotechnology. Under the aegis of the BMU and with the participation of the governmental research institutions, the so-called NanoKommission and its working groups discussed the opportunities and risks of nanotechnologies from 2006 to 2011 and worked out contributions for handling nanomaterials responsibly and sustainably. About 100 stakeholders from science, business, environmental, consumer and women's organisations, trade unions, the churches, ministries and government authorities took part together in the multifaceted discussion. The governmental research institutions dealt intensively in working groups with the question of possible risks to the environment and health and contributed their expert knowledge to the final reports.⁹ The Nano-Dialog is already in its third phase and will be continued in four specialist colloquia until the end of 2012. The governmental research institutions will make an important contribution to the success of the stakeholder dialogue here as well. As the leading department for nanotechnology, the BMBF has for several years carried out a "dialogue with the public" within the federal government, in which, among other things, nanotechnology was also a topic.¹⁰

⁸ http://www.bmbf.de/pub/akionsplan_nanotechnologie_2015_en.pdf

⁹ <http://www.bmub.bund.de/en/topics/health-chemical-safety-nanotechnology/nanotechnology/nanodialogue/>.

¹⁰ <http://www.nanotruck.de/initiative-nanotruck.html> (in German).

Another example of a structured public dialogue between experts and the lay public is the "consumer conference nanotechnology". This was intended to include the public in the discussion of opportunities and risks in the preliminary stages of a broad application of nanotechnology and to frame risk communication as a participatory dialogue. Two years later, "Nanotechnology in the Focus of Consumer Health Protection" was the motto of a consumer forum, in the framework of which 200 participants from politics, science, industry, public institutions and NGOs discussed the opportunities and risks of nanotechnology and the existing research demand. Occupational health and safety for the work with nanomaterials was the focus of another dialogue forum that was set up in 2011. The special exhibition "nano!" which was also shown at the 2011 World of Work (DASA), supplied the framework for a series of further public information and dialogue events in which the opportunities and risks of nanotechnology occupied centre stage.

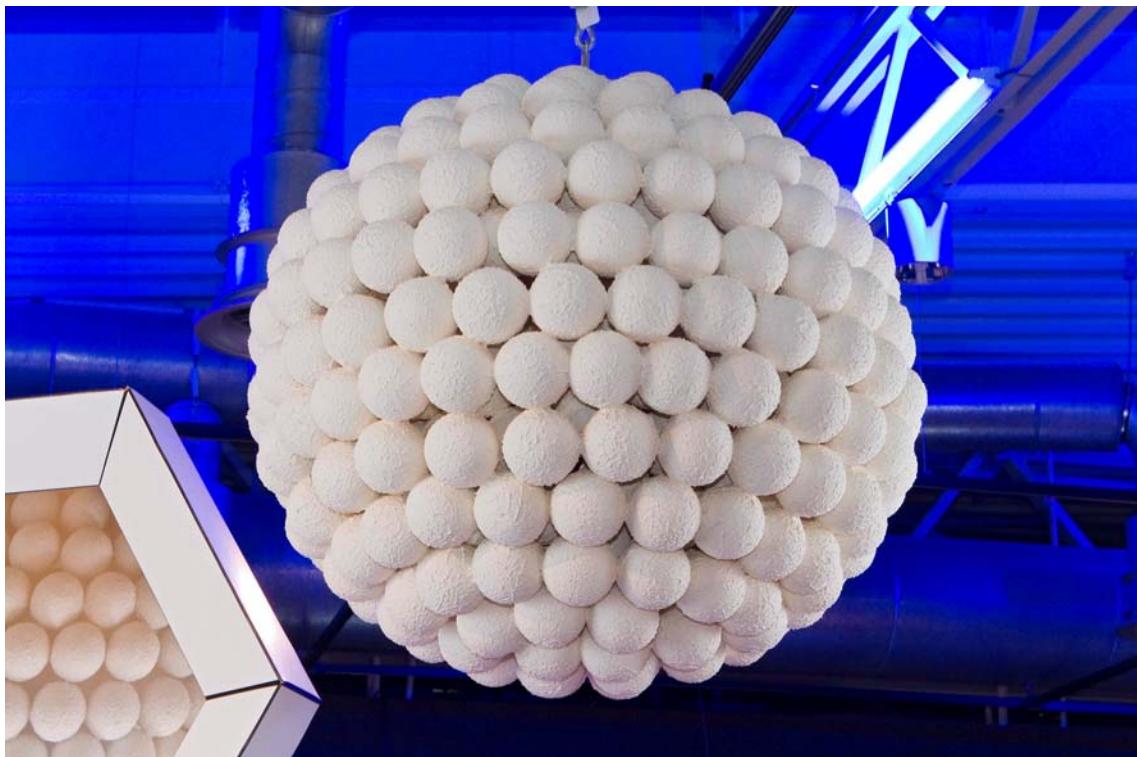


Figure 7: Model of a nanomaterial (photograph: BAuA/Fox)

2.6 Sustainability potential

In the framework of the debate on the opportunities and risks of nanotechnology the discussion is turning more and more to contributions to sustainable development. Nanotechnology provides great potential for energy efficiency and the protection of resources, for use in the protection of the environment and for the development of novel techniques and applications

in medicine. Many of these promising applications are still in the development phase. The sustainability of the applications is often propagated, but qualitative and quantitative verification exists in very few cases only, particularly as the methodological foundations for a systematic consideration have up to now largely been missing. At present, criteria are being developed for various areas in which nanotechnological applications are used that enable a comparison of beneficial and risk aspects and by means of which sustainability could be evaluated. The NanoKommission appointed by the federal government has published a process for comparing beneficial and risk aspects of nanotechnological processes and products.¹¹

A series of studies has dealt with the representation of sustainability aspects of nanotechnological products and processes. The focal point of the studies was on the analysis of the potential relief of the environment through energy saving, protection of resources and reduction of emissions of greenhouse gases. The findings showed in some cases clear potentials for relief. In addition, the assessments showed gaps in essential data, such as, for example, energy and raw material consumption in the production phase. At present, therefore, an eco-balance assessment is not yet worthwhile for some promising nanotechnological applications.

In an expert's report on the use of nanomaterials in antifouling paints, research was carried out on existing nanotechnological applications for coatings that are intended to prevent fouling and increased abrasion resistance underwater. It was stated in the findings that commercially available products containing nanomaterials cannot be seen as alternatives to conventional products containing biocides. There was insufficient evidence of the effectiveness of the new applications, and there was no information on the specification of the nanomaterials contained for an ecotoxicological assessment.

¹¹ <http://www.bmub.bund.de/en/topics/health-chemical-safety-nanotechnology/nanotechnology/nanodialogue/>

3 Conclusions for the future direction of research activities

In the first years of the research strategy, the focus was on early identification of risks for humans and the environment through new materials from nanotechnology, which was then still young. Since then, the discussion has reached political decision makers globally. In this way, the research requirement is changing clearly in the direction of support for government action (governance). One important goal is non-contradictory and coherent integration of the safety aspects of nanomaterials in existing statutory provisions governing material and product law, as well as occupational health and safety, environmental and consumer protection. But through their activities, governmental research institutions also want to support government programmes on sustainable development with their ecological, economic and social components. Questions on the safe design of workplaces and products over the complete life cycle, improvement of energy and resource efficiency and targeted risk communication provide a good foundation for further research activities and cooperation in the national, European and international framework.

The following subchapters show perspectives of safety research on innovative materials in the coming years, how it is constituted taking account of the special dynamism in nanotechnology today. In order to cope with this dynamism, along with concrete research projects developments have also been taken into consideration that are just starting, but are relevant for the safety of the various protected resources in the foreseeable future. The associated challenges for research and development result from the increasing application of nanomaterials in products and processes, the development of additional innovative materials with new chemical compositions, nanoscale and microscale structures and surface functionalisations whose effects on man and the environment are as yet unknown.

3.1 Further development of early risk detection

A whole series of innovative marketable nanomaterials is expected in the next few years. These include nanomaterials that are specifically coated on their surfaces with other substances, chemically altered or systematically restructured with the help of so-called bottom-up methods. There will also be hybrid materials that consist of an inorganic core and one or more layers of organic materials. A particular challenge is to adapt the set of instruments for the early detection of risks associated to these cases and to develop them further. The widening of safety research to other innovative materials ("advanced materials") that are not covered by the term nanomaterial will also be in the foreground of the research and political advisory activities of governmental research institutions in the coming years.

