Nano matters: building blocks for a precautionary approach

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Chapter 1

Introduction
1.1 Introduction and questions raised

Since the late nineties of last century the emergence of nanotechnologies\(^1\) has been the subject of public debate (‘nanodebate’). Nanotechnologies apply materials at the nanoscale, though it may be noted that the range of the nanoscale, which was formally recommended for legislative purposes by the European Commission as materials with a diameter of 1-100nm, is not precisely defined in terms of risk as will be further discussed in section 1.2. The stakeholder groups that committed themselves to take part in the nanodebate are quite divergent being NGOs (e.g. EEB nd-b, FoE 2007), consumer organizations (e.g. BEUC), insurance companies (Münchener Rück 2002; Swiss Re 2004; Allianz nd), religious organizations (Touney 2012), educational organizations and musea (Nanototouch nd), trade unions, and many others.

Contributions to the public debate have ranged from high expectations and ambitious road maps (e.g. Roco & Bainbridge 2001; Royal Society 2004, KNAW 2004, Roco 2007), to dire warnings (ETC 2003, FoE 2007). The matters raised have included its promises to solve so far not-easily solvable problems as finding new energy resources and reduction of energy use (e.g. Cientifica 2007, Lewis 2007), clean water supply (e.g. Hillie et al 2006, Grimshaw 2009), cleaner food production (e.g. Joseph et al 2006), medicines with targeted drug delivery (e.g. Park 2007), new cancer treatments (e.g. Maynard 2010), smart self-repairing coatings (e.g. Shchukin et al 2007), substitution of toxic substances in products (e.g. Ellenbecker et al 2011) and many others. Other topics in the nanodebate relate to the social and ethical issues of introducing nanotechnologies in society (e.g. Sandler 2009, Gammel 2009) and matters of hazard (potential to harm) and risk (chance that harm will occur). The importance of the latter matters is linked to findings that a specified mass of nanomaterials may be more hazardous than the same mass of larger sized materials. This is discussed in more detail in section 1.3. The differences in properties between nanosized and larger sized materials may require including factors like size, form, zeta-potential and other parameters in hazard assessment (SCENHIR 2009, Shvedova et al 2010). The properties of nanomaterials may require using new metrics for exposure assessment departing the conventional mass-based approach (Oberdörster et al 2005), which is an important issue for risk assessment and standard setting (see also section 1.6). With the growing attention to the occupational health risks of manufactured nanomaterials (MNMs) interest is also emerging in nanoparticles that are generated in processes (process-generated nanoparticles – PGNP), which may be similarly harmful. This is briefly discussed in section 1.5 and in later chapters.

Special attention in the nanodebate regards the matter of risk governance. One relevant matter in this respect is the question whether existing legislation covers the safe use of nanomaterials. Initial studies to identify possible gaps in existing legislation regarding

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\(^1\) The word nanotechnologies is used in the plural form as to express its nature as enabling technology. Nanomaterials and technologies that study and operate at the nanoscale are used in other technologies, like e.g. biotechnology, genomics, coating technology. As such nanotechnology does not exist as independent discipline, but is generally characterized as a converging technology.
control of potential hazards of nanomaterials resulted in early European and national governmental statements that existing legislation, in principle, covers the new risks of nanomaterials as well, and only slight adaptations should have to be made to address the nanoscale (EC2008; NL2008). More recent studies show that sometimes more fundamental changes in legislation should be considered (Vogelezang-Stoute et al 2010); other studies are still ongoing (DG Empl 2012). The legislation regarding the cosmetics directive has already been “nanonized” under the pressure of consumer organizations and after agreement in the European Parliament (EC 2009). Initiatives to include nanomaterials in the REACH regulation are ongoing; adaptations have been made in accompanying guidance documents addressing a nano-specific approach for identification, information requirement and risk assessment of nanomaterials, (ECHA 2012).

Given the present trend to deregulation, the ambition of governments to develop new legislation is limited and preference is given to self-regulating of social partners and soft instruments. The latter emphasize the responsibility of industry to take care for a safe and acceptable nanotechnological development and advocate a deliberative approach to give a critical voice to Civil Society Organizations (CSOs) (Renn et al 2006, Widmer et al 2010). In an effort to frame a responsible development of nanotechnologies the European Commission launched a voluntary Code of Conduct (CoC) for nanotechnological R&D and emphasized the need to invoke the precautionary principle when indications of hazard, uncertainties and ambiguities are at stake (EC CoC 2008, NanoCode 2012). Industry responded to this with their own CoCs or similar approaches, which is elaborated further in section 1.4.

More in general, in the debate of risk governance the operationalization of the precautionary principle (PP) has become important. All relevant actors having interests in nanomaterials on the European market, being industry, governments and CSOs, tend to agree on invoking the PP when ambiguity and uncertainty is at stake. It is however questionable whether they mean the same when they operationalize the PP. Indicative thereof is the emergence of the concept “precautionary approach”, as to which the use of the word ‘approach’ may be suggest a loose interpretation of the PP (Rip 2006).

Other matters that are important in the nanodebate are the balancing of the uncertainties regarding (health) risks and (economic) benefits, and the problem of trust. Many of the stakeholders have only a limited trust in the downstream information supply (Brun et al 2012). Problematic in this respect is the lack of transparency in the market of nanomaterials and the confidentiality of product compositions. Downstream users are kept ignorant to a large extent about the composition of nano-enabled products and are generally not informed about a possible release of nanomaterials during the intended use of their products (see chapter 5). This matter will be taken up in chapter 3.

This thesis will partly deal with the emerging position of European trade unions and environmental organizations in the nanodebate about hazard and risk. A larger part of this thesis will more specifically deal with hazard and risk linked to nanomaterials at the workplace. The latter part of the thesis is to be viewed against the background of major developments in workplace risk governance. These include REACH and ‘deregulation’ and the way to translate the precautionary principle into a precautionary approach that allows developing manufactured nanomaterials (MNMs) and applying these safely in products.
The questions raised in this thesis regard the following topics.

1. **The role of CSOs in the nano dialogue**

This thesis focuses on developing precautionary risk management strategies in situations where uncertainties prevail and economic interests force industries to go full speed ahead with new materials that can be manufactured at the nanosize and studies how CSOs built their capacity to position themselves in the nanodebate. Section 1.5 shortly introduces the dilemmas around making the precautionary principle operational. Chapter 2 goes into detail about the capacity building of CSOs and their initiative to develop “building blocks for a precautionary approach”.

