Nanotechnology:
Health and environmental risks of nanomaterials

– Research Strategy –

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A draft of the research strategy was published on the internet by the Federal Institute for Occupational Safety and Health (BAuA), the Federal Institute for Risk Assessment (BfR) and the Federal Environment Agency (UBA) in August 2006. The contents were presented at a joint dialogue conference organized by the Federal Environment Ministry (BMU), the Federal Ministry for Labour and Social Affairs (BMAS), the Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) and the Federal Ministry of Education and Research (BMBF) at the Federal Environment Ministry on the 30th November 2006 and discussed with 120 participants from the world of science and business as well as from associations and NGOs. National and international experts were additionally asked to provide their comments. We wish to express our thanks for the numerous and, in part, extensive comments that we received. They were given due consideration during the production of the current final version.

The current report is published on the following internet pages:

www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/Nanotechnology/Nanotechnology.html

www.bfr.bund.de/cd/template/index_en search term nanotechnology

www.umweltbundesamt.de/technik-verfahren-sicherheit-e/nanotechnologie/index.htm

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1 Summary

As an important future technology, nanotechnology[1] presents an opportunity for positively influencing economic development in the long term through intensive research and the effective translation of the research results into innovative products. In many areas it is currently not possible to assess the toxicological and ecotoxicological risks associated with this emerging technology. Nanotechnology is increasingly in the public eye. It is expected that the importance of nanotechnology will continue to increase and that workers, consumers and the environment will be exposed to an increasing extent. Hence, there is a need to monitor the development of the new technology, to weigh up the opportunities and risks in a transparent process and compare them with established technologies.

According to present knowledge, the insoluble and poorly soluble nanomaterials[2] are of particular toxicological relevance. For this reason, and in order to sensibly define the scope of the subject, this research strategy relates to these nanomaterials and to chemicals safety at the workplace and for consumer and the environment.

Chemicals legislation (e.g. REACH) does not provide for a specific procedure for testing (e.g. toxicological studies) and assessment of nanomaterials such as, for example, titanium dioxide, zinc oxide, iron oxide, silicon dioxide or carbon black which represent a nanoscale modification of an existing HPV[3] substance with the same CAS number. Up to now, there has been no specific regulation for nanomaterials in the areas foodstuffs, consumer products and cosmetic products, either. For example, no particle sizes have been defined in the purity criteria for the authorized food additives silicon dioxide (E 551) and titanium dioxide (E 171). In addition, nanomaterials can be used as auxiliaries in plant protection products and biocides and in formulation. Here, too, no guidelines or guidance documents for testing and no requirements regarding identification and size or other physico-chemical properties currently exist. Due to the small number of available studies, it is hardly possible to make comparative statements on the basis of the results available.

Since exposure of humans and the environment, the toxicological properties and risks cannot yet be evaluated, the need to conduct further investigations and close gaps in knowledge by means of research and assessment activities is generally recognized. Similar to technology-oriented research, in safety research, too, there are demands for a shift away from pure fundamental research and a new orientation which enables the translation of the results into risk-oriented and comprehensive assessments (or recommendations for measures) and the covering of the relevant toxicological and ecotoxicological end points. As a matter of principle, it is therefore necessary that the toxicological and ecotoxicological studies that are to be performed can be utilised in regulatory toxicology. In addition, the goal is to achieve a balance between *in vitro* and *in vivo* methods, which is influenced to a large extent by the validity of the *in vitro* methods. To achieve this, a validation of the *in vitro* methods by *in vivo* methods is required.

However, consideration should also be given to the fact that nanoscale particles are not entirely new. Natural and unintentionally produced particles of this size have long been entering the environment and resulting in the exposure of humans and the environment.

[1] Nanotechnology describes the production, investigation and application of structures, molecular materials and inner boundary surfaces having at least one critical dimension below 100 nm.

[2] Nanomaterials are composed of discrete functional parts, many of which having one or more dimensions of < 100 nm. In particular, intentionally produced granular particles, tubes and fibres with a diameter < 100 nm (including their agglomerates and aggregates) for at least one dimension are meant here.

[3] HPV chemicals: chemicals that are placed on the EU market in quantities greater than 1000 t/y per producer or importer.

The following strategic aims should be considered in order to achieve coordinated, targeted and effective research and promotion:

- Risk-oriented approach
- Comprehensive risk characterizations and risk assessments
- Integration into the statutory and sub-statutory regulatory framework
- Research that is application-oriented and relevant from the regulatory viewpoint
- Assessment of the novelty of nanomaterials
- International cooperation and coordination
- Sustainability and the precautionary principle
- More efficient structures for a targeted promotion of research
- Transparency and public discourse.

Key public-sector sponsors of research into impacts on health and the environment are, at national level, the Federal Ministry of Education and Research (BMBF) and, at European level, GD Research. Without comparable financial resources, the responsibility for assessment within the current statutory framework lies with the Federal Ministry for Labour and Social Affairs (BMAS), the Federal Environment Ministry (BMU) and the Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) and the corresponding institutions at European level. Bodies to prepare and support risk assessment within the current statutory framework have not been established and supported up to now. A transfer of the research funds to the spheres of responsibility of BMAS, BMU and BMELV is urgently required to enable efficient and targeted research that takes account of the statutory framework.

Since nanotechnology is a cross-cutting subject, there is an obvious need to examine, the extent to which nano-specific aspects and particularities have to be considered in the various areas of chemicals assessment and management. For the purpose of high-level structuring, the research and work areas can be assigned to various topics:

- Identification of nanomaterials and characterization of the physico-chemical properties, determination of the chemical reactivity
- Exposure of workers and consumers (oral, dermal, inhalative), development of measurement methods
- Exposure of environment (development of measurement methods for the use of nanomaterials in the environment, life-cycle analyses and exposure scenarios, accumulation and persistence etc.)
- Improvement of the comparability and standardization of the studies on toxicology/ecotoxicology and the behaviour of nanomaterials in the environment
- Toxicological assessment of nanomaterials (test methods: *in vitro*, *in vivo*, epidemiology/occupational medicine, relevant end points, kinetics, effect mechanisms etc.)
- Toxicological test strategies and risk-assessment procedures (formation of groups, SAR)
- Ecotoxicological assessment of nanomaterials (test methods, effect hypotheses, relevant end points etc.)
- Ecotoxicological test strategies and risk-assessment procedures (formation of groups, QSAR, intelligent test strategy)
- Risk management
- Information and communication (handling aids, safety data sheets, training of workers)
- Databases

- Public discourse: nanotechnology
- International cooperation and promotion of research.

The review status and the urgency of treatment vary, however, in the individual areas. Some topics follow on from each other so that sequential treatment is advisable. In current research practice, topics are often dealt with in parallel; one reason cited for this is that strictly sequential treatment would lead to a situation in which some topics would be tackled only in the distant future. What is required is a close and timely exchange of findings and experience between the topics dealt with simultaneously as well as an iterative and flexible development process in the course of further research in order to obtain results for use in risk assessment as soon as possible.

The following research projects and support initiatives are considered to be particularly urgent for the common needs of **occupational health, consumer protection and environmental protection**, whereby they in part follow on from each other:

1: Identification of relevant nanomaterials
2: Research initiative for the assessment of nanomaterials within the existing statutory framework
3: Minimum requirements for publications
4: *In vivo* studies for assessment of the risks of nanomaterials
5: Assessment and validation of the *in vitro* methods as a contribution to the assessment of the risks.

From the point of **occupational health**, research is urgently needed in the following areas:

O 1: Development of the measurement methodology and measurement strategies for the determination of exposures to nanomaterials by inhalation
O 2: Provisional handling aids for certain frequently occurring activities involving nanomaterials in the workplace.

From the point of view of **consumer protection**, research is urgently needed in the following areas:

C 1: Investigations into absorption, systemic availability, accumulation and elimination of nanomaterials after oral exposure (foodstuffs and food packaging materials)
C 2: Assessment of the toxicity of nanomaterials after oral exposure.

From the point of view of **environmental protection**, research is urgently needed in the following areas:

E 1: Identification of relevant parameters for behaviour and fate in the environment
E 2: Exposure, persistence and accumulation of nanomaterials in the compartments water, soil and sediment
E 3: Development of uniform standards for the testing of nanomaterials.

The currently foreseeable research topics and requisite activities in fundamental areas will require specific support in the next 5 to 10 years. In particular, this also applies to conceptual aspects relating to the procedures and strategies. With increasing experience and

consolidation of the procedures and methods for testing and assessment, it will be possible to change to a more routine form of investigation and assessment of nanomaterials (individual substances and substance classes) which will continue for as long as new nanomaterials with relevant exposure of humans and the environment are developed.

2 Introduction

2.1 General information

As an important future technology, nanotechnology presents an opportunity for positively influencing economic development in the long term through intensive research and the effective translation of the research results into innovative products. Nanotechnology describes the production, investigation and application of structures, molecular materials and inner boundary surfaces having at least one critical dimension below 100 nm. The low end of the nanometer range borders on the molecule size range which has long been shaped by targeted chemical reactions. The upper nanometer range encompasses microtechnology which is also undergoing a dynamic development through, for example, computer technology (integrated circuits). Nanotechnology closes a gap here and is increasingly in the public eye. NGOs have already taken up the subject (BUND 2007, Öko-Institut 2007). It is expected that the importance of nanotechnology will continue to grow and that workers, consumers and the environment will be increasingly exposed. Hence, there is the need to monitor the development of the new technology and to weigh up the opportunities and risks in a transparent process and to compare them with the opportunities and risks associated with established technologies. An EU experts survey in 2005 rated “nanoparticles and ultrafine particles” as the most important emerging risk in the area of occupational safety. It is particularly important to launch coordinated and effective research aimed at creating a sound and comprehensive knowledge base for toxicological and ecotoxicological risk assessments, which have to satisfy the demands imposed by the regulatory framework, and the resultant recommendations (e.g. classifications, limit values, recommendations for handling). In various international and national projects public funding is made available for the investigation of the technological opportunities. Up to now, the share of funding earmarked for the investigation of the risks has been less than 5 %. This research strategy, therefore, discusses the various research and topic areas and identifies projects which require funding and support. The strategic planning reveals mutual dependencies of the various topics and sets priorities in terms of the topics that are to be treated on a priority basis.

It should, however, also be taken into account that nanoscale particles are not entirely new. Natural and unintentionally produced particles of this size have long been entering the environment and leading to an exposure of humans and the environment. Historical examples (e.g. ruby glass) show that nanotechnology has by no means come into use only recently. However, the special interest it is generating is due to the enormous boost in development due to the improvement in measurement technology and, above all, the opportunities for new and targeted design on the nanometer scale.

2.2 Statutory background

The coverage of nanotechnology by the legal instruments is discussed by various authors (Franco 2007, Frater et al. 2007, Davies 2006, Dekkers et al. 2007, Meisterernst et al. 2006, Merenyi et al. 2007, VCI 2006). A number of legal instruments have the task of protecting workers, consumers and the environment without specifically dealing with nanotechnology (Dekkers et al. 2007) e.g.:

- Regulation (EC) No 1907/2006 of the European parliament and of the council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH); Regulation (EC) No. 1907/2006 (some of the following rules and regulations have been repealed by the REACH Regulation)
- Existing Substances Regulation; Regulation (EEC) No. 793/93

- Assessment of risks to humans and the environment of existing substances (EC) No. 1488/94
- Classification, packaging and labelling of dangerous substances, Directive 67/548/EEC
- Preparations Directive; Directive 1999/45/EC
- Laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations, Directive 76/769/EEC
- Biocide Directive; Directive 98/8/EC
- Directive concerning the placing of plant protection products on the market, 91/414/EEC
- Occupational safety directives; 89/391/EEC, 98/24/EC
- Directive on the safety of toys; Directive 88/378/EEC
- Directive on general product safety; Directive 2001/95/EC
- Cosmetics Directive; Directive 76/768/EEC
- Directive on the restriction of the use of certain hazardous substances in electrical and electronic equipment; Directive 2002/95/EC
- Consumer goods; Regulation 2004/1935/EC
- Foodstuffs legislation; inter alia, Regulation 2002/178/EC
- Waste-management directives (Directive 2006/12/EC on wastes; Directive 91/689/EEC on hazardous wastes; Directive 2000/53/EC on used vehicles)
- Waste Incineration Directive 2007/76/EC
- Water Framework Directive 2000/60/EC
- Directive on integrated pollution prevention and control (IPPC-RL); Directive 96/61/EC
- Federal soil protection ordinance
- Federal Immission Control Ordinance
- Sewage-sludge ordinance.

In the area of occupational safety, the fundamental statutory rules hold the employer responsible for protecting the health of workers (national: Occupational Safety and Health Act and the Hazardous Substances Ordinance; European: Framework Directive on health and safety 89/391/EC, protection of the health and safety of workers from the risks related to chemical agents at work 98/24/EC). However, in connection with the handling of chemicals, deficits with regard to implementation were identified, in particular in the case of small and medium-sized companies. Special rules and regulations relating to nanomaterials are not currently available. Since, as a rule, the nanomaterials (here in particular nanoparticles, tubes, platelets, threads etc. including their aggregates and agglomerates) bear the same CAS number as the larger objects made from the same basic material, the nanoscale fractions have not been assessed in a targeted manner in the existing substance-specific body of statutory rules and regulations (Chemicals Act, Existing Substances Ordinance). Up to now there has been no substance-specific statutory duty to perform studies specially for nanomaterials. Fullerenes represent an exception here since they are not an EINECS substance, have received their own CAS number and, on reaching a tonnage threshold, are subject to a duty of more extensive testing. The extent to which nanomaterials are to be assessed on their own within the framework of the new chemicals legislation (REACH) is not entirely clear. Suitable aids for the assessment of insoluble or nanoscale materials are not currently available. REACH enables the assessment of new uses. The extent to which this option is applicable to nanomaterials must be examined. Also, with regard to the areas foodstuffs, consumer goods and cosmetic products, there is currently no special regulation of nanomaterials. For example, no particle sizes are laid down in the purity criteria for the

authorized food additives silicon dioxide (E 551) and titanium dioxide (E 171). Nanomaterials may be added to products and articles in order to achieve a biocidal effect (e.g. silver). A notification duty exists in the case of biocides (Biocide Notification Ordinance, Biocide Directive). However, the particle size is not recorded here.

The Federal Environment Agency (UBA) has already produced an expert report (UBA, 2007) which analysed the statutory areas with regard to the current state of technology. Stock was taken here of the existing national and European environmental legislation. Gaps in regulation that exist at European and national level in connection with “nanotechnologies” were identified and possible regulatory approaches indicated. Recommendations for the further regulatory approach were additionally formulated. The analysis of the individual statutory areas has made clear that, with regard to the specific properties of nanomaterials, gaps exist at many points in the sectorial environmental legislation.

2.3 National and international activities

Since the exposure of humans and the environment as well as the toxicological and ecotoxicological properties and risks, in particular in connection with newer nanomaterials, cannot yet be assessed, there is general recognition of the need to perform further investigations and close gaps in knowledge through research and assessment activities. For example, the European Commission published an action plan which provides, inter alia, for contributions towards the investigation of the associated health risks (EC 2004, EC 2005). In a study outlining the status of European research, the Commission takes the view that appropriate risk assessments must be performed and a risk-management concept should be available before production and use take place on a large scale (EC 2006a).

