

Workplace exposure to nanoparticles



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1 Executive summary

The European Agency for Safety and Health at Work has published a series of expert forecasts providing an overview of the potential emerging risks in the world of work (physical, biological, psychosocial and chemical risks). Among the top ten emerging risks, three have in common their physico-chemical state as insoluble particles or fibres: nanoparticles and ultrafine particles, diesel exhaust, and man-made mineral fibres. The experts agreed that nanoparticles and ultrafine particles pose the strongest emerging risk.

Nanomaterials possess various new properties and their industrial use creates new opportunities, but they also present new risks and uncertainties. Growing production and use of nanomaterials result in an increasing number of workers and consumers exposed to nanomaterials. This leads to a greater need for information on possible health and environmental effects of nanomaterials. This report focuses on the possible adverse health effects of workplace exposure to engineered nanomaterials and possible subsequent activities taken to manage the risk. Nanomaterials originating from natural sources as well as non-intended nanoscale by-products, such as diesel engine exhaust and welding fumes, are not included in this review. In order to provide a broad overview, information from different sources such as scientific literature, policy documents, legislation and work programs were collected. Documents from the EU were given priority, although national and international activities have also been described. Studies published up to November 2008 have been considered in the report.

When particle size is decreased to the nanoscale range, physical and chemical properties often change with consequent new product opportunities. Thus a considerable future expansion of the nano-market is expected. Nevertheless it should be remembered that nanomaterials are not fully new: some established chemicals like amorphous silica or carbon black show a nanostructure. The knowledge about the occupational exposure to new nanomaterials is very limited. In addition, the measurement techniques to determine exposure are not fully developed. Various physical and chemical parameters have to be considered.

Different methods to investigate possible health effects of nanomaterials, such as in vivo- and in vitro-methods and methods to determine physico-chemical properties, are currently under discussion. The standardised in vivo-studies represent at present the best standard to detect toxicity evoked by nanomaterials. Effects like inflammation, fibrosis and tumours were induced by several granular nanomaterials in the lungs after respiratory exposure. Currently the mechanism of tumour formation is not fully understood and scientific uncertainties remain. Thus, the evaluation of toxicity is not only influenced by results from toxicity studies but also by the policy decision to what extent the precautionary principle is applied in case of scientific uncertainties. Skin exposure is not yet investigated in detail. Generally, in case of insoluble substances skin exposure is not as relevant as respiratory exposure.

The current principles of risk assessment seem to be in general appropriate; however, the validation of in vitro methods and the development of a testing strategy remain future tasks. Classification and labelling as well as occupational exposure limits, which are derived from toxicological data, are appropriate instruments for management of risks resulting from exposure to nanomaterials, but critically depend on the availability of studies on toxicity.

Several handling guidelines describing possible risk management activities and best practice were published. These are mainly based on technical feasibility and some of them recommend, based on the precautionary principle, to minimise exposure as far as possible. The protective measures that are typically used to protect against insoluble materials, like dusts, are often recommended also for nanomaterials. Because of the particular smallness of nanomaterials, especially the filter materials/media used in general ventilation systems, personal respiratory protective devices and the materials of gloves have to be examined. Preliminary studies indicate a protective effect, but further research is needed. In relation to filtering half masks, the lack of tightness (inadequate sealing) between face and the mask seems to be the most important risk factor. Control banding methods are used to assess occupational exposure in the case of non-existent occupational exposure limits or exposure measurements. First initiatives to adapt this method to nanomaterials have been developed, but need further elaboration. An important instrument of risk management providing information about hazards and appropriate control measures is the Material Safety Data Sheet. To what extent this instrument considers nanospecific properties sufficiently is currently under discussion.

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Several statutory instruments are in place to ensure an appropriate level of protection of workers. The general framework is provided by the regulation on occupational safety and health of workers (EU Directive 89/391/EEC) and specifically for chemical safety - the directive on the protection of the health and safety of workers from the risks related to chemical agents at work (Directive 98/24/EC). Substance-specific regulation is intended by the biocide Directive (Directive 98/8/EC) and the regulation No 1907/2006 (REACH – Registration, Evaluation, Authorisation and Restriction of Chemicals). Currently it is discussed how to consider appropriately the broad variety of nanomaterials in these regulations.

The Community strategy on health and safety at work for the period of 2007 – 2012 includes nanotechnology as an important topic to be worked on in the context of the identification of new, emerging risks. Furthermore a communication from the European Commission 'Towards a European Strategy for Nanotechnology' was published. The European Commission developed an "Action Plan" to implement a safe, integrated and responsible approach for nanosciences and nanotechnologies. To ensure a safe and ethical development and use of nanotechnologies, the European Commission issued a Code of Conduct. There are many ongoing initiatives/activities aiming at the development of a safe, sustainable, responsible research and development of this new technology. Large scale research and standardisation programmes have been started and partly finalised to establish standards, close data gaps and reduce uncertainties. European and global collaboration is recognized as an important aspect in achieving these goals. Activities have been initiated by organisations such as the International Organization for Standardization (ISO) and the Organization for Economic Co-operation and Development (OECD) to support a globally harmonised development. Collaboration between EU and US is also being developed to investigate the regulatory challenges posed by nanotechnologies and to assess the effectiveness of existing approaches on both sides of the Atlantic. The project takes a comparative perspective and contributes to the early identification of regulatory methodologies and best practices that promote regulatory convergence between the EU and US.

As the conclusion of this review of the most recent publications, the following topics are identified as priorities for future actions and activities:

- identification of nanomaterials and description of exposure
- measurement of exposures to nanomaterials and efficacy of protective measures
- risk assessment of nanomaterials in line with the current statutory framework
- in vivo studies for assessment of the health effects of nanomaterials
- validation of the in vitro methods and methods of physico-chemical properties as methods to determine health effects
- training of workers and practical handling guidelines for activities involving nanomaterials in the workplace.

2 Scope of the problem

Background

In the 19th and 20th centuries several technical and economic evolutions like the development and spread of steam engines, railways (19th century) as well as automobiles, computers, biotechnology and information & communication technology (20th century) have emerged. In the 21st century - nanotechnology is seen as one of the key technologies [1, 2]. The previous industrial revolution has taught us that rapid technological change impacts on society in a variety of ways. One of the challenges – still to be overcome - is the issue of occupational diseases and accidents resulting from industrial processes. Recent introduction of new technologies – such as nanotechnology – presents the same challenges [3]

Within its work program, the European Risk Observatory of the European Agency for Safety and Health at Work carried out a series of expert forecasts providing a picture of the potential emerging risks in the world of work (physical, biological, psychosocial and chemical risks) [4]. Among the top ten chemical emerging risks, three have in common their physico-chemical state as particles: nanoparticles and ultrafine particles; diesel exhaust; and man-made mineral fibres. The risks posed by nanoparticles and ultrafine particles are by far the strongest agreed as emerging by the experts.

Nanotechnology offers on the one hand various new properties and opportunities and on the other hand - brings new risks and uncertainties. The current report gives an overview on occupational health and safety aspects that have to be considered in case of exposure to engineered nanomaterials.

Nanotechnology and nanomaterials

Nanotechnology is mainly defined by size and comprises the visualisation, characterisation, production and manipulation of structures which are smaller than 100 nanometers (nm) [5, 6]. Nanoparticles are particles with one or more dimensions at the nanoscale [7]. According to the ISO / TR 27628 nanoparticles are particles with a nominal diameter smaller than 100 nm [8]. These particles originate from primary sources (natural sources, e.g. sea-air, volcanic ashes / pumicite) and / or secondary sources (artificial sources, such as. technical products and by-products, cigarette smoke, diesel engine exhaust, cutting and welding fumes, open fire) [5, 9]. Engineered nanoparticles are intentionally engineered and produced with specific properties [8]. Nanomaterials are materials with one or more external dimensions / internal structure on the nanoscale [6]. Nanomaterials / nanoparticles possess novel properties and characteristics that differ from the same non-nanoscale materials [6]. Nanoparticles / nanomaterials include, for example, metals or metal oxides, carbon black, carbon nanotubes, fullerenes, silicate, organic nanoparticles or nano composites [1, 10]. The term “nanoparticles” means only solitaire nanoparticles. Aggregates and agglomerates are not covered by this term. However in practice, aggregates and agglomerates are mostly also part of an investigated “nano-substance”. Currently many authors use the term “nanoparticles” including also agglomerates and aggregates.

Applications

The physical, chemical and biological properties of nanomaterials differ in fundamental and important ways from properties of individual atoms, molecules or larger sized bulk material [5, 11]. Therefore, such materials can be used for new applications in areas like information & communication technology, power engineering, industrial engineering, environmental engineering, chemical industry, medicine, in pharmaceuticals and cosmetics [12]. Some nanoscale materials have been used for decades (e.g. in window glass, sunglasses, car bumpers, paints), whereas others are newly-discovered (e.g. those used in sunscreens and cosmetics, textiles, coatings, sports goods, explosives, propellants and pyrotechnics) or their applications are currently under development (e.g. in batteries, solar cells, fuel cells, light sources, electronic storage media, display technologies, bioanalysis and biodetectors, drug delivery systems, medical implants and new organs) [5, 10, 13]. All in all, the number of nano products and methods of their use increase continually [7, 14].

Markets for nano products

Due to the wide range of possible applications in different fields, nanotechnology is a key technology with a high turnover potential [12]. The following table provides an overview on the amount of money spent on different markets in different regions. Many calculations are based on estimates and these vary to a large extent. Thus, specific and precise data is lacking.

Table 1: Nanotechnology regional & global market [1, 5, 7, 15]

Country / region	Year	Market	Amount	Source
worldwide	2003	estimated turnover with nano products	double-digit billion US dollar	[5]
worldwide	2003	public research funding	3 billion US dollar (estimation)	[5]
worldwide	2005	total investment in nanotechnology	5-7 billion US dollar (estimation)	[7]
USA	2006	money spent on nanotechnology	1.2 billion US dollar (estimation)	[7]
USA	2008	nanomaterials market	1.4 billion US dollar	[7]
worldwide	2008	global market for nano products	700 billion US dollar	[15]
worldwide	2008	global market for nano products	700 billion euro (estimation)	[1]
worldwide	2010	estimated turnover with nano products	triple-digit billion US dollar	[5]
worldwide	2010	global market for nano products	148 billion US dollar (estimation)	[1]
worldwide	2011	world nanomaterials demand	4.1 billion US dollar	[7]
worldwide	2015	estimated turnover with nano products	four-digit billion US dollar	[5]

According to CIENTIFICA (www.cientifica.eu) the global nanotech market in 2007 could be presented as shares of different products:

- chemicals 53%
- semiconductors 34%
- electronics 7%
- aerospace / defence 3%
- pharma / health care 2%
- automotive 1%.

Regardless of all these estimations and expectations, technical and socio-economic problems (so-called 'show stoppers') related to nanomaterials might inhibit the dynamic market growth [1, 2]. Due to vagueness of first available data on nano markets, trends for the global markets are difficult to predict [2]. However, nanotechnology is expected to have a significant impact on society and economy within the next ten to 15 years [10]. Therefore, that topic becomes a high priority in many countries [15]. New markets with prospect of high profits stimulate an international competition in the field of nanotechnology [2].

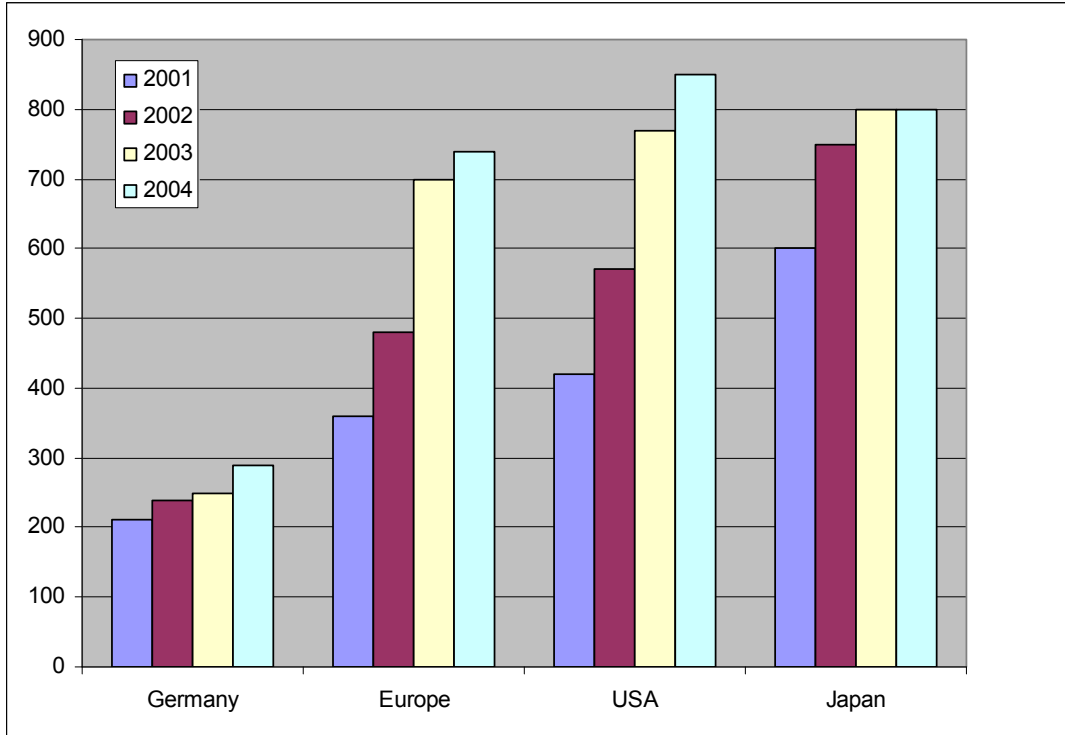
From 2001 to 2004 the public expenditures for the promotion of nanotechnology had grown steadily (see Figure 1) [1]. In 2004, 290 million euro (€) were spent for nanotechnology in Germany, whereas in Europe altogether 740 million euro were spent.

At the same time, 850 million euro were spent in the USA and 800 million euro in Japan on the promotion of nanotechnology. However, the comparability of these figures is in dispute: first, the definitions of "nanotechnology" vary, and second the figures had been calculated without considering,

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for example, the purchasing power in these countries and regions. Nevertheless, these figures illustrate to a certain extent the development of nanotechnology. That data is in line with figures on the estimated government nanotechnology research and development expenditures published by the OECD [16].

Figure 1: Promotion of nanotechnology in Germany, Europe, USA and Japan, expenditures in Million euro (2001, 2002, 2003, 2004)



Besides public expenditure, enterprises also invest in nanotechnology (research, development and production). At this juncture the financial sector plays a key role: venture capital is necessary in order to transfer the (gain in) technological knowledge from research centres to the industry and the markets [10]. Venture capitalists had by the end of 2004 invested one billion US dollars in companies working in the field of nanotechnology [10].

On company level barriers for development and/or implementation of innovations include high investments required (e.g. for research, new machines, new technologies), a lack of outside capital and insufficient subsidies [1, 2]. In comparison to big enterprises, small and medium-sized enterprises (SMEs) have different financing sources: SMEs have higher entry requirements to the money market than big enterprises [1]. Furthermore, innovation barriers for SMEs include also the access to market information as well as the availability of competent regional co-operation partners [1]. Therefore, collaboration between public research institutions and enterprises has become essential for the nano research progress [15]. These conditions influence the activities and development in the field of nanotechnology.

Players in the field of nanotechnology

Numerous players work in the field of nanotechnology:

- technology suppliers:
 - nano research (universities, non-university research institutions)
 - nano manufacturers (producers, technology service providers)
- technology users:
 - nano users (subsequent processing)
 - nano product users (consumer) [12].

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Further groups and professions play a role in for example safety and environmental aspects of nanotechnology: (accident) insurances, natural sciences (e.g. chemists, biologists, and toxicologists), engineering sciences (e.g. safety engineers) and medical sciences (e.g. occupational health physicians). These groups do not necessarily belong to the groups of technology suppliers and users. Each of these players has got its own view on nanotechnology. Whereas natural scientists work on the evaluation of possible health risks of nanomaterials, safety engineers and physicians deal with safety aspects (e.g. risk assessment) of nanomaterials for example in enterprises. Accident insurances are interested in the minimisation of occupational accidents and occupational diseases, whereas general insurances would like to minimise general impacts for example on the environment. Therefore the different players participate in the field of nanotechnology and nanomaterials on different levels.

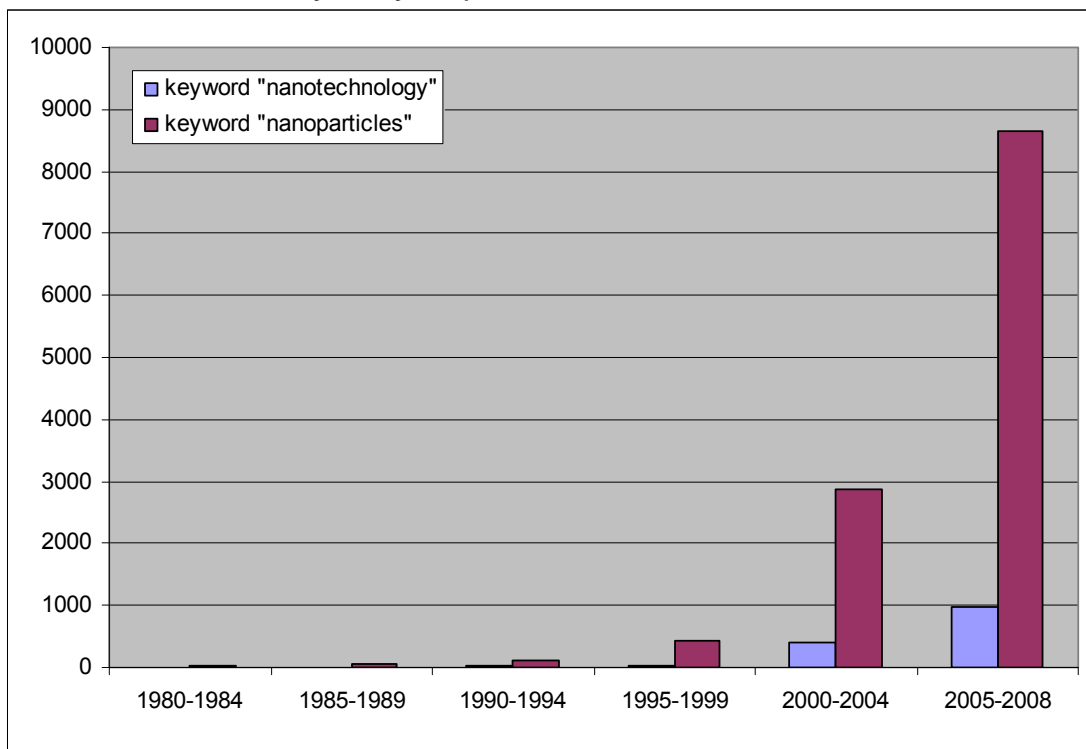
In 2003, most nanotech companies were located in the USA (430 companies), followed by Japan (110), Germany (94), UK (48), China (20), France (19) and Canada (18) [10]. According to further estimations, the field of nanotechnology comprised 1,500 companies worldwide, whereas 1,200 companies were start-ups [17]. In 2005, a total of 53 companies were involved in manufacturing, processing and / or using nanomaterials and 55 non-commercial organizations were undertaking nanotechnology-related research and development in the UK [18].

Between 20,000 and 114,000 jobs in 450 nanotechnology enterprises existed in Germany in 2004 [1]. According to tentative estimations for the increase of the number of jobs in the field of nanotechnology in Germany, 10,000 to 15,000 news jobs had been created by 2006 [2].

Publications & patents

Although market information and data on activities in the field of nanotechnology / nanomaterials are difficult to attain, the increase in the number of publications and patents underline the growing importance of nanotechnology. As an example, the number of published articles in relation to the keywords 'nanotechnology' and 'nanoparticles' in PUBMED (database for literature, service of the U.S. National Library of Medicine, <http://www.ncbi.nlm.nih.gov/sites/entrez>) increased very significantly within the last ten years (see Figure 2). Especially nanoparticles had been studied extensively (8,662 articles published between 1 January 2005 and 24 April 2008).