Questions raised are:

   a) *What is the role of CSOs in the dialogue on the responsible development of nanotechnologies?*
   
   b) *From their perspective, how can the precautionary principle be made operational?*

As will be explained in sections 1.3 and 1.6 there is empirical evidence for hazards and risks of nanomaterials but this evidence does only allow in a very limited number of cases to derive health based occupational exposure limits (HB-OELs). This has triggered unconventional approaches to safeguarding the workplace characterized by potential exposure to nanoparticles. One of these approaches essentially substitutes HB-OELs by nano reference values (NRVs). This approach is discussed in chapters 3-6. Another approach makes use of control banding. This approach is discussed in chapter 6.

2. **Downstream use of nanomaterials**

Workers along the full life cycle of nanomaterials are involved in handling and processing nanomaterials, but ignorance about the type of nanomaterials used in products, their potential release during use, as well as the limited knowledge about the hazards of MNMs may hinder making a full risk assessment and to develop an acceptable risk management. These issues are elaborated in a pilot in the construction industry, which described in chapter 3 of this thesis. The following questions were raised:

   a) *Which nano-enabled products are used in the European construction industry?*
   
   b) *Are employers and employees aware of the nanoparticulate character of those products and of its implications for occupational health?*
   
   c) *What are actual exposures to nanoparticles in a limited number of working environments where workers deal with nanoproducts?*
   
   d) *How do these exposures compare with preliminary nano reference values for workplace exposure based on a precautionary approach?*

In an epilogue to this chapter (3.2 and 3.3) the discussion of the downstream use of nanomaterials is extended to the furniture industry and the paint value chain (including car repair and painting contractors).
3. **Assessment of the usefulness of precautionary nano reference values**

To assess the provisional tool of number-based nano reference values a study was set up to apply them at workplaces using nanoparticles in settings as they occur in practice. Airborne nanoparticles’ concentrations were measured and compared with nano reference values. This approach was compared with the generic approach proposed by Pauluhn [2010] and with the mass-based approach as proposed by the British Standard Institute (BSI 2007). These issues were elaborated further in chapter 4. The following questions were raised:

- **a)** What is the actual exposure to NP during the use of nanomaterials in different occupational settings?
- **b)** Is the concept of NRVs a useful tool for risk management in industrial settings?
- **c)** How does the NRV-concept compare to the overload-based approach as proposed by Pauluhn [2010] and the mass-based approach as proposed by BSI [2007]?

4. **Lessons learned from the discussion and experience with nano reference values**

The introduction of a new precaution-based risk management tool like the NRV may not go without opposition. Therefore a study was set up involving companies using MNMs and regulators in the Netherlands with the aim to get insight into the acceptance of the NRV benchmarks, as well as into the use of these NRVs as a voluntary tool to minimize exposure at the workplace. Questions raised were:

- **a)** What can be learned from the discussion about and experience with Nano Reference Values in the Netherlands to minimize exposure to nanomaterials at the workplace effectively?
- **b)** Under which conditions are companies that produce and use nanomaterials able and willing to apply the NRVs?
- **c)** Is the voluntary nature of NRVs acceptable?

Chapter 5 seeks answers to the questions raised, and draws conclusions about the usability of NRVs as risk management tool to minimize exposure to nanomaterials at the workplace and regarding the potential to apply the NRVs as an instrument that can be used on a voluntary basis.

5. **Comparison of risk management tools to support safe working with nanomaterials**

Chapter 6 seeks to compare risk estimates and control measures that emerge from applying the laymen-oriented guidance for working safely with nanomaterials and two nano-specific Control Banding tools with the strategy to measure workplace concentrations and refer these with nano reference values (NRV). The matter of process-generated nanoparticles and whether these should be taken into account in risk modeling is discussed. Questions raised are:

- **a)** Do MNM-specific CB tools when applied at the same workplaces lead to similar risk estimates for control measures and how do these relate to measured concentrations?”
- **b)** Is it legitimate to ignore PGNPs in risk assessment and risk management when assessing MNMs?”

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6. **Reflection on the precautionary approach using NRVs in an international context**

The precautionary approach of NRVs was reflected at an international forum of small- and medium-size enterprises (SMEs), large companies, trade unions, governmental authorities, research institutions, and non-governmental organizations (NGOs) from many European countries, USA, India, and Brazil. The approaches towards risk management of nanomaterials with insufficient hazard data and opinions of the participants about the NRV-concept are further elaborated in chapter 7. The following questions were discussed:

- a) Are precaution-based NRVs for MNMs useful and acceptable as a substitute for HBR-OELs and derived no-effect levels (DNELs)?
- b) Are the metrics as used in the NRV useful for measuring NPs?
- c) Is it advisable to combine exposure assessment of MNMs and PGNPs?
- d) What is the opinion about applying the precautionary principle in risk assessment?
- e) How should a workplace deal with the lack of information regarding MNMs in products?
- f) Is it appropriate to use soft regulation for exposure control?

7. **General conclusions**

The study ends with drawing general conclusions in chapter 8.

This introduction further highlights a few topics that are (or should be) in the frontline of the discussion on the safe use of nanomaterials in practice. The first highlight (section 1.2) concerns the definition of nanomaterials, which is object of an ongoing debate regarding the purpose of defining nanomaterials exactly, being for legislative purposes for the industry e.g. for registration of the materials they market, or for the purpose of risk identification. The second highlight (section 1.3) regards the potential adverse effects of nanomaterials, what is known and what should be known to be able to make a reliable risk assessment. Section 1.4 reflects on the precautionary principle and the role this principle has in risk management. The fourth highlight (section 1.5) regards the background nanoparticles with a ‘natural’ origin and nanoparticles that might be formed at the workplace by processes and equipment used: the process-generated nanoparticles. So far this anthropogenic source is largely outside the debate on nanotechnologies, but arguments are brought forward to include this source as well in risk assessment. Section 1.6 finally discusses the definition and scope of occupational exposure limits and derived no-effect levels in Europe and precautionary approaches to standard setting.