The reports that appeared at an early stage in the United Kingdom (inter alia, United Kingdom 2005, Defra 2005, IOM 2005, Royal Society and the Royal Academy of Engineering 2004, CST 2007) describe in an exemplary manner an approach in the areas risk research, participation of the Competent Authorities and the public at large in a transparent discourse. Fair and early communication about the opportunities and risks of nanotechnology will be crucial for the way society deals with this technology. In Germany, the discourse is accompanied by various official events and activities (BMU-BAuA-UBA 2005, BfR 2006b, BMU-BAuA-BfR-UBA 2006, UBA 2006, BMBF 2007). In turn, the basis for risk communication and social discourse is provided by the availability of the most well-founded knowledge possible on the exposure and toxicity of nanomaterials, including the analysis required for the generation of knowledge.

Various authors have discussed the topic of a research strategy for nanomaterials (Balshaw et al. 2005, Borm et al. 2006a, Holsapple et al. 2005, NIOSH 2005a, NNI 2006, NNI 2007a, NNI 2007b, Oberdörster et al. 2005b, Powers et al. 2006, Thomas et al. 2005, Thomas et al. 2006, Tsuji et al. 2006). NIOSH (2005a) has structured the various research activities in a general strategy plan. In addition to the health risks that result from nanotechnology, the research also focuses on the avoidance of workplace-related diseases through the use of nanotechnology, practical aids and international cooperation. In a research strategy, Maynard (2006b) expresses the view, inter alia, that the official institutions tasked with the assessment of the risks have to be involved to a greater extent in guiding the research and that international coordination is required. Maynard et al. (2006c) discuss the various central topics of the research and propose working through the issues chronologically.

In a report on the ongoing research projects NIOSH (2007) also produced a schedule for the investigation into the effects on the health of workers. An overview of the ongoing and planned research in the United Kingdom and the international research activities was also produced by the UK Ministry of the Environment (Defra 2006, Defra 2007). The need for

research in the areas of occupational safety and health, consumer protection and environmental protection was also compiled from a US American perspective by NNI (2007a). In Germany, an investigation into the health effects is to be found, inter alia, in projects undertaken by the Federal Institute for Occupational Safety and Health (BAuA), the Federal Institute for Risk Assessment (BfR) and the Federal Environment Agency (UBA) as well as in the projects Nanocare, INOS and Tracer.

The Federal Government participates supra-departmentally in the discussion on the opportunities and risks of nanotechnology within the framework of its high-tech strategy. Stakeholders from the worlds of politics, business and science as well as authorities, NGOs and associations discuss the advantages and disadvantages of nanomaterials for sustainable development within the framework of the "Nano-Dialog 2006 – 2008". To this end, the Federal Environment Ministry (BMU) has set up a Nano Commission which coordinates and accompanies strategically the dialogue in three working groups. Representatives of various interest groups have been named for the working groups as well as for the Nano Commission. The working groups have the following foci of interest:

- Working group 1 Opportunities for the environment and health
- Working group 2 Risks and safety research
- Working group 3 Guidance document for responsible handing of nanomaterials.

The working groups started their work at the end of March 2007. Members of staff from the Higher Federal Authorities are involved here. Working group 1 is working on the assessment of the opportunities (e.g. resource conservation, environment-relieving effects and their assessment criteria). The draft research strategy devised by the Federal Institute for Occupational Safety and Health (BAuA), the Federal Institute for Risk Assessment (BfR) and the Federal Environment Agency (UBA) has influenced the work performed by the WG 2. The WG 3 is developing guidance documents for the protection of workers and emission reduction. In addition, in a working group created jointly by the German Chemical Industry Association (VCI) and DECHEMA, companies from the chemical industry discuss problems related to the impact on health and the environment ("Responsible Production and Use of Nanomaterials"). At international level the Higher Federal Authorities participate in the work performed by the Organization for Economic Cooperation and Development (OECD). A "Working Party on Safety of Manufactured Nanomaterials" (WPMN) that was established in 2006 focuses in its work programme on safety aspects relating to human health and the environment due to synthetic nanomaterials and the assessment of them. The topics that are required for a risk assessment are elaborated in 8 projects:

- Project 1: Development of an OECD database on EHS research
- Project 2: EHS Research strategies on manufactured nanomaterials
- Project 3: Safety testing of a representative set of manufactured nanomaterials
- Project 4: Manufactured nanomaterials and test guidelines
- Project 5: Co-operation on voluntary schemes and regulatory programmes
- Project 6: Co-operation on risk assessment
- Project 7: The role of alternative methods in nanotoxicology
- Project 8: Co-operation on exposure measurement and exposure mitigation.

The OECD working party therefore creates a very important platform for bringing together and agreeing at international level the diverse tasks and activities relating to the assessment of nanomaterials.

3 Strategic aims

The following aspects are of fundamental significance and should be considered generally during the conception of research:

- **Risk-oriented approach**

When determining the orientation of research, special importance should attach to the assumed risk.[4] Both the individual risk, which describes the level of the individual risk, and the population risk, which considers the number of affected persons, are relevant quantities which should crucially influence the process of determining the focus of interest of research. Characterization of a risk requires, inter alia, information on the extent to which humans and the environment may come into contact with nanomaterials (exposure) and, additionally, the dose-dependent toxicological and ecotoxicological properties of a substance. Only the combination of these two parameters enables a risk characterization and assessment. Essential characteristic variables are the extent of harm caused and the probability of harm occurring. Such considerations result in the finding that nanomaterials possess a higher toxicological/ecotoxicological effect potential and/or reveal a higher exposure of humans and the environment and have to be assessed as a priority. If no further exposure information is available, the annual production volume of a substance can be used as an estimated quantity for exposure.

- **Comprehensive risk characterizations and risk assessments**

The current uncertainties surrounding the risks posed by nanomaterials necessitate comprehensive risk characterization and assessment. This shall include all of the possible toxicological properties and end points as well as cover all of the various exposure situations throughout the life of a nanomaterial. The life-cycle analysis therefore forms part of the comprehensive risk characterization and assessment. In this process, the demands specified within the particular statutory framework must be considered and their suitability examined.

- **Integration into the statutory and sub-statutory regulatory framework**

A statutory and sub-statutory body of rules is available for the appropriate limitation of the risks. Since the options for action taken to limit the risks are oriented towards the body of rules and are derived from it, orientation and adaptation of the research activities to the demands of the statutory framing conditions are essential in order to be able to translate the results of the research into specific measures for the protection of humans and the environment should the need arise. In the public discourse, the question arises about whether the current statutory rules suffice or whether new laws are required. At present, integration into the existing statutory framework is envisaged and no attempts are being made to draw up a specific nano-law. Against this background, there is all the greater need to prove this by means of relevant assessments within the framework of the laws and to indicate any need for adaptation (UBA, 2007). It is unclear whether, in the statutory procedures which, as in the case of REACH, mainly proceed at the manufacturers' responsibility, greater participation by non-commercially oriented stakeholders or official institutions is required or is possible. There is a need for clarification here.

Against the background of current knowledge, a chemicals-related perspective, such as generally represented by REACH, is recommended. In the case of application-related rules (e.g. cosmetics, food additives etc.), this shall then be supplemented by these specific rules. With regard to a testing duty according to REACH, the minimum production quantities are set

[4] Risk is the qualitative and/or quantitative characterization of the type, severity and probability of any harm.

so high that many nanomaterials are not recorded. Discussions are currently taking place on whether it is sensible to lower the tonnage threshold for nanomaterials. Once improved knowledge on the use of nanomaterials in the individual technology sectors is available, technology-oriented considerations (nanoelectronics, nano-optics etc.) can be additionally applied.

- **Research that is application-oriented and relevant from the regulatory viewpoint**

Research activities with regard to the assessment of the risks are sensible if the research results may have an indirect or direct influence on the limitation of the risks. For this reason, safety-related research also calls for a shift away from pure basic research and a new orientation that enables the translation of the results into risk-oriented and comprehensive assessments and the derivation of specific instruments such as limit values, classifications and handling aids ("exploratory versus targeted research"). It is therefore necessary, as a matter of principle, for the toxicological and ecotoxicological studies to be performed in such a way that they can be used in regulatory toxicology.

- **Assessment of the novelty of nanomaterials**

Nanomaterials are understood as products of a new technology although a large percentage of the nano-structured materials currently on the market has for decades belonged to the established chemicals. To these are added recently produced nanomaterials that are indeed new. A large number of new nanomaterials is expected in future. In comparison with the established industrial chemicals, an increased need for information on the risks of the nanomaterials as a result of the new properties is justified from various quarters. These properties may lead to new risk scenarios for which empirical values are not currently available and for which special public interest exists. However, the new chemicals legislation REACH does not differentiate any longer between existing substances and new chemical substances as used to be stipulated in the previous regulations, the Chemicals Act and the Existing Substances Ordinance. It is necessary to examine the extent to which a particularly critical approach, one differing from other new or well-known chemicals, is justified in the case of the new nanomaterials.

- **International cooperation and coordination**

Nanotechnology is considered to be an important area of development by all industrial nations. Consequently, there is a recognized need for research at European and international level in order to be better able to assess the risks of the nanomaterials. Coordination of the research activities among the various nations and institutions should be targeted in order to enable a division of labour and to avoid duplication. In an increasingly globalized world, it is necessary to act at a supranational level while still taking due account of regional particularities.

- **Sustainability and the precautionary principle**

The need to consider aspects of sustainability when accompanying a new technology is of general importance and not specific to the assessment of the risks to health and the environment posed by nanomaterials. Long-term consequences with a harmful effect that only becomes apparent decades or generations later must be avoided. This is ensured by acting according to the demand for minimization. The same applies to the consideration of the precautionary principle which, as a fundamental principle, urges caution in the case of

knowledge gaps and is taken into account in test strategies as soon as the first grounds for suspicion become apparent.

- **More efficient structures for targeted promotion of research**

At national level, it is the Federal Ministry of Education and Research (BMBF) and, at European level, GD Research that assume the role of central promoters of the public sector in relation to investigating the impact on health and the environment. Without comparable financial means, the responsibility for the assessment within the current statutory framework lies with the Federal Ministry for Labour and Social Affairs (BMAS), the Federal Environment Ministry (BMU) and the Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) and the corresponding institutions at European level. Bodies which prepare and support the assessment of the risks within the current statutory framework have not yet been established and supported financially. A transfer of the research funds to the area of responsibility of BMAS, BMU and BMELV is urgently required to enable efficient and targeted research which takes account of the statutory framework.

- **Transparency and public discourse**

The consideration of social problems is a crucial factor in any attempt to do justice to a sustainable technological development. Due to the public interest, transparency and public discourse are essential elements of communication and discussion:

- The collation and compilation of current trends relating to the development of nanotechnology with regard to its positive and negative effects on the environment, health and safety.
- The assessment of the trends by the relevant players from the areas relating to society, politics, business and science.
- The development of dialogue offerings for a future-oriented public discussion alongside training and further training initiatives.

4 Research and work areas

The extent of the need to consider nanospecific aspects and particularities must be examined for the various specialist areas relating to chemicals assessment and management. If required, adaptations and changes must be undertaken in response to nanospecific characteristics. Consequently, research is basically needed for the topics presented in the following Chapter 4.

4.1 Definition and limitation of the topic

The definitions used in this text accord with the current status of the international discussion (OECD, ISO, SCENIHR 2007b; see 7.2 Definitions). Nanotechnology describes the production, investigation and application of structures, molecular materials and inner boundary surfaces with at least one critical dimension below 100 nm. In most cases the area from approx. 1 nm to 100 nm is the focus of attention. The limits are, however, fluid because in the low limit range the problems of complex molecules are also discussed and, in the upper limit range, the limit was shifted upwards in certain areas of nanotechnology product use (e.g. textile production). The agglomerates and aggregates of the nanoparticles, nanotubes, nanofibres etc. which are, in part, larger 100 nm, should also be the subject of consideration provided that a nano-structured form or the nanoscale functionality remain. According to the current knowledge on possible risks, insoluble and hardly soluble particles, fibres and tubes etc. or their agglomerates and aggregates are of particular toxicological relevance. Soluble nanomaterials lose their nanocharacter once they have come into contact with humans and the environment. For example, organic carrier substances (liposomes, micelles and vesicles) may be used. As a result, the bioavailability of the substances transported by the carrier substances is increased and the kinetics may be altered. Limitation to synthetically produced nanomaterials (“manufactured or engineered nanomaterials”) has already become the established procedure. Of special importance here are nanoparticles, nanotubes, nanofibres etc. or rather their agglomerates and aggregates. The already available insights into unintentionally produced nanomaterials (e.g. diesel engines emissions) or natural nanomaterials may provide supplementary data. Pharmacologically effective nanomaterials (e.g. cytostatics), which open up new possibilities in medicine, represent a particular area which, due to the special risk-benefit discussion and the specific statutory background, requires consideration in its own right and is not the subject of discussion here.

Working on future visions for nanotechnology for which no science-based clues for design and implementation exist is problematical. Molecular nanotechnology which brings atoms and molecules together in a targeted way, independent of biotechnological processes, to form highly complex and differentiated structures can, due to the lack of technical possibilities, not be the subject of discussion here, either. However, if technical innovations of practical relevance emerge, they must be considered contemporaneously.

This text provides a joint consideration of the safety of chemicals in the workplace, in the consumer area and the environmental compartment which concentrates on the release of synthetically produced nanomaterials during production, further processing and use as well as after use (from products).

4.2 Improvement in the comparability of studies on toxicology/ecotoxicology as well as on the environmental behaviour of nanomaterials

Published studies on the toxicological and ecotoxicological effects of nanomaterials are frequently the subject of intensive discussion in which experts also express conflicting views. At present, doubt is occasionally cast on the validity of studies on nanomaterials and their publications because information is missing or certain aspects were not considered in the

study design. This concerns in particular the characterization of the utilized material, the preparation of samples - in particular the production of suspension solutions in the aquatic compartment - as well as the issue of conducting suitable positive and negative controls. This makes the interpretation and comparability of results more difficult.

A research project undertaken by the Federal Environment Agency (Hund-Rinke and Herrchen 2007) evaluated studies in the area of ecotoxicology and environmental behaviour with the aim of identifying natural laws in the testing of nanomaterials. However, this assumes that relevant information is recorded and published in all of the studies. However, crucial gaps in information still remain here. As a result, inter alia, specific recommendations were made such as, for example, the systematic investigation of the connection between the property of a material and its behaviour/effect or the re-definition of the term stability (agglomerate formation, effectiveness and reversibility). In connection with test procedures in the environmental compartment, the recording of the stability of the suspensions is of vital importance, in particular in the prolonged tests (reproductive behaviour), since it is only thus that comprehensibility and comparability of the test results can be ensured.