Figure 2: Number of PUBMED listed publications, from 1 January 1980 to 24 April 2008 (period 2005-2008 covers only four years)



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Within the last five years the number of patents related to application of nanotechnology has doubled every second year (basis year 2004) [1, 2]. Between 1995 and 2003 the number of patents in Germany increased tenfold (2003: 368 patents in Germany; 2,658 patents worldwide) [12]. However, SMEs apply for patents less frequently than big companies [2]. The reasons for that difference might be the existence of development barriers, such as high investments required or insufficient subsidies for SMEs.

Occupational exposure

Up to now, a few studies on workplace exposure to nanomaterials have been carried out. Objects of investigation have been for example titanium dioxide (TiO₂), carbon black, nickel powder, silica fumes or by-products like welding fumes, metal fumes, beryllium or diesel exhaust [19, 20].

Whereas some nanomaterials are in use since several years / decades (like titanium dioxide, carbon black), other nanomaterials are quite new and manufacturing and handling occurs only on laboratory scale. In comparison to those nanomaterials already investigated, information on workplace exposure to new nanomaterials is very limited [18]. Maynard et al. carried out laboratory and field measurements on the exposure to single-walled nanotubes [21]. Mazzuckelli et al. investigated potential sources of workers' exposure to carbon nanofibres during polymer composite laboratory operations [22]. Schneider et al. summarized information on exposure to engineered nanoparticles [23]. In one study the exposure to amorphous SiO₂ fume in smelters were described. Further sources for exposure were cleaning operations in laboratories or drilling and cutting operations of carbon nanotube-doped concrete [23]. Regarding these measurements, the influences of background concentration (concentration of other particles than those of concern) as well as the potential temporal variations of exposure have to be taken into consideration [20, 22, 23]. However, official data on the number of workers exposed to nanomaterials are not available [4].

Risk potential

New properties of nanomaterials and therefore new market opportunities lead to broad discussions regarding potential advantages and disadvantages (risks). Particles and materials on nanoscale have other properties than the same particles / materials on micro-scale. Some experts suspect that nanoscale particles/materials affect health more than microscale particles/materials [5]. Furthermore, safety risks might occur (e.g. risk of explosion).

A variety of exposure paths are possible [12]. At the workplace, workers can be exposed during the production process (laboratory, factory), use of products, transport, storage or waste treatment. The release of (fixed) nanomaterials during the products' life cycle might affect consumer's health. Nanomaterials might be released everywhere (at the workplace, in the general environment, at home), affecting workers and/or consumers. Due to the environmental uptake, nanomaterials might also affect the environment (soil, water, air, flora and fauna). The environmental contamination again might affect people's health.

Some experts think that nanotechnology is the next industrial revolution influencing society and economy [5]. On the one hand, new technologies may support problem-solving. On the other hand, new technologies create new risks. A risk of forming negative public perception - difficult to change - should also be considered. However, wider availability of information on nanotechnology and nanomaterials with all its facets is necessary to avoid emerging unjustified and unfounded horror scenarios and fears [5].

Focus of the report

The increasing production and use of nanoparticles and nanomaterials lead to an increased need for information on these materials in order to recognise evaluate and avoid risks. Increasing opportunities due to new properties of nanoparticles induce a higher production with an increased number of workers and consumers exposed to nanoparticles.

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The current report focuses on the possible health effects of engineered nanoparticles and risks that might occur at workplaces as well as the characterisation and measurement of this type of nanomaterials. Nanoparticles originating from natural sources as well as non-intended nanoscale by-products like diesel engine exhaust and cutting and welding fumes are not included in this review. Studies published up to November 2008 have been considered in the report.

3 Terms and definitions

To describe potential and risks related to nanotechnology, a common terminology has to be used to avoid misunderstandings. The following terms that have been defined by institutions like ISO, British Standards Institution (BSI) or European Committee for Standardization (CEN), are used in this document.

General terms

Table 2: general terms

Term	Definition
nanoaerosol	aerosol comprised of, or consisting of, nanoparticles and nanostructured particles [8]
nanomaterial	material with one or more external dimensions, or an internal structure, on the nanoscale, which could exhibit novel characteristics compared to the same material without nanoscale features [6]
nano-object	material with one, two or three external dimensions at the nanoscale NOTE: generic term used for all discrete nanoscale objects [24]
nanoparticle	particle with a nominal diameter (such as geometric, aerodynamic, mobility, projected-area or otherwise) smaller than 100 nm [8] nano-object with all three external dimensions at the nanoscale NOTE: if the lengths of the longest and the shortest axes of the nano-object differ significantly, the terms nanorod and nanoplate should be considered. 'Significantly' is considered to be by more than three times [24]
nanoscale	having one or more dimensions of the order of 100 nm or less NOTE: also referred to as nanosize [6]
nanostructured particle	particle with structural features smaller than 100 nm, which may influence its physical, chemical and/or biological properties [8] NOTE: agglomerates and aggregates of nanoparticles are examples of nanostructured particles [6]
nanotechnology	design, characterization, production and application of structures, devices and systems by controlling shape and size at the nanoscale [6]

Particle terms

Table 3: particle terms

Term	Definition
agglomerate	(aerosols) group of particles held together by relatively weak forces, including Van der Waals forces, electrostatic forces and surface tension NOTE: the term is frequently used interchangeably with "aggregate" [8]
aggregate	(aerosols) heterogeneous particle in which the various components are held together by relatively strong forces and thus not easily broken apart NOTE: the term is frequently used interchangeably with "agglomerate" [8]
carbon black	elemental carbon in the form of near-spherical particles with major diameters less than one micrometer (μm), generally coalesced into aggregates [6]

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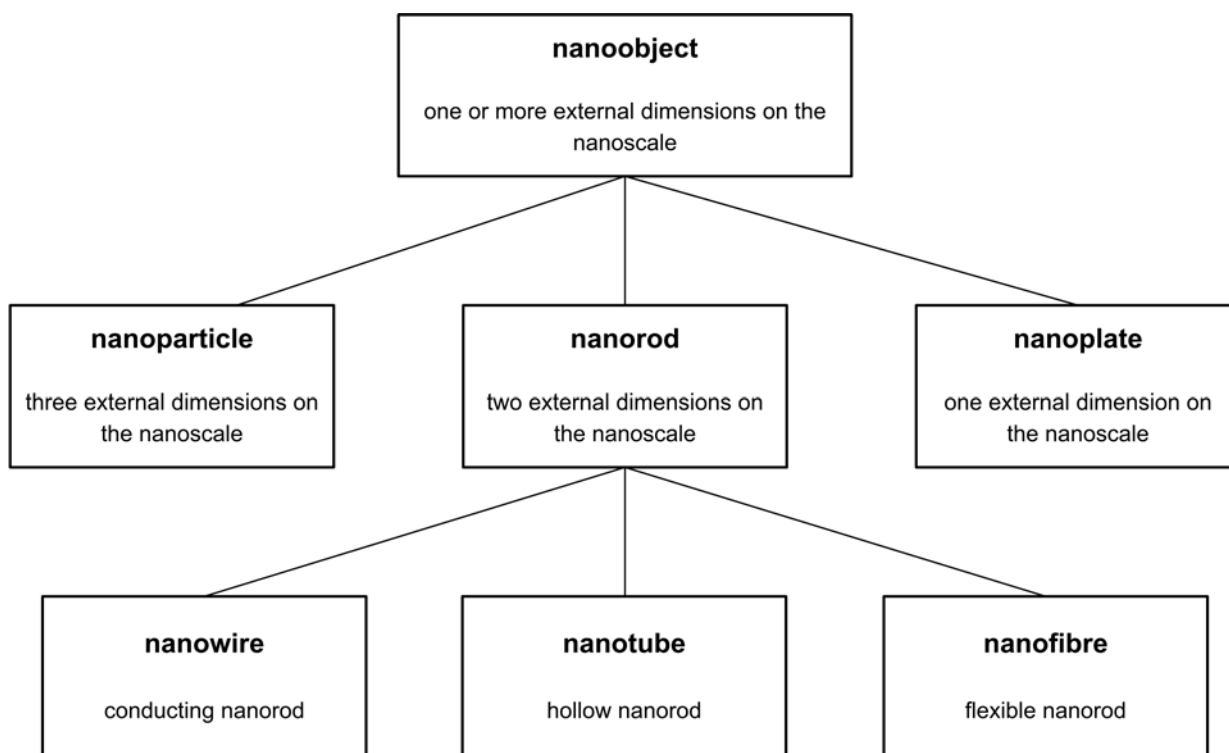
Term	Definition
carbon nanotube	nanotube consisting of carbon NOTE: This term is commonly used to a seamless tube constructed from graphene that can be either a single-wall carbon nanotube (SWCNT), comprising a single layer of carbon atoms, or a multi-wall carbon nanotube (MWCNT), comprising multiple concentric tubes [25]
dendrimer	synthetic, three-dimensional macromolecule built up from a monomer, with new branches added in a step-by-step fashion until a symmetrical branched structure is created NOTE: where there is perfect branching, the particle is referred to as a dendrimer; where the branching is imperfect, it is referred to as hyperbranched [6]
engineered nanoparticle	nanoparticle intentionally engineered and produced with specific properties [8]
fullerene	closed-cage structure having more than 20 carbon atoms consisting entirely of three-coordinate carbon atoms NOTE: a fullerene with 60 carbon atoms (C ₆₀) is sometimes called buckminsterfullerene [25]
fumed silica	bulk powered form of silicon dioxide produced from thermal pyrolysis, which could have primary particles sized at the nanoscale [6]
graphene	single sheet of trigonally bonded (sp ²) carbon atoms in a hexagonal structure [25]
nanocluster	non covalently or covalently bound group of atoms or molecules whose largest overall dimension is typically in the nanoscale [25]
nanocomposite	multiphase structure in which at least one of the phases has at least one dimension in the nanoscale [25]
nanocrystal	nanoscale solid formed with a periodic lattice of atoms, ions or molecules [6]
nanofibre	flexible nanorod [24, 25]
nanoplate	nano-object with one external dimension in the nanoscale and the two other external dimensions significantly larger NOTE 1: the smallest external dimension is the thickness of the nanoplate. NOTE 2: the two significantly larger dimensions are considered to differ from the nanoscale dimension by more than three times. NOTE 3: the larger external dimensions are not necessarily at the nanoscale [24, 25]
nanopowder	mass of dry nanoparticles [25]
nanorod	nano-object with two similar external dimensions in the nanoscale and the third dimension significantly larger than the other two external dimensions NOTE 1: the largest external dimension is the length of the nanorod and is not necessarily in the nanoscale. NOTE 2: the two similar external dimensions are considered to differ in size by less than three times and the significantly larger external dimension is considered to differ from the other two by more than three times. NOTE 3: a nanorod can take any cross-sectional shape consistent with the dimensional limits of the definition [24, 25]
nanotube	hollow nanorod [24, 25]

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Term	Definition
nanowire	conducting or semi-conducting nanorod [24]
primary particle	particle not formed from a collection of smaller particles NOTE: The term typically refers to particles formed through nucleation from the vapour phase before coagulation occurs [8]
quantum dot	semiconducting crystalline nanoparticle that exhibits size dependent properties due to quantum confinement effects on the electronic states [24]
secondary particle	particle formed through chemical reactions in the gas phase (gas to particle conversion) [8]
ultrafine particle	particle with a nominal diameter (such as geometric, aerodynamic, mobility, projected-area or otherwise) of 100 nm or less NOTE: The term is often used in the context of particles produced as a by-product of a process [8]

The hierarchical relationship between many of the above mentioned terms is presented in the following figure.

Figure 3: hierarchical relationship between terms [24]



Particle characteristics

Table 4: particle characteristics

Term	Definition
aerodynamic diameter	<p>diameter of a spherical particle with a density of 1000 kg/m³ that has the same settling velocity as the particle under consideration</p> <p>NOTE: aerodynamic diameter is related to the inertial properties of aerosol particles and is generally used to describe particles larger than approximately 100 nm [8]</p>
dustiness	propensity of materials to produce airborne dust during handling [26]
mobility	(aerosols) propensity for an aerosol particle to move in response to an external influence, such as an electrostatic field, thermal field or by diffusion [8]
mobility diameter	<p>diameter of a spherical particle that has the same mobility as the particle under consideration</p> <p>NOTE: mobility diameter is generally used to describe particles smaller than approximately 500 nm and is independent of the density of the particle [8]</p>
surface area, active	<p>surface area of a particle that is directly involved in interactions with surrounding gas molecules</p> <p>NOTE: active surface area varies with the square of particle diameter when particles are smaller than the gas mean free path (average distance molecules travel between collisions with other molecules in the gas), and is proportional to particle diameter for particles very much larger than the gas mean free path [8]</p>
surface area, specific	surface area per unit mass of a particle or material [8]
zeta potential	electrostatic potential at the slipping plane (which marks the region where the liquid molecules surrounding the particle first begin to move with respect to the surface) relative to the potential in the bulk solution [6]

4 Physico-chemical properties

Nanostructured particles make up a group of elements composed of primary particles smaller than 100 nm, which are combined in aggregate or agglomerate form. The way in which primary particles are interlinked determines whether they constitute aggregates or agglomerates. Aggregates are formed by association of primary particles strongly linked by molecular-type bonds, whilst agglomerates are formed by association of primary particles interlinked by Van der Waals-type lower energy bonds. Both aggregates and agglomerates can comprise identically or differently composed primary particles, which can make up either homogenous agglomerates or heterogeneous aggregates. Similarly, their primary particles can be subjected to chemical treatment, which modifies their surface. Table 1 below provides a summary of all these structures [27].

Table 5: classification scheme for nanostructured particles [27]

class	description
A	spherical or compact particles compositionally homogeneous
B	high aspect ratio particles compositionally homogeneous
C	<i>complex</i> non-spherical particles compositionally homogeneous
D	compositionally heterogeneous particles core-surface compositional variation
E	compositionally heterogeneous particles distributed compositional variation
F	homogeneous agglomerates (agglomerates of a single particle class)
G	heterogeneous aggregates aggregates of diverse particle types
H	active particles particle behaviour and properties depend on external stimuli
I	multifunctional particles particle behaviour and properties depend on functional responses to local environment and stimuli

When the particle size is decreased to the nanoscale range, fundamental physical and chemical properties appear to change, often resulting in completely new and different than before physical/chemical properties. For example, titanium dioxide particles lose their white colour and become colourless at decreasing size ranges below 50 nm. Other particle types, known for electrical insulating properties, may become conductive at the nanosize, or low soluble substances can increase their solubility when their size is below 100 nm [28, 29].

The behaviour of nanoparticles is similar to the behaviour of a gas or a vapour and it is related to the size of particles, which depends on their formation mechanism and the diffusion forces [30, 31]. Air diffusion is the principal mode of transport of particles smaller than 100 nm. The speed at which particles diffuse is determined by their 'coefficient of diffusion', which is inversely proportional to their

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size. Nano-size particles will diffuse much faster than micro-size particles. Thus nanomaterials can be found far away from their point of origin in the work environment.

Because of diffusion and Brownian motion (random movement of particles suspended in a gas or liquid), particles suspended in an aerosol are subjected to a multitude of collisions, which lead to their agglomeration or coagulation and thus increase in the diameter. The speed at which the particles agglomerate, depends on their numerical concentration and mobility. The mobility of particles is inversely proportional to their diameter [32].

Coagulation of very small particles quickly leads to the formation of larger particles in lower concentration. Particles from one nm to 100 nm tend to agglomerate quickly to form larger diameter particles. When they reach a size of around 100 nm, they grow at a slower pace, up to 2,000 nm. This slower growth zone, between 100 and 2,000 nm, is called 'accumulation mode'. The primary aerosol particles that come into contact with each other, adhere to each other due to short distance forces (a few atoms diameter) to form loosely larger particles or agglomerates. The aerosol coagulation process is caused by the relative motion among the particles. When the movement is due to the Brownian effect, the process is called Brownian coagulation or thermal coagulation, this is an spontaneous and ever present phenomena for aerosols. If the relative motion is caused by external forces (such as gravity, electrical or aerodynamic forces) the process is called kinematic coagulation [33].

Gravitational sedimentation is the phenomenon whereby particles fall into a medium under the effect of gravity. Sedimentation speed depends on the particle diameter and the characteristics of the fluid in which sedimentation occurs, particularly the friction coefficient. For big particles this friction coefficient is negligible, but it becomes more and more significant when the particle size diminishes. This is illustrated by the ratio of thermal diffusion displacement to the gravity displacement. For ten nanometer diameter particles the ratio is 4,800 (predominance of diffusion and a negligible sedimentation) while for ten microns diameter particles the ratio is 7.2×10^{-4} (negligible diffusion, predominance of sedimentation) [34]. As a conclusion the gravitational sedimentation cannot be considered an efficient mechanism for elimination of small particles, particularly nanoparticles [32].

Resuspension of particles from powder is extremely complex. Several factors can influence this process, particularly size, form, electrostatic particle charge and ambient humidity. The forces responsible for the particles adhesion to each other are also responsible for the particles adhesion to surfaces. The smaller the particles, the more difficult they will be to detach from any surface and re-suspend. Most nanoparticles, once they are attached, i.e., aggregated or agglomerated in powder form, will not be easy to separate or suspend in the air of the work environment [32].

Particle surface and interfaces are important components of nanoscale materials. As the particle size is reduced, the proportion of atoms found at the surface related to the atoms in the interior of the particle increases and as consequence, the nanoscale particles are more reactive. From a health effects perspective, reactive groups on a particle surface can modify the toxicological properties [35, 36].

Biological effects caused by nanoparticle deposition are related to their physical and chemical parameters. The nanomaterials may have different health impacts when compared to fine-sized (bulk) particle-types of similar chemical composition [37, 38]. In this regard, the knowledge of physical and chemical properties such as particle size distribution, morphology, particle composition, particle surface area, particle number concentration, surface chemistry and particle reactivity in solution are particularly important for the purpose of risk assessment. Table 6 below provides an exhaustive list of these parameters [27].

Table 6: nanostructured particle attributes

Attribute	Notes
Shape	physical shape or morphology of particles including surface structure at the nanoscale
surface area	ideally, the surface area of particles involved in biological interactions (biologically relevant particle surface area)
surface chemistry	surface chemistry associated with a particle's biological activity
composition	integrated particle chemical composition
core surface composition homogeneity	systematic nanoscale variations in core and surface composition which may influence particle behaviour
distributed composition heterogeneity	compositional variations distributed throughout a nanoscale particle
Solubility	solubility is used here to describe the rate of dissolving of a nanoscale material in a given biological environment, or release of a specific component of a nanoscale material through dissolution
charge (in biological fluid)	particle charge following deposition in the respiratory tract
crystal structure	internal crystal structure of a nanoscale particle
Porosity	internal porosity of a nanoscale particle
Changes in particle size and/or structure following deposition	changes in particle size and/or structure due to de-agglomeration the collapsing, the collapsing of open nanostructures or the expansion of previously dense structures
preferential release of constituent components following deposition	preferential release of individual particles or chemical components from composite particles, agglomerates and aggregates, following deposition
Stimulus associated behaviour	biological activity which is dependent on an external stimulus, such as light or a magnetic field
functional response to environment	biological activity which depends on the local biological environment, and may change in response to the local environment

According to information presented in the above table, it can be concluded that there is no universal physical / chemical parameter for assessing the toxicity of a nanostructured particle. Highly varied measuring methods have to be applied to characterise the different parameters. Some of these methods are already used in industrial environments for assessing the quality of a powdery product with a view to its later use in formulations. In relation to toxicological studies, investigation of all physical and chemical parameters would be ideal, but represents a major workload. A significant number of parameters can therefore be retained as a minimum for successfully conducting meaningful toxicological studies [28]. These would include:

- particle size,
- particle distribution,
- specific surface area,
- crystalline structure,

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- surface reactivity,
- surface composition,
- purity.

Murdock et al. (2007) also emphasises that an adequate characterization of physico-chemical properties is strongly recommended. The following physico-chemical properties should be characterized before performing hazard-evaluating studies

- particle size and size distribution (wet state) and surface area (dry state) in the relevant media being utilized depending upon the route of exposure,
- crystal structure / crystallinity,
- aggregation status in the relevant media,
- composition / surface coatings,
- surface reactivity,
- method of nanomaterial synthesis and/or preparation including post synthetic modifications (e.g., neutralization of ultrafine TiO₂ particle-types),
- purity of the sample [39].