### 1.2 A definition for nanomaterials

An essential element to structure the debate on nanotechnologies is to define what we are talking about when referring to nanoparticles and nanomaterials. Over the past decade there has been a considerable global effort to develop a suitable robust and comprehensive definition that allows the characterization of nanomaterials so as to facilitate scientific and, more particularly, regulatory and legislative discussions and agreement. For registration of substances under the REACH legislation a univocal definition for nanomaterials is needed, especially to distinguish whether new materials that are
markedly marketed should be considered as nanomaterials or should be considered to fall under the definition of existing substances. Arguments were brought forward concerning size- and surface- oriented definitions regarding statistical limitations of particle number size distributions (Lidèn 2011) and regarding the hazards of nanomaterials being not limited to number and size only, but being affected as well by different other factors like porosity and chemistry (Maynard 2011). Maynard states that a ‘one size fits all’ definition of nanomaterials will fail to capture what is important for addressing risk. He warns for science to be pushed aside when policy-makers would restrict health policy to limited, but clear nano-regulations. Scenihr (2010) stressed that “nanomaterial” is a categorization of a material by the size of its constituent parts and does not imply a specific risk, nor does it necessarily mean that this material actually has new hazard properties compared to its constituents. However, size will influence biodistribution (and distribution kinetics) in an organism or in an ecosystem.

The Joint Research Centre of the European Union gave an overview of current definitions and approaches (Lövestam et al 2010) and concluded that for pragmatic reasons and for the sake of uniqueness, broadness, clarity and enforceability, it was justified not to include properties other than size in a basic definition. For specific purposes it might however be relevant to adapt the general definition by including other properties as well.

The European Commission (EC) published its recommendation for a definition of nanomaterials in October 2011 (EC 2011) (box1). Its considerations are clarified in an accompanying Question and Answers document (EC 2012). A review is foreseen by 2014 in the light of experience and of scientific and technological developments with a particular focus on whether the number size distribution threshold of 50 % should be increased or decreased.

Box 1 The European Commission’s definition of nanomaterials

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

In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %.

In the absence of better arguments for other thresholds, the Commission decided to follow the most commonly applied approach, i.e. a size range between 1 and 100 nm.

The definition of the European Commission is intended for use as reference for legislative and policy purposes in the EU and does not define boundaries for occupational or environmental risks. The EC argues that a specific hazards or risks of the nanomaterial will only become clear as a result of a risk assessment. Another reason for not referring to properties specific to nanomaterials is legal clarity. The specific properties of (different) nanomaterials vary and it is often unclear whether such properties relate to the nano-size, to the chemical nature of the material or a combination of both. Nevertheless the Commission makes an implicit reference to potential risks by stating that it may in some
cases be necessary to include additional materials, such as some materials with a size smaller than 1 nm or greater than 100 nm in the scope of application of specific legislation or legislative provisions suited for a nanomaterial. Proposals for a higher upper-limit in the definition of nanomaterials >100nm were made by environmental NGOs (EEB nd-a). The EEB proposes a range of 0.3-300 nm to allow the definition to capture as much material as possible about which there is already concern. An upper-limit of 300nm was also suggested by the German Advisory Council on the Environment for precautionary reasons (SRU 2011) and earlier by Scenhir (2009).

Some scientists suggest an upper-limit lower than 100nm when the focus would be solely to identify nano-effects. Auffan et al (2009) suggested that nanoparticles larger than about 30 nm do not in general show properties that would require regulatory scrutiny beyond that required for their bulk counterparts. Auffan et al. (2009) also suggested that there is a critical size, which is strongly related to the exponential increase in the number of atoms localized at the surface as the size decreases and delineates a smaller set of nanoparticles, typically with diameters less than 20–30 nm and showing a size-dependent crystallinity. Choi et al (2011) have shown that there are major differences in translocation of nanoparticles from the lungs into the body at nanoparticle sizes well below 100 nm. Pan et al (2007) showed gold nanoclusters (1.4 nm) to be toxic to cells owing to their specific interaction with major grooves of DNA, whereas smaller or larger gold particles did not behave in this way.

The EC definition regards ‘natural’, ‘incidental’ and ‘manufactured’ nanomaterials. The starting point is to consider primary particles including particles in agglomerates or aggregates whenever the constituent particles are in the size range 1 nm - 100 nm. As defined by the EC, nanomaterials are not exclusively synthesized (manufactured or engineered) nanomaterials. The term nanomaterials also covers particles originating from natural processes and originating from heating and combustion processes (incidental nanoparticles), and assemblies of these with manufactured nanomaterials and non-nanoparticulate pollutants. In the part of this thesis, which focuses on workplace exposure the incidental nanoparticles are called process-generated nanoparticles (PGNP). The EC notes that nanoparticles are present in low quantities in most solid materials and that the percentage may be significant in certain powders. Their choice for the 50% number size distribution may refer to this phenomenon, and it will be subject to further review. Regarding potential risks it must be noted that a threshold for the number size distribution of 50% in nanomaterials does not guarantee the generated airborne nanoparticles’ concentration to remain within safe limits when using products that contain nanomaterials (Weir et al 2012). Nanoparticles have a high potency to become airborne, which is mainly determined by the handling procedures, also in batches with a concentration of <50% (p/p) (van Broekhuizen et al 2012). Additionally, the RIVM (Bleeker 2012) noted that it agrees with the Commission’s principle that a nanomaterial should not automatically be considered as hazardous, but conversely, materials not covered by the definition should not automatically be considered as safe. Such materials may pose a nano-size related risk, if a substantial number of the particles is in the nano-size range, depending on the degree of human and environmental exposure.

Regarding the use of nanomaterials in products the EC notes that if a nanomaterial is used
amongst other ingredients in a formulation the entire product will not become a nanomaterial. With this explanation the EC proposes to strongly limit the use of the wording “nanoproduct”.

In sum the recommendation of the European Commission for a definition of nanomaterials has an explicit legislative and policy orientation, and contains some elements regarding risks of nanomaterials. Under the definition the background and ‘incidental’ nanomaterials have to be taken into account. Risks in the practice of the downstream user using nanomaterial-enabled products have to be considered by specific risk assessments that take into account the release of MNMs during the handling of the products and the NMs that are generated at the workplace by the equipment and the use of conventional bulk materials.