The minimum requirements for the documentation and publication of toxicological and ecotoxicological studies have not yet been defined (see also 4.5.1). The information required for an estimation of the validity and comparability of studies with nanomaterials should be elaborated (e.g. the laying down of the characterization of the nanomaterials, impurities, preparation of samples). For the purpose of laying down the minimum requirements, a parameter set should be determined which, in an initial step, exactly characterizes parameters such as the chemical composition, the size of primary particles and agglomerates. In addition, the criteria for the definition of the term stability must be elaborated. These minimum requirements should be coordinated worldwide (e.g. with the criteria developed by the OECD). A similar concept already exists in the case of toxicogenomic technologies (MIAME = Minimum Information About a Microarray Experiment). The aim is to ensure that publications of toxicological and ecotoxicological studies as well as studies on the environmental behaviour include this information as a quality criterion. This would facilitate the discussion and recognition of study results.

Although worldwide coordination of the minimum requirements via the OECD is intended and desirable, in addition - following the current test methods - various variants for the determination of the same end points are being developed. In order to ensure that the results from these investigations can also be used and made comparable, the procedures must be tested on various nanomaterials in parallel and all of the relevant information must be published.

There is a particular need for research in this area which is concerned with the comparability of the studies and the definition of quality standards.

4.3 Identification of nanomaterials and characterization of their physico-chemical properties

4.3.1 Identification and differentiation of nanomaterials according to physico-chemical properties

It is particularly important to identify the relevant nanomaterials for the purpose of risk assessment. Since the assessment of the risks requires the assessment of the exposure it is recommended that the exposure be considered as a selection criteria for substances to be dealt with on a priority basis against the background of the large number of nanomaterials on offer. Nanomaterials with a high exposure potential must be identified and characterized as a priority. High-cost materials that are currently only available on a laboratory scale could only be relevant to risk in the future.

Titanium dioxide, silicon dioxide, zinc oxide, aluminium oxide, iron oxides, cerium oxide, silver, carbon black, carbon nanotubes, fullerenes etc. are mentioned as basic substances which are (also) placed on the market in nano-structured form. Initial results on the handling and use of nanomaterials are available (Plitzko and Gierke 2007, Stuer-Lauridsen et al. 2007). A systematic compilation which records the various substances in consideration of the morphological and chemical modifications is not yet available. The properties and morphological and chemical modifications concern, for example, solubility, size, surface area, form, degree of agglomeration/aggregation, surface modification or reactivity, number concentration and similar. These parameters are discussed as variables which may possibly have an influence on the toxicological and ecotoxicological properties. Since the possibility cannot currently be excluded that, as a result of modifications, not only technical properties but also toxicological and ecotoxicological properties can be altered, a systematic, differentiating overview is required. Such information is essential in order to be able to identify, in a risk-oriented procedure, those nanomaterials that must be assessed on a priority basis and tested more intensively.

Due to the considerable fundamental significance of these aspects, a considerable need for research exists (see also 5.2.1: Urgent projects of general importance).

4.3.2 Determination of the chemical reactivity

The physico-chemical parameters required for the assessment of the chemical reactivity are also relevant. For example, in the case of improper handling, flammable and oxidizing substances can result in sudden exothermal reactions and require particular protective measures. A particular catalytic activity can decisively accelerate reactions. It has not yet been clarified whether, in the case of a nanoscale modification of a substance, these properties differ significantly from, for example, microscale modification. The enlarged surface could have an influence here.

4.4 Exposure of humans and the environment

Considerable uncertainties currently attach to the characterizations of the exposure of nanomaterials to which humans and the environment are subject since, in particular, the following preconditions have not yet been sufficiently met:

- Sufficient information on the identity, distribution and use of nanomaterials
- Standardized measurement methodology and measurement strategies.

More precise knowledge is required in order to be able to assign a graduated information requirement regarding the health effects to the different nanomaterials in dependence on the extent and level of the current or expected exposure. The higher and more extensive the exposure of humans and the environment, the more intensively the nanomaterials must be investigated in terms of health effects.

4.4.1 Methods for the quantitative determination of nanomaterials

Validated and standardized quantitative measurement methods and measurement strategies in the various media are not currently available. In addition, there is still no international consensus about which combination of measurement parameters (solubility, size, surface area, form, degree of agglomeration/aggregation, surface modifications or reactivity, number concentration, mass or volume and others) has the greatest meaningfulness for the

estimation of the level of risk. In particular, the following are relevant as a source or locus of exposure:

- Workplaces
- Foodstuffs, cosmetics and other consumer products
- The environmental media air, water and soil as well as the occurrence in sewage sludge and in the case of disposal.

Up to now, measurement methods have been developed and discussed in the area of air exposures in particular (Maynard 2007, ISO 2007, Sioutas 2005, Kuhlbusch et al 2004, Kuhlbusch and Fissan, 2006). Various measurement systems are being tested:

- Cascade impactor
- Tapered Element Oscillating Microbalance (TEOM)
- Scanning Mobility Particle Sizer (SMPS)
- Electrical Low Pressure Impactor (ELPI)
- Condensation Particle Counters (CPC)
- Electron Microscopy
- Diffusion Charger
- TSI Model 3550 surface area monitor.

Additional challenges relating to measurement methodology result during the performance of the toxicological and ecotoxicological studies, for example, in the generation and standardization of the exposure atmosphere and the quantitative measurement in the biological material.

Since nanomaterials in the biological material cannot be made visible directly using light-microscopic methods, special methods (e.g. labelling of the materials, electron microscopy, fluorescence microscopy) are required in order to be able to identify the nanomaterials outside and inside the cell or cell compartments (e.g. cell nucleus). If labelling of the nanomaterials was performed for the purpose of quantitative detection, uncertainties remain about whether the labelling has altered the biological behaviour.

A particular need for research exists with regard to making image-generating methods methodologically reproducible and standardizing them using a quantitative statement or characterizing the kinetics of the nanomaterials in the organism.

Reference materials are needed in many measurement-technology areas to enable standardization, to create parameters and to ensure the comparability of results from different laboratories. Nanomaterials which can be used as a reference material have not yet been defined. Consequently, nanomaterials that are utilizable for standardization must be selected.

4.4.2 Exposures in the workplace

Inhalative and dermal exposure are of prime concern for the workplace. Due to better accessibility to measurement technology, the proven hazard after inhalation and the better barrier effect of the skin in comparison with the respiratory tract, the assessment of exposure has so far concentrated on the exposure by inhalation.

The above-mentioned measurement-technology systems that are available on the market for the recording of the particle concentrations are state-of-the-art. The checking and standardization of these various measurement technologies are to be described as priority

research tasks that are required to arrive at comparable assessment systems for the estimation of exposure. At the moment there are no standardized rules for the assessment of the performance of devices for the measurement of ultrafine aerosols (aerosols < 100 nm) in the workplace. The possibility of validation according to DIN EN 13205 or following this rule must be examined, adapted or elaborated anew.

A person-related measurement technology for the purpose of individual recording of the exposure is required for workplace-related measurement of nanomaterials and, in particular, as the basis for occupational-health epidemiological investigations. The person-related measurement devices must enable measurements for the recording of the mean exposure or exposure dose (shift-related). In addition to suitability for use in the workplace (robustness, good wearability, easy handling), further demands are the ability to also be used at high concentrations (inter alia, welding work) and the possibility for characterizing ultrafine particles (electron-microscopic analyses, the assessment of agglomerates and primary particles).

A further focus of research is the development of a simple calibration system for measurement devices intended for use in on-site measurements. A simple calibration system for measurement devices for the determination of the particle number concentration is not available at present. However, due to the transportation of the measurement device, the 'severe' conditions during on-site use associated with the need for relevance for practice, the varied climatic conditions and, last but not least, the ageing of devices (material wear and tear), calibration of the measurement devices prior to use in measurement is urgently required. The calibration should not, as is, for example, prescribed in the case of gravimetric measurement technology, only include a check of the volumetric flow rate of the air but instead consider the entire measurement system.

A uniform procedure during the measurement planning and documentation is required in order to ensure transparency in the processing of the measurement results and comparability between the measurement data. Standardized measurement strategies are both beneficial and necessary, particularly in the case of the complicated problem surrounding the measurement and assessment of ubiquitously occurring nanoparticles (incl. agglomerates and aggregates). The measurement strategies that are devised should be oriented towards the following measurement tasks:

- Routine measurements (workplace measurements for the purpose of obtaining an overview)
- Measurements within epidemiological studies
- Measurements within toxicological investigations.

A further main focus of research is the substance-related identification of the nanomaterials during the inhalative exposure measurements. Measurement devices for the determination of the particle number or surface concentrations are unable to distinguish between the nanomaterials that are to be determined according to their chemical composition. In a production process for the manufacture of nanomaterials or in connection with the handling of nanomaterials, it has so far not proved possible to make a distinction between product particles and further nanoparticles from the environment (concentration in the outside air) or from a different emitter in the work area (diesel vehicles, welding smoke). As long as this distinction cannot be made, any limit values for nanomaterials that may be discussed cannot be applied. A special need for research results for this area as well as for the development of reference materials (see also 5.2.2.1: urgent occupational safety projects).

The level of the exposure is essentially influenced by the on-site processes and protective measures. Production of the nanomaterials systems that are, as far as possible, closed as well as the use of further protective measures (e.g. air filtering in exhaust ventilation systems and filter masks, gloves) can essentially influence the exposure. Further influencing variables are, for example, processing occurring in dust-free form (pellets) or suspension in liquid media (solid in liquid) which are not nebulized to form liquid aerosols. The incorporation of the nanomaterials into a solid matrix (solid in solid) can drastically reduce the exposure. Consequently, the exposure in the three areas production, further processing/formulation and use in the workplace can change greatly.

In various systems relating to the assessment of risks and hazards, the level of exposure can be estimated quantitatively using model calculations. Before such models can be developed for nanomaterials, it is first necessary to develop the corresponding measurement methods and have available sufficient measurement data in order to identify the parameters (e.g. dust-forming behaviour, the form in which handling occurs, the substance quantity) that crucially determine the level of exposure from among the exposure conditions associated with the measurement data. Once the causal connections are demonstrated with sufficient certainty on the basis of various measurements, it is then possible to develop a model that permits the estimation of the approximate level of exposure even without the need for further measurements. In the case of dust-forming nanomaterials in particular it must be examined whether parallels to fine dusts result and whether the existing models for fine dusts can be adopted.

4.4.3 Exposure of consumers

In the same way as in the workplace, nanotechnology is also being increasingly used in the production of foodstuffs, food packaging materials, dietary supplements, cleaning products, biocides in the area relating to the household as well as in other consumer products. In addition, exposure via the water, soil and air is possible if nanomaterials enter these environmental media. Dermal, oral and inhalative exposure is fundamentally possible.

For example, dermal exposure is possible as a result of the use of cosmetic products as well as, however, via correspondingly treated textiles. In addition, nanomaterials in formulations of cosmetic products may influence the skin penetration of further constituents. The use of nanoscale titanium oxide and nanoscale zinc oxide as a UV filter in sunscreen products has been known for a long time. Little information is available with regard to further nanomaterials in cosmetic products and other consumer goods that might come into contact with the skin or mucous membrane.

Oral exposure may occur as a result of the consumption of foodstuffs that contain nanomaterials. It can, however, also come about if nanomaterials from packaging materials transfer to foodstuffs. In this connection, in addition to the need for information about such foodstuffs and packaging materials, there is also a need for research, both in connection with the question of absorption in the digestive tract and the systemic availability associated with it and a possible accumulation in certain compartments or organs as well as the migration behaviour of various nanomaterials from packaging materials for foodstuffs.

For example, exposure by inhalation occurs during the use of spray aerosols in the household. The case of a so-called “nano” sealing spray whose use led to severe lung diseases showed how unreliable the information on exposure is. It finally turned out that the “nano product” did not contain any nanomaterials at all (BfR 2006a).

Consequently, from the point of view of consumer health protection, knowledge about the occurrence of nanomaterials in household products (both articles and preparations) is of considerable interest. It would therefore be extraordinarily helpful if the use of nanomaterials

in consumer products was sufficiently documented. Special investigations involving oral exposure are presented in Chapter 4.5.4.2.

4.4.4 Exposure of the environment

Like exposure of workers and consumers, the exposure of the environment is currently largely unclear due to the absence of essential information on the type, distribution and use of nanomaterials. Likewise, little is known about the direct use of nanomaterials in the environment (e.g. treatment of waste water, restoration of soils or pest control).

In addition, the growing use of synthetic nanoparticles is likely to lead to increased releases to the environmental media soil, water and air in the future. Research findings on the behaviour and impact of natural ultrafine dust or ultrafine dust formed during incineration can only be partially applied to the risks of engineered nanoparticles. Further studies are needed for the adequate assessment of potential risks. Nanoparticles formed “naturally” vary considerably in form, composition and size whereas artificially - "intentionally" - engineered nanoparticles are normally manufactured and designed in a uniform way based on desired properties. The wide application possibilities for nanotechnology and the highly diverse nanoparticles require a differentiated approach when it comes to assessing a possible threat to the environment.

When assessing the exposure risk for nanoparticles, the decisive factor is the form in which these materials come into contact with humans and the environment. Key information concerns how nanoparticles released from materials behave in the environment, how stable and long-lived these forms are, whether they for instance disintegrate or agglomerate, are soluble in water or body fluids, interact with other nanoparticles, chemicals, surfaces or are degraded and how their properties change in these processes.

Given their small size nanoparticles can be widely distributed by air. In soil, because of their large, active surfaces, nanoparticles can bind and mobilise pollutants like heavy metals or organic substances and therefore pose a threat to ground water.

Stable nanoparticles can enter living cells and possibly accumulate there.

So far no findings have been reported about how organic nanomaterials are degraded in the environment. Fullerenes very rarely occur naturally, and nanotubes are not naturally occurring carbon modifications and they are stable. There are no indications about whether and how these carbon nanomaterials are degraded, disintegrated, aggregated.

4.4.4.1 Release of nanomaterials to the environment during production, further processing, use and disposal

Findings from research activities to identify nanomaterials and characterize their physico-chemical properties as described in Chapter 4.3.1 provide information on the sectors that produce nanomaterials and on the products that contain them. Information should also be generated on other sectors that handle nanomaterials in production because this may result in environmental exposure. Existing knowledge concerning the release of nanomaterials to the environment during production, further processing and use must be collated through further company surveys.

A further exposure route and, at the same time, research area is the intentional use of nanomaterials in the environment. Nanoscale substances are used to remove inorganic and organic pollutants from soils, water (e.g. removal of substances containing arsenic from drinking water with the aid of nanoparticulate iron oxide) and waste water, as well as in pest control (e.g. silver).

Both the areas of application and the likely exposure routes for each should be described. In addition, the knowledge that is available with regard to the behaviour and fate of these nanomaterials must be collated.

On the basis of the totality of the information that is to be generated, priority nanomaterials for investigation of environmental exposure can be identified to create a sound basis for subsequent determination of the environmental risk.

Research activities are required to clarify the release of nanomaterials to the environment during production, further processing, use and disposal. Furthermore, nanomaterials intentionally released to the environment should be identified and their fate clarified.