3.1.1 Methods for identifying, characterising and determining the dosage

The term nanomaterial implies structural complexity that is clearly greater than that of traditional materials. It requires the inclusion of chemical and morphological aspects in the characterisation of the material. Nanomaterials have a variety of material properties, for example, composition, size, shape, crystalline category, domain size, surface structure and surface chemistry, porosity. Which material modifications can be treated with analogue methods and standards for the risk assessment, and can thus be grouped together, has to be clarified. For this purpose, material variations have to be determined reliably and examined with regard to possible toxic and ecotoxic effects. The appropriate physical-chemical identification, characterisation and dosage determination is one of the greatest challenges, in order to generate reliable (eco-) toxicological data on individual nanomaterials. In addition, identification and characterisation of nanomaterials within the media surrounding them is gaining importance.

Creating preconditions for a substance safety assessment

Established methods for the safety assessment of chemical substances cannot be applied to nanomaterials without adaptation to specific peculiarities. The substance definition used in chemicals safety, for example as the basis for the EU's REACH and CLP Regulations, is oriented primarily towards the chemical composition. Possible risks based on morphological properties were regulated up to now only in relation to product groups, e.g. for fibrous materials such as asbestos and artificial mineral fibres, or for individual protective goals, e.g. fine and ultrafine dusts in the environment and at the workplace.

The problems of the identification of nanomaterials start with their designation. This is why the development of a suitable nomenclature represents a fundamental task, and one that has to be solved primarily, for a differentiated regulatory treatment of nanomaterials and other materials. A nomenclature should be comprehensive enough to name and differentiate existing material variants adequately. On the other hand, it should not name each nanomaterial individually, such as, for example, a description would do that is based on specifying all atomic coordinates of a nanoparticle. This means that it has to be in a position to name relevant material aspects. Developing a sufficiently but not overly differentiating nomenclature for nanomaterials therefore requires a categorization approach. The approaches that are under discussion at present classify nanomaterials by means of their shape as approximately spherical, elongated or flattened, cf. Fig. 8. In addition, for nanomaterials of a higher structural order special terms were coined that describe the morphology: nanowire, nanotubes, nanorod, nanoroll, nanocone, nanosphere.

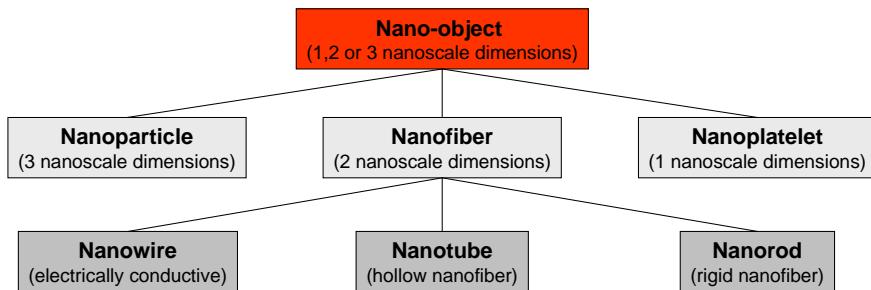


Figure 8: Order of nanomaterials by means of their shape through the introduction of the term nano-object in accordance with the proposal in DIN ISO/TS 27687:2010-02 “Nanotechnologies - Terminology and definitions for nano-objects – Nanoparticle, nanofibre and nanoplate”.

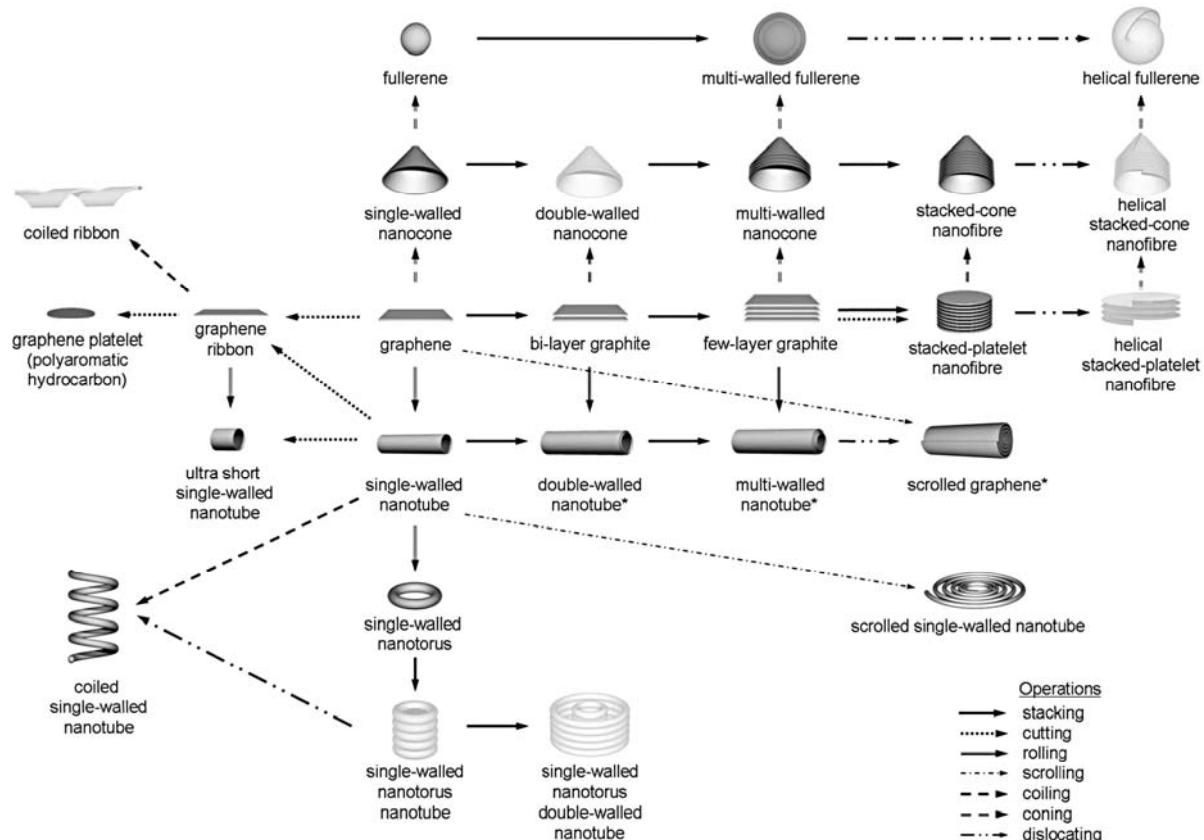


Figure 9: Proposal for a system of naming carbon nanoforms in accordance with [Suarez-Martinez I, Grobert N, Ewels CP. Nomenclature of sp₂ carbon nanoforms. Carbon. 2012; 50(3):741-747].

Even more than the categorization approach shown in Fig. 8, the system developed in Fig. 9 for naming structurally ordered carbon nanoforms makes the variety of the nanomaterials even clearer. Structural defects increase their degree of complexity still further.

With surfaced-modified, specially coated nanomaterials above all the question that is important for chemical law arises whether they represent only a material modification or a discrete substance. Also, questions on the solubility and adhesive strength of the coating would have to be answered in order to assess the risks of a coated nanomaterial suitably.

This makes it clear that categorization for nanomaterials solely under morphological aspects is not sufficient. Additional physical-chemical material aspects have to be taken into consideration. If too many are considered, the categorization scheme will become too complex and make it difficult to form equivalence classes. A sufficient categorization should comprise relevant aspects of nanomaterials for the safety assessment. This includes chemical and surface chemical substance properties, e.g. composition, solubility, reactivity, polarity, and (eco-) toxicologically important morphological specifics, such as fibre character and fibre stiffness, or tube geometry. It therefore appears now to be toxicologically necessary to differentiate rod-shaped from practically spherical particles, analogous to the schema in Fig. 8. In addition, numerous further properties will have to be described.¹²

In the coming years, categorization schemes for nanomaterials under an (eco-) toxicological aspect should be developed, in order to derive a sufficiently differentiating nomenclature for the purposes of legislation (e.g. classification in accordance with the CLP Regulation). A scheme of this type requires a comprehensive understanding of the structure activity relationships of nanomaterials and needs validation in experiments, as well as regular adaptation to the state of the art. For this purpose, nanomaterials that were or are being examined in (eco-) toxicological studies are characterised comprehensively on a materials science basis. The interlinking of these chemical-physical material data with (eco-) toxic effects or non-effects is intended to create a database that permits the identification of relevant material properties and the development of categorization approaches. For this it is necessary that not only study findings that show (eco-) toxic effects, but also those that show no effects, are published or made available in another form for a link of this kind. In addition, in case of government sponsored studies the archiving of (eco-) toxicologically examined nanoscale input materials in the form of so-called reference samples must be required. With these, material data that was not recognised until a later date as missing or not sufficiently exactly determined can be supplemented with higher developed, e.g. standardised methods. In this way it would be possible with the inclusion of material science expertise to differentiate elaborately generated (eco-) toxicological data at a later date in relation to the material and to evaluate them.