In addition to this minimum set of parameters, the following parameters have also been identified as being desirable: shape, zeta potential, solubility and hydrophobic potential.

Moreover, it would seem necessary to know the dispersion capacity of nanoparticles in the air for assessing risks associated with their inhalation. A so-called dustiness test has been developed for assessing this state [23]. Once it has been standardised, this test can provide a dustiness index for each nanostructured powder and will permit assessment of its handling-related risks.

Usual analytical techniques can be applied to the measurement of nanoparticles if modified correctly to allow for the specificity of nanomaterials. However, there are favoured techniques that are used currently to estimate the basic parameters. Analytical methods for the minimum set of parameters recommended and additional optional parameters are summarised by the Institute of Occupational Medicine (IOM) [40].

5 Occupational exposure

Even though nanotechnology is a relatively new branch of industry, numerous applications have already been developed. It is estimated that there are more than 400 consumer products on the market which include nanomaterials. The investment – and exposure of workers to related risks - in this technology is concentrated in following fields:

- Construction – in products improving wear-resistance, rigidity, but also used in pigments; windows, more efficient insulation materials
- Health care – in new drugs and active agents, drug-delivery systems, oral vaccines, tissue engineering and production of biocompatible materials
- Energy conversion and use – increasing efficiency of energy conversion and low-wastage storage of energy, including new generation photovoltaic cells, more economical lighting, compact combustion cells
- Automobile (and aerospace) industry – reinforced and stronger materials, sensors optimising engine use, fuel additives, scratch-resistant, dirt-repellent coatings
- Chemical industry – catalysts, adhesiveless bonding techniques, multi-functional and more efficient ceramics, products used for surface functionalisation and finishing, such as pigments, corrosion-inhibitors, self-cleaning surfaces, anti-static, functional layers: thermal insulation, but also extremely hard and resistant cutting tools
- Electronics and communication – optical/optoelectronic components including lasers, high-density memories, pocket electronic libraries, ultra fast compact computers

This list is not all-inclusive. Other areas where nanotechnologies are utilised include environmental applications, textile industry, manufacturing of instruments and tools, defence. The list of application will grow with the development of nanotechnology. At the same time, for some activities – such as cleaning and maintenance – exposure to nanomaterials has to be considered in increasing number of sectors. [17, 32]

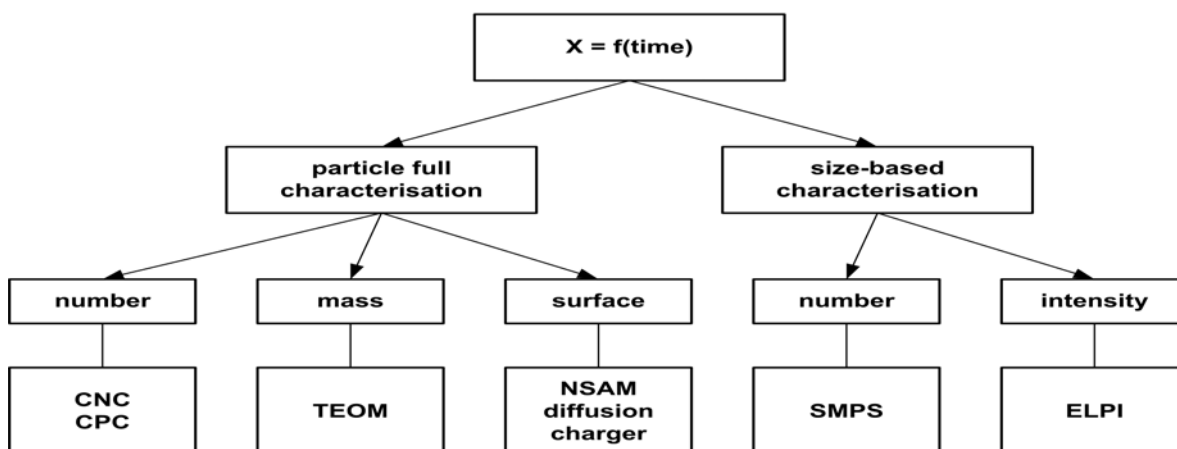
5.1 Occupational exposure measurement

Measuring aerosol mass concentration is a standard procedure in the workplace and environment. The simplest approach is to use a filter-based personal sampler comprising some form of inertial particle pre-selector. Conventional pump-based filter sampling of an aerosol is not the best solution for exposure assessment for an aerosol of nanostructured particles. There are two reasons for that:

- mass concentration, which is the parameter considered in this form of sampling, is not necessarily well-suited to the toxicity assessment of inhaled nanoparticles. Toxicity studies show that particle toxicity increases as they become smaller [41, 42];
- none of the existing instruments used for monitoring give specific information about particle concentration below 1 μm aerodynamic diameter.

More relevant indicators have emerged for describing nanoparticle aerosols, including particle number, surface and mass concentrations, and criteria relating to their size or shape. Some of the instrumentation developed around these indicators enable a continuous measurement. The sections 6.2 and 6.3 of ISO Standard TR 27628 include a classification of each instrument based on continuous measurement of size, number and surface area parameters for the collected aerosol. These parameters - $X = f(\text{time})$ - involve the whole aerosol or one of its particle size distribution fractions as shown in Figure 4 below.

Figure 4: classification of instruments [8]



(CNC= Condensation Nuclei Counter, CPC = Condensation Particle Counter, TEOM = Tapered Element Oscillating Microbalance, NSAM = Nanoparticle Surface Aerosol Monitor, SMPS = Scanning Mobility Particle Sizer, ELPI = Electrical Low Pressure Impactor)

Cascade impactor

The cascade impactor is an example of an aerosol sampling method, which provides the aerosol mass distribution for the aerosol with respect to the aerodynamic diameter (D_{ae}) of the collected particles. The instrument is composed of a series of collection stages, each of them being characterised by a specific cut-off diameter. Each stage constitutes a specific particle size selection for the sampled aerosol. Particles larger than the stage cut-off diameter impact the stage, whilst other particles are collected at lower, or smaller, cut-off diameter stages. The last, smallest diameter stage only allows nanoaerosols to be collected on a filter. Impactors include five to 10 stages; the cut-off diameter of their last stage varies between 0.25 μm (250 nanometres), for the Sioutas model and 0.4 μm (400 nanometres), for the Marple model [43]. Depending on its model, a cascade impactor can be used for fixed (stat) atmospheric sampling or operator-based (dynamic) personal sampling. Moreover, further analysis can be carried out on the collected particles on each stage (such as X-diffraction which provides information about crystalline structure or ICP which provides information about chemical composition of the nanoparticles).

Tapered Element Oscillating Microbalance (TEOM)

This instrument enables automatic measurement of aerosol mass concentration and it is currently the only instrument performing the measurement of the mass of a sampled aerosol in a single operation [44]. Measurement of the collected fraction is usually performed by collecting the aerosol on a filter, then measuring the deposited mass later. The TEOM enables the measurement of aerosol mass concentration ranging from $\mu\text{g}/\text{m}^3$ to g/m^3 . Particles are collected on a glass tube-mounted filter, the system being oscillated at a vibration frequency f . The variation in oscillation frequency is observed when the aerosol is collected. This variation is directly proportional to the mass of particles deposited on the filter (in fact the inverse of the square of the frequency).

The TEOM is the reference instrument for environmental air quality monitoring stations. Installation of PM_{10} , $\text{PM}_{2.5}$ and PM_1 selectors (PM_x Particulate Matter size) enable the sampling of environmental aerosols with aerodynamic cut-off diameters of 10, 2.5 or 1 μm to be sampled [45]. However, values

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given by these selectors, which are compatible with environmental standards, are rather different to aerosol fractions collected in industrial hygiene, especially in relation to the respirable fraction given for a four µm cut-off diameter. Furthermore, the weight and size of TEOM equipment means it can only be used for static environmental sampling; the version developed for operator-based personal sampling had to be abandoned.

Scanning Mobility Particle Sizer (SMPS)

This instrument measures the particle number size distribution. It is composed of a Differential Mobility Analyser (DMA) which is coupled in series with a Condensation Particle Counter (CPC). The DMA first selects a particle size interval of the sampled aerosol, then the CPC counts the particles exiting the classifier. The selection within the DMA is performed by applying an electric field between two concentric electrodes. Only a fraction of them, of given electrical mobility, moves along a trajectory, which allows them to reach the outlet. It should be noted that the particles must be previously neutralised at the DMA inlet using radioactive sources (Kr^{85} , Am^{241}) to reach a state of charge equilibrium. Electric field scanning then allows different particle size to be selected for building up the particle size distribution. The SMPS measurement range extends conventionally from a few nanometres to a micron. The considerable size and the weight of this instrument limit its use to environmental sampling. In some European countries, the presence of an internal radioactive source further restricts its use to laboratory applications [46].

Electrical Low Pressure Impactor (ELPI)

This instrument measures automatically the particle (number) concentration and generates the particle number size distribution of aerosols composed of particles with aerodynamic diameters between 28 nm and 10 µm. This is a low-pressure cascade impactor, which extends to cut-off diameters smaller than those reached by cascade impactors operating at atmospheric pressure. The number of particles deposited on each impaction stage is determined by current measurement. Sampled particles are effectively charged electrically by corona effect at the instrument inlet and neutralise their charge by depositing themselves at the collection stage corresponding to their aerodynamic diameter. Therefore, the current measured at each stage enables the determination of the particle number concentration. If the charge law governing conversion of the number of electric charges carried by each particle in relation to its diameter is known, the numerical particle size distribution can be calculated. It should be noted that the particle density is an essential parameter, which affects the impact location of each particle. However, this property is rarely known in an industrial environment. This instrument allows numerical particle size distribution to be monitored in real time. Its heaviness restricts its usage to only static, fixed station, sampling. In common with conventional impactors, subsequent chemical analysis can be performed at each of the impacting stages; this option is attractive for the last four stages, which cut-off diameters are in the nanometric range [46, 47].

Condensation Particle Counter (CPC) or Condensation Nuclei Counter (CNC)

This instrument measures the particles' numerical concentration in air sampled by laser optical detection. Optical reading restricted to particles with diameters less than 100 nm requires their artificial growth for detection purposes. To achieve this, sampled particles are used as alcohol or water vapour condensation nuclei. This particle growth operation then enables the detection of nanoparticles as small as three nm in diameter in the case of the most sensitive instruments. The CPC or CNC thus measures fully the sampled aerosol without discrimination between the particle sizes. It is mainly used for the monitoring of clean rooms that need a low level of environmental pollutants such as dust. For clean rooms standards are drawn up in terms of numerical particle concentrations. Furthermore, its size and weight only allow it to be used for environmental sampling [48, 49].

Nanoparticle Surface Aerosol Monitor (NSAM)

This instrument measures the surface concentration of an aerosol that would be deposited either in the tracheobronchial or alveolar section of the airway. Sampled aerosol particles are charged by a corona effect-induced ion diffusion at their surface. The number of charges carried by a particle is related to its surface area. Particles charged in this way are then collected on a filter, which current conduction, measured against time, allows to determine the surface concentration. Suitable adjustment of the ion trap provides access to the deposited surface area in the tracheobronchial or alveolar region. This is a full measurement, but it does not provide the particle size distribution of the collected particles. The weight of the instrument restricts its usage to static environmental sampling. However, a “field” version of the NSAM (TSI 3550) has been marketed more recently (AeroTrak 9000) [50, 51].

Conclusion

The operation of all presented instruments requires specialist skills. This effectively limits their usage to researchers in environment and occupational fields. Each instrument only provides data on a single parameter and a further development would be to combine their different measurement techniques to improve aerosol characterisation [34, 52].

One of the practical measurement difficulties is to avoid including in the measurement the nanoparticle ‘background noise’ of natural origin. The latter arises from natural sources by erosion or vapour condensation in the atmosphere. Production of these naturally occurring nanoparticles is evaluated at several hundreds of millions of tonnes per year in the world [53].

‘Background noise’ is also contributed to by human activities, especially fuel combustion, in which emissions of several billion nanoparticles per gram of fuel have been recorded [54]. This ‘background noise’ must be eliminated, especially when measuring the numerical particle concentration.

The nature of nanoparticle aerosols imposes a sampling strategy, which considers aerosol space-time variations in workplaces. This strategy must integrate the origin of the various nanoaerosol emission sources in workplaces and take into account both air movements therein and operators’ real activity [55].

These different considerations require foreseeing an universal instrument for aerosol measuring, which would have the ability to record various parameters permitting optimum, simultaneous evaluation of [27]:

- aerosol numerical, surface and mass concentration;
- an ultrafine fraction (which indeed requires definition as well as conventional respirable, inhalable and thoracic fractions who are defined in standard ISO 7708);
- rapidly collected data and their storage for later use.

This universal instrument must be portable for use by operators in the workplaces. Instruments currently monitoring continuously a single parameter can only be used for environmental sampling because of their weight. A European project, called Nanodevice is under development to satisfy this need. The overall goal of the Nanodevice project is to develop a family of devices for direct (in-situ) monitoring and measurement of a broad range of relevant engineering nanoparticle characteristics in the workplace air with high time resolution (on-line).

5.2 Occupational exposure assessment

The Working Party on Manufactured Nanomaterials (WPMN) of the Organization for Economic Co-operation and Development (OECD) has selected a list of representative manufactured nanomaterial considering those materials which are in commerce (or close to commercial use) [56]. This list includes the following nanomaterials:

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- fullerenes (C60)
- single-walled carbon nanotubes (SWCNTs)
- multi-walled carbon nanotubes (MWCNTs)
- silver nanoparticles
- iron nanoparticles
- carbon black
- titanium dioxide
- aluminium oxide
- cerium oxide
- silicon dioxide
- polystyrene
- dendrimers
- nanoclays.

As example, four of these nanomaterials (silicon dioxide, iron, silver, single-walled nanotubes) are presented in more detail later, describing the manufacturing processes and their applications, as far as currently are known.

Exposure to engineered nanomaterials can be found mainly in two ranges: one at industrial scale which means production of nanomaterials and subsequent formulation and application in products and the other, at research scale, which includes research and university laboratories.

Human exposure to engineered nanomaterials by inhalation is very limited during production because normally this process is performed in a closed reaction chamber, except in case of leaking during the process. Human exposure is more likely to occur after the manufacturing process, when the reaction chamber is opened or the product is dried, or during the handling of products after their manufacture or during the reactor cleanout operation [22, 57, 58]. At research scale, Tsai et al. (2008) found that the handling of dry powders consisting of nano-sized particles inside laboratory fume hoods can result in a significant release of airborne nanoparticles from the fume hood into the laboratory environment and the researcher's breathing zone [59]. Many variables were found to affect the extent of particle release including hood design, hood operation (sash height, face velocity), work practices, type and quantity of the material being handled, room conditions and the adequacy of the room exhaust.

One important point to consider in workplaces exposure is that most exposures to nanomaterials are in the form of aggregates/agglomerates. In those cases size measured by e.g. impactors or mobility analyzers can not reveal the agglomeration state and thus to which degree an agglomerate can break up into many smaller units in the lung fluid. Thus results of such measurements cannot be directly related to risk if particle number is a relevant measure of this risk [23, 57].

To assess occupational exposure to nanomaterials it is important to know background particles that include those particles that penetrate from outdoors to indoors and those that are suspended by background activities in the production facility like combustion engines, heating units or cleaners. The particle number size distribution and the particle number concentration are useful parameters for identifying sources of particles [22, 23, 57, 58].

One important basis of risk assessment is monitoring of exposure of workers to engineering nanomaterials. Currently, papers in the field of occupational exposure are limited. Most of them are related to potential exposure to engineering nanoparticles, because it is difficult to discriminate the background particles. Furthermore the influence of process (e.g. blending) to release nanosize particles is currently difficult to determine. Recently published papers are discussed below.

Potential particle exposure levels during chemical vapour deposition (CVD) growth and subsequent handling of vertically-aligned carbon nanotube films was investigated by Bello et al. [60]. The process was monitored on three different occasions over the course of six months. During each session, continuous information was collected on particle number concentration of the background and the

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surrounding air during the whole cycle of the furnace operation. These measurements were accomplished using a real-time particle sizer (FMPS) to measure number concentration of aerosol particles in the range 5.6 to 560 nm, a condensation particle counter (CPC) to measure total particles concentration from 10 nm to one μm and thermophoretic and electrostatic precipitators (TP, ESP) to evaluate particle size and morphology. No increase in the total particle number concentration and any particle size range were observed during each cycle of the furnace operation as compared to background (FMPS and CPC results). Electron microscopy of multiple copper (Cu) grids collected with TP and ESP did not reveal the presence of CNTs (carbon nanotubes). This is an important finding as many academic and industrial laboratories utilize similar systems and processes.

Fujitani et al investigated physical properties of aerosols in a fullerene factory for inhalation exposure assessment [57]. The authors used a scanning mobility particle sizer and an optical particle counter to measure the particle number size distributions of particles ranging in diameter (D_p) from 10 nm to more than 5000 nm and used scanning electron microscopy to examine the morphology of the particles. Comparisons of particle size distributions and morphology during non-work periods, during work periods, during an agitation process, and in the nearby outdoor air were conducted to identify the sources of the particles and to determine their physical properties. During the bagging operation, the particle number concentration at $D_p < 50$ nm increased by 40 % compared with that in the non-work period. Results indicate that the use of the vacuum cleaner increased the number concentration of particles with $D_p < 50$ nm compared with that in the non-work period. During agitation, which is not a normal procedure (compressed air was blown into an open bag of fullerene located nearby the storage tank to disperse the fullerene in the air) no increase in particle number concentration in the nanometer-size range occurred compared with that during the non-work period. This result corresponds to that of morphological analysis, in which many coarse particles were observed.

The possible exposure to multi-walled carbon nanotubes (MWCNTs) release in a carbon nanotube research laboratory was investigated by Han et al. [61]. To estimate the potential exposure of

researchers and evaluate the improvement of the workplace environment after the implementation of protective control measures, personal and area monitoring were conducted in a MWCNT research facility where the researchers handled unrefined materials. The gravimetric concentrations of total dust before any control measures ranged from 0.21 to 0.43 mg/m^3 , then decreased to a nondetectable level after implementing the control measures. The number of MWCNTs in the samples obtained from the MWCNT blending laboratory ranged from 172.9 to 193.6 MWCNTs/ cm^3 before the control measures, and decreased to 0.018-0.05 MWCNTs/ cm^3 after the protective improvements. The real-time monitoring of aerosol particles provided a signature of the MWCNTs released from the blending equipment. The black carbon mass concentration also increased significantly during the MWCNT release process. The present study suggests that the conventional industrial hygiene measures can significantly reduce exposure to airborne MWCNTs and other particulate materials in a nano research facility.

The National Institute for Occupational Safety and Health (NIOSH) examined various operations involved in the handling or processing of CNF (carbon nanofibre) materials and determined whether emission of these materials occurred [22]. The evaluated processes were: weighing out CNF material, mixing CNF with solvent, handling bulk – partially dry product, wet-saw cutting CNF composite. The mass of total carbon (TC) on the singular, filter-based samples, was employed as an element marker for the presence of CNFs. Air concentrations within the laboratory processing area were two to 64 times those in a nearby office area. The TC loading on a floor surface collected near the desk of a laboratory employee, suggested transfer of CNFs from the laboratory to a nearby office – the surface TC loading was 11 times that in a sample from a more remote office area. The CPC measurements show slight increases in particles concentration relative to laboratory background for weighing and mixing of CNFs as well as for wet-saw cutting of composite material. Particles having a diameter of about 400 nm or greater were found in greater number during wet-saw cutting, while the number of particles having a diameter of about 500 nm or greater were elevated during the weighing and mixing of CNFs. The majority fibres observed in TEM (transmission electron microscopy) grids appeared as loosely bundled agglomerates rather than as single fibres, an observation that is in general agreement with real-time aerosol instrument data.