4.4.4.2 Development or adaptation of measurement methods for environmental compartments (air, water, sediment, soil and sewage sludge) and for biota

To date, no knowledge exists with regard to methods suitable for the determination of the exposure and fate of nanomaterials in environmental compartments or biota. This knowledge is important for devising life-cycle analyses and exposure scenarios, for identifying those nanomaterials that must be examined on a priority basis or for determining the effective exposure level in subsequent ecotoxicological testing. Currently available measurement methods and findings from research area 4.4.1 (exposure and measurement technology) should be examined for their suitability for measuring nanomaterials in the environment. Since the current methods do not consider the special demands associated with the measurement of the parameters that are relevant to nanomaterials, it is necessary, alongside the adaptation of current analysis methods, to also develop new validated instruments for the measurement of particle mass concentration, surface concentration and size distribution in various systems. Waste water analysis should be a first focus of interest since this is a major release route. In addition to quantitative determination, it should also be possible to characterise the nanomaterials (e.g. chemical composition, particle size and distribution, solubility, hydrophilicity/lipophilicity, state of agglomeration, shape, surface, zeta-potential).

The development of measurement methods for environmental compartments (air, water, sediment, soil and sewage sludge) and for biota is a prerequisite for the development of life-cycle analyses and exposure analyses of nanomaterials. Consequently, there is a particular need for research in this area.

4.4.4.3 Life-cycle analyses and exposure scenarios for nanomaterials entering the environment

The methodology of life-cycle analyses and exposure scenarios should be examined with regard to the special demands of nanomaterials and, if necessary, adapted. For exposure assessment, the physico-chemical properties of released nanomaterials (e.g. chemical composition, particle size and distribution, solubility, hydrophilicity/lipophilicity, state of agglomeration, form, surface, surface charge) should be determined first. Depending on these properties, exposure routes with the relevant releases to the various media should be estimated. This should consider releases during production via waste gas, waste water and waste as well as during transportation and further processing to a finished product. Exposure during the use of finished products treated with nanomaterials, e.g. as a result of abrasion, wear and tear or washing, should also be examined. For example, it is highly probable that textiles which are surface-modified with nanomaterials release particles during the washing process. No data are available with regard to the size and number. One important aspect is the behaviour of the nanomaterials after use during disposal, landfilling, incineration or reutilization. The aim of the required research activities is the development of life-cycle

analyses and exposure scenarios. For this purpose, relevant influencing variables leading to exposure to nanomaterials during their entire lifecycle should be determined in order to be able to consider possibilities for reduction at an early stage within the production processes.

Research is required in this topic area due to the need for development of life-cycle analyses and exposure scenarios for further-going investigations into the behaviour and fate in the environment and the development of risk-reduction measures.

4.4.4.4 Investigation into the behaviour and fate in the environment

A crucial factor for the determination of a risk of exposure to nanomaterials is the form in which these materials come into contact with humans and the environment. It should therefore be examined how stable and long-lived these forms are, whether and under which conditions they, for example, decompose (e.g. under the effect of ozone or UV light) or agglomerate, are soluble in water or body fluids, interact with other nanomaterials, chemicals, surfaces or are degraded and how their properties alter as a result. In accordance with the exposure routes determined from production, processing and use, the fate of the starting products of nanoscale substances and their conversion products must be tracked and measured in the target compartments. The extent to which long-range atmospheric transport may occur must also be examined.

Nanomaterials are provided with special functions for their use. In the case of release to the environment, these properties can result in undesired effects in the environment. Besides having direct toxic properties, nanomaterials due to their specific form, surface or charge may interact with chemicals in an undesired way or bind nutrients. There has been little investigation of this so far. There are also few insights available with regard to the modification of nanomaterials through environmental impacts. Changes in their physico-chemical properties may result in undesired effects such as mobility, carrier effects or ecotoxicological effects.

There is a need to investigate the fate in the environment and in biota since knowledge about exposure forms part of the risk assessment of nanomaterials. The behaviour in the environment should be examined in a targeted manner, in particular with regard to the way that certain functionalities impact the environment, e.g. the mobilization of harmful substances, the binding of nutrients or the effect as catalysts. It is urgently necessary to clarify which relevant parameters can be taken as a basis for predicting environmental behaviour. In this context, it should also be clarified under what conditions such nanofunctions can be acquired, modified or altered and how (or whether) nanomaterials lose these functions and, for example, dissolve.

4.4.4.5 Investigations into persistence and bioaccumulation

Nanomaterials can enter the environment in the course of their lifecycle. How long they survive there, and in which form, i.e. how long they persist, is a matter for urgent investigation. Through the relevant release routes to the various media (water, sediment, soil, sewage sludge, air), nanomaterials can enter the compartment-specific biota. As a result, they have the potential to accumulate in organisms and via the food chain.

Investigation is required to determine the extent to which existing standard test procedures are suitable for generating information about the bioaccumulation potential or the persistence of nanomaterials or whether conclusions derived from physico-chemical data (e.g. logPow,-octanol/water partition coefficient of a substance) also apply to certain groups of nanomaterials. It may be necessary to elaborate proposals for modification of the guidelines. There is a general need to review the definition of the term “persistence” with regard to

whether it has to be modified for nanomaterials, since in their case the particle properties must be considered additionally. This is also an important aspect with regard to REACH since vB and vP substances ("very bioaccumulative, very persistent") belong to the substances of concern which must be subjected to an authorization procedure even if there is no evidence of toxicity.

Nanomaterials to be investigated as a priority include above all the numerous modifications of carbon nanotubes and fullerenes which do not occur in nature in these varied forms. In addition, it should be examined, as a function of quantity used and relevant exposure route, whether the spectrum of organisms used in determining a bioaccumulation potential must be extended.

Since the same materials may react very differently depending on their state (size, form, charge), one focus of attention, in addition to environmental behaviour, should be the investigation of the dependencies on the materials' intrinsic properties.

The investigation of persistence and bioaccumulation are important areas of research. Experiences with other persistent substances reveal that such substances cause long-term problems after their release to the environment and can no longer be recovered.

4.5 Toxicological assessment of nanomaterials

4.5.1 Methods for the determination of the toxicological properties

The acute and chronic toxicity, the irritant and corrosive effect, the sensitization and the CMR end points carcinogenicity, mutagenicity and reproductive toxicity (developmental toxicity, fertility impairment) are the key toxicological end points that must be examined with regard to chemicals. The toxicological end points are presented in greater detail, for example, under EC (2001) and EC (2003). In order to be able to assess the effects of chemical substances on health, various standardized test methods were developed which permit an assessment of the effects on various organs and organ systems (OECD 2007, EC 2006b):

- Methods for the determination of physico-chemical properties
- *in vitro* methods (cellular and cell-free)
- *in vivo* methods (animal experiments, occupational medicine/epidemiology).

At present, the validity of studies with nanomaterials and their publications is occasionally called into question because information is missing or because some aspects are not considered in the study design. This applies in particular to the characterization of the utilized material. In general, the process of checking the methods includes the identification of the relevant information that is essential to the study report and the publication of the study in order to ensure relevance for the assessment. SCENIHR (2006a, 2006b) discusses the suitability of the test methods and indicates possible additions.

4.5.1.1 Methods for the determination of the physico-chemical properties

Information on physico-chemical properties may contribute to the assessment of the toxicological properties of chemicals. They are of special importance due to the solid-substance character of most of the relevant nanomaterials. The situation is similar to the discussion on fine dusts and fibres. Inter alia, the following aspects are discussed as possible physico-chemical influencing variables:

- Solubility
- Size

- Surface
- Form
- Degree of agglomeration/aggregation
- Surface modification or reactivity
- Number concentration
- Mass
- Volume etc.

The influence of these variables on the toxicological dose-response-relationships of the nanomaterials has not yet been sufficiently characterized.

4.5.1.2 *in vitro* methods (cellular and cell-free)

By means of investigations involving biological material or cells, the toxicological *in vitro* methods of the OECD attempt to obtain indications of possible harmful effects in man. In addition to saving time and money, the aim here is animal welfare. The methods investigate, inter alia, the local damage to the skin and eye, the skin permeation and the genotoxicity. Various further *in vitro* methods are discussed specifically in connection with their application to nanomaterials. Cell-free *in vitro* studies provide information on the interactions with proteins, the activation of the complement system and the induction of oxidative stress. The cellular systems produce, inter alia, data on the translocation of the nanomaterials, on genotoxicity as well as on the biological effect mechanism in cells of the portal of entry and the systemic target organs.

For example, the Comet Assay and the measurement of 8-hydroxy-deoxyguanosine are given for the determination of a genotoxic effect component (Oberdörster et al. 2005b, Greim et al. 2001, Schins 2002a, Schins et al. 2002b). The oxidative stress, which is discussed as the cause of damage and activation of cells (Oberdörster et al. 2005b), can, in the opinion of various authors, be detected by means of the measurement of dichlorofluorescein and oxidized gluthathione as well as by the determination of nitrosated proteins (Hess et al. 2005, Janssen et al. 1993, Quinlan et al. 1995). The reactivity of the alveolar macrophages can be checked using the “vector model” which provides information on the metabolism, on the secretion of inflammation mediators and reactive oxygen species (Luther, 2004, p. 74, Bruch et al. 2004).

In vitro methods are currently not suited to assessing with sufficient certainty the effects of nanomaterials since the sensitivity and specificity required to predict the effects resulting from nanomaterials in humans are questioned (Sayes et al. 2007, Maynard 2006e). Furthermore, *in vitro* methods currently have a further methodological disadvantage since they were, as a rule, developed for dissolved substances. It is difficult to turn various nanomaterials into a finely dispersed suspension. They sediment or remain on the surface of the medium.

A special need for research exists with regard to examining the qualitative and quantitative meaningfulness of the *in vitro* studies using statistical parameters (e.g. sensitivity and specificity) so that *in vitro* methods can be employed in an optimal and statistically certain way for the purpose of assessment, promoting animal-substitution methods and making a contribution towards a specified test strategy (see also Chapter 5.2.1 Urgent projects of general importance).

4.5.1.3 *in vivo* methods

The *in vivo* test methods obtain information, for example, by means of histopathological procedures about whether, after oral, dermal or inhalative administration in the animal experiment, harmful effects occur at the portal of entry or the inner organs and whether the foetus is harmed or the fertility impaired. In addition, it is possible to acquire information about the deposition, the uptake into the blood-circulation system, the toxicokinetics and toxicodynamics as well as the biopersistence. The histopathological examination and the examinations of the BAL[5], the oxidative stress and the cell proliferation may make a contribution towards clarification of the mechanism. The additional determination of acute phase proteins and coagulation factors provides an insight into the effects on the cardiovascular system.

In recent years there have been discussions at national and international level about whether the established OECD test methods (EC 2006b, OECD 2007) that have been developed so far to examine the toxicological effects within the framework of the various statutory rules and regulations are perhaps not sensitive enough to demonstrate specific effects of nanomaterials on human health. It is certainly the case that the number of parameters measured in studies can be increased indefinitely. However, this not only applies to nanomaterials but, to the same extent, to other existing and new chemicals. If an organ, for example, the lung is known as a target organ for insoluble nanomaterials after inhalation, it is sensible to add certain measurement parameters such as, for example, the examination of the BAL. This already happens in the case of good studies on microscale fine dusts. Furthermore, there is currently the need to examine the inner organs in the case of exposure to nanomaterials if a systemic availability cannot be excluded. Oral OECD studies on the toxicity after repeated exposure already regularly provide for this. In accordance with the test design for oral studies, this approach must be added with regard to inhalation studies. Although the number of the aforementioned nanospecific additions is manageable, the appropriate consideration of a possible cardiovascular toxicity such as is indicated by the environmental epidemiological data is unclear. *In vivo* test approaches which consider cardiovascular parameters are already available. Their suitability and validity has, however, not been clarified. The insights from environmental epidemiology indicate that a phenomenon is involved here which also applies to fine dusts.

Research is required here in order to be able to coordinate the established OECD test methods internationally. The methods must be supplemented by test parameters for which indications of relevance to nanomaterials exist (e.g. BAL in the case of inhalation studies, cardiovascular parameters, investigations into systemic toxicity). Kinetics studies represent a special challenge because the problem of the quantitative detection of the relevant nanomaterials in biological materials has not yet been solved methodologically for a large number of nanomaterials. Besides this, a detection method must be developed for each nanomaterial on a case-by-case basis (see also Chapter 4.4.1).

Reference materials are required as a benchmark control in toxicological studies in order to check the correct performance of the test involving positive and negative controls. Standardization is required in order to create parameters as well as to ensure the comparability of the results from various laboratories. Nanomaterials utilizable as a reference material have not yet been defined. Consequently, there is a need for a selection of well-characterized nanomaterials which can be used for the purpose of standardization and as a parameter.

[5] BAL: Bronchoalveolarlavage: lavage of the lungs with a physiological salt solution in order to obtain lung fluid

4.5.1.4 Epidemiology/occupational medicine

Information about the effects on the health of workers and consumers can be obtained within the framework of epidemiological investigations and occupational-medicine studies. Thus it is possible to avoid the uncertainties that result from the extrapolation of effects in the animal experiment to man. Accompanying occupational-medicine and epidemiological research is an essential component in the assessment of the risks and the effects on human health. However, the meaningfulness of epidemiological investigations is dependent on reliable exposure data.

Epidemiological studies on the effect of synthetic nanomaterials in the workplace with statements about the specific effect of nanoscale particle sizes have not yet been performed. A considerable need for research in connection with the short-term and long-term effects of synthetic nanomaterials on workers in the case of inhalation and skin contact results from this. In the case of evidence of relevant occupational exposures to nanomaterials, the relationship to suitable effect parameters for exposure (in particular the parameters for respiratory and cardiovascular function) must be examined.

4.5.2 Toxicological properties of nanomaterials

It is becoming increasingly possible to design a basic chemical (e.g. titanium dioxide, silicon dioxide, zinc oxide, aluminium oxide, iron oxides, ceroxide, silver, carbon black, carbon nanotubes, fullerenes) in terms of its morphology and surface properties at the nano-level as well. In this way, new technological properties are achieved. The extent to which significantly altered toxicological properties may result from a change in the morphology or the surface (coating, covalent ligands) is currently unclear. Nanomaterials whose basic substances are soluble in biological fluids lose their nanostructure characteristics once they have come into contact with biological material. In the case of soluble materials, a nanospecific toxicity could still result from a change in the kinetics. However, the focus is currently on the hardly soluble nanomaterials that retain their nanostructure. Nanostructures which are incorporated into a stable material and thus do not come into contact with biological fluids or cannot be taken up by the organism are of less importance. They can possibly only be released after disposal of the products by means of incineration or decomposition. Consequently, the free nanomaterials that can be taken up via various routes are of special toxicological importance. Included here are the nanoobjects (nanoparticles, nanotubes, nanorods, nanoplates). Since they can only be stabilized as singular particles etc. under special conditions, their agglomerates and aggregates must be additionally considered. Insoluble microparticles with a nanoscale coating can also be understood as nanomaterials. The ability of the morphology and the particle size of an insoluble material to acquire toxicological relevance is not a new phenomenon. The established subdivision into respirable and alveolar dust and the morphology-dependent fibre toxicity adequately demonstrate this. Viewed from this perspective, the toxicity of the nanomaterials represents a further facet of the well-known particle and fibre toxicity.