Wide distributions of properties require advanced characterisation techniques

Progress in recent decades in the characterisation of materials and structures on the nano-scale has enabled scientists to examine the chemical-morphological results of their synthesis

¹² The following example shows how complex the designation of a nanomaterial for regulatory purposes would have to be: *Designation: "non-photocatalytically effective, transition metal contaminated, biopersistent, rigid, multiwalled carbon nanotubes coated with water-soluble negative-pole polymer".*

and modification approaches. In this way, the capabilities for targeted material developments were developed to an impressive extent and have led to a significant part of today's nanotechnology. However, the coherences between synthesis conditions and structure genesis are not yet sufficiently well understood, in particular for nanomaterials, in order to be able to guarantee a high level of structure control. The reasons for this, along with the complexity of structure forming processes are insufficiently developed methods for the characterisation of intermediate and end products. The new capabilities have led to a variety of nanomaterials that are available industrially or on laboratory scale that display the broad distributions of properties. On the one hand, different synthesis paths for a specific end product can lead to different characteristics of the material. On the other, variances can occur even between different batches of the same material from the same producer. This not only clearly increases the expense for chemical-morphological characterisation, but above all for (eco-) toxicological assessment. Reproducible synthesis with the least possible variability between individual batches is a basic requirement for further characterisation and assessment.

For this reason, rapid progress is necessary to increase the reliability and the information content of characterisation methods for nano-objects. This applies in particular to complex nano-objects in various surroundings. They are necessary not simply for the identification of nanomaterials that should be assessed (eco-) toxicologically and for clarification of structure-activity principles, but also contribute to the development of more specific approaches for the synthesis of nanomaterials.

Reproducible and structure-preserving sample preparation

Among the most urgent tasks in the field of nanomaterial characterisation is the development of protocols for reproducible sample preparation. Characterisation methods that require isolated nanoparticles demand particular attention.

The starting point is dispersions of isolated nanoparticles that are sufficiently stable over time. For microscopic solid matter analyses, particle dispersions must be fixed on a substrate while retaining particle isolation. For this, drying-related agglomerations must be minimised, such as can be caused, for example, through particle transport taking place in an evaporated solvent. Research activities are also planned on the stable generation of nanoscale aerosols and on processes that sort in accordance with particle size.

With regard to the structure preservation of nanoparticles that should be isolated, the question of the necessary and permissible energy input specific to the material is largely unexplained. Among other things, demarcation between agglomerated and aggregated particles, and between agglomerated and entwined fibres, that is not yet sufficiently clear is responsible for this. In principle, dispersion methods should be applied that isolate agglomerated, i.e. weakly connected primary particles without changing their structure. Aggregated, i.e. strongly connected particles on the other hand should not be isolated. Strongly intertwined fibres, on

the other hand, cannot be isolated without cutting, i.e. shortening the fibres. Available studies on dispersion processes usually lack a systematic materials science approach for examining the structural changes of the particles. Measuring the particle size or the fibre length of the input material cannot be carried out with many traditional methods without a dispersion step. In particular, with long, intertwined nanofibres the shortening effect through the dispersion step can only be examined with great effort.

To make things more complicated it has been seen that in many cases the isolation degree of agglomerating nanoparticles does not increase constantly with the input of dispersion energy. On the contrary, long ultrasound treatments of particles in a dispersion can lead to re-agglomeration, whose causes are still insufficiently understood. The use of a dispersion, e.g. in a toxicity test, therefore requires regular monitoring through simple and reliable methods. The most established method, dynamic light scattering (DLS), has proved to be unsuitable for polydisperse, i.e. non-uniform, particle sizes. In addition, there are only a few suitable processes that are able to map the particle dispersion of non-spherical nanomaterials, such as, for example, plates, or whose underlying mathematical models are suitable for this assessment. For this reason, the development of alternative processes is being pursued intensively. The focus here is on coupling processes from fractionating and analysing methods that are intended to be developed into compact, easy-to-operate appliances.

Increasing the reliability of characterisation methods

Against the backdrop of the EU Commission's recommendation for a definition of nanomaterials that applies to all legislation, the urgency to develop reliable measuring methods for the identification, characterisation and dosage measuring of nanomaterials becomes clear. The necessary improvement of the reliability of methods for the characterisation of complex nanomaterials in different surroundings will require considerable efforts in the coming years. The aim should be for standardised methods that, for example, can be applied for the physical-chemical characterisation of substances for the REACH registration process. These methods must be easy to implement practically and enable low-emission, reproducible and structure preserving specimen preparation.

Metrological traceability to the International System of Units (SI) and data on measuring uncertainty are indispensable for a reliable and internationally comparable assessment of measuring results. Because measuring uncertainties are enlarged with each step of forwarding measurands in the metrological traceability chain, reference measuring methods should be developed that permit the precise determination of the relevant measurands of nano-objects with the least possible measuring uncertainties. The traceable characterisation of the size distribution of nanoparticles by means of scanning electron microscopy (SEM) in transmission is shown here as an example of a reference measurement method. Here, along with the calibration of the image magnification, the electron transmission through the nanoparti-

cles is calculated on a model-supported basis in dependency on material property and particle size and used for the traceable determination of the particle size distribution for particle sizes down to about 7 nm with small measuring uncertainties of 1-2 nm.

The smallest measuring uncertainties can be achieved with the calibration of reference materials that are available in narrow size distributions (monomodal). More complex material specimens can only be characterised with enlarged measurement uncertainties. A still great demand is seen for the development and traceable characterisation of complex reference materials and for the development of adapted preparation methods.

Characterisation of the pure nanomaterial, as is usually demanded for chemical safety, is made difficult in case of consumer-oriented products, because the nanomaterial is already integrated in a material, a formulation, etc., and the identification of the nanoscale materials has to be carried out in the product. This applies analogously for verification in food.

The required sensitivity can be achieved in combination with a high selectivity of coupled methods only. Imaging processes can be used for statements on shape, size, surface, agglomeration and structure. However, statements on size distribution and concentration or exact chemical compensation are only possible in combination with further analytical processes (e.g. ICP-MS with field flow fractionation). In the process, the selection of the suitable analytical sequence depends not only on the type of nanomaterial, but also on the production method, and on the surrounding matrix. Together with further development of the method, the derivation of standards is particularly important for increasing reliability.



Figure 10: Scientists working with a scanning electron microscope (SEM) (photograph: BAuA/Fox).

Necessity of improved methods for number distribution

The EU Commission's recommendation for a definition of nanomaterials also results in an acute need for action for improved methods for determining particle number distribution. First of all, standardised, material-specific, optimised preparation regulations should be developed, and routinely usable processes for checking the primary particle size (dimension 1-100 nm) and particle size distribution (over 50 % of particle numbers under 100 nm). In this process, the difference in principle between individual and ensemble-based methods should be taken into account. While the former examine individual particles with microscopic methods and are able to identify a nanoscale directly, typically low counting statistics and possible preparation artefacts limit the significance of statements on size distribution. Ensemble-based methods, such as, for example, small-angle X-ray scattering and dynamic light scattering, do in fact determine the dominating particle size in a large number of particles, but are frequently unable to determine clearly wide or multimodal particle size distributions, unexpected agglomeration and artefacts. For this reason, ensemble methods should always be combined with individual measurement methods. Here as well, coupling processes and aerosol-based processes promise definite progress.

