DECHEMA e.V.

Society for Chemical Engineering and Biotechnology

VCI

German Chemical Industry Association

Roadmap for Safety Research on Nanomaterials

– with a priority list for the European 7th R&D Framework Programme and national research programmes –

5 July 2007

1. Introduction

Nanotechnology is the technology that characterises, designs, produces and uses structures and systems that require exact control of the size and form of matter on the nanometre scale. A nanometre is a billionth of a meter.

Nanotechnology will enable new developments and novel applications from biomedicine to information technology. Chemistry is the science that delivers basic materials for those technologies by producing “nanomaterials”.

Nanomaterials are understood to be either so-called *nano-objects* or *nanostructured materials* according to the draft definition of the ISO Technical Committee 229 "Nanotechnologies" which was taken over as working definition by the OECD. *Nano-objects* are materials which are confined in one, two, or three dimensions at the nanoscale (approximately 1 – 100 nm); typical examples are nanoplates, nanorods and nanoparticles. Nanoparticles are nano-objects with three dimensions at the nanoscale. *Nanostructured materials* have an internal structure at the nanoscale. Typical examples are aggregates and agglomerates of nano-objects. Chemically, nanomaterials can be, for example, pure or mixed oxides, salts, metals, and organic substances.

Nanomaterials may exhibit new substance properties, especially due to an increased surface/volume ratio, a higher surface energy and a smaller particle size, which may lead, in some cases, to other toxicological and ecotoxicological properties than the properties of the corresponding bulk materials. These possible changes in substance properties currently give rise to the question whether existing exposure measurement techniques and toxicological testing strategies are appropriate to assess potential hazards and analyse potential risks of nanomaterials. This is currently intensively studied worldwide by industry and academia.

Nanomaterials must be safe for man and the environment. As with any other emerging technology, safety research is necessary to ensure a responsible use of nanomaterials.

In Germany, DECHEMA and VCI have established as early as 2003 the joint working group "Responsible Production and Use of Nanomaterials" which consists of high-level European academic and industrial experts and is regularly joined by representatives from German authorities. The group shares scientific findings and best practices on safety aspects of the production and use of nanomaterials.

Mainzer Landstr. 55
60329 Frankfurt, Germany

Mail: info@vci.de
Web: www.vci.de

Phone +49 69 2556 - 0
Fax +49 69 2556 - 1471

The DECHEMA/VCI working group has already addressed safety aspects of nano-materials at a very early stage in a roadmap for safety research. This roadmap, shown in the Annex of this document, is continuously reviewed and updated. The roadmap contributed, i.a., to the “NanoCare” project, co-funded by the German Federal Ministry of Research (BMBF).

This document also provides recommendations which research issues should be addressed in the European 7th R&D Framework Programme, especially in the European Technology Platforms for Sustainable Chemistry (SusChem) and for Industrial Safety (ETPIS), and in national research programmes.

2. Overview of the most urgent issues and ongoing research projects concerning the safety and potential risks of nanomaterials

In close cooperation with academia, the chemical industry works already on almost all of the most urgent research issues:

- The BMBF project "NanoCare" project will
  - investigate decisive parameters which trigger toxic effects (size, chemical composition, effects of surface, morphology) by the end of 2007.
  - develop and assess toxicity testing methods with respect to their suitability to detect different specific effects in bodies under practical circumstances, e. g. at the working place, by mid 2008.
  - study the toxicology of other materials than titania and carbon black by the end of 2007.
  - develop methods to reproducibly provide inhalable atmospheres of nano-materials suitable for toxicological studies by the end of 2007.
  - investigate the stability of agglomerated nanoparticles in body fluids by mid 2008.

- The project "Nanosafe II" funded by the European Commission
  - develops and assesses toxicological testing methods with respect to their suitability to detect different specific effects in the body under practical circumstances, e. g. at the working place, by the end of 2008.
  - studies the toxicity of other materials than Titania and carbon black by the end of 2008.
  - develops methods to reproducibly provide nanoscaled aerosols for toxicological studies by mid 2008.
  - investigates mechanisms to take particles into the lung by the end of 2008.
  - investigates the real morphology (isolated, agglomerated) of nanoparticles and develops methods to detect the kind and concentration at the working place by the end of 2008.