Preliminary information indicates that a large percentage of the nanomaterials (in particular, nanoparticles, nanofibres and nanotubes or their agglomerates and aggregates) that are currently being placed on the market in larger quantities or are experiencing clear growth consist of the following basic substances:

- Carbon: carbon black
- Carbon: carbon nanotubes
- Carbon: fullerenes
- Silver

- Titanium dioxide
- Silicon dioxide: amorphous and crystalline
- Zinc oxide
- Aluminium oxide
- Iron oxides
- Cerium oxide.

In their diverse modifications, these nanomaterials probably result in a higher exposure of humans and the environment than other nanomaterials which are so far only being produced in low quantities.

Sufficient investigations into health effects are not available for many newer nanomaterials. In particular, studies which could be used for an assessment within the framework of chemicals legislation are rare. It is therefore not possible to make any sufficiently certain statement about these nanomaterials. By contrast, nanomaterials placed on the market for decades have frequently been investigated more thoroughly. In addition to a fairly large number of *in vitro* studies whose suitability for the assessment of the health effects on humans is not clear, *in vivo* studies have been performed, in particular for nanomaterials that have long been placed on the market. It is not the task of this text to collect and evaluate all of the studies that have been performed. Reference is made in this connection to a number of reviews on toxicology, the risks and the original literature that is cited there (Allianz 2005, BIA 2003, Borm et al. 2004, Borm et al 2006b, Borm and Kreyling 2004, Chen et al. 2007, Colvin 2003, Donaldson et al. 2006, Environmental Defense and DuPont 2007, Flinders Consulting Pty Ltd 2006, IOM 2004, HCN 2006, Helland 2007, HSE 2004, Hurt et al. 2006, IRSST 2006a, IRSST 2006b, Kreyling et al. 2005, Krug et al. 2007, Kuempel et al. 2006, Lam et al. 2006, Luther 2004, Maynard and Kuempel 2005, Maynard 2006a, Maynard 2006d, Meili 2006, Meili 2007, Nanoforum 2005, Nel et al. 2006, Oberdörster et al. 2005a, Oberdörster et al. 2005b, Panessa-Warren et al. 2006, Paschen et al. 2003, Royal Society and the Royal Academy of Engineering 2004, SCCP 2007, Schmid et al. 2006, Swiss Re 2005, Stern and McNeil 2008, United Kingdom 2005, Defra 2005, U. S. EPA 2007, NNI 2006).

Reference is only made here to a number of key findings. For example, prolonged oral and inhalative *in vivo* studies were performed with certain nanoscale forms of the amorphous silicic acid and titanium dioxide (ECETOC 2006, NIOSH 2005b). Consequently, it is possible to set a limit value for these probably widely distributed nanomaterials. This has already occurred for the workplace atmosphere in the case of amorphous silicic acid (Greim et al. 1989, TRGS 900 2007).

A toxic effect of nanomaterials was detected in the lung after inhalation in animal studies, inter alia, with nanoscale titanium dioxide which has long been placed on the market (e.g. NIOSH 2005b). Similar to larger fine-dust particles in the micrometre range, lung toxicity (inflammation, fibrosis) and the formation of tumours were revealed for a correspondingly high exposure. It should be assumed that such effects can occur in man, too, in the case of correspondingly high exposure. Similar findings were established in experiments in which exposure by inhalation was simulated by means of intratracheal instillation (inter alia, Mohr et al. 2006, Roller and Pott 2006). Similar to situation for many fine-dust particles, this effect is caused by an overloading of the lung with insoluble or hardly soluble particles. Consequently, it is assumed in various quarters that these effects do not occur in the case of realistic exposures of man. However, the mechanism of the tumour formation has not been fully clarified since, like fine dusts, some nanomaterials trigger oxidative stress whose contribution to the formation of tumours has not yet been quantified. Related to the mass per unit volume,

in part, a higher potency of effect was detected for the nanoscale modifications in connection with lung toxicity.

The particularly small size of the nanomaterials is the characteristic of these substances and is also associated with a possible nano-specific toxicity. The enlarged surface is in particular assumed to be the reason for an, in part, increased potency of effect. The small size of the nanomaterials can also result, for example, in their penetrating the organism after inhalation and reaching further organs in addition to the lung. For example, they were detected in various organs (inter alia, the liver, the brain). The biological relevance of these insights has not yet been sufficiently clarified since no detailed histopathological or functional investigations for the determination of a dose-response relationship are available for the aforementioned inner organs. A special need for research results with regard to the influence of the size of the nanomaterials on toxicity. It may perhaps be possible to jointly assess differently sized particles. The quantitative difference in terms of the potency of effect between nanoscale and microscale particles must be described better.

Epidemiological data on the toxicity of the heterogeneously composed environmental fine dusts (inter alia, diesel engine emissions) reveal an increased rate of cardiovascular diseases in the population. A similar effect is also assumed for the nanoscale (ultrafine) fraction of the environmental dusts. However, mixtures are involved here which cannot be traced back to intentionally produced nanomaterials.

The intentionally produced nanomaterials should not be considered to be an isolated research area. Due to their size, account must be taken of the features that are shared with the unintentionally arising (welding smoke, diesel engine emissions) and natural particles of this size. The data relating to the larger and better investigated fine-dust particles are also of importance because similarities exist between both particle fractions with regard to lung toxicity.

It is variously discussed that the provision of a mass-related dose is possibly not suitable and that, for example, the surface represents a better measure of the dose. In terms of measurement technology, it is easy to undertake a determination of the particle number in air. A further method which records geometric parameters is required for a more precise characterization. At least in the case of an idealized roundish particle, various measurement parameters that are being discussed can be converted to one another using geometric formulae. It is possible to calculate the mass from the volume via the density of the nanomaterial.

Overall, further experimental studies and assessment activities are considered to be very important for being able to sufficiently assess the toxicological properties. Here attention must be paid to ensuring that the studies are also suitable for the assessment within the framework of regulatory toxicology (e.g. classification/labelling, setting limit values).

4.5.3 Test strategies and risk-assessment procedures

Developed risk-oriented test strategies[6] or risk-assessment procedures[7] are available for industrial chemicals in general (inter alia, EC 2003, BMA 1998, BUA 2003, IPCS 2005, EC 2007, Risk Commission 2003). They are used nationally and internationally in the

6: Test strategy: a test strategy is understood as a programme of testing with a defined sequence which can be modified in dependence on information about the exposure and toxicology of the substance. The test strategy is applied to individual substances. As a result, a data base is created which, as a rule, enables a comprehensive characterization and assessment of the risks of a substance.

7: Risk-assessment procedure: in this context, a risk-assessment procedure is understood as a defined approach in the interpretation and assessment of the generated substance data which, in consideration of substance-specific particularities, permits consistent characterization and assessment of the risks. The assessment of the risks is not only based on scientific and medical insights but additionally includes social evaluations about which residual risks can still be considered acceptable. Results of individual-substance-related assessment are, for example, limit values for the workplace atmosphere, limit values for substances in foodstuffs and cosmetics, classifications and risk phrases or handling recommendations.

assessment of the risk and the possible derivation of measures for the limitation of the risks (classification, limit value, recommendations for handling, concepts for measures etc.). In a risk-oriented test strategy, toxicological information and exposure-related information influence the selection of the studies that are required. The lower the exposure, the lower are also the demands. Since the currently available test strategies and those planned under REACH contain risk-oriented elements, it is possible to use the current system for the testing of toxicological properties, the assessment and the limitation of health risks for nanomaterials, too and to modify them as required. Supplementing the test methods by study parameters which take account of specific aspects of the nanoparticulate effect mechanisms, e.g. after exposure by inhalation in the lung (BAL investigations), suggests itself (see under *in vivo* methods).

However, there is currently no consensus concerning the test strategy or the assessment procedures that should be employed to investigate and assess the health risks of the nanomaterials. Oberdörster et al. (2005b) concerned themselves with a "screening strategy" for nanomaterials in an overview study. It has not yet been possible to develop a detailed and specific test strategy for the assessment of the health risks. As a matter of principle, account must be taken of the results of the studies (see above) from the three areas:

- physico-chemical properties
- results from *in vitro* methods (cellular and cell-free)
- results from *in vivo* methods (animal experiments, occupational medicine/ epidemiology).

SCENIHR (2007a) discusses the suitability of the risk-assessment procedure as it is presented in the "Technical Guidance Documents". The body expresses the view that, in general, the methodology is suited to identifying a human-health hazard. Additions are possibly required. The German Chemical Industry Association's position is that, apart from the need for additions, the current assessment procedures are suitable (VCI 2005). Environmental Defense and DuPont (2007) have already developed an assessment aid ("Nano Risk Framework") which, in a risk-oriented approach, supports the assessment of the risks, the risk management and the assessment documentation.

It would desirable for low-cost and animal-saving studies to be available which would provide rapid and reliable results. Ideally, *in vitro* methods or physico-chemical (PC) data, for example, on solubility, size or surface coating should permit reliable conclusions about the effects in the human organism (low-cost high throughput *in vitro* assays, Luther 2004, p. 74). The extrapolation of the results to humans often occurs in the following series with increasing certainty the closer the measurement system is to man.

PC data[8] → *in vitro* animal/(human) → *in vivo* animal → *in vivo* human

However, simple PC investigations and *in vitro* methods are not sensible if they do not predict the effects in humans with sufficient sensitivity and specificity. Controversy surrounds, in particular, the predictive value of cell culture studies with (transformed) target tissue cells as a qualitative and quantitative indicator test for chronic effects. Since the currently available *in vitro* methods do not suffice, it is necessary to develop *in vitro* methods further or to devise new *in vitro* methods. The validation and establishment of *in vitro* test methods in a test strategy will be one important task for future research (see also 5.2.1: Urgent projects of general importance). So far no limit value has been derived when *in vitro* methods were used as the central data base. In order to be able to assess the suitability of *in vitro* methods, it is necessary to also perform suitable *in vivo* studies as reference studies for selected nano

[8] Substance identity, solubility, size, surface, coating, agglomeration, lipophilicity, crystallinity etc.

materials if they are not already available. Studies on larger particles (e.g. microscale particles) may possibly be considered if it is plausible that the results are transferable to the nanoscale fraction.

Meaningful publications on health effects on humans caused by nanomaterials are not yet available and only provide clear results for morbidity and mortality in the case of effects with a latency period if fairly large collectives have already suffered irreversible damage (see asbestos).

Consequently, special importance attaches to prolonged animal-experiment test methods with histopathological investigations into the determination of the dose-response relationship as a reference variable in the test strategy. They are a prerequisite for the assessment of the possible effects on the various target organs (lung, brain, liver etc.), not only after single exposure but also after chronic exposure for the purpose of deriving limit values. The OECD prolonged test methods which should include specific investigations, for example, with regard to the lung toxicity and cardiovascular effects in addition to a complete histopathology provide a good basis. Subchronic (and, possibly, also subacute) studies may likewise provide meaningful information (excluding carcinogenicity, though). It is only such studies with extensive histopathology etc. that permit (in addition to human data) the identification of the affected target organ.

In a further step, the mechanism of toxicity, in so far as it is relevant to assessment, can be clarified in more specific studies which concentrate on the target organ. In addition to the clarification of the chronic toxicity, the end points mutagenicity, carcinogenicity and reproductive toxicity are of particular importance. Information on the mutagenic effect potential can be obtained *in vitro*. If relevant grounds for suspicion exist, in particular in the case of systemic availability, *ex vivo* or *in vivo* studies are required for the purpose of further clarification of the mutagenicity. Positive mutagenicity data may provide indications of a possible carcinogenic potential. A chronic study would be required to clarify the grounds for suspicion. In the case of systemically available nanomaterials, the reproductive toxicity likewise represents an essential end point. The investigations into the gonads in studies with repeated exposure are already providing initial results. A final assessment will only be possible on the basis of teratogenicity and generation studies. Chronic toxicity and mutagenicity studies should be performed before those relating to reproductive toxicity. The examination of further toxicological end points (acute toxicity, sensitization etc.) is also integrated into the aforementioned existing test strategies for chemicals.

Since, with regard to most of the toxicological end points, the *in vivo* studies currently represent the only - also in the regulatory context - accepted data base, there is an urgent need to investigate the *in vivo* toxicity of the nanomaterials. A base data set must be established or supplemented on the basis of *in vivo* studies in order to identify the target organs and establish a dose-response relationship. Due to the considerable fundamental importance of this area of research, there is great need for research here (see also 5.2.1: urgent projects of general importance).

Since nanomaterials were detected in inner organs after inhalative administration, it is first necessary to consider all of the possible target organs. Studies on the kinetics of the substance in the organism could clarify substance-specifically whether certain target organs cannot be reached and whether, at least, these organs cannot be directly damaged. However, this would require a sensitive method for the detection of the nanomaterials in the organs and body fluids, something which in most cases represents a new methodological development. Besides this, there is also the uncertainty about whether the prior labelling of the nanomaterial which is, as a rule, required for detection can influence the toxicity. Research is required to determine the absorption, distribution, metabolism and the

elimination of nanomaterials in the organism in order to clarify the toxicokinetics of these in part novel substances.

Once the primary target organs have been identified via the above-mentioned studies, for the assessment of the risks and the derivation of a limit value, it may be necessary to examine the mechanism of toxicity by performing special investigations of the target tissue. For example, the hypothesis was advanced in connection with the lung as a target organ that the pulmonary tumours are the result of a chronic inflammatory reaction and a secondary genotoxicity. On the other hand, nanomaterials can form reactive oxygen species and trigger oxidative stress which might have a direct influence on the integrity of the DNA. Dependent on the mechanism, various limit values and classifications may result within the framework of the risk assessment. Further investigations into the mechanism of toxicity are required in consideration of parameters of inflammation, immunotoxicity and genotoxicity. Consequently, there is also need for research to also undertake investigations which clarify the mechanism of toxicity.

A lack of experimental data and uncertainties about the suitability of the currently available test methods, test strategies and assessment procedures have resulted in no appropriate risk assessments being performed. Unfortunately, mature and internationally coordinated test strategies and assessment procedures are only to be expected in the long term. On the other hand, it has so far not emerged that the previously employed procedures (in particular the *in vivo* test methods) are fundamentally unsuited. Consequently, it is in the public interest to now undertake full collation, characterization and assessment of the studies on nanomaterials that already result in high exposures. In the case of some of the nanomaterials (e.g. silicon dioxide, titanium dioxide), numerous results from toxicological studies are available (ECETOC 2006, NIOSH 2005b) which have so far not been examined and assessed in consideration of the demands of the regulatory framework. It is only possible to identify the gaps in the data from which an additional need for testing may result once the available data have been inspected. Such assessments are provisional assessments required in order to be able to add future insights to the test strategy etc. Dependent on the regulatory context (e.g REACH, biocides, food additives, cosmetic products etc.), these assessment activities must take account of the corresponding sub-statutory instructions (“Technical Guidance Documents” etc.). In this way, the assessment activities that are required anyhow (e.g. in REACH) are prepared and the primarily responsible industry is supported in the task of appropriately characterizing and assessing the nanomaterials. Since integration into the existing statutory framework is currently envisaged and since no specific “nano law” is planned, there is all the more need to demonstrate this by means of corresponding assessments within the framework of the statutory rules on substance assessment.

Owing to the high fundamental importance of this area, there is a special need to start a research initiative for the purpose of assessing the nanomaterials within the existing statutory framework (see also 5.2.1: urgent projects of general importance).