Emission of nanoparticles in the process of developing new polymers was investigated by Jankowska et al. [62]. Measurements were carried out in the laboratory equipped with a switched-on fume cupboard, the polymer was however prepared in the middle of the room, about 1.5 m from the fume

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cupboard. SMPS with long DMA results showed that curves of the number concentration in the function of particle size were similar for measurements done before the beginning of the process of polymer preparation (background) and for those during the process of cleaning and preparing the form, weighing the chemicals, and also at the beginning of blending the chemicals. An increase in the number concentration of nanoparticles in laboratory air was observed just after blending was stopped (time of blending - two minutes). For 15 nm nanoparticles, the number concentration increased from 185 particles/cm³ (background) to 1,017 particles/cm³ (three minutes after blending stopped) to 3,536 particles/cm³ (nine minutes after blending stopped). 30 minutes after blending was stopped the concentration of 15nm nanoparticles was equal to the background concentration. The number concentrations obtained with SMPS and P-TRAK were similar.

Tsai S-J et al. concluded that manual handling of nanoparticles is a fundamental task of most nanomaterial research - such handling may expose workers to ultrafine or nanoparticles [59]. Nanoalumina (with primary particles size ranging from 27 to 56 nm and 200 nm agglomerates when dried) and nanosilver (with average particle size of 60 nm) were selected to perform handling experiments in the fume hoods. Handling tasks included transferring particles from beaker to beaker by spatula and by pouring. Measurement locations were the room background, the researcher's breathing zone and upstream and downstream sides of releasing source. Airborne particle concentrations measured at breathing zone locations were analyzed to characterize exposure level. The concentrations of airborne particles with diameter from 5.6 to 560 nm were measured using a Fast Mobility Particle Sizer (FMPS). The test results found that the handling of dry powders consisting of nano-sized particles inside laboratory fume hoods can result in a significant release of airborne nanoparticles from the fume hood into the laboratory environment and the researcher's breathing zone

Particle number concentration measured at the researcher's breathing zone using the conventional hood (with the highest face velocity of one m/s) increased significantly during handling of 100 g nanoalumina particle – during pouring the concentration increased to 13,000 particles/cm³.

Dustiness of nanoparticles is directly related to the exposure levels and the health risks during handling of nanomaterials. Tsai C-J et al. determine the dustiness of two nanoscale TiO₂ and ZnO, in standard one minute tests [63]. Then, the sampling train was modified to determine the number and mass distributions of the generated particles in the respirable size range using a Scanning Mobility Particle Sizer (SMPS), an Aerodynamic Particle Sizer (APS) and a Multi-orifice Uniform Deposit Impactor (MOUDI) in the 30-min tests. Authors found that very few particles below 100 nm were generated and the released rate of particles decreased with increasing rotation time for both nanopowders in the 30-min tests. Due to the fluffy structure of the released TiO₂ agglomerated particles, the mass distributions measured by the MOUDI showed large differences compared to those determined by the APS assuming the apparent bulk densities of the powders. The differences were small for the ZnO agglomerates, which were more compact than the TiO₂ agglomerates.

Plitzko and Gierke performed a survey in cooperation with the German association of the chemical industry on exposure to nanomaterials in Germany [64]. Twenty one percent of the 217 participating companies performed activities involving nanomaterials. 31% of the companies carried out regular or exploratory measurements.

A US survey of New England-based nanotechnology companies has found that these firms lack a clear roadmap of government environmental, health and safety (EHS) expectations and regulations for successful commercialization, as well as the information needed to meet those expectations. One of the survey findings was that while 80% of large firms were taking steps to manage nanotechnology EHS risks, only 33% of small and micro companies and 12% of firms at start-up stage. At present, the majority of survey participants expect to rely on suppliers to provide nanomaterial risk management information in the form of Materials Safety Data Sheets (MSDS). But these do not always reflect the latest health and safety information, and regulatory or consensus guidance for these new materials is lacking [65].

In the following four of these before mentioned nanomaterials are shown as examples, detailing the manufacturing processes and their applications.

5.2.1 Silica nanoparticles

Silicon dioxide (SiO₂) nanomaterials, silica nanoparticles or nanodots are high surface area particles. The size of nanoscale silicon dioxide nanoparticles or silica particles is typically five to 100 nm with specific surface area (SSA) in the 25 - 50 m²/g range. The main forms of nanosized silica are precipitated silica, silica gels, colloidal silica, silica sols and fumed and pyrogenic silica [66].

Silica nanoparticles are used as additives in plastics and rubbers to improve mechanical properties of elastomers and in liquid systems to improve the suspension behaviour [71].

Silicon dioxide nanoparticles are either superconductors, electrical conductors or semiconductor particles, or quantum dots with far reaching potential in electronics, high speed computing, telecommunication and space travel.

Nanoscale silica is being used as filler in a range of products, including dental fillings [243].

Chemical mechanical planarization (CMP), a precision polishing technique used during the production of semiconductor chips, is the largest market application for nanosized silica, in particular fumed silica and silica sols is [66].

Different methods have been used to prepare silicon dioxide nanoparticles:

- the sol-gel method [67]
- flame aerosol reactors [68-70]
- high-temperature hydrolysis of silicon tetrachloride in the flame reactor [70]
- gas phase thermal oxidation of tetraethylorthosilicate (TEOS) [71, 72]
- SiO₂ supported Palladium (Pd) catalyst particles can be generated by chemical vapor synthesis, followed by chemical vapor deposition (CVS/CVD) [73]
- Pd / SiO₂ nanosized particles have been synthesized using a reverse micelle technique combined with metal alkoxide hydrolysis and condensation [74]
- silicon dioxide nanowires can be prepared by
- direct thermal treatment of a commercial silicon powder [75].

Amorphous and crystalline silica have to be discriminated because of their different toxic potential.

5.2.2 Iron (Fe) nanoparticles

Iron (Fe) and iron oxides nanoparticles present magnetic properties [76, 77]. Nanoparticles made of a ferro- or ferrimagnetic material, and below a certain size (generally 10 to 20 nm) can exhibit a unique form of magnetism called superparamagnetism. This property has made it a popular choice in magnetic recording media for analog and digital data recording [66]. But Fe magnetic nanoparticles have other important applications as electrical components (e.g. transformers) and in sensor and transducer applications [76].

Magnetic nanoparticles have also a number of biomedical applications, such as the labelling and magnetic separation of biological materials, directed drug delivery, magnetic resonance imaging (MRI) contrast enhancement and hyperthermia treatment. In those cases typically iron oxides have been used, because iron reacts quickly to non magnetic oxyhydrides. However iron has potential advantages over the oxides due to its higher magnetic moment and that it can maintain superparamagnetism at larger sizes than its oxides [76].

Fe⁰ (zero-valent iron), especially at nanoscale, presents a great reactivity [78]. In consequence its chemistry is dominated by an extreme reactivity with oxidizing agents: it presents, for instance, a high electrocatalytic activity [79]. In the case of reactions in absence of oxidants nanosized iron is an excellent catalyst, especially in reactions that involve making and breaking carbon-carbon bonds [76,

80]. Some studies also describe the potential uses nano-Fe reactivity with organic pollutants such as benzoquinone, carbon tetrachloride and chloroform, for developing new technologies for water remediation [81].

Different methods have been used to prepare nanosized iron or iron oxides:

- thermal decomposition of iron pentacarbonyl or other iron organometallics by high heat [76], laser irradiation [30, 77] or spark discharging [77, 82]
- sonochemical decomposition of iron carbonyl [76, 83]
- reduction of iron salts and oxides [76] including the microemulsion method [79]
- vapour phase methods [76, 84]
- mechanical methods as high energy milling or grinding [76, 85].

No data of assessment of exposure to iron or iron oxides in manufacturing these products were found. However some studies of measurements surface area by BET (Brauner-Emmett-Teller) analysis and/or size distribution by scanning mobility particle sizer (SMPS) have been performed for toxicological purposes [82, 86, 87] and also some field studies of secondary generated iron nanoparticles in workplaces such as in iron foundries [88].

5.2.3 Silver nanoparticles

Metallic silver displays unique properties normally associated with the noble metals (chemical stability, excellent electrical conductivity, catalytic activity) along with other more specific ones (antibacterial properties, nonlinear optical behaviour). Nowadays, according to Woodrow Wilson inventory, where the available information on nanomaterials used in the 606 currently available consumer products is listed, silver is the most commonly used new nanomaterial [89].

Silver nanoparticles can be synthesized by chemical and physical methods. The chemical methods are based on the reduction of a silver salt using a reducing agent such as sodium borohydride, N,N-dimethylformamide (DMF), ethylene glycol, etc. in the presence of appropriate surfactants like poly(vinylpyrrolidone) (PVP) to prevent aggregation processes [90, 91]. The particle size, shape and morphology of silver nanoparticles depend on the solvents, reducers and surfactants used in the reaction. Nanowires, nanoprisms and nanocubes of silver have also been obtained [92-94]. Nanoparticles of other noble and near-noble metals such as gold and platinum have been generated by similar methods [91].

Gas phase methods are the main physical methods to obtain silver nanoparticles. Those methods are based on homogeneous nucleation of a supersaturated vapour and subsequent particle growth by condensation, coagulation and capture. Among the different available heating or evaporation processes, furnace flow reactors, spray pyrolysis and laser ablation are used [30, 95-99].

Microorganisms also have the ability to reduce silver salts, thus besides chemical and physical methods, biosynthetic procedures can be used to prepare silver nanoparticles under normal air pressure and at room temperature [100, 101].

The main application of silver nanoparticles is related to their antimicrobial properties, i.e. antibacterial, antifungal, antiviral and anti-drug resistant pathogens. Silver nanoparticles can be applied in biomedicine (dressing and bandages, biological implants, diseases' treatments), in household items (nano-silver lined refrigerators, air conditioners, washing machines), in clothing (footwear, socks, home textiles), in food storage containers, in cosmetics and personal care products, for water purification, etc. [89].

Silver nanoparticles present high conductivity and can be used in glues, inks, pastes, polymers, coatings, etc. to make them thinner conducting pastes and coatings than using conventional silver powders. Some of its applications are as component for integrated circuits, catalysts or EMI/RFI (Electromagnetic Interference / Radio Frequency Interference) shielding [102].

Another interesting property of silver nanoparticles is their high optical nonlinearity. Silver nanoparticles can modify optical properties – such as colour - of other materials, because their plasma frequency lies in the visible light range and therefore they can be used as optical filters, optical devices, photonic crystals, chemical sensors or biomarkers and biodiagnostics.

No data on exposure assessment to silver nanoparticles in workplaces have been found.

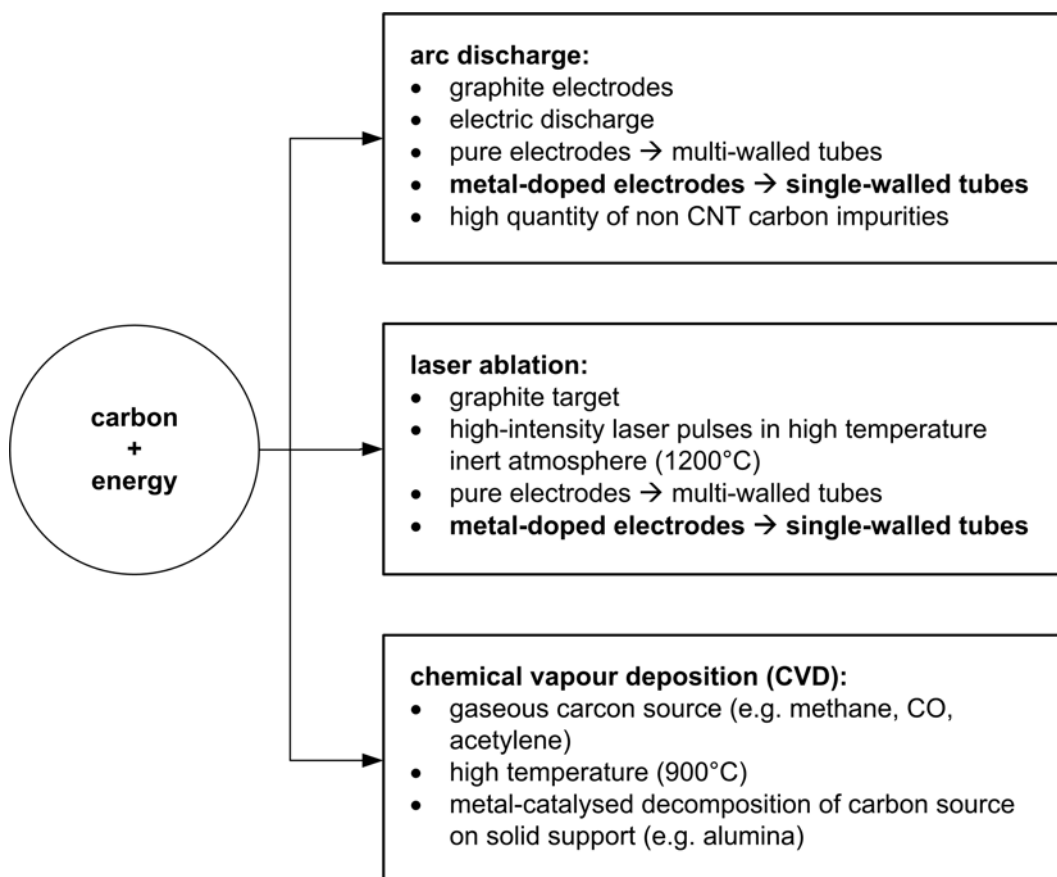
5.2.4 Single-walled carbon nanotubes

The single-walled carbon nanotubes (SWCNTs) are cylindrical structures built of a single graphite leaf rolled up on itself, they can be closed by its ends by one semi fullerene molecule (conical, polygonal or spherical). Most single-walled nanotubes have a diameter of close to one nanometer, with a tube length that can be many thousands of times longer - that can vary significantly depending on the synthetic procedure [103]. The diameters of SWCNT are controlled by the sizes of the metal nanomaterial from which they are grown, which vary between about 0.7 and three nm [104].

Synthesis of SWCNT

Three common methods to synthesize SWCNT are used: arc discharge, chemical vapour deposition (CVD), and laser ablation. All of them have in common a supply of energy to the carbon source to produce fragments (groups or single C atoms) that can recombine to generate CNT. The energy source may be electricity from an arc discharge, heat from furnace for CVD, or the high-intensity light from laser ablation. Depending on the synthesis conditions the result is richer in SWCNT or multi-walled carbon nanotubes (MWCNTs) (see Figure 5) [105].

Figure 5: methods to synthesize single-walled nanotubes [105]



Arc discharge

This method creates nanotubes through arc-vaporisation of two carbon rods placed end to end, separated by approximately one millimetre (mm), in an enclosure that is usually filled with an inert gas (helium, argon) at low pressure (between 50 and 700 mbar). A direct current of 50 to 100 ampere (A) driven by approximately 20 volt (V) creates a high temperature discharge between the two electrodes. The discharge vaporises one of the carbon rods and forms a small rod cylindrical-shaped deposit on the other rod. For SWNTs synthesis the anode has to be seeded with metal catalyst such as iron (Fe), cobalt (Co), nickel (Ni), yttrium (Y) or molybdenum (Mo) [106].

Laser ablation

In the laser ablation technique, a high-power laser beam impinges on a graphite target in an oven at 1,200°C in presence of an inert gas at pressure of about 500 Tor. Carbon molecules and atoms vaporise and condense in refrigerated forming clusters. These initial clusters grow into single-wall carbon nanotubes. At the moment, laser ablation method produces a small amount of clean nanotubes, whereas arc discharge methods are generally used to produce large quantities of impure material [106].

Chemical vapour deposition (CVD)

Chemical vapour deposition (CVD) synthesis is based on cracking a gaseous carbon molecules (methane, Carbon monoxide or acetylene) to reactive atomic carbon, which diffuses towards a heated substrate, coated with a catalyst (usually a first row transition metal such as Ni, Fe or Co) where it binds and carbon nanotubes will be formed. Excellent alignment, as well as positional control on nanometre scale, diameter and growth rate can be achieved. Choosing the appropriate metal catalyst can control the production of either single or multiwall nanotubes.

CVD carbon nanotube synthesis is essentially a two-step process consisting of a catalyst preparation step followed by the actual synthesis of the nanotube. The catalyst is generally prepared by sputtering a transition metal onto a substrate and then using either chemical etching or thermal annealing to induce catalyst particle nucleation. Thermal annealing results in cluster formation on the substrate, from which the nanotubes grow. Ammonia may be used as the etching agent. The process is usually occurring in the temperatures ranges within the 650-900°C. Typical yields for CVD are approximately 30%. This method is very easy to scale up, and favours commercial production.

In the recent years, different techniques of CVD have been developed, such as plasma enhanced CVD, thermal chemical CVD, alcohol catalytic CVD, vapour phase growth, aero gel-supported CVD and laser assisted CVD [106].

Baron et al. 2003 have studied the tendency to form aerosols of SWCNT obtained under two different manufacturing processes, the laser ablation method and the high-pressure carbon monoxide (HiPCO) method, both using Ni and Fe ultrafine particles as catalyst [107]. They found that the material obtained with laser ablation was more compact than the one produced with high-pressure carbon monoxide (HiPCO). Both methods produce aggregates or clumps of nanotubes, known as nanoropes, which retain particles of metal catalyst up to a proportion of 30% by mass.

The tendency of aerosol formation was studied in the laboratory by agitating the bulk SWCNT under a current of filtered air in a vortex shaker, either in the presence of bronze beads for the more dense material obtained through laser ablation or without the bronze beads, with the more porous material obtained in high pressure carbon monoxide method.

The aerosol generation under laboratory conditions is inefficient. But several conclusions can be drawn:

- when unrefined SWCNT material is subjected to a gentle agitation it releases large airborne clumps visible to the naked eye, with the presence of very few small particles;

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- laser ablation generates very low particle concentrations below 100 nm. The HiPCO (high pressure carbon monoxide) process generated particles smaller than 100 nm, which remained consistent over a period of 15 minutes. It was not determined whether these particles were nanotubes, catalyst particles, or compact carbonaceous particles;
- the generation of aerosols of SWCNT was much lower (two orders of magnitude) than those obtained with the fumed alumina, a low density material used as comparison. Both generated in the same conditions (see above).

A field evaluation of the airborne contamination, while manipulating the bulk SWCNT, was conducted in four manufacturing facilities (two laser ablation and two of high pressure carbon monoxide (HiPCO)).

The bulk material was removed from the reactors and manipulated (poured from one container into another one) in a closed area with inlet of filtered air, with a continuous monitoring of aerosol number and mass concentration, as well as personal and area filter samples.

There was no clear evidence of increased aerosol mass concentrations during the handling of unrefined nanotube material in the field. Mass concentrations during handling were generally below those associated with re-suspension of ambient dust due to personal movement, and cleaning operations following handling of material. The aerosol nanotube concentrations during material handling were estimated to be lower than $53 \mu\text{g}/\text{m}^3$. The dermal contamination was also determined by placing cotton gloves over the rubber gloves normally used by the workers. The gloves were analysed for iron as an estimation of the total SWCNT. The clumps of nanotubes were visible in the gloves. The estimated material deposited on the gloves ranged between 0.2-6.0 mg per glove [21, 107].

Properties

SWCNT structure makes them mechanically stronger, electrically and thermally more conductive, and chemically and biologically more active than graphite [108]. The properties of nanotubes depend on the atomic arrangement (how the sheets of graphite are 'rolled'), the diameter and length of the tubes, and the morphology, or nano structure. They are also deeply influenced by the synthetic procedure and the purification method [109].

Electrical properties

The electrical properties are one of the greatest fields of interest for SWCNT. Their extremely small size and the highly symmetric structure allow for remarkable quantum effects and electronic, magnetic, and lattice properties. They can either perform as metals (transporting current densities of about 100 times greater than metals), semiconductors or as insulators. The electronic properties have been correlated with mechanical, chemical, biological, thermal, and magnetic interactions with nanotubes [108].

Mechanical properties

In general, various types of nanotubes are stronger than graphite. The Young modulus (stiffness) depends on the diameter of the nanotube: the highest value is an attribute of diameters between one and two nm, with a Young modulus fivefold that of steel [110].

The elastic response to deformation is also very remarkable. Contrary to most hard materials that fail with a strain of one percent or less Carbon nanotubes can sustain up to 15% tensile strain before fracture. The hardness of some nanotubes is higher than diamond's.

Thermal properties

The thermal conductivity of SWCNT is much superior to that of good thermal conductive materials like Cu, Ag or diamond.

SWNT, as well as multi-walled nanotubes (MWN), materials and composites are being studied for thermal management applications, either as “heat pipes” or as alternatives to metallic or alumina particle additives to low thermal resistance adhesives.