Developing advanced characterisation methods

Because of the large number of properties of nanoscale materials that have to be identified, it is important to develop characterisation methods with a high information content. One example is analytical transmission microscopic (TEM) methods, such as scanning transmission electron microscopy with element analysis (STEM/EDX), with which not only the shape and the size distribution can be examined, but also chemical composition and crystallinity. Another example, time-of-flight secondary ion mass spectrometry (ToF-SIMS), enables statements on the molecular composition, or on the surface structure of nanomaterials that can be combined with the mapping of the respective nanomaterials, which permits not only statements on the shape and the size distribution, but also the preparation of a depth profile. This technique can be used not only for complex materials such as packing material or cosmetics, but also to identify and map nanomaterials in cells or in tissue.

Progress in specimen preparation should be achieved through cryogenic processes, i.e. shock-frozen dispersions and tissue samples and focused-ion-beam based thin section techniques. In addition, facilities for automated analysis and assessment should be improved. If their crystallinity (atomic resolution) is not in the foreground during the characterisation of nanomaterials, scanning electron microscopy in transmission can be an interesting variant method. Other promising new developments for a combined characterisation of particle size, composition and shape are based on X-ray fluorescence analyses of nanoparticles isolated on a smooth, clean substrate, aerosol mass spectrometry and a coupling of field flow fractionation with small-angle X-ray scattering and other analysis methods. In order to be able to

manage the task of nanomaterial characterisation, these methods should be developed further in the coming years into standard measuring methods.

For routine tasks, inductively coupled plasma mass spectrometry (ICP-MS) in the so-called "single particle" mode, which can be combined with field flow fractionation (AF4) or liquid chromatography (LC) or size exclusion chromatography (GPC), should be developed further. Initial findings indicate that these methods are suitable in particular for the analysis of nanomaterials in complex matrices (e.g. coffee, soup, sun cream).

One problem that is still largely open is characterising the coating condition, the adhesive strength of a coating and the surface chemistry of functionalised or coated nanoparticles. In particular for particles with a diameter of less than 20 nm it is not possible to differentiate sufficiently precisely between surface functionalisation and particle composition, because the analysis depth even of low-range processes such X-ray photo electron spectroscopy (XPS) is insufficient here. In this case, derivatisation methods of reactive surface groups should be tested in order to generate a contrast between particle volume and surface by coupling foreign atoms. In order to be able to derive quantitative information on the surface reactivity from such reactions, systematic examinations on determining the implementation efficiency should be carried out.

Particle dispersions for (eco-)toxicological testing

In recent years, clear progress was achieved for selected material systems on the examination of the conditions and necessary additives (surfactants) for a stable dispersion of nanoparticles. Because of the size of the interface between nanomaterials and the medium, the interface interaction should be optimised, so that the result is wetted particles, and also the strong reagglomeration tendency of the particles with one another should be suppressed, e.g. through electrostatic repulsion or steric spacers. For stable dispersions therefore, solvents have to be selected on the basis of the substances or – with a given medium - the particle surfaces have to be functionalised or coated sufficiently. This raises a fundamental problem of an approach for (eco-) toxicological nanomaterial assessment based on stable dispersions. Stable isolated nanoparticles appear to be particularly suitable for provoking nano-specific effects in (eco-) toxicological tests and in this way simulating worst-case scenarios. These worst-case based tests appear in principle to be suitable to be able to determine the (eco-) toxicological potential of a nanomaterial. However, a nanomaterial that was coated or functionalised for the retention of a stable dispersion usually differs significantly from the original test material.

For this reason, in ecotoxicological examinations the best possible dispersing would take place doing without a solvent and nanomaterial coating and an attempt should be made to keep the dispersion constant over the test period. The chemical composition of the medium

(e.g. ion content) can be optimised here (realistic worst case) and should be documented.

Insofar as it is not possible to preserve any stable dispersions of unmodified nanoparticles in relevant test media, fundamental examinations should be carried out of the stabilisation of nanoparticles by means of natural components of biological fluids (cell culture media, surface waters, bodily fluids). Because the nanomaterials are modified by these natural components during uptake and distribution in the organism, characterisation *in situ*, i.e. in the biological surroundings, is of decisive significance for the examination of possible (eco-) toxicological effects.

3.1.2 Estimating release and exposure

Because of their central role for risk assessment and risk management, questions on determining and assessing the exposure of man and the environment to nanomaterials will continue to take up a broad area in future research activities of the governmental research institutions. While producers and importers are initially responsible for the safety of their products, as a monitoring and controlling instance, the state must provide appropriate expertise.

One challenge still exists for the metrology for verifying small amounts of synthetic nanomaterials in areas that display background contamination with other ultrafine particles. It must be clarified whether, in what amount and in what shape nanomaterials are released during the production process, when a product is used, through ageing and degradation, and on disposal and recycling. Material changes caused by ageing (corrosion, physical and biological disintegration and degradation processes) may intensify release.

Nanomaterials are used in the development of innovative pesticides, care and strengthening agent for plants and biocide products as carrier substances for the improved release of the active ingredients, so that in this context, additional examinations of the behaviour of these substances in the environment are necessary. In addition, in the coming years products should be examined in particular that come on the market as nondurable mass-produced goods (e.g. packaging). Along with the release potential, the stability and persistence of the nanomaterials released into the environment are also of interest, as are interactions with other nanomaterials and chemical substances (mixed exposure). For example, research is being carried out as to whether and how carbon-based nanomaterials such as fullerenes and nanotubes are degraded in organisms and the environment. Another focus will be on the release of nanomaterials from foodstuff contact materials, textiles, wall paints in various scenarios (e.g. sanding, heating up), as well as product ageing processes (e.g. weathering, brittleness). In this process tests will have to be made to see whether such releases of nanomaterials change the air in interiors. In addition, methods for determining exposure frequency and duration should be developed.

The broad range of consumer-oriented products and application forms means that routes through which substances enter organisms can also vary greatly. This concerns both intended and unintended uptake.

Even when used as intended, nanomaterials can be absorbed by the body through the three classical routes: 'oral' (e.g. foodstuffs and feedstuffs), 'dermal' (e.g. cosmetics, textiles) and 'inhalative' (e.g. sprays, powders, cleaning agents). From today's aspect, inhalative absorption through the use of sprays tends to cause the most concern, because in this way nanoparticles and non-nanoscale co-formulants can reach the deep lungs and cause inflammation processes there, or reach other organs from there. While the risk of uptake of specific nanomaterials, e.g. titanium dioxide, via the skin (e.g. by using sunscreens containing nanomaterials) is regarded as minor for healthy skin, there are still open questions with regard to absorption via damaged skin or the gastro-intestinal tract and the associated effects.

Substances absorbed orally can enter the trachea through aspiration, skin-care products or cleaners can be unintentionally swallowed. The latter cases are no doubt exceptions, but should not be neglected from the aspect of all-round consumer protection. This applies to a special degree as well to rather unusual entrances for nanomaterials, e.g. via mucous membranes, the eyes (intraocular) or even under the skin (subcutaneous), as in the case of contact lens containers coated with nanosilver, or nanoparticulate tattoo ink pigments. The possible distribution or enrichment of nanomaterials via these particular consumer-oriented absorption routes is therefore a component of future research activities.

A further focal point of future activities is the search for suitable mathematical models for estimating exposure to nanomaterials. Investigations should be carried out to see whether the models already in use for the substance assessment under REACH can be used for nanomaterials, or whether extended or independent model approaches are necessary. The models should be checked in the framework of field studies through measurements.

Detection and quantification in products, environmental media and organisms

For many material classes, the problems of characterising nanomaterials in real milieus (atmosphere, surface waters, soils, cell culture media, body fluids) have only been solved rudimentary up to now. Traceability of nanomaterials is usually based on differences between their chemical composition and the matrix surrounding them. Carbon-based materials can be identifiable in organic matrices, for instance by means of impurities remaining in the material, for example originating from the synthesis, and be quantifiable with elementary analytical processes. If there is no chemical contrast, isotope marking can be of great value, as was demonstrated with ¹⁴C-carbon nanotubes for verification in aquatic organisms and systems in

toxicological bioavailability and biokinetic studies.¹³ Purely structure-based verification, such as is possible in principle for fibre-shaped carbon nanotubes, has proved to date to be unsuitable for quantifying because of the great analytical complexity of transmission microscopic screening examinations. Approaches for verifying and quantifying nanomaterials solely through the particle size can fail in biological media through naturally occurring nano-scale components, such as, for example, micelles. In addition, their type and concentration are subject to serious natural fluctuations, particularly in the case of non-synthetic cell culture media.