Once the toxicological studies laid down in the OECD test guidelines have been performed or experiences from the human area are available, the system of classification and labelling can be used to indicate toxic properties in order to limit or avoid exposures of humans (EC 2001). For the purpose of deriving limit values, there is a need, in particular, for studies that are suitable for permitting the assessment of the chronic toxicity. Apart from substances that are used in cosmetic products, according to the current guidelines for the classification/labelling and the establishment of limit values for the toxicological end points, mainly *in vivo* studies are required.

In regulatory toxicology, substances are jointly subject to a particular rule (classification, limit values) if it is plausible that a similar toxicity is to be assumed (SAR considerations). The formation of groups is undertaken in particular in cases where a representative substance has been sufficiently examined and comparable substances (possessing, for example, a similar structure, surface or similar physico-chemical properties) have only been examined to an insufficient extent. For example, in the case of the coarser particles (fine dust; granular particles without specific toxicity), various substances are grouped together within the framework of setting a limit value because a similar toxicity on the part of various particles of the same size can be assumed. The discussion about the suitable measurement parameter (surface or other measurement parameter) also serves the aim of forming groups. Should it turn out that the toxicity is dependent on the surface, studies with differently sized nanomaterials of identical composition would be superfluous. It would then not be necessary to test each size modification. The precondition for the formation of groups is a connection between structural (or physico-chemical) parameters and the toxicity, something which should be examined on the basis of valid *in vivo* or *in vitro* studies. It is currently unclear whether a subdivision according to physico-chemical criteria or results from *in vitro* studies is biologically sensible.

As with other chemicals, the joint exposure of nanomaterials together with other chemicals could lead to new effects which the individual substances do not reveal. These combined effects (mixed toxicology) could change both the toxicodynamics and the toxicokinetics. In general, however, the precondition for the assessment of mixtures is the prior testing and assessment of the individual substances.

An increased need for information on the risks of nanotechnology in comparison with other industrial chemicals is justified in part by the fact that nanotechnology is understood as a new technology (“emerging techniques”) and new risk scenarios become apparent for which no empirical values are available and for which a special public interest exists. However, the new chemicals legislation REACH does not distinguish between existing substances and new chemical substances as was stipulated in the previous rules and regulations in the form of the Chemicals Act and the Existing Substances Regulation. Previously, more studies have been required for new substances of the same tonnage than for existing substances. This indicates that the social attitude towards a dynamically changing technological world also represents a position parameter that influences the need for information during the investigation of health and environmental risks.

In order to be able to compare the risks of the substances resulting from “old” and “new” technology in a transparent process, taking account of the particularities of the nanomaterials, the test strategies and assessment procedures should have common basic structures, also for the purpose of being able to undertake a comparative assessment within the framework of a discussion about substitute substances. For this reason, too, the recommended course of action is to consider the current test strategies and assessment procedures (EC 2003, BMA 1998, BUA 2003, IPCS 2005, EC 2007, Risikokommission 2003) as the basis and to adapt them to the specific situation pertaining to nanomaterials as required. It also becomes clear that the risk assessment (including measures such as limit values, classifications etc.) is not only influenced by exposure and toxicology but also reveals a social/political influencing variable (risk acceptance discussion).

4.5.4 Test strategies and assessment procedures in individual areas of occupational health and consumer protection

The development of a mature test strategy is understood as an iterative process. Individual elements of a test strategy are already available due to the previous experience with industrial chemicals and can be applied. *In vivo* test methods are able to provide essential information on the toxicity of nanomaterials. The investigations into subchronic and chronic toxicity are of particular importance and can be regarded as available elements of a test strategy.

As already mentioned, the exposure route of humans must be considered when selecting the exposure route for the *in vivo* studies and the cell system for the *in vitro* methods (see above). Consequently, different study demands may result according to the collective of exposed persons. This is presented in the following.

4.5.4.1 Investigation and assessment of the toxicity of nanomaterials in the workplace

Mainly dermal and inhalative exposures occur in the workplace. The currently available data indicate that the skin represents a barrier if it can fulfil its protective function and is free from damage and heavy mechanical strain. However, the protective function could be limited by skin lesions, strong mechanical strain and small nanoparticles (< 5 – 10 nm). Since, according to current insights, the systemic availability is much greater after inhalation than after dermal exposure and since, in addition, the harmful effects in the lung have already been demonstrated (similar to the case of fine dusts in the micrometre range), from the point of view of occupational safety, priority is given to the inhalative route in the selection of the route of administration in animal studies.

Since a repeated daily exposure can be assumed, there is a need for investigations which are also suitable for the assessment of chronic toxicity. Against the background of the present uncertain meaningfulness of *in vitro* methods, the subchronic and chronic *in vivo* studies acquire special significance. Should it be possible to show that a systemic availability does not exist, the detailed histopathological investigation can be limited to the respiratory tract. In addition, the accompanying occupational-medicine and epidemiological research plays an essential part in the assessment of the risks and the effects on human health.

A special need for research results for this area (see also 5.2.1: Urgent projects of general importance).

4.5.4.2 Investigations into the absorption, systemic availability, accumulation and elimination of nanomaterials after oral exposure (foodstuffs and food packaging materials)

For the purpose of health-related assessment of the oral exposure of consumers to nanoscale materials that are used in the production of foodstuffs and food packaging materials, it is necessary to determine the extent of the absorption, systemic availability, accumulation and elimination of nanomaterials after oral exposure. The *in vivo* studies that are required here should be integrated into the toxicological studies that must be performed anyway in order to avoid unnecessary animal studies. The influence of modifications (e.g. of the coating) on the kinetic parameters as well as the toxicological properties of the nanomaterials should be examined here.

A special need for research results for this area (see also 5.2.2.2: Urgent projects for consumer protection).

4.5.4.3 Investigations into the skin penetration of nanomaterials from cosmetic products and consumer goods

For the purpose of health-related assessment of the dermal exposure of consumers to nanoscale materials which are used in both cosmetic products and other consumer products, it is necessary to determine the extent of the systemic availability of nanomaterials after dermal exposure. The skin penetration could be examined initially using suitable *ex-vivo-in-vitro* skin models. It would subsequently have to be examined *in vivo*. *In vivo* studies are required in order to examine the systemic availability and determine the toxicity. The influence of modifications (e.g. of the coating) on the systemic availability and on the toxicological properties of the nanomaterials should also be examined here. As a result, it would additionally be possible to avoid further animal studies.

4.6 Ecotoxicological assessment of nanomaterials

There are only very few studies and overviews on the effects of nanomaterials on the environment (Krug 2005, Nowack and Bucheli 2007). The results of these studies are provoking a great deal of discussion among experts about the assessment and validity of such investigations.

Up to now only a few organisms have been examined in aquatic ecosystems. For example, depending on the type of administration, C60 molecules ("buckyballs") and nanoscale titanium oxide are lethal to water fleas even at relatively low concentrations in water (Lovern et al. 2006). Experiments with juvenile largemouth bass show that C60 nanomaterials are taken up via the gills and penetrate the blood-brain-barrier, and that brain damage occurs already at low concentrations of C60 molecules (Oberdörster 2004). In zebra fish embryos, carbon nanotubes delay hatching (Cheng and Cheng 2005). Since agglomerates are assumed to undergo sedimentation in the environment, specific studies with sediment organisms should be performed. However, this presupposes the availability of uniform standards/methods for the application of nanomaterials to sediment. The bactericidal effect of some nanomaterials such as silver could also cause negative effects in waste-water treatment plants by leading to a change in the microbial composition of the water.

For terrestrial ecosystems, studies on the effects of nanomaterials are also scarce. In mammals, the results of laboratory studies for modelling the effect on human health may also be applied to wild animals. Up to now there are no studies on non-mammal species and invertebrates. Experiments with aluminium nanomaterials revealed reduced root growth in various crops (maize, cucumber, soya, carrot); this effect did not occur with larger particles (Yang and Watts, 2005). The microbial composition of soil may be impaired as a result of the biocidal effect of nanomaterials in soil.

Similar to the considerations for toxicology, existing test systems must be examined for their validity and transferability to other organisms. The testing of nanomaterials can be undertaken with two aims in mind. A decision must be taken about whether the primary concern is to obtain statements about the intrinsic properties of the materials or whether the main focus is to be on environmental relevance/ecotoxicity.

4.6.1 Grouping of nanomaterials on the basis of their ecotoxicological effect

Given the large number of nanomaterials with numerous modifications, the effort involved in ecotoxicological testing is enormous. There is therefore the need to group together nanomaterials with similar toxicity. To this end, the extent to which nanomaterials can be subdivided into groups on the basis of similar toxicity must be examined using results from

human toxicology and ecotoxicology in order to then examine one representative substance from the particular group. Here it is sensible to form classes with similar effect mechanisms and to define suitable reference parameters (for example, mass, particle count, surface).

Physico-chemical parameters of nanomaterials must be examined with regard to their suitability for grouping.

In particular, the following additional aspects should be considered when defining these groups:

- Differentiation according to inorganic and organic nanomaterials
- Various sizes of one material → general statements on the influence of the surface
- Various materials of the same size → general statements about the influence of the material properties
- One material with a number of variants (e. g. surface modification, crystal structure, form) → general statements about the influence of surface and material modifications.

Research is needed to clarify the grouping of nanomaterials with regard to their ecotoxicological effect. As a result, the number of animal studies that have to be conducted can be reduced and an assessment performed more rapidly.

4.6.2 Further development of ecotoxicological test methods

Due to the combination of size and chemical composition, it is to be assumed that there will also be a very large number of nanomaterials in the environment. However, it will not be possible to test all of them with regard to their ecotoxicological effects. In order to keep the testing effort to an acceptable level, synergies must be identified in the preparation of samples from different investigations. Only in this way is it possible to recognize at an early stage regularities with regard to behaviour and effect which enable conclusions to be drawn from the investigation of selected materials to the behaviour of other materials.

Standardized tests to determine relevant properties have been developed for the testing of “classical” chemicals. These are designed for the testing of soluble or poorly soluble substances. However, at least some nanomaterials, for example, metal oxides, occur in particulate form. For aquatic ecotoxicological studies, a suspension solution must first be prepared of the nanomaterials to be tested. However, existing test systems are not intended for use for the testing of suspensions.

4.6.2.1 Production of stable suspensions of organic and inorganic nanomaterials for the recording of intrinsic properties

The production of stable suspension solutions is a precondition for tests to determine the intrinsic properties of nanomaterials. Little experience with the production of these solutions exists so far (see 4.2). A methodology must be developed for keeping nanomaterials in an even suspension during the test. Since test organisms react very differently to external stimuli (e.g. stirring), this must be done specifically for all of the standard test organisms. Methods for the production of stable suspensions must be developed, taking into account specific properties (formation of agglomerates, size, form) of various groups of nanomaterials. There is a special need for research in this area.

4.6.2.2 Development of a methodology for the application of nanomaterials to various soils/sediments

The sensitivity to nanomaterials of standard test organisms for soil/sediment is still largely unknown. For this reason, there is a particular need for research here. However, suitable testing methods must first be developed. Methods for the application of nanomaterials that occur in suspended or powder form should be developed, based on the soils or sediments recommended for the standard tests. The methods should show the potential dependence of the effect on the form of application for defined nanomaterial groups (according to 4.6.1). The results should be incorporated into the existing standard test guidelines.

4.6.2.3 Evaluation of performed studies with regard to relevant ecotoxicological end points, development of effect hypotheses, identification of suitable test systems

Based on a literature review, the studies on environmental impact and human health effects conducted so far should be analysed and assessed in terms of their relevance to ecotoxicology. The results obtained by the project “Technical Procedure for the Testing of Nanomaterials” (Hund-Rinke and Herrchen 2007) should be taken as a starting point. Including new publications and studies from the area of human health, it should be determined whether the test systems used, and the corresponding test design allow conclusions to be drawn about acute and chronic effects on organisms. The described methodology should be reviewed for sufficient accompanying tests as well as for information on particle characterization, form of application, production of suspensions, the methodology used to determine the concentrations of the nanomaterials, incubation conditions of the test organisms etc.

These research activities would aim to identify relevant end points, advance effect hypotheses and make recommendations as to what the minimum requirements for reporting on test methods used should be in order to be able to validate and compare results.

4.6.2.4 Review and adaptation of ecotoxicological test methods and standardization of nano-specific test systems

The results from the research described in Chapters 4.6.2.1 to 4.6.2.3 should subsequently be used to examine already validated ecotoxicological test methods and test strategies for their suitability for assessing acute and chronic effects of nanomaterials. Standardized test procedures should form the basis for this because they are accepted and are already widely performed.

It should be examined here whether the available test methods suffice in their existing form or with an adaptation to the particular properties of nanomaterials, or whether new endpoints need to be taken into account for assessment or test methods have to be developed and standardized.

Consequently, there is a particular need for research to review and, if necessary, adapt existing ecotoxicological test guidelines.

4.6.3 Ecotoxicological testing of nanomaterials

Taking the results from 4.6.2 into account, the nanomaterials that are to be examined on a priority basis should be tested for their acute and chronic effects. Results and findings from previous research should serve as the basis here. In coordination with the activities of other

countries, acute and chronic ecotoxicological tests should be performed on materials to be tested.

As very little is known about the ecotoxicological effects of nanomaterials, there is a particular need for research in this area.

4.6.4 Elaboration of a test and assessment strategy to determine the risk from nanomaterials in the environment

The risk posed by environmental chemicals is generally determined by comparing exposure and effect (PEC/PNEC). Using the information obtained in the aforementioned projects, an intelligent test strategy (ITS) shall first be elaborated in order to determine the concentrations in the environmental compartments as well as relevant effect thresholds. For reasons of animal welfare and cost, a suitable test strategy for acute and chronic studies, on the basis of which the risk can finally be determined, should be devised using suitable (Q)SAR estimations, substance-group considerations, read-across opportunities and *in vitro* tests. The scale of the studies should be determined by the scale of exposure.

It is clear from the above that there is need for research to develop an intelligent test strategy and an assessment strategy for determining the risk posed by nanomaterials in the environment in which all of the available information is utilized and integrated into the assessment.

4.7 Occupational risk management

Besides substitution, technical, organizational and personal protective measures are employed in the workplace in order to limit the exposures of the respiratory tract and the skin. The protective measures hitherto used in connection with insoluble materials that occur as dusts and suspensions cannot be transferred per se to nanomaterials (in particular, nanoparticles, nanofibres, nanotubes etc. including agglomerates and aggregates). Due to the particularly small size of the nanomaterials, in particular the filter materials used in cleaning the air and the glove materials intended to protect the hands from dermal contact must be examined for suitability. The extent to which the methods that have been employed so far to examine the protective measures are also suitable for nanomaterials has not been finally clarified. Consequently, it is necessary to examine the previous methodology, if appropriate, to adapt it to the nanospecific aspects and, subsequently, to apply it systematically to nanomaterials. Initial insights indicate that nanoparticulate sodium chloride is held back by air filters (P2, P3). This should also be demonstrated for insoluble or hardly soluble nanomaterials that are in use in the workplace.