Chemical properties

Single-walled carbon nanotubes are chemically inert. However, adsorption is easy and allows important modifications to their physical properties and potential applications [111]. There is much more reactivity at the end of the tubes (caps) and at mechanical strained points [103].

Molecular adsorption

SWCNT have the ability to adsorb various gas molecules with modification of their electrical properties. When semi-conducting SWNT are exposed to low concentrations of nitrogen dioxide (NO₂) and ammonia (NH₃) the conductance increases by up to three or two orders of magnitude. These results suggest the potential benefits of application of SWCNT as chemical sensors with high sensitivity [111]. A big potential in the use of hydrogen in the field, is the property of Hydrogen physisorption and gas storage, allowing an increase of the storage capacity of five to 10 mass percent of the total sample [108].

Chemical reactivity

The most reactive part of the SWCNT are the open ends or caps. A simple way to functionalise them is by carboxylation with a mixture of H₂SO₄ with different oxidants (HNO₃, H₂O₂, KMnO₄, etc.) [109].

When the open end of a SWNT is rich with –COOH group, it can be used for reaction with primary amines. A similar method can be used to functionalize the open end of a SWNT with a peptide nucleic acid (PNA). The modified carbon nanotubes were used as biosensors [108].

Opening of the nanocarbon tubes

The capped SWCNT must be open so the end caps must be destroyed to allow the flow of fluids through their pores. That presents a big potential in molecule separation devices, biocatalysis, molecule detection, and as encapsulation media. This is accomplished by oxidation in liquid or gaseous media.

Filling the internal cavity of the SWCNT

The internal cavity of the SWCNT has the ability to retain atoms or molecules, either in solid, liquid, or gaseous state. The fillers includes metals (Cs, Cu, Ag, Au, Sn, Fe, Co, Ni, Pd, Rh, etc.), alloys (Fe–Ni, Fe–Pt, Pt–Ru, Nd₂Fe₁₄B), non-metals (Ge, S, Se, Te, I₂, etc.), oxides (SnO, Sb₂O₃, NiO, UO_{2-x}), hydroxides (Ni(OH)₂), halides (KI, LaCl₃, ZrCl₄), salts (AgNO₃), carbides (B₄C, LaC_x, NbC_x, FeC_x), sulfides (AuS_x, CdS, CoS_x), nitrides (BN, GaN), organic substances (CHCl₃), acids (HNO₃), polymers (polystyrene), complex inorganic compounds and eutectic mixtures (FeBiO₃, CoFe₂O₄, AgCl–AgBr, KCl–UCl₄), and fullerene and endofullerene molecules (C₆₀, Gd@C82), complex hybrid materials (FeCl₃–C₆₀, K–C₆₀, Pt–WO, as well as diverse nanomaterials [109].

Applications

Medical applications: SWCNTs offer the opportunity for improved medical treatments:

- implantable defibrillators (pacemakers),
- portable/field equipment,
- implantable biosensors,
- improved hearing aids,
- electrochemical analysis of biological materials,
- delivery of medicines and other treatments at the cellular level.

Microelectronics: SWCNTs offer low resistance low mass density, and high stability for improved:

- microcircuits, nanowires, and transistors for miniature electronics,
- consumer products, including pagers, cell phones, laptop and hand-held computers, toys, power tools, and automotive components,
- scanning force / tunnelling.

Microscopy: probing tips made with SWCNTs last longer and perform better than conventional silicon tips, improving:

- materials science research and development,
- production quality control of semiconductor materials and data storage media,
- evaluation of biological samples.

Materials: SWCNTs do not affect a polymer's mechanical properties, allowing stress, transition, and thermal strain to be observed. SWCNTs also can be used to reinforce composites. Applications include:

- dopants to create electrically conductive polymers,
- composites for long-lasting bone and joint implants,
- easier monitoring of composites in critical applications (e.g., aircraft),
- molecular containment - SWCNTs can be used to contain various elements:
- hydrogen for fuel cells,
- lithium boron hydrate for radiation shielding.

6 Health effects of nanomaterials

6.1 Methods for the assessment of health effects

For the assessment of the diversity of toxicological properties such as acute and chronic toxicity, sensitisation, reproductive toxicity, genotoxicity or carcinogenicity [112, 113] testing recommended methods have been published by the European Commission and the Organisation for Economic Co-operation and Development (OECD) [114, 115]. These methods have been developed for chemicals in general.

The methods can be divided into four groups according to the kind of study and the object of investigation:

- occupational medicine / epidemiology,
- in vivo-methods in animals,
- in vitro-methods,
- methods for the determination of physico-chemical properties.

The appropriateness and validity of methods to investigate health effects of nanomaterials is debated at present. Especially the need for a detailed physico-chemical characterisation of the tested nanomaterials is of high importance to clearly discriminate nanomaterials that are made of the same basic material but differ in specific characteristics like primary particle size, surface agglomeration state etc. Furthermore it has to be considered that the sample preparation before testing can have an influence on the results because of differences in agglomeration and solubilisation [116, 117].

Epidemiology / occupational medicine

Epidemiological studies and findings of occupational medicine offer insights into effects on humans which are evoked by exogenic factors like chemicals (e. g. nanomaterials). The uncertainties surrounding the extrapolation of results of animal studies to humans are avoided by investigating effects directly in human population. In case of respiratory exposure to nanomaterials special attention is to be given to the respiratory system and the cardio-vascular system. The role of occupational medicine as a tool to limit adverse health effects of nanomaterials is discussed by Schulte et al. (2008) [118]. They conclude that first priority should be to implement appropriate primary preventive measures. Additional efforts to monitor workers' health may be warranted. Continued research is needed, and the collection of such information for exposure registries may be useful for future epidemiologic studies. Nasterlack et al. (2008) also discuss occupational health surveillance of workers being (potentially) exposed to nanoparticles [119]. They conclude that there is at present no evidence-based foundation for a "nano-specific" occupational medical screening. One can perform general medical screening with methods targeted at some of the health outcomes under discussion. The results of such examinations can provide a basis for future epidemiologic studies. Therefore, the establishment of exposure registries to enable the conduct of large-scale multi-centric prospective epidemiologic studies is recommended.

In vivo-methods with animals

In vivo-methods determine health effects in animals after oral, dermal and inhalation exposure depending on the prevailing route of human exposure. Effects on the whole body can be detected by e. g. histopathological examination or the determination of functional deficits. The interdependencies within the entire organism are considered. In addition the fate of a chemical substance within the organism can be determined in studies on kinetics. A whole battery of in vivo-methods has been developed for routine testing of chemical substances in general [114, 115].

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The appropriateness of these testing methods for the examination of health effects evoked by nanomaterials was discussed by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). It was stated that the *in vivo* methods are in principle appropriate though some amendments and new developments, such as detailed particle characterisation, will be needed [116, 117].

Concerning effects on occupational health, inhalation exposure is a major field of concern. For the detection of possible lung toxicity by inhalation of nanomaterials additional investigations in the bronchoalveolar lavage (examination of cell proliferation and oxidative stress) could improve the sensitivity of inhalation studies [120]. For the detection of effects on the cardio-vascular system acute phase proteins and coagulation factors in blood could be determined. Furthermore, a detailed investigation of other organs (such as brain, liver, heart, kidneys) is indicated, as long as it cannot be excluded that the substance reaches the circulatory system and further organs apart from the respiratory tract. In addition to the typical inhalation studies inhalation exposure can be simulated by intratracheal instillation. However dose selection, the atypical kinetics by accumulated, non-continuous application and the different deposition pattern compared to inhalation have to be considered evaluating the results of these studies.

A further exposure route of importance at workplace is the dermal exposure. The corresponding dermal *in vivo* toxicity studies are in principle provided by the institutions mentioned above [114, 115]. The need for amendment of nanospecific requirements has not been discussed in detail.

In vitro-methods (cellular und cell-free)

Some *in vitro*-methods have been validated by OECD-programs for chemicals in general, which refer *inter alia* to local effects on the eye and skin, skin permeation and genotoxicity. For other toxicological endpoints like chronic toxicity or carcinogenicity no validated *in vitro* studies are available [121, 122].

In vitro testing refers for example to possible effects in the respiratory system, especially the lungs. Inflammation, cytotoxicity or genotoxicity, which contribute to lung toxicity *in vivo* (such as fibrosis or tumour formation) are examined. The comet-assay and the determination of 8-hydroxy-desoxyguanosine are discussed to determine a genotoxic property [123-126]. According to Hess et al. (2005), Janssen et al. (1993), Oberdörster et al. (2005) and Quinlan et al. (1995) the determination of dichlorofluoresceine, oxidized glutathione and nitrosized proteins is a model to characterize the oxidative stress, which damages cell function [42, 123, 127-129]. Information about the secretion of mediators of inflammation, reactive oxygen species and the metabolism in alveolar macrophages is proposed to be gained by the vector model [130, 131]. Presently the *in vitro*-methods need a better validation to predict effects in humans evoked by nanomaterials.

Physico-chemical properties

Most of currently relevant nanomaterials occur in a solid aggregate state and have a (very) low solubility. Physico-chemical properties describing the characteristics of solids are discussed to influence the toxicological profile of nanomaterials. Some of these properties, which are suggested to indicate toxicological properties are:

- morphology
- size
- surface
- solubility
- agglomeration / aggregation
- mass
- surface modifications

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- particle concentration
- volume etc..

Presently it is uncertain which parameters represent the best predictive value for toxicity. The corresponding methods to determine these properties are partly established. Other need further development and standardisation.

6.2 Toxicological properties of nanomaterials

It becomes increasingly possible to modify a basic material in its morphology and surface in the nanometer scale. New technological properties are achieved. It remains uncertain to what extent toxicological properties are changed too. From a toxicological point of view nanomaterials of poor solubility in biological fluids are of special importance, because they maintain their nanostructure after contact with the human body. Nanomaterials that are enclosed in an insoluble matrix are of minor importance, but may become relevant as soon as they are released by e.g. mechanical forces. So, the most important nanomaterials are at present nano-objects like nanoparticles, nanotubes, nanorods or nanoplates, including their aggregates and agglomerates that are 'available' for skin contact or inhalation. Preliminary information suggests that the majority of nanomaterials which are marketed in large volumes or will experience a considerable increase in nano-market share in near future are composed, inter alia, of the following basic materials [56]:

- aluminium oxide
- carbon: carbon black
- carbon: carbon nanotubes
- cerium oxide
- dendrimers
- fullerene
- iron oxide
- nanoclays
- polystyrene
- silicon dioxide: amorphous and crystalline
- silver
- titanium dioxide
- zinc oxide.

In the previous chapter, some of these materials were introduced in more detail. A significant number of publications review or discuss the toxicological properties of nanomaterials [29, 30, 32, 105, 132-155] [3, 36, 41, 42, 130, 156-177].

Inhalation exposure and dermal contact are the occupational exposure routes of primary importance. Oral uptake is not considered here, because at workplaces it is of limited relevance. In the following, a selection of studies of high importance is presented.

6.2.1 Human data

Human data on nanomaterials mainly refer to carbon black which is one of the nanostructured materials to which workers have been exposed for a long time and in a variety of occupational scenarios.

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The relation of carbon black exposure to lung tumours is discussed in a number of publications [178-183]. Valberg et al. (2006) reviewed the epidemiological data on carbon black exposure [184]. All in all, no clear evidence of carcinogenicity could be found, though some uncertainties remain. In addition, it is not certain in all studies whether workers were exposed to nanoscale or microscale carbon black. In other epidemiological studies (e.g. on titanium dioxide) it is also uncertain whether workers were exposed to a nanoscale or a microscale modification.

One volunteer study was performed with nanostructured zinc oxide. Inhalation exposure led to a deposition in the respiratory tract, which was higher than that of microscale zinc oxide and that predicted by models [185].

Epidemiological data presenting the toxicity of heterogenous environmental microscale fine dusts suggest an increased rate of cardio-vascular diseases. A similar effect is assumed by some authors to be caused by the nanoscale fraction of environmental dusts. Those effects are attributed to non-intended materials like e. g. combustion products. It is uncertain to what extent such effects can be expected from engineered nanomaterials. However, it should be considered that nanostructured non-intended material (welding fumes, combustion products) shows some similarities (poor solubility, persistence in the lungs) that might indicate some common properties.

6.2.2 Animal data

In vivo animal studies represent currently the best database for assessing the hazard of nanomaterials, since epidemiological evidence is currently limited and in vitro studies have not been validated for nanomaterials.

Animal studies of short- and mid-term duration

In the last years several studies with a duration up to one year have been performed which mainly inform about toxicity to the lung. Several authors detected inflammation, cytotoxicity and tissue damage induced by carbon black nanomaterials in the lungs [186-193]. Rats have demonstrated higher sensitivity than mice and hamsters. Niwa et al. (2007) in addition described some cardiovascular effects as a consequence of carbon black exposure [194].

Inflammation, cytotoxicity and tissue damage in the lungs were also observed after titanium dioxide exposure [195-200]. Surface properties as well as size and surface area were identified to influence toxicity [196, 197, 199, 201]. An increased sensitivity of rats compared to hamsters and mice was also confirmed for titanium dioxide by Bermudez et al. (2004) and Hext et al. (2005) [196, 201]. Warheit et al. (2007) reported a set of in vivo toxicity tests in rats, rabbits and mice in line with the OECD methodology for nanoscale titanium dioxide [198]. Apart from lung toxicity which was tested additionally by intratracheal instillation, a low toxicity was observed.

Nanoscale amorphous silicon dioxide also induced inflammation, cytotoxicity and tissue damage in the lungs [202-204]. A higher potency of nanomaterials compared to microsized particles was detected by Kaewamatawong et al. (2005) [204]. Contrary to this Chen et al. (2004) observed a higher potency of microsized silicon dioxide compared to nanosized silicon dioxide [203]. Warheit et al. (2006) used crystalline silicon dioxide and determined an influence of the surface activity on lung toxicity [202].

Increased manganese levels were also found in the brain in an inhalation study in rats with manganese oxide [205]. In addition markers of inflammation were observed in the brain, while lung lavage analysis showed no indications of lung inflammation.

Different modifications of C₆₀-fullerenes also induced lung toxicity like inflammation, cytotoxicity and tissue damage [206]. Differences in toxicity, which were observed in preceding in vitro studies could not be confirmed in vivo.

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Lung toxicity (inflammation, cytotoxicity and tissue damage) was observed after carbon nanotube exposure [207-209]. Takagi et al. (2008) and Poland et al. (2008) detected in preliminary studies that specific modifications of carbon nanotubes showed effects similar to that of asbestos [210, 211].

The smallness of nanomaterials can lead to an increased potential to cross barriers in living organisms which increases the number of organs that can be affected. A review of studies that focus on the distribution in the organism is given by Hagens et al. (2007) [212]. These studies in general do not include a detailed analysis of toxic effects, but focus on the detection in different parts of the organism. After inhalation exposure for example silver nanoparticles were detected in the lungs, but also in the liver and the brain [213]. Gold nanoparticles were detected after inhalation exposure also in many organs [214]. The highest concentration was reached in the lungs. Oberdörster et al. (2004) demonstrated in a rat inhalation study that nanosized carbon reaches the brain (olfactory bulb) via the olfactory mucosa [215]. Increased manganese levels were also found in the brain in an inhalation study in rats with manganese oxide [205]. In addition markers of inflammation were observed in the brain, while lung lavage analysis showed no indications of lung inflammation. Further studies on systemic availability via the circulatory system after inhalation were performed for example by Semmler et al. (2004), Takenaka et al. (2001), Takenaka et al. (2000) and Oberdörster et al. (2002) [125, 216-218]. Overall it can be stated that some nanomaterials entered blood circulation after respiratory exposure and reach other organs, but others showed no detectable transfer from lungs to blood circulation. As mentioned above a transfer from nose directly to the brain is also possible. The biological relevance and possible toxic consequences of the availability in further organs of the organism is not sufficiently clarified.

In general the skin reveals a better barrier function compared to the respiratory tract. The effects of nanomaterials like titanium dioxide on the skin have been tested by Butz et al. (2008) [219]. Effects on the skin or a relevant skin penetration were not observed. However the barrier function of the skin could be limited by skin lesions, strong mechanical strain or small nanoparticles (< five to 10 nm). Nanoscale titanium dioxide was also tested according the OECD guidelines for skin irritation, skin sensitisation and ocular irritation. No skin irritating or skin sensitising property was observed. The eyes responded by a transient redness, the cornea was not affected.

Animal studies of long-term duration

Of special importance for the assessment of occupational health are studies with long-term (chronic) inhalation exposure, because these studies detect chronic toxicity as well as carcinogenicity in the lung. Lung toxicity was investigated in long-term inhalation studies in rats and mice exposed to nanostructured carbon black and titanium dioxide [220-222]. Both substances induced inflammation, cytotoxicity and tissue damage in both species. Lung tumors were evoked in rats, but not in mice.

Furthermore long-term studies with intratracheal instillation were performed with nanostructured carbon black, aluminium oxide, aluminium silicate, titanium dioxide (hydrophilic and hydrophobic) and amorphous silicon dioxide [223-227]. Tumors were induced by all tested nanomaterials. Microsized fine particles also evoked tumours in these studies, but a five to 10-fold higher potency of the nanomaterials (calculated on a volume basis) was calculated.

6.2.3 In vitro data

The reliability of in vitro-methods to assess health effects of nanomaterials in humans is uncertain at present. Furthermore, some toxicological effects such as chronic toxicity cannot be determined sufficiently with in vitro studies, also for chemicals in general. Thus, a detailed description of performed in vitro studies is not included here. Many in vitro-studies are described in the reviews referred to in the beginning of chapter 6.2. The review of Lewinski et al. (2008) specifically addresses cytotoxicity of nanomaterials in vitro and concludes that further research is needed [228].

6.2.4 Summary evaluation of toxicity

The most important toxic effects that were induced by nanomaterials after exposure of the respiratory tract are chronic toxicity and carcinogenicity in the lungs. Effects like inflammation, fibrosis and lung tumours were induced by several granular nanomaterials. Similar effects have also been observed with micro-sized fine dust.

Hamsters and mice did not respond as sensitively as rats to micro-sized fine particles, neither did they respond to some dusts that are confirmed or suspected human carcinogens [226, 229]. So, rats seem to be an appropriate and sensitive model to predict effects in human population, while mice and hamsters can be suspected to be not sensitive enough, thus providing false negative results. It could be assumed that effects corresponding to those in rats can occur in humans, if the exposure at workplaces is sufficiently high and long-lasting.

Especially the increased surface area and the decreased particle diameter are thought to be the cause of a partly increased toxicity of granular nanomaterials in the lungs (calculated on mass or volume basis).

Some authors argue that lung tumours can only occur in case of lung overload and subsequent reactions such as inflammation and fibrosis. In this theory the tumour development is clearly pending on non-neoplastic prelesions (e.g. inflammation, fibrosis) and tumours can be avoided by preventing occurrence of these prelesions (secondary mechanism of tumour development) (e.g. Greim and Ziegler, 2007, Oberdörster et al. 2004) [215, 230]. Other authors consider this theory as not sufficiently supported and argue in favour of a more cautious theory on the mechanism of tumour development [226, 231, 232]. A direct interaction of particles (or compounds generated by particles) with DNA is considered possible, which implies a higher risk of carcinogenicity (primary mechanism of tumour development). Currently this dispute cannot be clearly decided and scientific uncertainties remain about the mechanism of tumour development. Thus, the evaluation of the tumour potential and the risk management that follows is also influenced by a policy decision how to pay attention to the precautionary principle, which is intended to be applied in case of scientific uncertainties.

Lung toxicity, evidenced by inflammation and tissue damage, was also proven to be induced by fibrous nanomaterials such as carbon nanotubes. There are also indications from pilot studies that a carcinogenic potential is possible but further studies are needed to clarify this.

Further toxic effects in other organs are possible, because some nanomaterials enter blood circulation or reach the brain via the olfactory nerves. The biological relevance and possible toxic consequences of this availability in further organs of the organism is not sufficiently clarified.

In a limited set of studies effects on the skin or a relevant skin penetration were not observed. However the barrier function of the skin could be breached by the presence of skin lesions, strong mechanical strain or small-sized nanoparticles (< five to 10 nm). Skin sensitisation was detected. Direct exposure of the eyes showed some transient redness. The cornea was not affected.