The development of concepts to verify nanomaterials using characteristic spectroscopic properties requires the study of intrinsic quantum effects of nanomaterials in different matrices. In this way, quantum dots, for example, or metallic nanomaterials can be detected through their fluorescence or plasmon resonance phenomena. Promising research approaches exist for a characteristic marking of synthetic nanomaterials on their synthesis with infrared fluorescent dyes, which in this way become verifiable *in vivo* in the so-called water window in the cell tissue. In principle, nanomaterials can be marked using various methods (radioactive isotopes, stable isotopes, luminescence, fluorescence). Up to now there has been little information on how far a label of this type influences quantification or the materials' toxicological properties.

A further challenge is to determine the interface condition in a matrix *in situ*, in order to examine interaction processes of nanomaterials in cells. Here, innovative preparation and analysis concepts should be developed in order, for example, to analyse or extract nanoparticles in their respective coating states within a cell. Spectroscopic properties of metallic nanomaterials, so-called plasmon resonances, that are to be researched in greater detail, could be suitable, for example, for acquiring information on the composition of the interface configuration and the embedding matrix through the dielectric properties of the particle surroundings. ToF-SIMS is also suitable for analyses in cells and tissue and in addition to this is of particular importance for verification in consumer-oriented products.

3.1.3 Testing and assessment of adverse effects on humans and environment

Determining toxicologically relevant properties

The hazard characteristics of nanomaterials reflect the complete range width and characteristic of the toxicological properties of conventional chemical substances. Categorization of the bulk material is therefore an important, but not sufficient, starting point for the risk assessment of the corresponding nanomaterial. In addition, there are hazard potentials that are

¹³ http://www.inno-cnt.de/de/backgrounder_carbosafe.php (in German).

connected to the particle properties (in particular size) and the extremely large surface-volume ratio of the nanomaterials. The following specific features for the characterisation of the toxicological properties of nanomaterials can be derived from this:

1. With nanomaterials it is particularly important to ascertain the chemical surface properties. They determine possible catalytic effects, their reactivity, solubility and adsorption properties that can be important for toxicological mechanisms of action. Depending on the nanomaterial, for example, catalytic surfaces can lead to the formation of reactive oxygen species. Nanoparticles have a particularly "sticky" surface. As a result of this, they tend not only to agglomerate with each other, but can also interact with other molecules (metabolically relevant biomolecules, but also foreign substances) and thus influence their availability or localisation. Conversely, sheathing with endogenous proteins and lipids ("corona") has an influence on the bioavailability and localisation of the nanomaterials themselves.

The type of released substances and the release rate are, like the rate of surface-induced reactions and adsorption processes, dependent on the substance properties of the nanomaterial itself, and on the surrounding milieu. Systematic research is necessary regarding how far the surface properties and the resulting consequences have an effect on human health if released nanomaterials enter the body, and whether categorization possibilities for estimating a toxic potential can be derived from this.

2. Fibre-shaped nanomaterials must be tested to see whether they fall under the so-called fibre principle and could display an asbestos-type effect. The material properties fibre length, fibre diameter and the bio-persistency are to be ascertained for this purpose. Fibre stiffness also appears to be an important parameter, because according to the current state of scientific knowledge nanofibres with low stiffness do not display any typical fibre character with regard to their toxicology.
3. In addition, nanomaterials are to be tested to see whether they are to be classified as respirable **granular biopersistent particles** (GBP) without known significant specific toxicity. These GBP do not possess any substance-specific toxicity beyond a particle effect and are by definition, persistent in the biological milieu. This material class comprises, for example, many nanomaterials on the basis of titanium dioxide or industrial soot manufactured on an industrial scale. GBDs are also characterised by an aerodynamic diameter of up to about 10 µm. For this reason they can penetrate deep into the lungs, i.e. into the alveoli, and cause inflammatory processes there, among other things. On the assessment of possible risks to health of such GBD nanomaterials along with an inflammatory effect the question of a suspected carcinogenic effect in the lungs is in the foreground.

The information system of the European Chemicals Agency and the step-by-step registration of further chemical substances under REACH provide the governmental research institutions with additional knowledge that can be supplemented where necessary through specific examinations in the framework of research projects.

Mechanisms of action and toxicokinetics

In spite of numerous in vivo and in vitro studies of the toxic effects of nanomaterials, knowledge of the basic mechanisms, and of the fate and whereabouts of nanomaterials after absorption into the organism, is still incomplete. The reason for this is, on the one hand, the great variety of materials and difficulties in handling the test materials. On the other hand, there is a lack of sufficiently worked out analytical concepts for recording nanomaterials in tissue qualitatively and quantitatively. The practical implementation of broad toxicological studies is hindered above all, however, by a lack of apparatus and methodological standards. To meet this challenge, great efforts are being made globally, not only in the framework of the OECD WPMN, but also through numerous research cooperations at EU level in the so-called European NanoSafety Cluster. With regard to toxicokinetic studies, absorption, distribution and elimination in the test organism are to be examined quantitatively. In the case of biopersistent nanomaterials, possible enrichment in target organs at low but chronic exposure, and the possible health consequences this leads to, is of particular scientific interest.

These studies on distribution and enrichment should be supplemented practically by suitable cell penetration and barrier studies in vitro with cell or organ systems selected on the basis of the exposure route, in particular for new materials with low production volumes (e.g. air-liquid interface, three-dimensional multiple cell models). What kinds of cell types preferably absorb nanomaterials in vivo should also be examined, as well as the shape in which this takes place and the consequences. This should be examined separately in vivo for each exposure route and modelled in vitro.

Kinetic studies are also used to determine relevant dosages for toxicity studies of animals and in cell cultures. Much of the previously published data on the toxic effects is based on unrealistically high exposure concentrations with which measurable effects were provoked whose validity for exposures that are relevant to reality is limited. In addition, inferences must be drawn regarding the suitable dosage measure (mass, number or particle surface per volume, etc.). The standard dosage measure for deriving limit values in quantitative risk assessment is a concentration relative to mass or volume (e.g. mg/kg body weight; mg/l). There are a number of indications that show that dosage measurements other than mass describe harmful effects caused by nanomaterials better, e.g. the surface. A solution to this question is highly relevant, not least with regard to the comparability of nanomaterials (including with the

basic substance) and study findings, and depends on clarification of mechanisms of action and toxicological equivalence, that is, the correlation of material properties and toxic effects. At present, indication of the mass concentration is without doubt the more practicable way, but conversions should be possible.

One research field that will be expedited – not least in order to be able to deal with the enormous variety of shapes resulting from group formation with appropriate regulations – concerns the predictability of biological properties and/or toxic effects based on the physical-chemical properties of nanomaterials. Useful toxicological equivalence criteria and structure-activity relationships should be developed. In addition, contributions should be made for the clarification of the importance of the formation of oxygen radicals (reactive oxygen species - ROS) through nanoparticles (material-mediated and/or cell-mediated) for the activation of immunological and inflammatory reactions through to tumour formation or influencing chronic-degenerative processes (ROS/inflammatory theory).

Clarifying the long-term effects of GBP nanomaterials

Statements on the inhalative long-term effect of nanomaterials are to be acquired by means of a large-scale in vivo study under the aegis of the Federal Ministry of the Environment, Nature Conservancy and Nuclear Safety. A particular focus here is on the examination of effects in the area of low exposure, which have great significance for the workplace and the environment. The study is planned to last four years and is based on the OECD's test specifications. BASF SE is carrying out the inhalation studies in the framework of the project as the industry partner, BAuA, UBA and BfR will undertake the subsequent examinations for the assessment of the study as independent specialist agencies. An external independent group of advisers, consisting of high-ranking, internationally renowned experts, provides scientific supervision for the examinations. The study is also part of a major European research programme that from 2013 (term: 5 years) will contribute to further improving the scientific foundations for appropriate regulation of nanomaterials in the framework of chemicals and product safety.

Further development and standardisation of test procedures

For the adaptation of existing and the generation of new test procedures for testing possible hazardous properties of nanomaterials further research activities on the standardisation of test substance dosages and on the standardisation of cell models are to be initiated. International validation studies taking into account certified reference nanomaterials should then follow. There is a research need both for the adaptation of toxicological and ecotoxicological endpoints and for physical-chemical endpoints (e.g. dust generation and redox potential). This necessitates a sufficient physical-chemical characterisation of the nanomaterials in the test system (in vitro, in vivo) and in various ecosystems (environmental performance).