The classification/labelling and the setting of occupational exposure limits or the consequences of this are an essential part of risk management. At national level, a specific occupational exposure limit for nanomaterials only currently exists for amourpous silicic acid (TRGS 900 2007). Initial orientating “benchmark exposure levels”, which are not understood as health-based occupational exposure limits in the narrow sense, were published by BSI (2007) for further nanomaterials. In addition NIOSH developed in a draft document exposure levels for nanoscale titanium dioxide (NIOSH 2005b).

The “control banding” procedure is applied in the workplace in order to perform an assessment and recommend protective measures for substances without an occupational exposure limit or for which no exposure measurements are available (HSE 2006, BAuA 2007a). For this purpose, the substances are subdivided into categories of toxicity (“hazard bands”) and categories of exposure (“exposure bands”). An initial approach for the application to nanomaterials is being developed (NIA 2007). In particular against the

background of the enormous diversity of various modifications, the “control banding” procedure might offer a possibility for recommending protective measures in the case of more poorly investigated nanomaterials, too.

4.8 Information and communication

Problems relating to the varied aspects of risks associated with nanotechnology are being worked on at national and international level. The quantity of data involved is becoming increasingly large and requires structures that enable a trouble-free exchange of information and communication. Effective communication structures are also required within the framework of the coordination of the international efforts with regard to the setting of standards and the development of methods. It is additionally necessary to communicate risks transparently and make information available to practitioners. To fulfil this task, congresses, conferences, symposia, seminars, information days, workshops and dialogue events are currently taking place in relatively quick succession (see BAuA (2007d) for an exemplary compilation).

4.8.1 Provisional handling aids for nanomaterials in the workplace

Nanomaterials are increasingly being produced, further processed and used as a product component, for example, in small and medium-sized companies. Consequently, there is a need for help to be provided in connection with handling in these various areas of work. Since it is currently still not possible to finally assess the health effects, especially with regard to new nanomaterials, such handling aids are at present oriented towards the state of technology and should attempt, as far as possible, to limit and minimize the exposure. For example, in cooperation with the German Chemical Industry Association (VCI), the Federal Institute for Occupational Safety and Health (BAuA) has elaborated a guidance document for activities involving the use of nanomaterials in the workplace (VCI-BAuA 2007) and collected further aids that are described in varying degrees of detail (BAuA 2007b). The task is now to specify these handling aids for substances, branches and applications.

4.8.2 Safety data sheets and the training of workers

Safety data sheets are an important instrument for informing workers and employers about the chemicals and their risk potential and recommending appropriate protection measures. This instrument needs to be supplemented and checked for relevance to nanomaterials so that workers and employers are informed in a suitable way about nanospecific aspects. In an overview, Schneider et al. (2007) concern themselves, inter alia, with the quality and level of detail provided in the safety data sheets for nanomaterials. The training of workers in this regard is also sensible.

4.8.3 Databases

It is becoming increasingly difficult to maintain an overview of the mass of data in the scientific literature and the relevant information on nanotechnology. Efficient research and assessment require the ability to rapidly access relevant publications. The Federal Institute for Occupational Safety and Health (BAuA) has produced an overview of the literature databases that are currently available with regard to the topic EHS aspects of nanotechnology (BAuA 2007c).

4.8.4 Discourse: nanotechnology

The three higher federal authorities discern a need for research and action in the discourse-related accompaniment of the further development of nanotechnology. In addition to the research in innovation and safety, the accompanying social-science research including the performance of dialogue processes, should form the third pillar in the promotion of nanotechnology. However, the dialogue cannot limit itself to the communication of risks but must equally introduce aspects relating to the benefits of nanotechnology into the public discourse.

A number of discourse activities already exist today. One deserving of special mention is the dialogue on the assessment of synthetic nanomaterials in the occupational and environmental areas organized by the Federal Environment Ministry, the Federal Environmentl Agency and the Federal Institute for Occupational Safety and Health (BMU-BAuA-UBA-iku 2005). This process is currently being continued as “NanoDialog 2006 - 2008”. In the NanoDialog, the stakeholders from the world of politics, business and science as well as the relevant authorities and associations discuss the opportunities and risks of nanomaterials and elaborate recommendations for the responsible handling of them. In November 2006 the Federal Environment Ministry set up the Nano-Commission for the purpose of coordinating the dialogue. Since March 2007 the stakeholders have been working in three working groups on the topics: “Opportunities for the Environment and Health”, “Research into Risks and Safety” as well on a “Guidance document for responsible handling of nanomaterials”. The Federal Institute for Risk Assessment has initiated various projects in this area. Within the framework of its activities relating to risk communication, an Expert-Delphi-Survey and a consumer conference on the risks of nanotechnology in the areas foodstuffs, cosmetics and consumer products were carried out in 2006 and a representative survey of the population and a media analysis were initiated in 2007.

However the social dimension of the development of nanotechnology requires comprehensive concepts for accompanying social-science research and a variety of dialogue offerings which bring together scientists, politicians, the representatives of interest groups from the world of business and NGOs as well as consumers. Processes must be organized and forums made available within the framework of a public nano-dialogue in which nano-players from research and production come together to discuss the health and environment-related risks of nanotechnology. In addition, within this framework, methods of participation and dialogue could be developed and tried out which enable various social players to be included in the debate surrounding nanotechnology at the earliest possible stage. In order to examine the factors influencing the perception of nanotechnology and to attempt to undertake prognoses about the direction in which public opinion is developing, the regular performance of representative surveys and media analyses continue to be necessary.

4.8.4.1 Accompanying social-science research and nano-dialogues

The consideration of social problems should occur within the framework of a public nano-dialogue. In particular, three areas of action are considered to be relevant for work performed on the social dimension of nanotechnology research and development:

- The collation and compilation of current trends in the development of nanotechnology with regard to their positive and negative effects on the environment, health and safety
- Assessment of the trends by the relevant players from society as well as the world of politics, business and science

- The development of dialogue offerings for a future-oriented public discussion as well as training and further training initiatives.

4.8.5 International cooperation and research promotion

The research undertaken in the area of the risks associated with nanotechnology occurs in parallel in various national and international support projects. Coordination of the research activities performed by the various nations and institutions should be aimed for at EU and OECD level in order to enable division of labour and avoid the duplication of work. As far as possible, attempts should be made to ensure an internationally coordinated procedure with regard to the definitions, the setting of standards, the formation of categories, the determination of criterias and assessment activities (e.g.: ISO, OECD, SCENIHR 2007b).

5 Linking and prioritizing the various research topics and work areas

5.1 Linking and time-related coordination

From the overview of the topics provided in Chapter 4 it becomes clear that the various areas relating to chemicals assessment and chemicals management should be examined for nano-specific aspects and particularities. A general need for support and research therefore exists in these areas. However, the development status of the checking and the urgency differ.

The inadequate knowledge about the type and modification of the nanomaterials, which lead to an exposure of humans and the environment to a very different degree, currently makes difficult a targeted and risk-oriented selection of the substances that are to be assessed primarily. The substances selected for primary assessment should also be given preference in the development and improvement of detection methods. Equally, these substances are also highly suitable for the performance of toxicological and ecotoxicological investigations for the individual-substance assessment as well as for the validation of the *in vitro* studies and the further development of the test strategies and the assessment procedures on the basis of a data set that is as relevant to exposure as possible. Since at least the toxicological data set of those nanomaterials that have long been in use is extensive for one part of the modifications and since valid investigations should not be repeated unnecessarily, there is a clear need for recording the data systematically in databases and assessing the quality and regulatory relevance of the studies before further studies are performed. The substance associated with high exposure should likewise find special consideration with regard to the development of the risk management and in the area of information and communication. Since, as a rule, reductions in exposure, should these be necessary as a result of the research, can only be implemented effectively using the instruments of regulatory toxicology, the demands of regulatory toxicology must be considered during the conception of the research as a matter of priority and to a much greater extent than hitherto.

The selection of the key physico-chemical measurement parameters within the framework of the characterization of the nanomaterials and the measurement of the exposure should be influenced in particular, in addition to the possibilities offered by measurement technology, by the toxicological relevance of the measurement parameters. In turn, the toxicological relevance is influenced by the suitability of the measurement parameter for mirroring a dose-response-relationship or recording the toxicological mode of action.

The methodology relating to measurement in the various exposure media has not yet been finally developed and standardized. It is slightly more advanced in the area of the air concentration than in the other areas. Decisions about the risk-related need for testing can, however, already be made on the basis of the qualitative or semi-quantitative exposure data. In particular in the area of inhalative and oral exposures, the measurement technology is an essential element which should be available at an early stage.

Apart from a clear number of necessary additions, the *in vivo* OECD methods for the recording of toxicological effects are suitable for recording potential damage to health in the context of regulatory toxicology. Consequently, *in vivo* testing is available in principle and, as an established element of the test strategies, represents an essential precondition for the assessment of individual substances, the validation of the *in vitro* studies and the development of the test strategies and assessment procedures. No specific evaluations are available with regard to the suitability of the ecotoxicological OECD methods.

Since the suitability of the *in vitro* methods for regulatory toxicology is not certain at present, there is a need to rapidly undertake a systematic determination of the sensitivity and specificity by means of a comparison with the results from *in vivo* studies or perform the studies required for this. A key future challenge will consist in validating *in vitro* methods and,

in the case of suitability, integrating them into test strategies in order to be able to justify dispensing with *in vivo* methods without putting at risk human health as a result of the higher uncertainty that attaches to the *in vitro* methods.

The definitive formation of substance classes within the nanomaterials so that the investigation of a representative substance suffices for the assessment of the class and regulatory decisions can be taken for substance classes is also a topic that belongs more to the future. Since the integration of the *in vitro* methods and the formation of substance classes are essential parts of a mature test strategy, one optimized with regard to the resources, this is also not achievable in the short term.

The activities relating to information and communication continuously accompany the individual specialized topics. Since the provisional handling aids are oriented towards the current technical possibilities, they can be produced in a way that is largely independent of the risk assessment and are, in part, also already available. The discourse on nanotechnology is conceived as accompanying social-science research and extends throughout the entire period of research and assessment.

Some of the priorities and dependencies of the individual topics which would support sequential treatment are presented in the above. In current research practice, the topics are frequently worked on in parallel, also against the background of the fact that strictly sequential processing would result in a situation in which some topics could only be treated in the distant future. A mutual close exchange of information between the topics that are to be worked on simultaneously, one which informs about current insights contemporaneously and an iterative and flexible development process in the further research would contribute to an effective and targeted form of research. This task becomes particularly demanding against the background that an international division of labour and coordination are sensible but time-consuming and that important results are frequently published before they are publicly discussed. Further hindrances result from the confidentiality of some of the information whose transfer might lead to competitive disadvantages for the companies concerned.

The currently predictable research topics and necessary activities will require special support in the fundamental areas in the next 5 - 10 years, particularly also with regard to conceptional questions relating to the procedures and strategies. With increasing experience and consolidation of the procedures and methods, a transition to a more highly routine-related research and assessment of nanomaterials (individual substances as well as substance classes) will be possible. This will continue for as long as new nanomaterials are developed and result in corresponding exposures of humans and the environment.

Research topics and projects which must be worked on at present on a priority and urgent basis are presented in the following Chapter.

5.2 Urgent need for research

Against the background of the current and predicted research at national and international level and the fact that regulatory toxicology and the integration of the assessment of nanomaterials into the existing legal framework have so far hardly been supported by research work, a support and research priority results for the following topics. First of all, those projects are named which are of general importance for the assessment of the risks for humans and the environment. In part, they follow on from each other. Topics subsequently follow which have specific relevance in the areas of occupational safety and health, consumer protection and environmental protection.

5.2.1 Urgent projects of general importance for occupational safety, consumer protection and environmental protection

1: Identification of relevant nanomaterials

Once the definitions of the nanomaterials have been harmonized at international level, an essential fundamental requirement is the identification of the nanomaterials which are to be assessed. The available information on the type, structure, size, surface, solubility, coating etc. of the nanomaterials is currently superficial in nature since transparency in this area can lead to competitive disadvantages for the manufacturing and processing companies. Since it cannot currently be excluded that the modification of a nanomaterial (e.g. altered coating) not only implies new technical properties but also new risks, it becomes clear that the characterization of the nanomaterials cannot be limited to the naming of the basic substance but that, instead, a more specific characterization of the modification is required.

Data on the type, structure, size, surface, solubility, coating etc. as well as the annual production volume which allow sufficient differentiation of the nanomaterials are to be compiled systematically in a cooperation project with the companies that produce and process nanomaterials. Additionally, more specific information on the use of nanomaterials in consumer products is required. If no targeted exposure of humans is intended, for example, in foodstuffs or cosmetic products, due to the decreasing assumption of exposure, modifications of nanomaterials with an annual production volume below 1 tonne are not a priority. The identification of modifications of nanomaterials that are currently produced in low quantities but which will in future be produced at a high production volume would, of course, also be conceivable. However, such a prognosis of the market development can probably not be justified with sufficient certainty. Consequently, consideration of this aspect should be deferred. In addition to the evaluation of the publicly available sources, dialogue with the manufacturers and users must be started and clarification achieved in this sensitive area about whether sufficient information is to be provided by manufacturing and processing companies via a coordinated procedure.

This information is essential for a targeted and risk-oriented selection of the substances that are to be assessed primarily. Primary assessment is required of those substances for which a targeted exposure of humans is intended (for example, via a use in foodstuffs, materials that are in contact with foodstuffs, cosmetic products, textiles and other consumer products) and nanomaterials used directly in the environment as well as substances with a production volume of at least one tonne. Equally, these substances that are to be assessed primarily are also highly suitable for the performance of toxicological and ecotoxicological investigations for the individual substance assessment as well as for the validation of the *in vitro* studies and the further development of the test strategies and the assessment procedures on the basis of a data set that is as relevant to exposure as possible.

Time Period: 2008 - 2009

2: Research initiative for the assessment of nanomaterials within the current statutory framework

Since integration into the existing statutory framework is currently envisaged and there are no plans for any specific statutory instrument for the regulation of nanomaterials, it is all the more necessary to demonstrate this using corresponding assessments and rules within the framework of the statutory instruments for substance assessment. The following regulations are the centre of attention here:

- Regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH); Regulation (EC) No. 1907/2006

- Classification, packaging and labelling of dangerous substances, Directive 67/548/EEC
- Biocide Directive; Directive 98/8/EC
- Cosmetics Directive; Directive 76/768/EEC
- Consumer goods; Regulation 2004/1935/EC
- Foodstuffs legislation; inter alia Regulation 2002/178/EC.

Nanomaterials are ready for assessment in the bodies responsible for an assessment within the statutory framework in consideration of the current status of scientific knowledge. The sub-statutory body of rules (e.g. Technical Guidance Documents, REACH Implementation Plans) do not currently deal with the specific problem posed by nanomaterials. Consequently, there is the need for greater orientation of the research and support activities towards the support of the assessment in the enforcement of the law.

As a basis for this, the collation, description and assessment of the available studies on nanomaterials should be started or continued. Numerous results from toxicological studies are available for some of the nanomaterials (e.g. silicon dioxide, titanium dioxide). To date, they have not yet been examined and assessed in detail in consideration of the regulatory framing conditions so as to enable identification of gaps in the data and, possibly, also the identification of synergies from the various investigations. Both must take place in a first step in order to provide a basis for the definition of an additional need for research and testing. As a matter of principle, it is necessary to ensure that the toxicological and ecotoxicological studies that are to be performed are utilizable in regulatory toxicology.