Given the EC definition and existing legislation such as the Chemical Agents Directive (CAD 1998) and in REACH (EC 2006) the manufacturer and supplier have to provide information about the potential release of MNMs and the associated risks during intended use. It remains questionable whether the manufacturer or the OEM (original equipment manufacturer) has a responsibility as well to inform the downstream and end user about the possible release of PGNPs during the intended use of his equipment.

This thesis considers nanomaterials in accordance with the EC-definition within the size-range of 1-100nm. However, when measurements are carried out, the detection limits of the measuring equipment of 10-300nm are used, taking into account the likeliness that assemblies are formed at the workplace that may have a larger diameter that 100nm.

1.3 Adverse effects of Nanomaterials

When released in the workplace or in the environment nanoparticles may be potentially dangerous. The lung, skin, gastrointestinal tract, nasal olfactory structures, and eyes are the major portals through which nanoparticles can enter the body as a result of occupational or environmental exposures (Borm et al 2006). After exposure the nanoparticles could translocate into the blood and lymph circulating system and travel to distant organs including the cardiovascular system and brain (Nel et al 2006, Choi et al 2010). Of primary concern in occupational settings are inhalation and skin exposure. So far the healthy skin has shown little penetration, yet there are several studies that point at the condition of the skin (barrier integrity, anatomic structure, skin diseases such as allergic and irritant contact dermatitis, atopic eczema, psoriasis) that may influence uptake (Monteiro-Riviere et al 2012). On the other hand, calcium carbonate and calcium phosphate NPs were shown to be able to inhibit skin penetration of nickel ions (Vermula et al 2011). Inhalation is the most relevant exposure route of MNMs and the lungs and pleura the major primary targets for adverse effects (Donaldson et al 2012). Larger particles deposit higher up in the nose and upper respiratory tract, while only the smaller size particles deposit in the more peripheral bronchioles and proximal alveolar region (Donaldson et al 2012). The inhalation deposition probability, as a function of the particles’ diameter is represented in figure 1, showing that the particles at the nanosize (between 1
– 100nm) have the highest probability to deposit in the alveolar region. Deposition may increase further with exercise, to a degree greater than that predicted by modeling (Daigle et al 2003).

In the lungs several clearing mechanisms are active. In the upper-airways particles are trapped in the mucus and removed upwards by the mucociliary escalator to the throat and swallowed. In the terminal bronchioles and alveolar region the clearing mechanism is predominantly by macrophage action (Donaldson 2012).

When nanomaterials are deposited in the lungs other organs may also be affected. One possibility is that nanomaterials translocate from the lungs into the lymphatic and circulatory systems. Choi et al (2011) demonstrated in rat models that nanoparticles with a hydrodynamic diameter (HD) less than ~34 nm translocate rapidly from the lung to lymph nodes, while below this size the surface charge is a major factor determining the translocation with dipolar, anionic or nonionic surfaces being permissive and cationic surfaces being restrictive. They demonstrate as well that nanoparticles with a HD < 6 nm and a dipolar surface charge can translocate rapidly from the lungs to lymph nodes and the bloodstream, and can be subsequently cleared by the kidneys. Choi et al. (2011) suggest that the smaller nanoparticles, with a HD ~5 nm are of concern for carcinogenesis and distal inflammation because they are capable of traveling from the lung to the bloodstream, and once in the bloodstream, they can potentially reach every tissue and organ in the body. Kreyling et al (2009) show that iridium and carbon primary particles, their agglomerates and aggregates with a size between 20 and 80nm (and a primary size of <10nm) are found 24h after translocation from the lung to the blood circulation in the liver, spleen, kidneys, heart, and brain, and in the soft tissue and bone.
Other possibilities are that inflammation of the lungs triggers the release of metabolic stressors and platelet-leukocyte aggregates which might affect other organs and that there is an impact on activity of the autonomous nervous system (Reijnders 2012). Epidemiological studies have associated exposure to ambient nanoparticles with systemic effects, such as cardio-vascular diseases (Simko et al. 2010, Brook et al 2010), which is a reason to investigate this issue for MNMs as well (Colognato et al 2012).

Of interest is also the exposure route via the nose and the olfactory nerve that may give direct access to the brain. Elder et al (2006) found in inhalation experiments with nano-MnO in rats a higher accumulation of these particles in the olfactory bulb than in the lungs, and found increased levels of Mn in the brain tissue. The authors concluded that the olfactory neuronal pathway might be a relevant exposure route subsequent to inhalation for Mn oxide nanoparticles also in humans. Savolainen (2010) suggests that these observations are of special importance because the doses were low to moderate, and because the translocation pathway was intraneuronal.

An overview of possible mechanisms by which nanomaterials might react with biological tissue was graphically represented by Nel et al (2006) see figure 2.

**Figure 2** Possible mechanisms by which nanomaterials interact with biological tissue (from Nel et al 2006).
nanoparticles’ surface properties are the material’s chemical composition, surface functionalization, surface charge, shape and angle of curvature, porosity and surface crystallinity, heterogeneity, roughness, and hydrophobicity or hydrophilicity (Nel et al 2009). When nanoparticles enter the blood, plasma or interstitial fluid they are coated with proteins, the nanoparticle–protein corona. The corona is of further significance because it influences the surface properties of the particle and the hydrodynamic size and is subject to continuous dynamic changes in reaction with proteins in the surrounding medium. It influences association, dissociation and exchange of elements (Savolainen 2010).

The high reactivity of, and high adsorption by the smaller nanoparticles is explained by the number of atoms residing at the surface of the particle. A nanoparticle with a diameter of 300nm has 5% of its atoms at the surface of the particle and 50% when the diameter is 30nm (Colognato et al 2012). Thermodynamic analysis reveals that the surface tension decreases with decreasing particle size as a result of the increase in the potential energy of the bulk atoms of the particles. Smaller particles with increased molar free energy are more prone to absorb molecules or ions per unit area onto their surfaces in order to decrease the total free energy and to become more stable. Hence adsorption onto smaller particles has a higher adsorption coefficient (Zhang et al 1999).

Figure 3 indicates potential interactions of MNM with cells and subcellular structures.