Because of the amendments to the European Cosmetics Directive, animal testing for cosmetic products will be prohibited in the future. The development of reliable in vitro procedures for testing the hazards to health is essential, because otherwise use of nanomaterials in cosmetics will no longer be permitted.

Those in vitro test systems for skin and eye irritation, genotoxicity, phototoxicity and sensitisation that have already been recognised by the OECD are suitable for testing nanomaterials to a limited extent only, and, depending on the nanomaterial, must be checked with sufficient positive and negative controls and controls in the cell-free system.

At present, toxicity following repeated administration in the animal model is simulated for chemicals in vitro in complex reconstructed multiorgan systems (intestines – vascular system - liver - lungs - skin), and here, too, there is a need for more research with regard to applicability to nanomaterials. In vitro cultures of individual cell types are unable to map the complexity of surrounding tissue or organs. Barrier functions as well are not pronounced in these simplified models and repair functions for genetic defects are often missing. Today, however, new developments in regenerative medicine enable epithelial cell layers to be reconstructed from human cells for both skin and lung tissue. They constitute both a physiological barrier and express DNA repair enzymes. The development of new three-dimensional models of the human intestines and the blood-brain barrier is being driven forward intensively as well. These models are basically suitable for testing nanomaterials as well with regard to their capability to overcome physiological barriers; in particular, 3-D skin and lung models are being adapted and developed further accordingly at present.

In the medium term it is essential to check the significance of in vitro mutation tests that are usually used for chemicals. For example, the Ames test does not cover particle-induced effects. Mutation tests with mammal cells are only significant if it can be proven that the cells used in fact absorb the respective nanomaterials. In addition, for in vitro mutation tests the cytotoxicity of the nanomaterials in the test system must be known.

The test directives and guidelines for human toxicology are at present under scrutiny in the OECD WPMN programme. The German delegation is playing a leading role in the nano-relevant adaptation and redevelopment of these internationally valid guidelines documents. At present there are proposals for adaptations for the endpoints inhalation toxicology after repeated dosage and toxicokinetics, which are also to be discussed in the framework of a meeting of international experts organised by Korea and Germany. The endpoints sensitisation and genotoxicity also need to be adapted. Endpoints that are to be newly developed or integrated (e.g. on the barrier mobility of nanomaterials) are being prepared at present in the WPMN steering group "alternative methods". The regulatory framework conditions for testing itself and adaptation of the test guidelines are being adapted or harmonised in the risk assessment steering group. Germany is playing a leading role in both steering groups.

Closing knowledge gaps in the field of ecotoxicology and environmental behaviour

The OECD has developed numerous test guidelines for recording the environmental behaviour and the effects of chemicals on organisms in various environmental compartments. Those OECD test guidelines that teams of international experts found to be in need of adaptation for examining nanomaterials now have to be revised and proved for the definitive applicability. The focus here should be above all on dispersion methods, the necessary nanomaterial characterisation and analysis, and a possibly necessary change of the test performance (e.g. application, number of replications, endpoints). With a comparative examination of nanomaterials with different chemical origins (e.g. metals, metal oxides and carbon-based nanomaterials) the transferability of the findings to necessary adaptations from one nanomaterial to other nanomaterials is to be ascertained.

For a better understanding of the behaviour of nanomaterials in the environment data on transport, carrier effects, degradation and accumulation in the environment are to be collected for selected nanomaterials.

Development of integrated test strategies

Building on previous knowledge, future research by the governmental research institutions on human toxicology or the ecotoxicology of nanomaterials should have as its object the development of an integrated test strategy. Alternative test methods (among others, *in vitro*, *in silico*) should be used here. For the area of ecotoxicology an integrated test strategy should also include tests with organisms that are particularly affected, depending on the exposure route (e.g. filter feeders, sediment organisms) and, where applicable, additional or alternative endpoints (such as fish ventilation rates, pathology of fish brains or other organs, heart rate of daphnias, behaviour patterns). The general aim is to enable a prediction of the (eco-) toxicological effects of new materials through a combination of different experimental test methods and mathematical models, and at the same time to reduce the number of test animals.

Promoting collaboration between impact research and material sciences

The integration of material science expertise should become a precondition for research work of the governmental research institutions on the (eco-) toxicology of nanomaterials. Material science expertise is required above all for the selection of relevant nanomaterials as well as for the preparation and comprehensive characterisation of individual batches. Material scientists who are included in the clarification of structure-activity principles and learn to understand the clearing mechanisms of biological organisms and systems are also enabled to develop concepts for the synthesis of alternative, inherently safe materials. One example might be biodegradable nanofibres, which – analogously to microscale mineral wool insulation materials – enable progress in occupational health and safety, environmental and consumer protection without complex accompanying measures. Because avoidance of a spread

of risky materials has to start from the beginning of the product development chain, it is particularly important to integrate material scientists as early as possible into the safety assessment.

It is precisely the wealth of variants of nanomaterials that, together with the increasing abilities of material researchers to control structures through targeted synthesis, offers very good possibilities for permanently furthering the chances of nanotechnology through pro-active material selection and optimisation, i.e. taking account of possible risk aspects.

3.1.4 Identification and assessment of risk situations

The redirection of European chemicals policies and the creation of two central EU regulations (CLP, REACH) that are directly binding in the whole of the single market were linked to a reversal of the burden of proof for distributors of chemical products. Producers and importers are responsible for the safety of man and the environment over the complete life cycle of their products. This includes providing information on hazardous properties by means of labelling and the assessment and information on safe handling on the basis of a risk assessment.

The medium- and long-term objectives of the governmental research institutions are concerned with detecting, assessing and classifying the risk potentials of nanomaterials, supported by their own governmental research activities, in order to derive reliable scientific foundations for government action. In this, information is also very important that the governmental research institutions request in the framework of their official duties with regard to chemicals and product safety, or which is available to them in the form of dossiers from producers, e.g. substance and dossier assessment under REACH, applications for approval for biocidal agents and products, and others. They can help, for example, to identify nanomaterials with particularly high (eco-) toxic potential for basic research on structure-activity principles. But also the findings of specialist panels, such as EU panels, the hazardous substances committee and standardisation committees should be interlinked and used for a further structuring of future (governmental) research programmes.

Although European law provides for the comprehensive responsibility of producers and importers of chemical products, practical realisation is frequently driven by statutorily prescribed obligations to test and to provide information. Looking at REACH, for example, this means that with nanomaterials long-term risks for humans and the environment that are under discussion are assessed graduated on the basis of production volumes. Because nanomaterials usually do not reach the tonnage limits stipulated under traditional substances law, thorough systematic risk research and assessment of nanomaterials selected as examples is particularly important. In this way, prognoses can be made on the risk potential of other nanomaterials that were not tested because of low production volumes. With this in mind, the govern-

mental research institutions are continuing their participation in the OECD WPMN projects on the examination of selected nanomaterials, which should be intensified still further because the nanomaterials tested in the framework of the programme are very important for industry in Germany as well.

3.1.5 Risk perception and risk communication

One aspect of technology development whose importance should not be underestimated concerns risk perception by the population. For a key technology special importance should be attached to providing comprehensive and transparent information on the opportunities, but also on the possible risks of nanotechnology and its use in consumer-oriented products. Only in this way can a new technology find permanent acceptance and justify the investment in it. Examinations of consumer behaviour and confidence will be continued on this basis.

The development of nanotechnology was monitored at a very early stage by dialogue processes and systematic examinations of perception, so that fundamental findings on communicating the risks of new technologies can be derived from the findings of previous research activities. In addition, the possibility of continuous monitoring provides an opportunity to observe changes in perception and in consumer behaviour over a longer period of time.

Corresponding follow-up studies of perception in various media are already running. In addition, analyses of reporting in other countries as well were and are being carried out, so that not only can trends be seen over time, but European and international comparisons will be possible. Because the use of new Internet forums and above all mobile communication has increased greatly in recent years, these media are to be included increasingly in studies of risk perception and communication. International comparisons are of particular interest because of the varied distribution of these new media.

Along with the perceptions of consumers, the representation of nanotechnology in the media also plays a central role. As consumers still have little experience of nanotechnology, and because the latter also cannot be experienced with the senses, the image that consumers are able to make of nanotechnology is influenced among others by the media. Insofar, the question arises of the representation of nanotechnology in the media, and in particular the representation of possible risks.