- The Centre for Functional Nanostructures of the Deutsche Forschungsgemeinschaft (DFG; German Research Foundation) has launched a project that
  - has investigated the transport of nanoparticles into and through cells and the crossing of organ barriers (blood-brain barrier, placenta barrier, etc.)

- The research project "Nanoparticle Exposure on Workplaces (NEW)" at the Institute for Environmental Technology and Analytics (IUTA) and the “NanoCare” project will
  - investigate the real morphology (isolated, agglomerated) of nanoparticles and develop methods to detect the kind and concentration at the work place by mid 2008.

- The DFG Priority Programme SPP 1313 "Biological Responses to Nanoscale Particles" investigates the manufacturing and characterisation of nanoparticles, the transition of nanoparticles into and interaction with the biological environment, and the impact of nanoparticles on fundamental biological functions.

- "TRACER" is a project of several German companies within one value chain, co-funded by the German BMBF, which evaluates cytotoxity and biocompatibility of carbon nanotubes (CNT) and will derive recommendations for a safe processing, handling and use of these products.

- "INOS" (UFZ Dresden) will evaluate possible adverse health effects at production, characterization and processing of nanoscale powders.

- The FP 6 EU project "IMPART" reviews the latest scientific and technological developments related to the risks of nanoparticle exposure on human health and the environment and will in the end formulate guidelines and recommendations for future nanoparticle standards and exposure limits.

- FP 6's "Nanotox" project analyses information on the toxicological impact of nanoparticles by reviewing information on
  - physical and chemical properties of different types of nanoparticles and agglomerated nanocrystals, manufacturing and use, human health effects including side effects, animal toxicology; environmental impacts, mutagenicity/ genotoxicity, metabolism/pharmacokinetics, standards for safe use, safe laboratory methods, etc.
  - the potential methods of dispersal of, and contamination by, nanoparticles and agglomerated nanocrystals (e.g. adsorption, desorption, transport, aggregation, deposition, biological-uptake).

- The EU Project "NEST Particle Risk" is devoted to study the health hazards posed by new types of particles like nanotubes or fullerenes. The partners will also develop methods to detect and quantify the presence of the particles in living tissues. Mice will be used to assess the uptake and transport of the particles in living systems. In-vivo toxicity testing will use a mouse model, in vitro-tests will use cultured cells.

- The EU project "Nanoderm" investigated the uptake of titania and zinc oxide nanoparticles via the skin. The project has been finalized; the final report is still pending. The interim results confirm the effectiveness of the healthy skin as protective barrier.

- A German company investigated the skin penetration of zinc oxide and titania nanoparticles according to OECD guidelines: No skin penetration was found.

- The EU project "NANOTRANSPORT" addresses the behaviour of aerosols released to ambient air from nanoparticle manufacturing. The proposed pre-normative study has the objective of bringing into light and to document the need for standardised test aerosols adapted to the scope of nano-toxicology and occupational health studies.

Further issues not mentioned here but identified by the DECHEMA-VCI working group (see roadmap in the Annex) are addressed in company projects and in projects of the Institute for Environmental Medicine at the Heinrich-Heine-University, Duesseldorf.

As demonstrated in the Annex, almost all of the important issues concerning the safety and potential risks of nanomaterials are already under evaluation. Issues to be addressed within the European 7th R&D Framework Programme and within national research programmes and to promote European co-operation are described in the following chapter.

3. Recommendations for the European 7th R&D Framework Programme and national research programmes

Nanoparticles are mostly produced in closed systems, thus avoiding the release of particles and side products in the workplace and the environment. Most applications do use free isolated nanoparticles. Characteristically, nanoparticles firmly stick together in the course of the formulation processes or are firmly embedded in products. Great efforts have to be made to generate stable isolated nanoparticles for special applications. Therefore, to assess potential risks of nanomaterials, DECHEMA and VCI jointly recommend focusing in the first step on the exposure assessment.