**Figure 3. Possible interactions of MNMs with the cell and subcellular structures.**

Suggested mechanisms underlying nanoparticle-induced responses at the cellular level, which, in sufficiently high or persistent levels, potentially can lead to, altered tissue function. (Figure from Colognato et al 2012)

Much is still unknown, but it is clear that nanomaterials are likely to interfere with cellular organization and affect biological functions in ways that cannot be deduced from previous experience with macro- or microsized particles (Kagan et al 2010). Many nanomaterials
show a high activity in the formation of reactive oxygen species (ROS) leading to oxidative stress. Oxidative stress, which is effected by the initiation and propagation of free radical oxidation reactions and excessive accumulation of their products, is one of the most prominent effects associated with the adverse effects of nanomaterials (Shvedova et al 2010). Oxidative stress is defined as an imbalance between oxidants and antioxidants inside cells, in lung lining fluid or tissue fluid, such that there is more oxidation. ROS are produced by particles themselves by chemical reactions and by cells as part of normal respiration. Excessive oxidative stress has been proposed as a common paradigm for the toxicities of engineered nanoparticles (Shvedova et al 2010). Many studies support this hypothesis (see for example Fadeel et al 2012, Reijnders 2012). For example for the low-toxic, fine- and nano-TiO$_2$ it was shown that local persistence in the lung may lead to chronic inflammation and may cause non-genotoxic induction of lung tumors in rats (NIOSH 2011). There are however also contradicting studies that find no direct correlation between ROS production and cell toxicity (Diaz 2008).

The form of nanomaterials is an important issue in hazard and risk assessment. Carbon nanotubes (CNT) were shown to be able to induce asbestos-like alterations in the mesothelium of the mouse peritoneal cavity (Poland et al., 2008) and increase the likelihood of mesotheliomas in sensitive mouse strains (Takagi et al., 2008). Long CNTs may give an acute inflammation leading to progressive fibrosis of the pleura, while this is not the case for short CNTs (Murphy et al. 2011). Based on this type of findings SCENIHR (2009) advises to consider the possibility that free fibers, rods and tubes that are chemically/biologically persistent, are rigid and have a high aspect ratio (i.e. µm in length and nm in diameter) may have similar properties to asbestos.

Nel et al (2009) summarized the mechanisms of nanomaterial cytotoxicity of different nanomaterials (see table 1). A general overview of effects as the basis for pathophysiology and toxicity is given in table 2.

Table 1 Summary nanomaterial cytotoxicity (from NEL et al 2009)

<table>
<thead>
<tr>
<th>Nanomaterial</th>
<th>Cytotoxicity mechanism</th>
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| TiO$_2$      | ROS production mediated by electron–hole-pairs  
Glutathione depletion and toxic oxidative stress as a result of photoactivity and redox properties  
Nanoparticle-mediated cell membrane disruption lead to cell death; protein fibrillation |
| ZnO          | ROS production  
Dissolution and release of toxic cations  
Lyposomal damage inflammation |
| Ag           | Dissolution and Ag$^+$ release inhibits respiratory enzymes and ATP production  
ROS production  
Disruption of membrane integrity and transport processes |
| Au NPs and nanorods | Disruption of protein conformation |
| CdSe        | Dissolution and release of toxic Cd and Se ions |
| SiO$_2$      | ROS production by surface defects and impurities  
Protein unfolding  
Membrane disruption |
| Fe$_3$O$_4$  | ROS production and oxidative stress  
Liberation of toxic Fe$^{2+}$  
Disturbance of the electronic and/or ion transport activity in the cell membrane |
<table>
<thead>
<tr>
<th>Nanomaterial</th>
<th>Cytotoxicity mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>CeO2</td>
<td>Protein aggregation and fibrillation</td>
</tr>
<tr>
<td>MWCNT</td>
<td>Frustrated phagocytosis causes chronic tissue inflammation and DNA oxidative injury</td>
</tr>
<tr>
<td>SWCNT and MWCNT</td>
<td>Generation of ROS due to the metal impurities trapped inside CNTs</td>
</tr>
<tr>
<td></td>
<td>Pro-inflammatory effects due to oxidant injury</td>
</tr>
<tr>
<td></td>
<td>Granulomatous inflammation due to hydrophobic CNT aggregation Interstitial pulmonary</td>
</tr>
<tr>
<td></td>
<td>fibrosis due to fibroblast-mediated collagen production</td>
</tr>
<tr>
<td>Fullerenes</td>
<td>ROS production (spontaneous or photoactivated) Hydrophobic surface increases aggregation</td>
</tr>
<tr>
<td></td>
<td>but promotes intramembranous localization</td>
</tr>
<tr>
<td>Cationic nanospheres and dendrimers</td>
<td>Membrane damage, thinning and leakage</td>
</tr>
<tr>
<td></td>
<td>Damage to the acidifying endosomal compartment by the proton sponge effect that allows</td>
</tr>
<tr>
<td></td>
<td>entry into the cytosol</td>
</tr>
<tr>
<td>Co/Ni ferrite NPs, magnetic metallic NP</td>
<td>Liberation of toxic cations</td>
</tr>
<tr>
<td>AI2O3</td>
<td>ROS production Pro-inflammatory response</td>
</tr>
<tr>
<td>Cu/CuO</td>
<td>DNA damage and oxidative stress</td>
</tr>
<tr>
<td>MoO3</td>
<td>Membrane disruption</td>
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<table>
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<tr>
<th>Experimental NM effects</th>
<th>Possible pathophysiological outcomes</th>
</tr>
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<tbody>
<tr>
<td>ROS generation*</td>
<td>Protein, DNA and membrane injury *, oxidative stress†</td>
</tr>
<tr>
<td>Oxidative stress*</td>
<td>Phase II enzyme induction, inflammation†, mitochondrial perturbation*</td>
</tr>
<tr>
<td>Mitochondrial perturbation*</td>
<td>Inner membrane damage*, permeability transition (PT) pore opening*, energy failure*,</td>
</tr>
<tr>
<td></td>
<td>apoptosis*, apo-necrosis, cytotoxicity</td>
</tr>
<tr>
<td>Inflammation*</td>
<td>Tissue infiltration with inflammatory cells†, fibrosis†, granulomas†, atherosclerosis†,</td>
</tr>
<tr>
<td></td>
<td>acute phase protein expression (e.g., C-reactive protein)</td>
</tr>
<tr>
<td>Uptake by reticulo-endothelial system*</td>
<td>Asymptomatic sequestration and storage in liver*, spleen, lymph nodes*, possible organ</td>
</tr>
<tr>
<td></td>
<td>enlargement and dysfunction</td>
</tr>
<tr>
<td>Protein denaturation, degradation*</td>
<td>Loss of enzyme activity*, auto-antigenicity</td>
</tr>
<tr>
<td>Nuclear uptake*</td>
<td>DNA damage, nucleoprotein clumping*, autoantigens</td>
</tr>
<tr>
<td>Uptake in neuronal tissue*</td>
<td>Brain and peripheral nervous system injury</td>
</tr>
<tr>
<td>Perturbation of phagocytic function*; “particle overload,” mediator release*</td>
<td>Chronic inflammation†, fibrosis†, granulomas†, interference in clearance of infectious agents†</td>
</tr>
<tr>
<td>Endothelial dysfunction, effects on</td>
<td>Atherogenesis*, thrombosis*, stroke, myocardial infarction</td>
</tr>
<tr>
<td>blood clotting*</td>
<td></td>
</tr>
<tr>
<td>Generation of neoantigens, breakdown in</td>
<td>Autoimmunity, adjuvant effects</td>
</tr>
<tr>
<td>immune tolerance</td>
<td></td>
</tr>
<tr>
<td>Altered cell cycle regulation</td>
<td>Proliferation, cell cycle arrest, senescence</td>
</tr>
<tr>
<td>DNA damage</td>
<td>Mutagenesis, metaplasia, carcinogenesis</td>
</tr>
</tbody>
</table>