As is to be assumed that, with the increasing advent of nanotechnology in everyday life, and also through various public activities in the field, both reporting and, associated with this, the perception of consumers will change, population surveys on the perception of nanotechnology and analyses of media reporting will still be carried out in the future.

3.2 Supporting governmental action

Science-based policy advice for the federal government's departments is one of the main tasks of the governmental research institutions. The expertise for high-quality policy advice has to be developed through the institutions' own R&D activities and maintained at the state of the art. Through their proximity at the same time to science and politics, the governmental research institutions have a key function in disseminating scientific issues and findings. Policy advice comprises on the one hand contributions to the further development of statutory and sub-statutory regulations as an intrinsic government task; on the other hand, it is to support initiatives and programmes that go beyond legislation. The latter include in particular sustainable technical and regulatory development, whose social, ethical, ecological and economic dimensions are covered by the departments represented in the research strategy and is extremely important for future technologies in particular.

3.2.1 Legislative framework on chemicals

In the current global discussions on the integration of nanomaterials in existing statutory regulations governing the safety of chemicals deficiencies are becoming clear that raise an issue that extends beyond nanomaterials. It must be clarified how physical-morphological material properties that can have an effect on man and the environment can be integrated into substances law that is characterised by chemical activity profiles. Up to now, these questions were considered in substances law in individual cases only (e.g. asbestos, synthetic mineral fibres) or were regulated in parallel regulations (e.g. in the Hazardous Substances Regulations). With the rapid development of nanotechnology and new nanomaterials, but also of other innovative materials (advanced materials), public pressure increased for the development of a systematic regulatory approach. Because of its central importance for chemicals safety in Europe, the REACH Regulation is the focal point of activities in the governmental research institutions. The variety of nanoforms and nano-applications makes this into an exceptional regulatory challenge.

With the preparation of the position paper on the integration of nanomaterials in REACH, the governmental research institutions (BAuA, BfR and UBA) have faced up to this challenge and prepared suggestions that were brought into the discussion on a European level.

In the next few years the foundation is to be created for integrating nanospecific material properties in chemicals law. Along with systematic reprocessing of the theoretical basis on the interconnection between substance and material, the formation where necessary of toxicological equivalence classes based in individual cases (asbestos, etc.) that have already been thoroughly examined offers a practical starting point. Above all, it is important to validate methods for a morphological characterisation of substances and to entrench them in

legislation. The shaker procedure developed by the BAuA and the planned automated analysis of REM images form a good starting point here that is to be pursued further. Even greater challenges, which therefore can only be solved in the long term, are regulatory questions on morphological aspects for which there is no previous experience on which to fall back. This concerns, for example, nanomaterials and other composites whose surfaces are coated completely or only partly with other substances or mixtures. It also has to be expected that developments in synthetic biology will be combined with nanotechnology and the border between chemical and biological agents will be watered down.

Along with these research and development activities the governmental research institutions will use their opportunities in the framework of providing policy advice and official duties to develop statutes and regulations on nanomaterials and comparable substances systematically further. Along with collaborating in standards, technical guidelines and codes, this includes as well suggesting harmonised classification and labelling (CLP Regulation) and substance assessment of selected nanomaterials by the authorities in accordance with REACH. In addition, above all with regard to the safe configuration or work procedures and processes, standardised work procedures and exposure scenarios are to be established, or the applicability of already existing suggested measures be reviewed.

3.2.2 Consumer protection and product safety

Pesticides and biocides

Pesticides and biocidal products must be authorised before they are permitted to be sold and used. Authorisation presupposes that if they are used correctly, protection of the health of all groups of persons who may come into contact with the pesticide or biocidal product or their residues is guaranteed. In addition, if these products are used for the intended purpose there is no fear of unwarrantable effects on the environment. It must be possible to determine any residues that occur practically and reliability in an analysis. Only in this way is monitoring possible. In Germany, the use of pesticides is regulated by the Plant Protection Act and associated statutory regulations, and by European regulations.

Pursuant to the EU Biocides Regulation, which comes into effect in 2013, materials treated with nanoscale substances are to be labelled with an appropriate notation. This concerns, for example, textiles into which nanosilver is worked. In addition, from 2013 separate test dossiers will be prepared for nanoforms of active biocidal agents. Directives for the risk assessment of nanomaterials are also to be adapted or developed as well. Higher federal authorities are taking part in the configuration of a risk assessment harmonised on an international level.

Foods

Up to now, synthetic nanomaterials have not been used in foods. If applications arise in future, as with other foods, general food law regulations will apply, in particular those contained in Regulation (EC) No 178/2002 and the German Food and Feed Code (LFGB), which state that only safe foods may be placed on the market. Regulation (EC) No 258/97 concerning novel food and novel food additives has to be observed as well if there are significant changes to the structure or composition of the food or the food additive. In the EU, novel foods may only be placed on the market if they are approved after a safety assessment. If nanoparticles are used, for example as flavouring or colouring, this falls under Regulation (EC) No 1333/2008 concerning food additives and Regulation (EC) No 1331/2008, which requires a safety assessment and authorisation for each application. Use of the nanoscale form of an already authorised substance requires a new assessment and new authorisation. The Food Information Regulation, which came into force in 2011, prescribes labelling of foods that have additives in nanoscale form from 2014.

Food contact materials

Pursuant to the applicable statutory framework provisions of Regulation (EC) No 1935/2004, during normal or foreseeable use food contact materials may not release substances into food that are likely to endanger human health, cause an unacceptable change to the composition of the food or cause impairment of aroma, taste, texture or appearance of the food. Defined authorisation procedures are prescribed at EU level for specific components in food contact materials made of plastic or regenerated cellulose film.

Cosmetics

The requirements for cosmetic products are regulated at EU level in the framework of Directive 76/768/EEC, which was transposed in Germany in the framework of the Food and Feed Code and the Cosmetic Products Regulations. According to this, only safe products may be brought on the market. Cosmetic products do not require authorisation. Only defined ingredients and additives, such as preservatives, colourings or UV filters need to be authorised. However, in all cases producers of cosmetic products must guarantee the harmlessness of their products through safety assessments. In future, the requirements for cosmetic products will be governed in the framework of Regulation (EC) No 1223/2009, which comes into effect in 2013. This Regulation also contains rules on nanomaterials; for example, their use in cosmetics must be labelled.

3.2.3 Occupational safety and health

In contrast to specifications for chemicals safety, the statutory provisions governing occupational safety are stipulated on the basis of individual states. However, this must take account of minimum standards pursuant to Art. 153 of the Treaty on the Functioning of the European Union. In questions of protecting employees against chemical hazards at the workplace, the further development of the Hazardous Substance Regulations and their substantiating in Technical Rules for Hazardous Substances (TRGS), the Federal Ministry of Labour and Social Affairs is advised by the Hazardous Substances Committee (AGS). At present, the AGS does not see any direct need for adaptation at regulatory level for occupational safety where nanomaterials are involved. The AGS is currently working on practical recommendations for procedures for risk assessment and monitoring of safety measures¹⁴. One significant item is substantiation of the specifications of § 6(12) Hazardous Substance Regulations, which describes the stipulation of occupational safety measures for hazardous substances where there is no, or only insufficient, information on the hazard characteristics, e.g. from toxicological tests. There is a need here for practical and low-cost screening methods with which at least partial relief from the high occupational safety standards for substances whose hazard characteristics are not yet known can be reasonably justified for companies. This is of particular importance for start-up companies in the nanotechnology sector, because fulfilment of the standard "enclosed system" in the laboratory area is an established standard (e.g. a glove-box), but represents a significant cost factor as early as the transition to pilot production.

A further focal point of the current work of the AGS is setting an occupational exposure limit for granular, biopersistent fine particles (GBP) on the basis of a proposal from the DFG's senate commission on hazardous substances (MAK Commission). In the opinion of the BAuA, the limit value can be extended to nanoscale ultrafine dusts, among other things on the basis of findings from projects of the joint research strategy. In the medium term, a corresponding specification in annex No 2 "Particulate hazardous substances" of the Hazardous Substances Ordinance may be taken into account.