Skin disease attributed to exposure to dendrimers: case study

A case of erythema multiforme-like contact dermatitis – result of allergic response - was described in a person exposed to dendrimers.

A 22-year old student involved in work leading to synthesis of dendrimers has developed erythema multiforme-like contact dermatitis on his hands. Despite treatment with topical steroids and anti-histamines the disease has progressed to involve other areas of the body. He required hospitalisation for more than 3 weeks. Afterwards, the symptoms were reoccurring when he entered the office and laboratory he was working in.

Dendrimers are considered as a possible drug-carrier. However, the possibility of skin rashes has to be considered in those exposed to them.

Source: Toyama T., Matsuda H., Ishida I., Tani M., Kitaba S., Sano S., Katayama I., A case of toxic epidermal necrolysis-like dermatitis evolving from contact dermatitis of the hands associated with exposure to dendrimers, *Contact Dermatitis* 2008, July 28; 59(2): 122-123.

6.3 Testing strategies and risk assessment

Testing strategies and methods of risk assessment have been harmonized for industrial chemicals in general on national, European and international level for regulatory purposes [113, 233-237]. Currently there is no consensus what testing strategies and methods of risk assessment can be applied for nanomaterials. A general overview is given by Oberdörster et al. (2005), who identified methods for characterisation of physico-chemical properties and methods for in vitro- and in vivo-toxicity as relevant for testing of nanomaterials [123]. SCENIHR (2007) evaluated the current methods of risk assessment as described in the “Technical Guidance Documents” and came to the conclusion that the methods in general are appropriate, but some amendments are eventually necessary [113]. Rocks et al. (2008) compared the risk assessment approaches for manufactured nanomaterials and state that the current toxicological tests are, in principle, appropriate for risk assessment purposes [238].

Since valid epidemiological evidence is limited and in vitro studies have in general not been validated for nanomaterials, in vivo studies represent currently the best benchmark for assessing the hazard of nanomaterials and deriving specific classification and labelling. Of special importance are studies with repeated inhalation, because these are a prerequisite for deriving occupational exposure limits. Risk estimates associated with a specific air concentration of nanomaterials (titanium dioxide, carbon black) have been calculated by Kuempel et al. (2006) and Roller and Pott (2006) for particles of different sizes including nanomaterials [226, 239].

As a future task the integration of validated in vitro-studies into testing strategies is important because of animal welfare and the fact that in vitro testing is less expensive, time-consuming and laborious.

6.4 Classification, labelling and occupational exposure limits

Generally data on health effects are condensed into classification/labelling and occupational exposure limits to enable an appropriate and health based risk management. In principle a substance, identified by the CAS number (chemical abstracts service) can have different classifications and labellings, depending on specific properties, that are expressed, among other, by the particle size. Thus, properties of a nanomaterial which are different from a bulk material can be reflected by classification and labelling.

Official occupational exposure limits for nanomaterials have been set only for amorphous silicon dioxide (e.g. in Germany: Greim et al. 1989, TRGS 900 2007) [240, 241]. A draft occupational exposure limit for nanoscale titanium dioxide is also available from the US-American National Institute for Occupational Safety and Health [232]. Furthermore, so called “benchmark levels” that represent a pragmatic guidance level have been developed for four classes of nanomaterials by the British Standard Institution [242]. For insoluble nanomaterials a general benchmark level of $0.066 \times$ occupational exposure limit (OEL) of the corresponding micro-sized bulk material (expressed as mass concentration) is proposed. This factor of 0.066 is in line with the potency difference of microscale and nanoscale titanium dioxide as described by the US-American National Institute for Occupational Safety and Health [232]. For fibrous nanomaterials a benchmark level of 0.01 fibres/ml is proposed. This level is derived from the current limit value in asbestos removal activities in the UK. For highly soluble nanomaterials a benchmark of $0.5 \times$ OEL is proposed. For CMAR (carcinogenic, mutagenic, asthmagenic or reproductive) nanomaterials a benchmark level of $0.1 \times$ OEL of the corresponding micro-sized bulk material (expressed as mass concentration) is suggested.

7 Safety hazards

All the literature reviewed agrees on the lack of knowledge regarding the safety risks related to nanopowders and the need of further research.

In general, catalytic effects and the risk of fire or explosion should be taken into account in the assessment of safety risk when handling nanopowders [32]. Depending on the specific production methods being used, other possible hazards should be considered such as electrocution associated with the generation of a plasma via the use of high currents or asphyxiation hazards owing to possible leaks of inert protective gases during some processes [78].

Even if there is little information about the assessment of the fire and explosion risks associated with ultrafine powders, it is feasible that nanopowder could present a higher risk than coarser material with a similar mass concentration given its increased particle surface area [243]. This larger surface area, also favours their catalytic activity and may result in unexpected reactions, in some cases violent or explosive [32].

Fire and explosion hazards

In many cases where an explosive atmosphere can form, any ignition source will cause a fire rather than an explosion. Both fire and explosion cause dangers to workers, and in many cases the precautions required to prevent the event are the same.

When studying the flammability and explosivity of dust, it generally is important to determinate the minimal ignition energy (MIE) and the minimal explosion concentration (MEC), also known as lower explosion limit (LEL), to assess the impact of effects, the explosion severity which considers parameters like the maximum pressure of explosion and maximum rate of pressure. The maximum rate of pressure (Kst) is used to calculate the maximum rate of pressure rise. Considering Kst the atmosphere can be classified as follows.

Table 7: classification according to the maximum rate of pressure [244]

Dust explosion class	Kst (bar m/s)	Characteristics
St 0	0	no explosion
St 1	>0 - <200	weak explosion
St 2	>200 - <300	strong explosion
St 3	>300	very strong explosion

In any case, it is important to consider that the presence of a flammable solvent on the dust or the presence of flammable gas or vapour in the same atmosphere will increase the likelihood of ignition and the violence of the explosion [13].

More information about basic knowledge of explosive dust and other factors affecting the probability of ignition or explosion such as moisture or solvent content, oxygen concentration, degree of dispersion of the dust, temperature, or presence of other compounds in the air can be found in Pritchard 2004 and Beck 1997 [13, 245].

Dust of particle size in the range of microns may present an explosion or fire risk by ignition or even spontaneous combustion. In the case of nanopowders with a greater surface area, the particles can be easily charged electrostatically increasing the risk of ignition [167, 246]. The small size of

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nanoparticles makes them able to remain airborne for longer time and creating potentially explosive dust clouds.

The most important factor regarding ignition sensitivity and the violence of an explosion is the specific surface area that may increase the risk in the case of combustible nanopowders, though the explosion risk appears to plateau at particle sizes in the order of tens of microns for many dusts [13].

However for some kinds of dust such as very reactive metals (aluminium, magnesium) or PVC this limiting size seems to be even lower, and scarcely any data could be found in literature. For instance, literature data for aluminium nanopowder indicate that it has a minimum ignition energy low enough to be ignited with static electricity, and depending on the particle size could be classified as moderately or severely explosive [78].

The Nanosafe2 project, has carried out research about the flammability and explosivity of nanopowders [247]. Firstly, it has developed new devices to measure the MIE and to assess the impact effects, more suited for nanopowders than the devices existing up to date. The project has studied the MIE, MEC, maximum pressure of explosion and maximum rate of pressure and assigned an explosion class to the powders evaluated (various carbon black powders, aluminium nanoparticles of different sizes and carbon nanotubes). Carbon black and carbon nanotubes showed explosion sensibilities and severities of the same order, and their explosion class was assessed as St1, while the aluminium powders had a much lower MIE making it more likely to ignite and the severity of the explosion was classified as strong or very strong (St2 or St3) depending on the particle size.

It was furthermore concluded from the results of the project, that aluminium nanopowder was less explosive than micropowder due to the oxide layer on nanoparticles and that if a nanopowder tends to agglomerate it shows explosion severity of the same order as micropowder of the same substance.

Prevention

Handling the combustible nanopowders in liquid form, when possible, will avoid the risk of ignition and machinery must be designed to handle hazardous powders to prevent the ignitions and minimise the risk associated to the production of sparks [78, 167].

Other alternatives to reduce the risks of fire and deflagration include avoiding the dust to be airborne or to use controlled-atmosphere production and storage processes [32, 167].

The operation temperature of electrical equipment and the increased risks of auto-ignition of nanoparticles should also be considered [32].

8 Handling of nanomaterials

8.1 Occupational risk management

In order to limit the occupational exposure of the respiratory tract and the skin several protective measures like substitution, technical, organisational and personal protection measures could be applied. In addition classification and labelling and occupational exposure limits are important instruments of risk management, but critically depending on the availability of studies on toxicity. Risk management approaches for nanomaterials have been described by some authors [161, 248]. Many nanomaterials (e.g. particles, tubes and their agglomerates and aggregates) show a low solubility in water and biological fluids. Thus, the protective measures, that are used to protect against insoluble material like dusts are often taken as a starting point to be checked for their appropriateness also for nanomaterials. Because of the particular smallness of nanomaterials, especially the filter materials to clean the air and the materials of gloves have to be analysed. More detailed information was identified on engineering control, respiratory protection and protective clothing which is described in the following.

Engineering control methods

Elimination or reduction of the exposure to nanoparticles at workplaces has been, as priority, realised by using engineering control systems as: enclosure, local exhaust ventilation (LEV) and general ventilation [30, 32, 249]. The best ways of protection is to enclose the sources of nanoparticles. If that is not possible, LEV with different types of hoods depending on the requirements of the process can be used. Local ventilation has to be assisted by general ventilation systems. Effective performance of ventilation systems depends to a large extent on their appropriate use and maintenance.

Lu et al. (2007) evaluated the efficiencies of LEV (a 30 m³ mechanically ventilated test cabin) using Engine Exhaust Particle Sizer (EEPS) [250]. Nanoparticles with diameter between four to 100 nm were generated with a spray-drying type of aerosol generator. The evaluation of LEV capture efficiency was conducted for two aerosol emitters with different emission velocity and direction. The LEV system was also evaluated using a tracer gas (SF₆ diluted in air). Test results showed that the capture efficiency of LEV did not vary significantly as a function of particle size for nanoparticles. No significant difference was found between the efficiencies measured using the tracer gas (SF₆) and nanoparticles.

Tsai et al. (2007) measured the exposure to aluminium nanopowder during handling nanoparticles in fume hoods in two laboratory rooms [59]. Concentrations of airborne particles with diameter from five to 560 nm were measured using a Fast Mobility Particle Sizer (FMPS). Particles handling (transferring particles from beaker to beaker by spatula and by pouring action) took place 15 cm from the hood's face. Variable factors studied were the hood design, transfer method, face velocity/sash location and vertical height. The authors concluded that more particles were extracted while the hood performed at highest face velocity of one m/s and as the sash was lowered to the operator's low chest height.

Field study were carried out by NIOSH in a company that uses four gas-phase condensation reactors to produce approximately one kilogram of nanoparticles per day [251]. Manganese, silver, and cobalt nanoparticles in a diameter range from 15 to 50 nm were produced. Investigations were done before and after the installation of portable fume extractor typically used in the welding industry. The fume extractor was a standard six inch duct-type attached to a HEPA (high efficiency) filtered air-handler with a carbon prefilter. The LEV study used both direct sampling and filter-based sampling methods to determine the effectiveness of the implemented (LEV) control technology. NIOSH reports that filter-based tests showed a reduction in ambient nanoparticles ranging from 74% to 96%, with a mean reduction of 88%. Direct-reading test reductions ranged from 78% to 100%, with a mean reduction of 96%. The transmission electron microscope analysis confirmed a notable increase in nanoparticle capture when the LEV was used, and TEM images, regardless of the use of LEV, indicated that the majority of ENM's are emitted as agglomerates.

For removing nanoparticles from the exhausted air, an appropriate filtration system has to be used, which usually contains multi-stage filters with high efficiency particulate air filter (HEPA) or ultra low

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penetration air filters (ULPA) as final filter. In European standards (EN 1822-1 to EN 1822-5) procedures for determination of filter efficiency for their classification are described [252-256]. Air filter must be tested with the most penetrating particles – MPPS obtained for filtering material from the range 150 to 300 nm of the test aerosol (preferably DEHS). This range of particles is typical for MPPS for most filtering material used in air filters. HEPA and ULPA air filters are classified on the basis of their overall and local (leakage) value of penetration.

The European standards EN 1822-1 to EN 1822-5 are now revised. According to drafts of standards (issue from April 2008) high efficiency air filters will be classified into three groups: EPA (efficient particulate air filter), HEPA and ULPA, depending on their penetration obtained for the MPPS from the range 120 to 250 nm. Methods for testing filters with MPPS ≤ 100 nm are also described in those drafts, which apply e.g. to membrane medium filters (MPPS for commonly used PTFE membranes is approx. 70 nm). The classification of high efficiency air filters according to current and draft standards is shown in table.

Table 8: classification of high efficiency air filters according to current and draft standards [252]

EN 1822-1:1998			prEN 1822-1:2008		
Filter class	Penetration		Filter class	Penetration	
	Overall value ¹	Local value ²		Overall value ¹	Local value ²
H10	15	-	E10	≤ 15	-
H11	5	-	E11	≤ 5	-
H12	0,5	-	E12	$\leq 0,5$	-
H13	0,05	0,25	H13	$\leq 0,05$	$\leq 0,25$
H14	0,005	0,025	H14	$\leq 0,005$	$\leq 0,025$
U15	0,000 5	0,002 5	U15	$\leq 0,000 5$	$\leq 0,002 5$
U16	0,000 05	0,000 25	U16	$\leq 0,000 05$	$\leq 0,000 25$
U17	0,000 005	0,000 1	U17	$\leq 0,000 005$	$\leq 0,000 1$

¹ Overall value determined with procedure described in EN 1822-5:2000 or prEN 1822-5:2008
² Local value (leakage) determined with procedure described in EN 1822-4:2000 or prEN 1822-4:2008

According to the theory of filtration, penetration of particles through filtering materials is critical (max) for MPPS (e.g. Brown 1992) [257]. Particles with diameter less than MPPS can be deposited on the filter with Brownian diffusion.

However, a question arises - whether the thermal bounce of particles with diameter less than 20 nm occurs during filtration process [258-263]. Investigations were carried out for solid (silver, sodium chloride, graphite) and liquid (DEHS) particles. In most investigations (except Balazy 2004 [259]) it was found that the thermal bounce is not detected down to two and three nanometer particles at room temperature. Particles with diameter less than MPPS are deposited on air filters with higher efficiency than that with MPPS diameter.

Kim et al. (2007) investigated the nanoparticles penetration through wide range filter media (four electrets filter media and nanofibres medium) using silver nanoparticles from three to 20 nm at face velocities of 5.3, 10 and 15 cm/s [264]. Silver particles were generated by heating a pure silver powder source via an electric furnace with a temperature of 870°C. The number concentrations of nanoparticles were measured upstream and downstream of the test filter using a nano-DMA and an Ultrafine Condensation Particle Counter (UCPC). The authors reported that nano-DMA calibration and adequate leakage tests showed that the system can produce repeatable and reliable data. The furnace setting temperature and particle sampling time were determined experimentally in order to generate enough amounts of silver nanoparticles in the size range of three to 20 nm, so that 99.99% of efficiency can be measured for the high efficiency filter media.

Wang et al. studied the filtration of nanoparticles' agglomerates [265]. The particles generator consisted of two in-series furnaces to produce and subsequently sinter particles, and it was capable of generating spherical or agglomerated fractal-like silver particles. Filtration tests were performed using silver agglomerates. The authors reported that in case where the mobility diameter of the particles was

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small (e.g. 50 nm), the penetration of agglomerates was similar to that of spherical particles. If the mobility diameter of particles was large (e.g. 300 nm), the penetration of agglomerates was considerably lower than that of spherical particles.

As concluded in NanoAlert Service very few papers in the field of engineering control for nanoparticles have been published [14]. At least these studies show that well designed, installed and properly used engineering control can protect workers against nanoparticles. However, monitoring and maintenance of ventilation and filtration systems has to be conducted to avoid release of nanoparticles to working environment by leakages and from air filters overloaded by particles.

Respiratory protection

Fibrous filtration media are widely used for particle filtration of contaminated air. Filtering materials (melt-blown, electret, fiber glass) are commonly used as a basic material for filtration in filtering half masks and filters used as respiratory protection equipment against aerosols. The protective properties (level of aerosol penetration) are evaluated according to EN standards (EN 143 for filters and EN 149 for filtering half masks). These requirements define levels of protection for three different classes (class 1 = lowest protection, class 2 = medium protection and class 3 = highest protection). Polydisperse aerosol with particles of diameter larger than 1,000 nm is used for penetration assessment. Thus, the question arises, what is the performance of available filtering materials and filtering half masks against nanoparticles.

There was some research work done in this field. Within the Nanosafe project (NANOSAFE, Dissemination report 2008) tests of filtering media (used for respiratory protection) against graphite nanoparticles with a diameter from 10 to 400 nm were carried out [266]. The results showed that traditional filters made of glass fibres and electret fibres were efficient and had good performances for the nanoparticles used.

There has also been some research conducted with filtering half masks made of electret filtering media. The penetration test used polydisperse and monodisperse NaCl aerosol as the test agent with a diameter of particles from 40 to 400 nm. The test results showed that, in case of polydisperse aerosol filtering, half masks were efficient and in case of monodisperse filtration efficiency depended on the diameter of particles. The highest level of penetration was for particles with 40 nm of diameter [267].

The filtering half mask N95 (according to NIOSH) may not always provide the expected respiratory protection for workers. The highest penetration values (representing the poorest respirator protection conditions) were observed in the particle diameter range of ~30 - 70 nm. Based on the theoretical simulation, it has been concluded that for respirators utilizing mechanical filters, the peak penetration indeed occurs at the particle diameter of ~300 nm. However, for pre-charged fibre filters - which are commonly used for N95 respirators - the peak shifts toward nano-sizes. In the study it has been confirmed that the neutralization of particles is a crucial element in evaluating the efficiency of a respirator. The variability of the respirator's performance was determined for both models and both flow rates. The analysis revealed that the coefficient of variation of the penetration ranged from 0.10 to 0.54 for particles of 20 to 100 nm in diameter. The fraction of N95 respirators for which the performance test at 85 l/min demonstrated an excessive penetration of nanoparticles (>5%) was as high as 9/10. The test results obtained in a relatively small (0.096 m³) test chamber and in a large (24.3 m³) walk-in chamber were essentially the same, thus, suggesting that laboratory-based evaluations have a good potential to adequately represent the workplace-based respirator performance [268].

The filtration efficiency for nanoparticles down to one nm in size through glass fibrous filters can be measured using an improved Particle Size Magnifier -Condensation Nucleus Counter (PSM-CNC) System. In addition, the effects of relative humidity and particle charge may be investigated for various nanoparticle diameters. The results showed that the filtration efficiencies were independent of humidity and affected by particle charge in the case of particles below 100 nm in size. For particles smaller than two nm, the particle penetration increased with decreasing particle size [269].

It should also be noted that while filtration efficiency is important, other factors such as fit, maintenance, and wear time of respirators may have a greater influence on exposure mitigation. Many countries have assigned nominal protection factors for various classes or types of respirators. These may or may not be related to the filtration efficiency. Thus, from the point of view of industrial

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occupational hygiene, exposure reduction is calculated from the given respirator protection factor and not only by the filter efficiency.

The respirator's fit to the face does appear to be a significant issue for reducing exposure to engineered nanoparticles (ENPs). One commercially available fit test device (TSI PortaCount® Plus with N95-Companion™) measures fit by sampling particles of nominally 40 nanometers from inside and outside the respirator. This appears to be near the MMPS (Maximum Penetrating Particle Size) of many respirators, so it could include both filter penetration and face seal leakage and thus could be considered as "worst case" test for face seal leakage. For filtering half masks the risk is clearly coming from the lack of tightness (inadequate sealing) between face and the mask [270].

Protective clothing

Tests performed by Huang had shown that weaved fabrics behave as fibrous media in filters [271]. Nanoparticles between 100 and 500 nm experience maximum penetration, and efficiency increases as particle size decreases. The study also found that non-woven polyethylene textile (Tyvex) provided a superior barrier to nanoparticles compared to cotton and paper. Accordingly, the study suggested avoiding the use of protective clothing made with cotton fabrics when working with nanoparticles. These tests had been performed with an imposed air flow, like those carried out to test filtering devices.