In sum: based on (still limited) experimental animal and cell tissue studies with MNMs and epidemiological studies on the effects of airborne particulate pollutants it is likely that exposure to MNMs may lead to adverse health effects. Oxidative stress leading to inflammation is likely one of the key mechanisms exhibited by many nanoparticles of
different size, chemical composition and form. As a result of prolonged high exposure to more reactive NPs oxidative stress may give rise to an ongoing inflammation, which is likely to worsen bronchitis or asthma in those who already have a lung disease and even may cause lung fibrosis. Ongoing inflammation or genotoxic effects of reactive NP could lead to lung cancer if exposures are high enough and for a prolonged period. Asbestos-like effects, including mesothelioma might be expected from exposure to rigid, chemically/biologically persistent free nanofibers with a high aspect ratio (length >20 μm). Also there might be effects of nanoparticles on other organs. Savolainen et al (2010) emphasize that available observations on the toxicity of manufactured nanoparticles and the early stage of risk assessment with a lack of data justifies applying a precautionary approach in assessing the risks of manufactured nanomaterials.

1.4 Precautionary Principle

The Precautionary Principle emerged at a worldwide policy forum in 1992 at the UN Conference on Environment and Development in the Rio Declaration on Environment and Development included in principle 15 among principles of general rights and obligations of national authorities (UNEP 1992) (see box 2). It was launched as a principle to protect against adverse effects to the environment, but it should not be seen as restricted to the environment. The scope of its applicability is much broader and includes occupational health and consumer safety.

Box 2 Rio Declaration, principle 15: Precautionary Principle

Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.

The PP is a deliberative principle and, as von Schomberg (2006) notes, its application involves deliberation on a range of normative dimensions, which need to be taken into account while making the principle operational in the public policy context. These regard issues such as when to invoke the precautionary principle (act rather than not to act), the level of protection aimed at, a cost-benefit analysis balanced with health considerations, the burden of proof of adverse effects and the timing, the proportionality of precautionary actions, deliberation about uncertainties and lack of knowledge, the seriousness of possible adverse effects, and what level to use as provisional standard. The precautionary principle is subject to extensive debates and is frequently reformulated as to make it better comprehensible. It is used as basis in many European Directives and International treaties and is subject of rulings of the European Court of Justice (Von Schomberg 2006).

A significant policy document relating to the precautionary principle is the 2000 Commission Communication on the Precautionary Principle (EC 2000). While this document does not have a legally binding status, it provides a comprehensive EU level policy guidance on the application of the principle and provides insights into issues relating to both the scope of the principle’s applicability in EU law, as well as into conditions for its invocation. The European Commission does not provide a definition for the precautionary principle. Nevertheless they note in their communication that the precautionary principle
applies under defined conditions (box 3), but in view of ongoing discussions on the philosophy behind the principle, its interpretations and its non-strictly binding character there is room to make the principle operational into a precautionary approach for industrial practice:

Box 3  Application of the precautionary principle according to the European Commission

The precautionary principle applies where scientific evidence is insufficient, inconclusive or uncertain and preliminary scientific evaluation indicates that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level of protection chosen by the EU.

In the Code of Conduct for Responsible Nanosciences and Nanotechnologies Research the European Commission emphasizes the importance of conducting research activities in accordance with the precautionary principle, anticipating potential environmental, health and safety impacts of nanosciences and nanotechnologies and taking due precautions, proportional to the level of protection, while encouraging progress for the benefit of society and the environment (EC CoC 2008). Invoking the precautionary principle in matters regarding the development of nanotechnologies and use of materials manufactured with these technologies is accepted by many of participants in discussions explicitly addressing the matters of hazard and risk (Swiss Re 2004; GR 2006; WWR 2008, SER 2009, EC 2010). Governments advocate applying the precautionary principle whenever uncertainties and ambiguities are at stake when using nanomaterials (EC CoC 2008, SRU 2011, Gans et al 2012). Several industrial participants have publicly given notice of their intentions to contribute to a responsible development of nanotechnologies but do not refer to the precautionary principle. They include the control of risks in Codes of Conduct (Dupont 2007, Bayer 2007, BASF 2008, PACTE 2008, Evonik nd) or refer to their commitment to the Responsible Care Initiative (CEFIC 2011). Industrial stakeholders acknowledge the large uncertainties and ambiguities regarding the risks of manufactured nanomaterials and show awareness that the collection of hazard and exposure data of the nanomaterials used does not keep pace with the rapid developing technologies and the marketing of nanoproducts (NanoCap 2009, this thesis chapter 5). However the meaning of the precautionary principle as perceived by those in industry may be variable. Helland et al (2008) conclude from their study in the Swiss industry using MNMs that that industry did not convey a clear opinion as to who should be responsible for managing the potential environmental health impacts or how to regulate NPMs throughout their life cycle. They note that industry does not necessarily see monitoring and demonstrating specific characteristics of irreversibility as its responsibility. Engeman et al (2012) demonstrated that despite the reported uncertainty and perceived risk regarding MNMs (which should motivate to apply a precautionary approach), companies reported preference for autonomy from government regulation, and a majority of 58% agreed that workers are ultimately responsible for their own safety at work. Jostman (2007), Executive Director of the Programme Product Stewardship of CEFIC (European Chemical Industry Council) has invoked scientific uncertainty as reason not to apply the precautionary principle. Such responses suggest ambiguous views on responsibility and demonstrate tensions between the roles and the values of regulators, industry leaders, industrial hygienists, and workers in creating a safe workplace.
In order to apply the precautionary principle properly, it must be clear what is precisely understood by ‘scientific uncertainty’ and what types of uncertainties are relevant for the invocation of the precautionary principle. Von Schomberg (2006) categorizes four types of uncertainties related to the state of affairs in science and the possible corresponding responses by risk management.