Establishment of national occupational safety standards on European and international levels is absolutely essential for the competitiveness of German nanotechnology companies. This will take place in the near future through joint projects in the EU's 7th Research Framework Programme and collaboration in the preparation of standards for occupational safety with nanomaterials by the World Health Organisation (WHO). The scientific foundations for this will be created through a transdisciplinary field study on good working practice in research

¹⁴ www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/TRGS/pdf/Announcement-527.pdf

institutions and nanotechnology start-up companies. In addition, these activities will focus on the simplification and international standardisation of risk communication between producers and users of nanomaterials via control banding approaches.

3.2.4 Protection of the environment

Provisions on disposal, emission limit values and environmental quality standards in air and water law are to be reviewed to see whether adaptation is required for the appropriate addressing of the risks of nanomaterials. Necessary control and monitoring methods are to be developed for the enforcement of environmental law.

Waste legislation

Up to now there have not been any separate requirements for waste containing nanomaterials. It is to be checked first of all what the sources and volume flows are for wastes that contain nanomaterials with a high level of concern (e.g. rigid CNTs). Following this, the question of the behaviour of such wastes during reprocessing, incineration or landfilling, and whether separate disposal makes sense for these wastes, is to be dealt with.

Water protection legislation

Water quality targets and monitoring methods for the aquatic environment are to be developed for nanomaterials of concern.

For the field of wastewater a possible effect of specific nanomaterials on the efficiency of sewage treatment plants is to be further clarified. Nanomaterials that have been examined as examples, such as nanoscale silver, cerium oxide and titanium dioxide, have up to now, under the chosen laboratory conditions, not shown any effect on the efficiency of sewage treatment plants in the simulation. Some nanomaterials are bound to approx. 90 % to sewage sludge, whereas others are hardly separated at all through sewage sludge. In future, further relevant nanomaterials are to be included in the simulation experiments. The question then arises of how far a threshold value for a non-nanoscale input substance that applies to sewage sludge can be transferred to the nanoform.

Air quality directive

At present, environmental monitoring methods are not designed for specifically determining the nanoscale fraction when measuring dust. However, a proportion of these particles falls under the categorization of PM10 and PM25 and is thus covered indirectly. In addition, ultrafine particles and nanomaterials require a different sampling and a differently configured consideration of the natural background.



Figure 11: Measuring the outside air (photograph: BAuA/Fox).

3.2.5 Promoting sustainable development

Improving the risk-benefit assessment

The further development of instruments for the safety of nanomaterials and corresponding products is generally desired, including by the German Nano Commission in its second final report in 2011.¹⁵ Instruments for the safety assessment of nanomaterials and corresponding products are to be further developed so that they ensure risk management as defined by the precautionary principle. In an integrated approach taking account of a product's complete life cycle ("from the cradle to the grave"), instruments of this kind can provide early orientation for both potential risks and for potential benefits.¹⁶ A comprehensive assessment of benefits and risks is reserved for more extensive instruments, such as the ecobalance. These instruments should also be adapted to issues specific to nanotechnology. A risks-benefits assessment must also take account of social science aspects that have to do with confidence, dealing

¹⁵ <http://www.bmub.bund.de/en/topics/health-chemical-safety-nanotechnology/nanotechnology/nanodialogue/>

¹⁶ http://www.bmub.bund.de/fileadmin/bmu-import/files/pdfs/allgemein/application/pdf/nanotechnologien_fachdialog1_bericht_en.pdf

with uncertainties and questions of controllability. What is also important is a clear and harmonised terminology for the description of possible risks for humans and the environment. Defining standardised terms and procedures for risk assessment is a task for governmental research. Active participation in public dialogues and risk communication, in particular in dealing with novel technologies, not only permits the further development and harmonisation of appropriate standards, but also counteracts a loss of confidence and thus helps to avoid crisis situations.

Driving early risk detection forward

Previous applications of nanotechnology are based almost exclusively on the possibilities of the first generation of nanomaterials, which contains passive nanostructures (metals, metal oxides, polymers). Because of the applications of subsequent generations that can be expected in the medium term (e.g. with active nanostructures),¹⁷ the assessment of load and relief potentials of nanoproducts should be adapted continuously to the state of developments. To ensure the early detection of possible risks, future possible applications of nanotechnology must be known. It is particularly important here that governmental research is located at the interface between policy advice, authorisation or official control and research, and thus can detect and assess developments and trends at an early stage. Networking through national and international bodies – in the case of nanomaterials above all at OECD level – is a suitable possibility for an exchange with the relevant experts in all areas that are important for risk assessment and for the findings to flow directly into the applied research.

In addition, for early detection it is important to develop prognosis instruments still further. This includes deriving structure-activity relationships and suitable mathematical models that permit a prognosis of risks based on the characteristics of the nanomaterials that are used.

Intensifying safety research

Previous findings from the activities on the joint research strategy make it clear that the federal government's high-tech strategy must still be closely linked to parallel safety research. Only in this way can the high standards of sustainable development be accommodated. This approach will be all the more successful, the earlier that safety research starts. If a new technology and the substances and products that it enables are developed from the start under the aspect as well of minimising risks for humans and the environment, this promotes sustainable development. Retrospective risk minimising through expensive and usually less efficient retrofitting of production plant for occupational safety and protection of the environment, or even prohibitions on production based on risk factors that were identified late, as in

¹⁷ Renn, O. und Roco, M. (2006): Nanotechnology Risk Governance. International Risk Governance Council White Paper No 2.

the case of asbestos, will be unlikely. The positive image of safer substances and products strengthens their marketability. Employees, consumers and the environment also profit from the application safety that is inherent in a product. A good example of this is biosoluble mineral wool, which was first developed in Germany and with which, in contrast to earlier products, the risk of cancer is practically ruled out.

A series of research projects on the safety of nanomaterials was and still is being supported above all at EU level, including some with a regulatory focus, i.e. with the aim of preparing Council Directives or transposing existing Directives.

Strengthening safety consciousness

Encouraging and continuously increasing safety consciousness in research and development is a central challenge of this research strategy. The current continuation of the EU's research framework programme ("Horizon 2020") provides a good base for corresponding activities of the governmental research institutions, because at EU level the realisation and practical application of findings, and also of training measures, are given particular support. Training concepts for nanotechnology startup companies are already being developed in the framework of EU joint projects. In the framework of the 2015 Nanotechnology Action Plan the BAuA wants to intensify consultancy services for research institutions and startup companies. Along with government institutions, companies in particular bear great responsibility for minimising risks and for risk management.

From the aspect of governmental research a particular challenge consist of imparting expertise for the assessment of risks and appropriate science-based policy advice, in order to obtain suitable graduates. Students of natural and material sciences should be familiarised with the necessary instruments for risk assessment, management and communication in their bachelor's and master's degree courses. There are pilot projects for this at the TU Dortmund and a master's degree in Toxicology at the Charité Universitätsmedizin Berlin in cooperation with Potsdam University. In the course of globalisation it is particularly important to communicate corresponding safety standards to experts from partner countries as well.

Developing innovative, safe-to-use products

While for occupational safety purposes an application is possible under additional technical and organisational safety measures, for consumers an inherent safety has to be demonstrated.

A promising approach for nanomaterials is the so-called safety by design concept (cf. 3.2.4), which takes into account guidances on risk analysis and risk minimising in product development. For example, through the targeted modification or functionalisation of the surface the oxidative properties of the material can be reduced or surface charges shielded with the aim of minimising a damaging interaction with biological structures and molecules. This results in

considerable potentials for the development of novel materials with simultaneous reduction of risks for humans and the environment. This concept is therefore to be regarded as an integrative strategy for sustainable growth at the interface between innovations and safety research.

Further development of assessment concepts for handling novel materials

The insight from previous findings of the R&D projects are also to be emphasised, namely that recognised key aspects of hazards for man and the environment are not limited at any point to nanoscaled substances and nanotechnology products. Analogous risks can also occur with other innovative materials that do not conform to the definition of nanomaterials, for example, through the release of biopersistent fibre dusts. It is therefore essential to keep these material innovations as well in the focus of future activities. Close attention must also be paid to the development of further generations of nanomaterials, through to synthetic biology products that blur the lines between chemical and biological working substances. It is essential that a new chapter on "late lessons from early warnings"¹⁸ is averted by anticipatory, high-quality initial research by the governmental research institutions.

¹⁸ http://www.eea.europa.eu/de/publications/environmental_issue_report_2001_22.