In a complementary way (project NANOSAFE), closer to use conditions of protective clothing were tested without any air flow, using the diffusion cell. The through diffusion method based on the standard EN ISO 6529 and EN 374 uses a diffusion cell in which a constant particle concentration is imposed in the upper flow part. Diffusion coefficients are calculated from the measurement of nanoparticles flowing in the down flow part of the cell. The test results obtained for graphite nanoparticles centred at 30 nm and 80 nm showed that high density polyethylene textile seemed to be better than cotton and paper.

In November 2008 more results on experimental evaluation of individual protection devices against different types of nanoaerosols: graphite, TiO₂ and Pt were presented in Grenoble (NANOSAFE 2008 - International Conference on safe production and use of nanomaterials) [272]. It was concluded that protective clothing made from air-tight fabrics consisting of non woven textile seem much more efficient to protect workers against Pt and TiO₂ nanoparticles than cotton and polypropylene. Concerning gloves it was concluded that Nitrile, Latex, Neoprene are efficient for TiO₂ and Pt nanoparticles of around 10 nm diameter, when exposing the glove for few minutes.

8.2 Good practice guidelines and information tools

Nanomaterials are already in use at many workplaces. Examples of comprehensive and specific risk assessments are currently not sufficiently available. Nevertheless guidance on the use of nanomaterials is urgently needed. Since risk-related guidance is currently quite rare, the different approaches, that have been published until now, are mainly based on technical feasibility [14, 242, 243, 273-282]. ICON (2007) and Brouwer and Mikkers (2008) reviewed and compared available guidance documents [283, 284]. In general, these guidance documents suggest using what is currently recommended for protection against aerosols from fine dust. Sometimes, based on the precautionary principle, it is recommended to minimize exposure as far as possible. Specific uncertainties surround the efficacy of protective gloves and air filters.

The „Control Banding“-method is applied at workplaces to assess occupational exposure in case of missing occupational limits or missing exposure measurements [285, 286]. Chemical substances and exposure to them are grouped in categories of toxicity (hazard bands) and exposure (exposure bands). First initiatives to adapt this principle to nanomaterials have been developed [248, 287, 288].

A further important instrument of risk management to inform on hazards and appropriate measures is the Material Safety Data Sheet, which is discussed by Schneider et al. (2007) concerning nano-specific aspects [23]. The Association of the German chemical industry (VCI) issued guidance on submitting information along the supply chain about the safe transportation, storage, use, processing and disposal of nanoscale products [280, 289].

9 Regulatory background, policies and programs

9.1 Regulatory background

In Europe regulations regarding nanoparticles are based at present on existing laws and regulations applicable to chemicals.

According to the information given in the Communication “Regulatory Aspects of Nanomaterials” [290] all nanoparticles in chemical substances must meet the requirements of the REACH (Registration, Evaluation and Authorisation of Chemicals) [291]. Although there are no provisions in REACH referring explicitly to nanomaterials, they are included by the definition of a “substance”. The principal objective of the directive is to ensure a high level of relevant protection of human health and the environment. Until REACH is fully implemented, the notification scheme under the Directive 67/548/EEC applies for new substances and notified substances with significant new uses [292].

The general requirements in relation to occupational safety and health of workers at workplaces are presented in the EU Directive 89/391/EEC [293]. The aim of this framework directive is to ensure a high level of protection of workers at work – including those exposed to nanomaterials - through the implementation of preventive measures to guard against exposure to risks, and through provision of information, consultation, balanced participation and training of workers and their representatives.

The framework Directive foresees the possibility of adopting individual directives including more specific provisions in relation to particular aspects of safety and health and workplace exposures. Relevant directives thus adopted relate to risks related to exposure to carcinogens or mutagens at work [294], risks related to chemical agents at work [295], the use of work equipment by workers at work [296], the use of personal protective equipment at the workplace [297] and safety and health protection of workers potentially at risk from explosive atmospheres [298].

The Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work presents minimum requirements for the protection of workers from risks to their safety and health arising, or likely to arise, from the effects of chemical agents that are present at the workplace or as a result of any work activity involving chemical agents [295]. The text of the document includes employers' obligations related to identification and assessment of risk due to use of hazardous chemical agents, implementation of prevention measures, provision of information and training of workers. There are also definitions of chemical agents and hazardous chemical agents, but nanomaterials are not mentioned specifically.

Product legislation lays down requirements regarding specific products, such as medicinal products, plant protection products, cosmetics, food and feed additives. Consumer products that are not a subject of specific legislation have to meet the requirements of the General Product Safety Directive [299]. Community regulation in these areas contains provisions in relation to health and safety of consumers, workers, patients and users. As nanomaterials contained in such products are a subject of REACH legislation, therefore an assessment on their environmental impact must be conducted. All product legislation imposes a risk assessment and the adoption of risk management measures. Nanomaterials are not excluded from this obligation.

The European Directive 98/8/EC on Biocidal Products provides a framework of rules that apply to the marketing of biocidal (including nanomaterials) substances and products [300]. A biocidal product is any substance which is used to control or kill harmful organisms, such as bacteria, fungi, moulds and yeasts. Sterilisers and disinfectants are good examples of a biocidal product. The goal of the directive is to harmonise the European market for biocidal products and their active substances. The directive is intended to provide a high level of protection for humans, animals and the environment against results of use of biocidal substances. The Directive 98/8/EC requires the authorisation for use and placing on the market or registration of a wide range of biocide products currently not requiring authorisation including disinfectants, preservatives and a number of other specialist products as well as non-agricultural pesticides. (i.e. wood preservatives, public hygiene insecticides, rodenticides, surface biocides and antifouling paints). Only biocidal products which contain an active substance listed in Annex I of the Directive will be authorised for use. Existing and new active substances have to be evaluated to ascertain whether or not they can be included in the Annex I list [300].

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Environmental regulation relevant in the nanotechnology and nanomaterials context relates in particular to integrated pollution prevention and control (IPPC), the control of major accident hazards involving dangerous substances (Seveso II), the water framework directive and a number of waste directives.

In principle, the IPPC Directive could be used to control environmental impacts of nanomaterials and nanomaterials issues at IPPC installations through the inclusion of such considerations into the Commission's BAT Reference Document (BREFs) process should the need arise [301].

The Seveso II Directive applies to establishments where named dangerous substances (or substances falling within certain classification categories) are present above specific quantities (or thresholds) [302]. It imposes a general obligation on operators to take all measures necessary to prevent major accidents and to limit their consequences for man and the environment. If certain nanomaterials are found to demonstrate a major accident hazard, they may be categorised, together with appropriate thresholds, in the context of the Directive.

The Water Framework Directive sets common principles and an overall framework for action to improve the aquatic environment and to progressively reduce the pollution from priority substances and phasing out emissions, discharges and losses of priority hazardous substances to water [303]. Nanomaterials could be included among the Priority Substances depending on their hazardous properties.

For groundwater Member States will have to establish quality standards for pollutants representing a risk, in which case nanomaterials may also be included [304].

The Directive 2006/12/EC on waste sets the general framework and imposes an obligation on Member States to ensure that waste treatment does not adversely affect health and the environment [305]. The hazardous waste Directive defines which wastes are hazardous and lays down stricter provisions regarding such waste [306]. Hazardous waste must display certain properties set out in an Annex to the Directive and feature on the European Waste List as hazardous. Wastes containing nanomaterials could be classified as hazardous, if the nanomaterial displays relevant properties which render the waste hazardous.

Specific legislation has been adopted to deal with particular waste streams or specific waste treatment processes, such as incineration [307] and landfill [308].

Current EU waste legislation covers general requirements for the protection of health and the environment during waste management. It also includes requirements for the management of specific waste materials that may contain nanomaterials whilst not explicitly addressing the risks of nanomaterials.

9.2 European and international policies

The Community Strategy for health and safety at work has been published by the EC for the period of 2007 – 2012 [309]. Nanotechnology is addressed there as an important topic in context of the identification of new risks. Furthermore a communication from the European commission towards a European strategy for nanotechnology was published [310]. It has stated that activities connected with research and development as well as technological progress need to be accompanied by scientific studies and assessment of possible health or environmental risks associated with nanotechnology. In relation to health and safety issues the commission highlights the need:

- to identify and address safety concerns (real or perceived) at the earliest possible stage
- to reinforce support for the integration of health, environmental, risk and other related aspects into R&D activities together with specific studies
- to support the generation of data on toxicology and ecotoxicology (including dose response data) and evaluate potential human and environmental exposure.

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In 2005, the European Commission adopted the Communication "Nanosciences and nanotechnologies: an Action Plan for Europe 2005-2009" [311]. This Action Plan defines a series of articulated and interconnected actions for the immediate implementation of a safe, integrated and responsible approach for nanosciences and nanotechnologies. A risk assessment related to human health, the environment, consumer and workers should be responsibly integrated into all stages of the life cycle of the technology, starting at the point of conception and including R&D, manufacturing, distribution, use and disposal or recycling. Appropriate ex ante assessments should be carried out and risk management procedures developed and implemented before e.g. commencing with the mass production (10 tonnes/year or above) of engineered nanomaterials. Particular attention should be paid to products that are already on the market, or close to being put on the market, such as household products, cosmetics, pesticides, food contact materials, and medical products and devices. In 2007, the European Commission adopted the Communication of the first implementation report 2005-2007 of the above mentioned action plan [312]. This reports progress in virtually all areas of the Action Plan.

The European Commission issued a code of conduct to ensure a safe and ethical development and use of nanotechnologies. Seven principles have been developed [313]:

- **Meaning:** research activities should be comprehensible to the public. They should respect fundamental rights and be conducted in the interest of the well-being of individuals and society in their design, implementation, dissemination and use.
- **Sustainability:** research activities should be safe, ethical and contribute to sustainable development. They should not harm or threaten people, animals, plants or the environment, at present or in the future.
- **Precaution:** research activities should be conducted in accordance with the precautionary principle, anticipating potential environmental, health and safety impacts of outcomes and taking due precautions, proportional to the level of protection, while encouraging progress for the benefit of society and the environment.
- **Inclusiveness:** governance of research activities should be guided by the principles of openness to all stakeholders, transparency and respect for the legitimate right of access to information. It should allow the participation in decision-making processes of all stakeholders involved in or concerned by research activities.
- **Excellence:** research activities should meet the best scientific standards, including integrity of research and good laboratory practices.
- **Innovation:** governance of research activities should encourage maximum creativity, flexibility and planning ability for innovation and growth.
- **Accountability:** researchers and research organisations should remain accountable for the social, environmental and human health impacts of their work.

Furthermore the above mentioned policy documents from the European Commission have been compiled in a summary document [314].

Code of conducts were also developed by a British consortium and a producing company [315, 316].

Additionally national policy documents on the development of nanotechnology including health and safety issues have been published by several countries or organisations. To consider the precautionary principle is mentioned repeatedly (inter alia [317-321]).

Policy-guided activities of OECD member countries are summarized in a document that includes, among other, the following action points [322]:

- research and development programs and strategies
- investigations on the regulatory framework
- foundation of advisory committee and working groups
- voluntary stewardship programs
- good practice documents
- information programs and stakeholder consultation.

Nanoscale Materials Stewardship Program

In January 2008 the Environmental Protection Agency (EPA) of the United States launched the Nanoscale Materials Stewardship Program (NMSP). The NMSP will help to provide a firmer scientific foundation for regulatory decisions by encouraging submission and development of information including risk management practices for nanoscale materials.

The program is intended to:

- Help to assemble existing data and information from manufacturers and processors of existing chemical nanoscale materials;
- Identify and encourage use of risk management practices in developing and commercializing nanoscale materials;
- Encourage the development of test data needed to provide a firmer scientific foundation for future work and regulatory/policy decisions;
- Encourage responsible development, defined as the balancing of efforts to maximize the technology's positive contributions and minimize its negative consequences.

The participants of the program would include persons or entities that:

- Manufacture or import engineered nanoscale materials
- Physically or chemically modify an engineered nanoscale material
- Physically or chemically modify a non-nanoscale material to create an engineered nanoscale material
- Use engineered nanoscale materials in the manufacture of a product

Participation in the program is voluntary. It is designed in two parts: a 'basic' program, requires the participants to report all known or reasonably ascertainable information regarding specific nanoscale materials, and implement a risk management program. The other part, an "in-depth" portion, entails development of more sophisticated data, such as review of existing data, conducting preliminary assessments, identification of additional data needed to better characterize hazard, risk, and exposure issues for the material.

EPA will use the data to gain more detailed information in relation to which nanoscale materials are produced, in what quantities, how they are used, and the data that is available for such materials. Data collected through this program, will also aid in determining how and whether certain nanoscale materials or categories of nanoscale materials may present risks to human health and the environment.

The information submitted to the program could also be used to identify the data that are missing to conduct an informed risk assessment of a specific nanoscale material, but also to identify nanoscale materials or categories of nanoscale materials that may not warrant future concerns or actions, or should otherwise be treated as a lower priority for further consideration.

EPA believes that participation in the program will encourage responsible development of nanoscale materials and will benefit all stakeholders. Development and sharing of data on nanoscale materials to the fullest extent possible will enhance each stakeholder's ability to make informed decisions regarding nanoscale materials. Applying a stewardship approach will help participants to identify and adopt environmental health and safety practices throughout an industrial supply chain.

An interim report on the program will be published in approximately a year from its launching on January 28, 2008. A more detailed report and program evaluation will be published after approximately two years.

By October 2008 - 25 organizations (more than 113 nanoscale materials) have joined the basic program and further 3 companies have made a commitment to participate in the 'in-depth' program [289].

9.3 Research, standardisation and collaboration programs

9.3.1 Research programs

The European Commission has boosted support for specific collaborative research into the potential impact of nanomaterials on human health and the environment through the different Framework Programmes (FP) [323].

5th Framework Programme

The 5th Framework Programme (1998-2002) was implemented to help solve problems and respond to major socio-economic challenges, the European Union was facing [324]. The completed research projects addressing environmental, health and safety issues are shown in the following table.

Table 9: research projects in the 5th Framework Programme related to nano-and ultrafine particles (1998-2002) [325]

Acronym	Title	Duration & start	Partners	Website
Nano-Pathology	The role of micro and nanoparticles in biomaterial-inducing pathologies.	42 months January 2002	5	http://nanopathology.it/paginei/menu.htm
Nanoderm	Quality of skin as a barrier to ultra-fine particles.	42 months January 2003	7	http://www.uni-leipzig.de/
Nanosafe	Risk assessment in production and use of nanoparticles with development of preventive measures and practice codes.	15 months April 2003	9	http://www.nanosafe.org

The research project “Nanoderm” developed and applied different methods for analysing the quality of skin as a barrier against nanoparticles and investigated the nanoparticle activity and the skin response [326]. Different techniques were employed for the visualization of putative penetration pathways of TiO₂ nanoparticles through skin. According to the results, they do not expect any health effects for the application of sunscreen containing TiO₂ nanoparticles (especially when coated) on healthy skin because of the lack of penetration into vital tissue. The project “Nanosafe” assessed risks involved in production, handling and use of nanoparticles in industrial processes and products, as well as in consumer products [327]. The conclusions of the project were presented in previous sections of this report.

6th Framework Programme

The 6th Framework Programme (2002-2006) had as priority thematic area of research on Nanotechnology, knowledge-based materials and new industrial processes (NMP). The main objective of this thematic area was the creation of a scientific base for the transition of European production industry from resource-based towards knowledge-based, more environment-friendly approaches [328]. The research projects addressing environmental, health and safety issues in FP6 are shown in the following table.

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Table 10: research projects in the 6th Framework Programme related to nanotechnology (2002-2006) [325]

Acronym	Title	Duration & start	Partners	Website
Cellnanotox	Cellular interaction and toxicology with engineered nanoparticles.	36 months November 2006	8	http://fp6-cellnanotox.net
Dipna	Development of an integrated platform for nanoparticle analysis to verify their possible toxicity and the ecotoxicity.	36 months November 2006	10	http://dipna.eu
Impart	Improving the understanding of the impact of nanoparticles on human health and the environment.	42 months February 2005	18	http://www.temas.ch/Impart/ImpartProj.nsf/fmPubsByType?ReadForm&count=12&lang=en
Nanointeract	Development of a platform and toolkit for understanding interactions between nanoparticles and the living world.	36 months January 2007	17	http://nanointeract.net
Nanosh	Inflammatory and genotoxic effects of engineered nanomaterials.	36 months November 2006	7	http://www.nanointeract.net/
Particle-risk	Risk assessment for particle exposure.	36 months June 2005	7	http://iom-world.com/particlerisk
Nanosafe2	Safe production and use of nanomaterials.	48 months February 2005	22	http://www.nanosafe.org
Nanotransport	The behaviour of aerosols released to ambient air from nanoparticle manufacturing - a pre-normative study.	18 months September 2006	2	http://research.dnv.com/nanotransport
Nanocap	Nanotechnology capacity building NGOs.	36 months September 2006	17	http://www.nanocap.eu
Saphir	Safe, integrated & controlled production of high-tech multifunctional materials and their recycling.	48 months October 2006	22	http://www.saphir-project.eu/
Nanotox	Nano-particle characterization and toxicity.	24 months December 2006	1	http://nanotox.com

The objectives of “Nanosafe2” project are the development of an integrated system addressing potential hazards related to nanomaterials, in particular for health and environmental protection and also, the development of detection and characterisation techniques, hazard assessment, safe production processes and applications [327]. First results are presented in two dissemination reports. The first report is about conventional protective devices such as fibrous filter media, respirator cartridges, protective clothing and gloves and their efficiency against nanoaerosols. The second report presents information in relation to the explosivity and flammability of nanopowders. Safety parameters of nanopowders and their associated techniques and practices have been characterised for a representative set of particles of industrial relevance [327].

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More results have been presented in November 2008 at the NANOSAFE 2008 - International Conference on safe production and use of nanomaterials, 3-7 November 2008 in Grenoble, France [329].

The “Nanotransport” project addresses the behaviour of aerosols released to ambient air from nanomaterial manufacturing [330]. The aim of the project is to analyse and typify relevant exposure scenarios of workers to manufactured nanomaterial aerosols at industrial workplaces and to develop recommendations to the European Commission regarding realistic test conditions in terms of test aerosol characteristics for use within toxicology studies, but also for testing the efficiency of existing engineering control systems and personal protective equipment. The experimental results allow drawing a number of conclusions:

“The nanoaerosols evolve considerably with time. The average particle size increases while the number concentration decreases due to homogeneous coagulation processes.

The natural background aerosols are scavengers for nanomaterials by heterogeneous coagulation. This leads to the occurrence of physical/chemical presence of nanomaterials in size classes other than the one in which they were originally emitted.

Filtration of nanomaterials can be done with high efficiency using state of the art filters. However, the shift of nanomaterials to larger size classes by both homogeneous and heterogeneous coagulation may lead to the occurrence of nanomaterials in the size range where the filters are least efficient, the most penetrating particle size (MPPS) in the range of about 80 nm – 200 nm.”

Based on the experimental results, some recommendations to the European Commission regarding test aerosols for nanotoxicology studies, testing of filters and protective equipment in the workplace and metrology have been prepared but they are still under discussions with experts and stakeholders [331].

The “Nanocap” project is set up to develop the understanding of Non-governmental organizations (NGOs) and trade unions on impact of nanotechnology on environmental issues, occupational health and safety issues, ethical issues and critical assessment of benefits [332]. The project has developed an occupational hygiene strategy for a workplace to nanomaterials that includes:

- elimination of the emission source (full containment process, substitution)
- exhaust ventilation direct at the source
- personal protective equipment: perfect fitting respirators with high efficiency particulate air (HEPA) filters with fibrous filters
- non-woven fabrics against nanoparticle penetration
- use two layers of gloves [331].

7th Framework Programme

The 7th Framework Programme (FP7, 2006-2013) is continuing with the thematic area of research on nanotechnology, knowledge-based materials and new industrial processes (NMP). Other important activities, also for FP7, are Technology Platforms, that bring together companies, research institutions, the financial world and the regulatory authorities at the European level to define a common research agenda with should mobilise a critical mass of national and European public and private resources. Within nanotechnology, two Technology Platforms are set up:

- nanoelectronics and
- nanomedicine [328].