**Table 3** Overview of State of Affairs in Science and the possible corresponding responses by Risk Management *(source von Schomberg 2006)*

<table>
<thead>
<tr>
<th>Circumstances</th>
<th>State of Affairs in Science</th>
<th>Policy Framework/ Regulatory action/ Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Known effects, quantifiable probabilities, uncertainties may have statistical (e.g. stochastically) nature</td>
<td>Risk Management by defining thresholds on the basis of chosen level of protection, exercising prevention, minimization of risk and or precautionary minimization of risks by feasible management measures: applying the ALARA principle etc.</td>
</tr>
<tr>
<td>Unquantifiable Risk, lack of knowledge</td>
<td>Known effects/unknown or uncertain cause-effect relations, therefore unknown probabilities</td>
<td>Antibiotics in feeding stuff/Protection of the North Sea. Invocation of precautionary principle is justified; preventive measures to take away the possible causes can be justified.</td>
</tr>
<tr>
<td>Epistemic uncertainty: scientific controversies, lack of knowledge</td>
<td>Unknown scope of effects, however, degree and or nature of their ‘seriousness’ (in relation to the chosen level of protection) can only be estimated in qualitative terms.</td>
<td>Invocation of the precautionary principle is justified: example: GMOs, Climate Change, Ozone depletion</td>
</tr>
<tr>
<td>Hypothetical effect/ imaginary risk</td>
<td>Arguments on the basis of a fully conjectural knowledge base, no scientific indication for their possible occurrence</td>
<td>Invocation of precautionary principle is not justified.</td>
</tr>
</tbody>
</table>

**Remark PvB:** It would be better to use the wording “preventive minimization” instead of “precautionary minimization”

Based on his elaborations of the precautionary principle, its use by the European Court of Justice, the broad EU endorsement of European Guidelines on the precautionary principle and on International Treaties such as of the WTO and the UN, von Schomberg (2006) proposes a definition to bring the precautionary principle in line with the growing recognition of the normative challenges involved while invoking the precautionary principle (see box 4).
Box 4. Policy definition of the precautionary principle (von Schomberg (2006))

Where, following an assessment of available scientific information, there are reasonable grounds for concern for the possibility of adverse effects but scientific uncertainty persists, provisional risk management measures based on a broad cost/benefit analysis whereby priority will be given to human health and the environment, necessary to ensure the chosen high level of protection in the Community and proportionate to this level of protection, may be adopted, pending further scientific information for a more comprehensive risk assessment, without having to wait until the reality and seriousness of those adverse effects become fully apparent.

Von Schomberg (2012) further elaborates on how the normative qualifier “reasonable grounds” is relevant for invocation of the precautionary principle and refers to the type of circumstances as listed in table 3. It is the second and especially the third type of circumstances in table 3 that give rise to the use of precautionary principle. The ‘quality of the information’ relevant to the precautionary principle relates especially to what type of information is known or should be known and of which information one is ignorant. Still, as Rip (2006) remarks, this formulation of the precautionary principle is not immediately applicable to nanotechnologies as broad umbrella term of enabling technologies. What should be considered as ‘reasonable grounds’ remains unclear especially in case of promises and concerns about nanotechnologies. Rip (2006) shows that there are possibilities for precautionary approaches even when the precautionary principle (as defined by von Schomberg) cannot handle speculative technologies (where there is ignorance, not just uncertainty). The PP can handle manufactured nanomaterials, in R&D, intended or already applied in concrete products, which are on the market.

Against this background in discussions a distinction should be made between the broad umbrella term “nanotechnologies”, for which no general adverse effects can be assessed, and terms such as “nanoparticles”. Regarding the positive stance of the involved actors towards invocation of the precautionary principle in discussions between industry, governments and CSOs, it seems that industry actors refer to the nanomaterials as they are currently under development or on the market.

In sum, the precautionary principle has a deliberative nature and it is based on normative qualifiers. The precautionary principle is also a fundamental principle in the EU legislative framework and as such it may stimulate industrial users of nanotechnologies to formulate a way in which they intend to apply the novel nanomaterials in their products and processes; the novel nanomaterials that lack the essential hazard data needed for a reliable risk assessment. As a complement to existing legislation industry may also develop codes of conduct to frame their responsible and sustainable approach towards nanotechnologies and operationalize how they intend to deal with uncertain, ambivalent human and environmental risks. The precautionary principle allows CSOs to give an interpretation of normative qualifiers used for defining safe and sustainable nanomaterials and nanoproducts and to contribute to the formulation of a socially acceptable precautionary approach. Transparency and openness, especially by the industry about known, and uncertain risks are key elements in this, including information on where in the production chain and by what use of nanoproducts release of nanomaterials might occur.