DECHEMA and VCI recommend:

- the development of a robust and effective standard analytical method to measure surface and number concentration, morphology and chemical composition of individual particles and agglomerates under real workplace and environmental conditions and to determine the size distribution for high number concentrations. Especially, methods for environmental analysis for particles between 0.5 nm and 20 nm and processes to analyze non-spherical forms of nanoparticles (tubes, plates, etc.) are called for.

- The development of new methods to determine the particle number, size, composition, and the real morphology (isolated nanoparticles, aggregates, agglomerates, particle/protein or particle/DNA complexes, etc.) of nanoscale products in liquid media.

- The international harmonization of analytical standards (methods for reproducible particle generation, detection and characterisation of atmospheric nanoparticles and of nanoparticles in biological tissue, reference materials).

- The development of basic toxicology test protocols or guidelines for short term testing (genetic toxicity, extra-pulmonary distribution, bioavailability) and long term testing (long-term pulmonary inflammation, chronic effects).

- The investigation of life cycle aspects of selected articles containing nanomaterials (esp. accumulation potential and fate at the end of the life cycle).

Annex

Roadmap of the DECHEMA/VCI working group for safety research on nanomaterials

The roadmap summarizes the most urgent issues for safety research on nanomaterials and for a deepened understanding of biological effects and mechanisms. The issues already undertaken in ongoing projects are marked and scheduled.

Expected results of high prioritized (DECHEMA/VCI) topics

Priority and description		2005		2006		2007		2008	
		1st	2nd	1st	2nd	1st	2nd	1st	2nd
1	Decisive parameters for toxicity of nanoparticles			INOS NC FZK GSF Nanotox Tracer	**INOS** **NC** **FZK** **GSF** Nanotox Tracer	**INOS** **NC** **FZK** **GSF** Nanotox Tracer	INOS GSF Nanotox Tracer	INOS	INOS
2	Development of the validated toxicological methods			NS GSF	NC FZK NS GSF	INOS NC FZK NS GSF	**INOS** **NC** **FZK** **NS** **GSF**	**INOS** **NC** **FZK** **NS** **GSF**	INOS NS
3	Studies on materials other than TiO_2 and Carbon Black		NC FZK NS Tracer INOS	**INOS** **NC** **FZK** **NS** **GSF** **PR** INOS	**NC** **FZK** **NS** **GSF** **PR** INOS	**NC** **FZK** **NS** **GSF** **PR** INOS	**NC** **FZK** **NS** **GSF** **PR** INOS	NC NS FZK GSF PR INOS	INOS NS
4	Development of methods to reproducibly produce nano-aerosols		NC FZK ASO	NC FZK ASO GSF	NC FZK ASO NS GSF	**NC** **FZK** **ASO** **NS** **GSF**	**NC** **FZK** **ASO** **NS** **GSF**	NS	
5	Transport mechanisms of particles in/through cells		CFN	**CFN** **PR** **NS**	**CFN** **PR** **NS**	PR NS INOS	PR DFG NS INOS	DFG INOS	DFG INOS
6	Mechanism to take in particles through skin	**BA**	ND	**ND**					
7	Mechanism to take in particles by lung	**GSF** **LS**	**GSF** **LS**	**PDL** **GSF** **NS** **LS**	**PDL** **GSF** **NS** **LS**	**PDL** **GSF** **NS** **LS**	**PDL** **GSF** **NS** **LS**	NC LS	NC LS
8	Exposure Assessment (Methods to measure/identify conc., morphology and type of nanoparticles in environment and at the working place)		NEW NS	NEW GSF	NEW GSF	NEW GSF	NEW GSF	DFG NEW	DFG NEW
9	Stability of agglomerates under practical conditions			NC GSF	NC GSF	NC GSF	NC GSF	NC	NC
10	State of particle aggregation/agglomeration in human body			GSF NEW NS	GSF NEW NS	GSF NEW NS	NS NC GSF NEW	NS NC GSF NEW	NS NC GSF NEW
11	Disintegration of agglomerates in body fluids		DE	**DE** **INOS**	INOS	INOS	NC INOS	**NC** **INOS**	INOS