The directly related topics in the first call for research proposals in FP7 are [325]:

- NMP-2007-1.3-1 specific, easy-to-use portable devices for measurement and analysis
- NMP-2007-1.3-2 risk assessment of engineered nanoparticles on health and the environment

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- NMP-2007-1.3-3 scientific review of the data and studies on the potential impact of engineered nanoparticles on health, safety and the environment
- NMP-2007-1.3-4 creation of a critical and commented database on the health, safety and environment impact of nanoparticles
- NMP-2007-1.3-5 coordination in studying the environmental, safety and health impact of engineered nanoparticles and nanotechnology based materials and products
- HEALTH-2007-1.3-4: alternative testing strategies for the assessment of the toxicological profile of nanoparticles used in medical diagnostics. Call coordinated with NMP-2007-4.1.3-2/4.4.4.

Some of the projects of the FP7 are:

- NanoImpactNet (<http://nanoimpactnet.eu>) - The European network on the health and environmental impact of nanomaterials
- NanoTEST - Development of methodology for alternative testing strategies for the assessment of the toxicological profile of nanoparticles used in medical diagnosis
- Nanodevice (proposal under negotiation) - Novel concepts, methods and technologies for the production of portable easy-to-use devices for the measurement and analysis of airborne engineered nanoparticles in workplace air
- Nanoimmune (proposal under negotiation) - Comprehensive assessment of hazardous effects of engineered nanomaterials on immune system
- NanoReTox (proposal under negotiation) - The reactivity and toxicity of engineered nanoparticles, risks to the environment and human health
- Neuronano (proposal under negotiation) - The brain will be explored as NP target organ [331].

Researchers from the London School of Economics and Political Sciences, the Chatham House, the Environmental Law Institute and the Project on Emerging Nanotechnologies at the Woodrow Wilson International Center for Scholars launched a collaborative EU-US research project on the regulation of nanotechnologies in the European Union and United States. With a rapidly expanding range of scientific and commercial applications, nanotechnologies have emerged as a new focus of both EU and US regulatory efforts that seek to promote innovation while ensuring safety and enhancing public acceptability.

The goal of the project is to investigate the regulatory challenges posed by nanotechnologies and to assess the effectiveness of existing approaches on both sides of the Atlantic.

The aims of the project include:

- high quality analysis of the comparative dimensions of nanotechnologies regulation in the EU and US;
- to publish and widely disseminate policy-relevant research results that will assist policy processes and debates on both sides of the Atlantic; and
- to create greater awareness among decision-makers and opinion formers for congruent approaches and transatlantic convergence in nanotech regulation.

The known gaps and inadequacies in existing regulatory approaches to nanotechnology will be addressed to effectively promote innovation, while ensuring safety and enhancing public acceptability of the new technology.

The project will result in a research report and analytical papers based on comparative research. A major international conference is to be held at Chatham House and a series of outreach events in Brussels, Berlin, Paris and Washington throughout 2009. The project findings will feed into a major EU conference in 2009 and into the policy recommendations that are to be presented at the 2010 EU-US Summit. [333]

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As well as the European Commission, the European Union Member States and other European countries also fund research to analyse the impact of nanomaterials on health, environment and safety [325]. Due to the large number of projects involved, only some of the topic areas are presented below.

Table 11: projects funded by the different European countries [325]

Country	Number of projects	Title (examples)
Belgium	1	risk assessment of nanoparticles on human health using in vitro and in vivo models
Czech Republic	1	study of transport of inhaled nano-sized particles (Ag, Pb, Cd) and their distribution in organs
Denmark	12	evaluation and control of occupational health risks from nanoparticles
		NanoKem: nanoparticles in the paint and lacquer industry. Exposure and toxic properties
		Nanoplast: nano-technological materials and products in the plastic industry. Exposure assessment and toxicological properties
		Susano: risk assessment of free nanoparticles
		risk analysis and governance of nanomaterials
Germany	3	research project to study the safe handling of nanomaterials
Greece	1	technology development for optimising air quality in industrial buildings: Characterization of air quality in industrial buildings
Italy	1	European center for the sustainable development of nanotechnology
Finland	3	Nanosafety in Finland
United Kingdom	46	Nanoparticle occupational safety and health consortium
		reference materials for engineered nanoparticle toxicology and metrology
		new tools for nanometrology
		nanotechnology safety network
		an outline scoping study to determine whether high aspect ratio nanoparticles (HARN) should raise the same concerns as do asbestos
Switzerland	24	nanotechnology and health. Technical options, risk evaluation and preventive strategies
		Nanorisk: safety and risks of carbon nanotubes
		comparison of the effect of asbestos fibres and carbon-nanotubes
		use of nanoparticles in industry: Safety aspects
		how to assess the adequacy of safety measures for manufactured nanoparticles

9.3.2 Standardization activities

The European Committee for Standardization (CEN) and the International Organization for Standardization (ISO) have two Technical Committees, CEN/TC 137 "Assessment of workplace exposure to chemical and biological agents" and ISO/TC 146/SC-2 "Air Quality, Workplace Atmospheres", working in the field of assessment of workplace exposure to different agents. Recently, they have started to develop documents on the topic of the exposure to nanomaterials [334, 335].

The only published standard related to nanomaterials exposure is the ISO/TR 27628 (2007) "Workplace atmospheres: ultrafine, nanoparticle and nano-structured aerosols. Inhalation exposure characterization and assessment" prepared by the Technical Committee ISO/TC 146/SC22 [8]. The standard ISO/TR 27628 (2007) contains guidelines on characterizing occupational nanoaerosol exposures and represents the current state-of-the-art, with an emphasis on nanometre-diameter particles [8]. Furthermore, background information is provided on the mechanisms of nanoaerosol formation and transportation within an occupational setting and on industrial processes associated with nanoaerosol exposure. Exposure metrics appropriate to nanoaerosols are discussed and specific methods of characterizing exposures with reference to these metrics are presented. Specific information is provided on methods for bulk aerosol characterization and single particle analysis.

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Both committees are working in parallel to develop the project “Workplace atmospheres. Characterization of ultrafine aerosols/nanoaerosols. Determining the size distribution and number concentration using mobility particle sizers/differential mobility analysers” [336]. The pre-standard prEN ISO 28439 (2008) specifies the sampling of ultrafine aerosols, nanoparticles and nanostructured particles in the range of five nm to 800 nm using particle mobility analysers in order to get the number concentration and size distribution [336]. A measurement procedure is described for the use of particle mobility analysers at workplaces. Recommendations are also given for the evaluation of data [336]. The standard is expected to be released by 2011 [336].

Besides committees mentioned before, two other committees created in 2005, deal specifically with nanotechnologies: ISO/TC 229 and CEN/TC 352.

The ISO/TC 229 consists of four working groups (WG) with the following names and scopes of activities:

- WG1 - Terminology and Nomenclature: Define and develop unambiguous and uniform terminology and nomenclature in the field of nanotechnologies to facilitate communication and to promote common understanding.
- WG2 - Measurement and Characterization: The development of standards for measurement, characterization and test methods for nanotechnologies, taking into consideration needs for metrology and reference materials.
- WG3 - Health, Safety and Environment: The development of science-based standards in the areas of health, safety and environmental aspects of nanotechnologies.
- WG4 - Material specifications: (new work) [335].

The Technical Committee ISO/TC 229 is in contact with external standards bodies and research institutes as well as a number of ISO’s committees and subcommittees, highlighting among them, the Technical Committee ISO/TC 24/SC-4 “Particle characterization including sieving” and the Technical Committee ISO/TC 146/SC-2 “Air Quality. Workplace Atmospheres”.

The Technical Committee CEN/TC 352 will develop a set of standards addressing the following aspects on nanotechnologies:

- classification, terminology and nomenclature
- metrology, measurement and characterization (including procedures for calibration)
- health, safety and environmental issues
- nanotechnology products and processes.

The committee CEN/TC 352 will work closely together with the Technical Committee ISO/TC 229 and liaise with other European and international bodies as well as a number of CEN’s committees such as the Technical Committee CEN/TC 137 “Assessment of workplace exposure to chemical and biological agents”.

Some of the more relevant standards under development by the referenced committees are shown in the following table:

Table 12: Standards and standards under development by the referenced committees [334, 335]

Committee	Reference	Title	Current state	DAV/ stage codes
ISO/TC 146/SC 2	ISO/TR 27628	Workplace atmospheres. Ultrafine, nanoparticle and nano-structured aerosols. Inhalation exposure characterization and assessment.	published	

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Committee	Reference	Title	Current state	DAV/ stage codes
	ISO/CD 28439	Workplace atmospheres. Characterization of ultrafine aerosols/nanoaerosols. Determining the size distribution and number concentration using mobility particle sizers/differential mobility analysers.	under development	30.60
CEN/TC 137	prEN ISO 28439	Workplace atmospheres. Characterization of ultrafine aerosols/nanoaerosols. Determining the size distribution and number concentration using mobility particle sizers/differential mobility analysers.	under development	2011-04
CEN/TC 352	CEN ISO/TS 27687	Nanotechnologies. Terminology and definitions for nano-objects. Nanoparticle, nanofibre and nanoplate (ISO/TS 27687:2008).	published	
ISO/TC 229	ISO/TR 12885	Nanotechnologies. Health and safety practices in occupational settings relevant to nanotechnologies.	published	
	ISO/TS 27687	Nanotechnologies. Terminology and definitions for nano-objects. Nanoparticle, nanofibre and nanoplate.	published	
	ISO/AWI TS 11751	Terminology and definitions for carbon nanomaterials.	under development	20.00
	ISO/AWI TR 11808	Nanotechnologies. Guide to nanoparticles measurement methods and their limitations.	under development	20.00

NOTE: The following codes have been mentioned in the table: DAV: Date of availability. Date when the definitive text in the official language versions of an approved CEN publication is distributed by CEN Central Secretariat; 20.00: Preparatory stage. New project registered in TC/SC work programme; 30.60: Committee stage. Close of voting/comment period.

9.3.3 Organisation for Economic Cooperation and Development (OECD)

An international collaboration on Environment and Health Safety aspects (EHS) of nanotechnology is organized by the Organisation for Economic Cooperation and Development (OECD). A “Working Party on Safety of Manufactured Nanomaterials” (WPMN) was established in 2006 that consists of OECD member countries and organisations. It focuses on safety aspects relating to human health and the environment over the whole lifecycle [337]. Eight projects have been selected to be worked on in subgroups:

- 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.

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The OECD working party therefore creates a very important platform for the diverse tasks and activities relating to the assessment of nanomaterials at international level. The results of this ongoing activity are presented at the OECD website [337].

9.3.4 World Health Organization (WHO)

The Work plan of the World Health Organization (WHO) [338] Collaborating Centres in Occupational Health (2006-2010) includes six Activity Areas [339]. Projects connected with nanomaterials are presented in subgroup NM Nanomaterials of the Activity Area 6 Communication and Networking. General information about projects is shown in following table [340, 341].

Table 13: WHO projects connected with nanomaterials [340, 341]

WHO number	New AA code	Title	Lead organisation and country
21	AA6:NM 1	Dialogue on Nanoparticles	Federal Institute of Occupational Safety & Health – BAuA, Germany
22	AA6:NM 2	How to assess the adequacy of safety measures for manufactured nanoparticles	Institute for Work and Health, Lausanne, Switzerland
23	AA6:NM 3	Best practices globally for working with nanomaterials	NIOSH – National Institute for Occupational Safety and Health, USA
24	AA6:NM 4	NANO-Comms: A Technical observatory for the dissemination of information regarding nanoparticles health and safety issues	HSL, - Health and Safety Laboratory, UK
25	AA6:NM 5	Assessing the Hazard of Nanoparticles	Institute of Occupational Medicine – IOM, UK

Projects aim at the following objectives and outcomes:

Dialogue on nanoparticles:

- identify and evaluate the occupational and environmental exposure
- identify and evaluate health and environmental effects and risks
- specify the need for research, action and coordination
- initiate a dialogue and exchange view between different stakeholders (industry, research, administration, trade units, media, non-governmental organisations, political parties etc.).

How to assess the adequacy of safety measures for manufactured nanoparticles:

- identify work processes that involve manufactured nanoparticles
- categorize the health risks associated with these processes with regard to particle type and quantity used
- describe existing and new safety measures
- develop guidelines for the assessment of safety measures used in production, application, use and disposal of nanoparticles and nanoparticle-containing products.

Best practices globally for working with nanomaterials:

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- develop and maintain NIOSH best practice documents such as web-based “Nanotechnology Information Exchange”
- develop a NIOSH “Current Intelligence Bulletin” on working with engineered nanomaterials
- contribute to ISO standardization best practice guidelines and validated testing protocols for exposure assessment and protective equipment and provide them to developing nations with nanotechnology facilities (through 2010)
- provide ongoing analysis of occupational health and safety issues and practices regarding nanomaterials (through 2010)

NANO-Comms - a technical observatory for the dissemination of information regarding nanoparticles health and safety issues:

- develop a network of international experts in the field of health and safety issues of nanoparticles
- identify processes that involve manufacturing of nanoparticles which may lead to exposure
- review exposure modelling processes
- categorise and map health risks associated with exposure
- assist the development of standards
- engage with regulators, manufacturers, down-stream users and researchers to ensure communications meet the need of the audience

Assessing the hazard of nanoparticles:

- determine which nanoparticle attributes are most influential in driving toxicity on different target organs and species
- use results to inform a risk assessment framework for nanoparticles in an occupational setting
- disseminate the results to existing networks on nanomaterials health and safety issues.

10 Conclusions

Based on the information presented in the previous chapters it becomes obvious that there are many information deficits requiring research activities. Furthermore research results need to be transcribed into standards and guidelines in different areas such as exposure measurement or toxicological testing. To be effective this transfer of information into standards and guidelines must be interrelated to the regulatory background (for example REACH, regulations on biocides) and harmonised on a European and international level. In addition, voluntary standards and activities of industry, such as product stewardship, can contribute to an appropriate occupational health protection. Against the background of the current and predicted research at national and international level, the following priority fields in research, development and transfer are identified.

Identification of nanomaterials and description of exposure

The available information on the nanomaterials at workplaces is currently superficial, since transparency in this area can lead to competitive disadvantages for the manufacturing and processing companies. Also limited is the information on the industry branches, where nanomaterials are produced or used and the exposure conditions of the workforce.

The dialogue with the manufacturers and users must be intensified. Initiatives such as product stewardship and the Swiss code of conduct are steps in the right direction.

Measurement of exposures to nanomaterials and efficacy of protective measures

Measurement technology to determine nanomaterials in the air and on skin has to be developed for routine, workplace application. A focus must be on the further development of person-related measurement technology. At the same time, workplace measurements performed with the currently available measurement technology should be intensified. In particular in the workplace, differentiation between the ubiquitously occurring ultrafine aerosols and the intentionally produced nanomaterials is required. In addition the efficacy of protective measures, both collective and individual, used at workplaces has to be determined and evaluated.

Risk assessment of nanomaterials in line with the current statutory framework

Since integration into the existing statutory framework is currently envisaged, it is all the more necessary to demonstrate this using corresponding risk assessments. While the framework Directive [293] provides the requirement for all workplaces to conduct risk assessments, the following specific regulations are the centre of attention here:

- Regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) [291]
- Directive 98/24/EC on the protection of the health and safety of workers from the risks arising from exposure to chemical agents at work
- Classification, packaging and labelling of dangerous substances, Directive 67/548/EEC [292]
- Biocide Directive; Directive 98/8/EC [300].

The sub-statutory body of rules (e.g. Technical Guidance Documents, REACH Implementation Plans) do not currently address the specific problem posed by nanomaterials. Thus, these rules need further development to support the primarily responsible industry/ies with the appropriate characterization and assessment of the nanomaterials. 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.

In vivo studies for assessment of the health effects of nanomaterials

To date, the promotion of research has mainly supported the performance of in vitro studies due to animal welfare, ethical reasons related to human studies, costs. However, in general in vivo data represent a more reliable data base and are the European standard in regulatory toxicology in the case of existing chemicals. The quality of the necessary toxicological investigations should also meet these standards in the case of nanomaterials. Data sets of in vivo studies involving high exposure nanomaterials must be established or supplemented. A recently developed code of conduct assists in development of research programs maintaining high ethical standard.

Validation of the in vitro methods and methods of physico-chemical properties as methods to determine health effects

Due to the high costs, the long duration and for reasons of animal welfare in vivo methods have to be supplemented by in vitro methods and methods to determine physico-chemical properties, being predictive of health effects in humans. However, a comprehensive validation and evaluation of which in vitro method (including PC method) is sufficiently sensitive and specific for long-term effects does not yet exist. This is necessary in order to demonstrate the relevance of these studies for regulatory toxicology and to permit categorisation of nanomaterials and prediction of health damage.

Training of workers and practical handling guidelines for 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. General handling aids have already been produced. More specific handling guidelines should be added for activities that possess a relevant exposure potential. In addition workers have to be prepared and trained to behave appropriately.

It needs to be remembered that researchers working on the development of materials are among the first ones that may be exposed to new, potentially toxic substances. One of the main challenges is to ensure their health and safety - and to maintain the development of the technology [3].

The conclusions based on hard lessons learned following previous industrial revolutions instigate a cautious approach to any new inventions. However, sufficient foresight and strategically directed research can – in combination – lead to successful development of nanotechnology not only as a very highly beneficial and profitable new technology, but also to ensuring that those working in this field can do so safely.

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12 Annex

12.1 Abbreviations

Abbreviation	Long version
µm	micrometre
A	Ampere
Ag	silver
Am	americium
APS	Aerodynamic Particle Sizer
BET	Brauner-Emmett-Teller
BREF	Commission's BAT Reference Document
BSI	British Standards Institution
C	carbon
CAS	Chemical Abstracts Service
CEN	European Committee for Standardization
CMP	chemical mechanical planarization
CNC	Condensation Nuclei Counter
CNT	carbon nanotube
Co	cobalt
CPC	Condensation Particle Counter
Cu	copper
CVD	chemical vapour deposition
CVS	chemical vapor synthesis
Dae	aerodynamic diameter
DMA	Differential Mobility Analyser
DMF	N,N-dimethylformamide
EC	European Commission
EEC	European Economic Community
EEPS	Engine Exhaust Particle Sizer
EHS	Environment and Health Safety
ELPI	Electrical Low Pressure Impactor
ESP	electrostatic precipitator
f	frequency
Fe	iron
FMPS	Fast Mobility Particle Sizer
FP	Framework Programme
HEPA	high efficiency particulate air filter
HiPCO	high-pressure carbon monoxide
IOM	Institute of Occupational Medicine
ISO	International Organization for Standardization
kg	kilogram
Kr	krypton
Kst	maximum rate of pressure
LEL	lower explosion limit
LEV	local exhaust ventilation
m	metre

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Abbreviation	Long version
MEC	minimal explosion concentration
mg	milligram
MIE	minimal ignition energy
mm	millimetre
Mo	molybdenum
MOUDI	Multi-orifice Uniform Deposit Impactor
MRI	magnetic resonance imaging
MWCNTs	multi-walled carbon nanotubes
MWN	multi-walled nanotubes
NGO	Non-governmental organization
NH ₃	ammonia
Ni	Nickel
NIOSH	National Institute for Occupational Safety and Health
nm	nanometer
NO ₂	nitrogen dioxide
NSAM	Nanoparticle Surface Aerosol Monitor
OECD	Organisation for Economic Cooperation and Development
OEL	occupational exposure limit
PM	particulate matter size
PNA	peptide nucleic acid
PVP	poly(vinylpyrrolidone)
PSM-CNC	Particle Size Magnifier-Condensation Nucleus Counter
R&D	research and development
REACH	Registration, Evaluation and Authorisation of Chemicals
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SiO ₂	silicon dioxide
SME	small and medium-sized enterprises
SMPS	Scanning Mobility Particle Sizer
SSA	specific surface area
SWCNTs	single-walled carbon nanotubes
TEOM	Tapered Element Oscillating Microbalance
TEOS	tetraethylorthosilicate
TiO ₂	titanium dioxide
TP	thermophoretic precipitator
UCPC	Ultrafine Condensation Particle Counter
ULPA	ultra low penetration air filters
V	Volt
WG	working group
WPMN	Working Party on Manufactured Nanomaterials
Y	yttrium
ZnO	zinc oxide

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