An additional aim is to support the further development of the sub-statutory body of rules and regulations in the particular regulatory context (e.g REACH, biocides, food additives, cosmetic products etc.) by means of research and support activities in consideration of the current state of scientific knowledge. This approach prepares the assessment activities that are required anyway (e.g. in REACH) and supports the primarily responsible industry with the appropriate characterization and assessment of the nanomaterials. Once REACH is implemented, in the area of “evaluation”, only a small part of the assessments produced by industry is worked on content-wise by non-industrial institutions. The selection of the substances/substance classes that are to be worked on here should be oriented towards current knowledge and integrate results from the previous project. Silicon dioxide, titanium dioxide, zinc oxide, carbon black (including modifications, derivatives etc.) are cited as examples here. Only a few relevant data are now available for further relevant substances such as silver, carbon nanotubes and fullerenes. Consequently, after they have been collated, characterized and assessed, it can be expected that, in particular, the derivation of the need for further testing will be deduced. The data set relating to aluminium oxide and iron oxides is unclear. The data collection as well as the characterization and assessment of risks must be shaped in cooperation with competent bodies and companies and communicated transparently.

Time period: 2008 -

3: Minimum requirements for publications

In the scientific literature many studies on nanomaterials are published which then cannot be correctly assessed and compared with other results due to missing relevant data relating to the characterization of the nanomaterials, the measurement procedure or the test design. Consequently, together with experts from the particular areas, minimum demands for publications should be elaborated which lay down which minimum information is required for the estimation of the validity and comparability of studies. This applies to studies on

measurement methods, toxic and ecotoxicological effects and on the behaviour in the environment. The parameters should be agreed internationally as quality criteria.

The concept MIAME ("Minimum Information About a Microarray Experiment") for toxicogenomic technologies can serve as a model here.

Time period: 2008 - 2009

4: *In vivo* studies for assessment of the risks of nanomaterials

To date, the promotion of research has mainly supported the performance of *in vitro* studies (animal welfare, costs). However, in general *in vivo* data represent a more reliable data base and are the European standard in regulatory toxicology and decision-making in the case of known existing chemicals in dependence on the annual tonnage placed on the market. The quality of the necessary toxicological investigations should meet these standards in the case of nanomaterials, too. The novelty of many nanomaterials provides additional justification for the demand for a reliable data base.

A base data set derived from *in vivo* studies on nanomaterials involving high exposure must be established or supplemented in order to identify the target organs and produce a dose-response-relationship. In addition, this data set shall contribute to the validation of the *in vitro* studies and the assessment of the particular substance.

Time period: 2009 - 2010

5: Assessment and validation of the *in vitro* methods as a contribution to the assessment of the risks

Due to the high costs, the long duration and for reasons of animal welfare, the need to use *in vitro* methods in addition to *in vivo* methods is recognized. Consequently, meaningful *in vitro* methods are important (low-cost high throughput *in vitro* assays) in order to be able to estimate the effects of nanomaterials on humans with sufficient certainty. In addition to the *in vitro* studies, studies relating to the characterization of physico-chemical properties might also provide results that permit conclusions about effects on humans to be drawn. However, a comprehensive description of which *in vitro* method (including PC method) is sufficiently sensitive and specific for which long-term effects does not yet exist. The published data on nanomaterials, fine-dust particles and fibres must be evaluated systematically in order to check the qualitative meaningfulness of the *in vitro* methods on the basis of statistical parameters (sensitivity and specificity) and to propose further investigations.

This is necessary in order to demonstrate the relevance of the *in vitro* studies for regulatory toxicology. Due to their size, features shared with the unintentionally produced and natural particles of this size must be considered. In addition, the data relating to the larger and better examined fine-dust particles are of importance because similarities exist between the two particle fractions in terms of the lung toxicity. The extent to which the data on the fine dusts and fibres in the micrometre range are transferable to nanomaterials (including nanofibres) results from the analysis of the data and plausibility considerations relating to the mechanism of toxicity. With regard to the lung toxicity, common features between nanomaterials and fine dusts have been observed. However, the effect potential of the nanoscale particles is currently estimated to be higher. The aim of the project is to use *in vitro* methods for the purpose of assessment in an optimal and statistically certain way, to promote animal-substitute methods and make a contribution towards specifying the test strategy.

Time period: 2008 -

5.2.2 Urgent research projects for individual areas targeted for protection

5.2.2.1 Occupational health

O 1: Development of the measurement methodology and measurement strategies for the determination of exposures to nanomaterials by inhalation

The checking of the measurement technology currently available for the determination of exposure should serve as the starting point for further research planning. Furthermore, the focus here must be on the development or further development of person-related measurement technology in particular as a crucial precondition for the performance of later epidemiological studies.

At the same time, company measurements performed with the currently available measurement technology should be intensified, on the one hand, to obtain initial insights into the levels of exposure to nanomaterials and, on the other, to create the knowledge base for the elaboration of standardized measurement strategies for "routine workplace measurements" as well as toxicological and epidemiological investigations. The measurements undertaken in industrial practice must be of advantage to the companies that produce, process and use the nanomaterials since their cooperation is a precondition for the performance of the measurements.

A further urgent aim is the substance-related identification of the nanomaterials during the measurements of the exposures by inhalation. In particular in the workplace, differentiation between the ubiquitously occurring ultrafine aerosols and the intentionally produced nanomaterials is urgently required. Practicable analysis methods which distinguish the product particles from the background concentrations of the ultrafine aerosols must be developed here.

Time period: 2008 – 2009

O 2: Provisional handling aids for certain frequently occurring activities involving nanomaterials in the workplace

Nanomaterials are increasingly produced, processed and used as a component of products, for example, in small and medium-sized companies. Consequently, there is the need to provide aids for handling in various work areas. Since it is not currently possible to finally assess the health effects of new nanomaterials in particular, such handling aids are at present oriented towards the state of technology and should attempt to achieve, as far as possible, a limitation and minimization of the exposure. General handling aids have already been produced. More specific provisional handling aids should be added (e.g. spray applications with compressed gas packages) for specific activities that possess a relevant exposure potential.

Time period: 2008 – 2009

5.2.2.2 Consumer protection

C 1: Investigations into absorption, systemic availability, accumulation and elimination of nanomaterials after oral exposure (foodstuffs and food packaging materials)

The health-related assessment of the oral exposure of consumers to nanomaterials used in the production of foodstuffs and food packaging materials requires determination of the extent of the absorption, systemic availability, accumulation and elimination of nanomaterials after oral exposure. The requisite *in vivo* studies should be integrated into the toxicological studies that must be performed anyway in order to avoid unnecessary animal testing. The

influence of modifications (e.g. of the coating) on the clinical parameters as well as on the toxicological properties of the nanomaterials should be examined here.

Time period: 2008 – 2009

C 2: Assessment of the toxicity of nanomaterials after oral exposure

Silicon dioxide (E 551) and titanium dioxide (E 171) are, for example, authorized food additives which are also produced in nanoscale form in many modifications. It is currently unclear whether these nanoscale modifications possess toxicologically relevant differences or which modifications are ultimately used. For this reason, there is a need to assess transparently the possible risks that may be posed by nanomaterials that are taken in orally.

Time period: 2008 – 2009

5.2.2.3 Environment protection

E 1: Identification of relevant parameters for behaviour and fate in the environment

In order to be able to make statements about the fate and the accumulation of nanomaterials in the various environmental compartments and under changing environmental conditions, it is first necessary to identify the relevant parameters which influence the environmental behaviour of various groups of nanomaterials. Current test methods developed for the purpose of determining the persistence and degradability in the area of chemicals assessment do not consider the specific properties of nanomaterials and can therefore either not be used at all or only to a limited extent. Parameters may be: agglomeration, particle size and distribution, absorption, interactions with environmentally relevant chemicals, stability, catalytic activity, carrier function, zeta potential etc. The identification of the relevant parameters will permit improved predictability of the environmental behaviour.

Time period: 2008 - 2010

E 2: Exposure, persistence and accumulation of nanomaterials in the compartments water, soil and sediment

To date, only little knowledge is available about the distribution, accumulation and persistence of nanomaterials in the environment and in environmental organisms. In accordance with the exposure routes resulting from production, processing and use, the fate of the starting products of nanoscale substances and their transformation products must be followed (life-cycle analyses, exposure scenarios) and measured in the target compartments. The methodology of life-cycle analyses should be examined here with regard to the special demands of the nanomaterials and, if necessary, adapted. Only thus can materials be identified which are persistent and accumulate in the environment. In a further step, these must then be tested for ecotoxicity on a priority basis.

First, suitable measurement methods for the identification of nanomaterials in the compartments water, soil and sediment must be developed or existing technologies tested for their utilizability. The use of these methods should allow statements about the fate and the accumulation in the various environmental compartments in consideration of the properties identified under E1.

Time period: 2008 -

E 3: Development of uniform standards for the testing of nanomaterials

The procedures developed for the assessment of chemicals can only be applied to a limited extent in the testing of nanomaterials. Since extended guidelines have not yet been produced, a highly varying and, in part, insufficiently documented methodology has been

applied in the investigations performed to date. One example is the production of suspension solutions for ecotoxicological test procedures in the aquatic compartment. As a result, it is difficult to compare with each other and assess the investigations that have been performed so far. Uniform standards should be developed which ensure the comparability of the study results and reveal natural laws. Only in this way is it possible to extrapolate from investigations into selected materials to other materials and, against the background of the large number of nanomaterials, keep the effort required by the investigation to an acceptable level.

The existing test procedures should be adapted to the special requirements of nanomaterials such as, for example, the influence of the particle size, agglomerate formation, charge or certain demands on the production of suspensions. The focus here should be on the standardized test procedures since they are incorporated into the statutory framework, are accepted and widely performed. Expanding from this, guidance documents should be elaborated which can be implemented more rapidly than the introduction of new test guidelines.

The aim of assessment and regulation must be central here.

Time period: 2008 - 2010

5.3 Need for research in the medium and long term

Once the urgent research projects have delivered the first results, further topics that follow on from the results of the urgent projects or represent independent areas must be worked on. As already mentioned, the extent of the need to consider nanospecific aspects and particularities must be examined for the different areas of chemicals assessment and chemicals management. A general need for support and research therefore results in these areas. For example, the following topics will assume particular importance in the medium and long term and require targeted support (see also the presentation in Chapter 4):

- Development of the test strategy and integration of the *in vitro* methods as screening studies
- Formation of groups of similar nanomaterials which, as a result of the toxicological investigation of a representative nanomaterial, have been sufficiently investigated.
- Assessment of the protective measures in the workplace
- Guidance documents on the handling of nanomaterials in the workplace
- Accompanying occupational-medicine/epidemiological research
- Investigations into the skin penetration of nanomaterials from cosmetic and consumer products
- Assessment of the toxicity of nanomaterials after dermal exposure
- Accompanying social-science research and dialogue
- Investigation of possible ecotoxicological effects of nanomaterials in dependence on systemic properties such as particle size, agglomerate formation, charge
- Investigations into the bioaccumulation of nanomaterials
- Clarification of the distribution behaviour of nanomaterials between the various environmental media (e.g. water/soil)
- Investigations into the influence of nanomaterials (household and pharmaceuticals) on processes in waste-water treatment plants
- Uptake mechanisms for aquatic and terrestrial organisms
- Influence of nanomaterials on the function and structure of the soil microflora
- Development of an intelligent test strategy for the assessment of the ecotoxicological risks.

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7 Appendix

7.1 Abbreviations

BAL	Broncho-alveolar lavage
BAuA	Federal Institute for Occupational Safety and Health (Germany)
BfR	Federal Institute for Risk Assessment (Germany)
BMAS	Federal Ministry for Labour and Social Affairs (Germany)
BMELV	Federal Ministry of Food, Agriculture and Consumer Protection (Germany)
BMU	Federal Environment Ministry (Germany)
CMR	Carcinogenicity, mutagenicity and reproductive toxicity
EC	European Commission
EHS	Environmental health and safety
GVO	Genetically modified organisms
HSE	Health and Safety Executive (UK)
HPV	High production volume
IOM	Institute of Occupational Medicine (UK)
IPCS	International programme on chemical safety
ISO	International standards organisation
ITS	Intelligent test strategy
MIAME	Minimum information about a microarray experiment
NGO	Non governmental organisation
NIOSH	National Institute for Occupational Safety and Health (USA)
OECD	Organisation for Economic Co-operation and Development
PEC/PNEC	predicted environmental concentration versus predicted no-effectconcentration
PC	Physico-chemical
(Q)SAR	(Quantitative) structure activity relationship
REACH	Registration, Evaluation and Authorisation of Chemicals
SCCNFP	Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
UBA	Federal Environment Agency (Germany)
UFP	Ultrafine particles
U. S. EPA	Environmental Protection Agency (USA)
VCI	Chemical Industry Association (Germany)

7.2 Definitions

The definition of the terms relating to nanotechnology etc. accord with the current status of international discussion (OECD, ISO, SCENIHR 2007b).

Nanotechnology:

It describes the production, investigation and use of structures, molecular materials, inner boundary surfaces with at least one critical dimension below 100 nm.

Nanomaterials:

Nanomaterials are composed of discrete functional parts, many of which having one or more dimensions of < 100 nm. In particular, intentionally produced granular particles, tubes and fibres with a diameter < 100 nm (including their agglomerates and aggregates) in at least one dimension are meant here.

Nanoobjects:

Material whose extension is limited to the nanoscale in at least one dimension. For example, nanoparticles, nanotubes, nanorods and nanoplates belong to the group of nanoobjects.

Nano-structured:

is characterized by inner or outer structures in the nanoscale range.

Nanoscale:

The size range between 1 nm and 100 nm.

Nanoparticles, nanotubes and nanofibres:

Nanoparticles, nanotubes and nanofibres are understood here as intentionally produced granulate particles, tubes and fibres with a diameter of < 100 nm in at least one dimension. The more general term nanomaterials is suitable for considering their agglomerates and aggregates.

Research strategy:

As a generic term, a research strategy is understood as the comprehensive, risk-related research programme which creates the conditions for the derivation of a test strategy, an assessment procedure and effective and consistent testing of individual substances. Additionally included are projects relating to communication or further topics for the characterization of the total need for research in a holistic approach.

Test strategy:

A test strategy is understood as a sequentially defined programme of testing which can be modified in dependence on information about the exposure and toxicology of the substance. The test strategy is applied to individual substances. In this way, a data base is created which, as a rule, permits a comprehensive characterization and assessment of the risks of the substance.

Risk assessment procedures:

In this context, risk assessment procedures are understood as a defined approach in the interpretation and assessment of the generated substance data which, in consideration of substance-specific particularities, enables a consistent characterization and assessment of the risks. The assessment of the risks is not only based on scientific-medical insights but additionally includes social evaluations about which residual risks are to still be considered acceptable. Results of the individual substance related assessment are, for example, exposure limits for the workplace atmosphere, exposure limits for substances in foodstuffs and cosmetics, classifications and risk phrases or handling recommendations.