This thesis applies the definition for the precautionary principle as given in box 4.
1.5 Background concentrations and Process-Generated Nanoparticles

Ambient “background” nanoparticles

Nanoparticles (in many environmental studies denominated as ultrafine particles (FP)) are around us in our daily life as particles originating from natural processes like volcanic activities, fires, and erosion processes and from anthropogenic sources as traffic, smoking, heating and cooking. Dynamic processes in the atmosphere play a role of which agglomeration and aggregation (the formation of assemblies) are important processes. In natural environments the formation of new particles is of importance, of which the main mechanism is nucleation of low-volatile gas-phase compounds, followed by their growth into small particles (Morawska et al 2008). The background of nanoparticles in ambient air consists of a mixture of inorganic and organic particles that varies in (chemical) composition. Particles composed of substances such as metal oxides, polycyclic aromatic hydrocarbons, oxidized organic structures, soot in many different forms and sizes may be present. Sources of ultrafine particles are abundant, but in urban environments traffic, (especially emissions from diesel engines) may be dominating (Matti Maricq 2007, Morawska et al 2008). In urban centers in Finland concentrations up to 140,000 particles/cm\(^3\) were measured, while along highways number concentrations of >60,000/cm\(^3\) were measured (Hussein et al 2005). Nanoparticle or ultrafine particle (UFP) exposure for pedestrians in Leicester, UK was suggested to be up to 50% higher than in cars (Gulliver et al 2007); at car parkings in Leeds mean UFP exposure levels of attendants were reported up to 40,000 particles/cm\(^3\), while peak levels may be as high as 400,000 particles/cm\(^3\) (Tiwary et al 2012). Dahl et al (2006) identified that due to wear the rubber car tires emit significant amount of UFPs originating from the carbon reinforcing filler material (soot agglomerates) and the plasticizers (mineral oils). Emissions from aircraft engines were measured under varying conditions at concentrations from 700,000 nanoparticles/cm\(^3\) up to > 5,000,000 nanoparticles/cm\(^3\) with a particles’ diameter varying from \(\approx 10\)nm - \(\approx 30\)nm (EPA 2009).

The ambient nanoparticles may influence the indoor nanoparticles’ concentrations. Van Broekhuizen et al (2012) (see chapter 4) measured mean indoor background concentrations in Dutch industrial plants varying between 6,000 and 21,000 nanoparticles/cm\(^3\), with an occasional high mean concentration of 28,000 nanoparticles/cm\(^3\).

Particle number concentrations in clean air in the high mountains were measured in the Himalaya’s at a height of 4520m (above sea level) varying from 80 – 8,000 particles/cm\(^3\) with a mean at 1150 particles/cm\(^3\) (Moorthy et al 2011).

Cigarette smoking is another not process-related anthropogenic source of workplace airborne nanoparticles. Van Broekhuizen (2011b) found in a smokers’ room of a company nanoparticles’ number concentration up to >500,000particles/cm\(^3\).

Some background concentrations are summarized in figure 4.
Figure 4  
**Indication of some “environmental” background concentrations**

<table>
<thead>
<tr>
<th>Source</th>
<th>Concentration (particles/cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airport</td>
<td>&gt;700.000</td>
</tr>
<tr>
<td>Seriously polluted environment</td>
<td>&gt;100.000</td>
</tr>
<tr>
<td>Highways</td>
<td>&gt;60.000</td>
</tr>
<tr>
<td>Clean air in town</td>
<td>&lt;10.000</td>
</tr>
<tr>
<td>Clean air mountains</td>
<td>=1.000</td>
</tr>
</tbody>
</table>

Sources: see previous text

**Process-generated nanoparticles**

Exposure assessment to MNMs in industrial workplaces shows that the handling of nanomaterials and nano-enabled products may give rise to exposure to primary MNMs and agglomerates (Brouwer 2010), and simultaneously to nanoparticles formed by work-related processes. This thesis will show that nanoparticles generated at the workplace by processes and equipment used may even dominate the airborne nanoparticles’ number concentration. Industrial processes (also conventional processes, without any relation to nanotechnology and manufacturing or processing of nanomaterials) may generate airborne nanoparticles, sometimes up to levels of several millions of particles/cm³. Characterization of these nanoparticles is generally highly complex and may complicate risk assessment. The potential hazard of the PGNPs, similar to MNMs, depends on factors like size, surface, form, composition etc. and may be comparable to the anticipated and proved hazards for MNMs (SCENIHR 2009). Therefore, when carrying out a workplace risk assessment identification and characterization of PGNPs cannot be ignored (SER 2012, EU/US 2012). An example is diesel exhaust particulates (DEP), as a listed carcinogen (SDU 2011). DEP is a highly complex mixture containing nano-, fine- and coarse-mode particles as well as a variety of gaseous components of toxicological relevance (e.g. nitrogen oxides, carbon monoxide, aldehydes). The dominant carbon-based chemical composition of diesel soot NPs bears similarities to that of several commercially important classes of MNMs (e.g., carbon-based fullerenes, nanotubes), whereas their physical structure (i.e., agglomerates of spherical primary particles) bears similarities to others that also have a strong tendency to agglomerate (e.g., titanium dioxides and other metal oxides) (Hesterberg et al 2010).

The type of the airborne process-generated nanoparticles (PGNPs) is highly specific for the materials processed, the way of processing, machinery used, temperature etc. Typical sources for the formation of nanoparticles at workplaces are combustion processes (Donaldson et al 2005), soldering, welding, use of electrical equipment and fracturing and abrasion activities like sanding, milling and drilling. Scymczak et al (2007) demonstrated that universal electrical motors emit nanoparticles with a high content of copper. During the operation of a universal motor, brushes made of graphite slide over commutator contact bars made of copper. This movement causes the formation of particles not only by mechanical abrasion, but also by brush sparks. Scymczak suggests that domestic appliances and electric power tools using power control by phase angle modulation can be a strong source of nanoparticles with a high content of copper. Plasma cutting, metal inert gas and tungsten inert gas welding, metal grinding, aircraft maintenance, brazing, food
preservation (smoking), smelting and laser ablation were shown to emit nanoparticles’ number concentrations ranging from $2 \times 10^4$ to $4 \times 10^7$ particles/cm$^3$ near various processes (Riediger et al. 2007; Pfefferkorn et al. 2010). Evans et al (2007) reported spatially and temporally varying nanoparticle number concentration within an automotive grey iron foundry from process emissions in incoming make-up air and the heating with direct fire natural gas burners, melting and pouring operations ranging from $1.9 \times 10^4$ to $3.5 \times 10^6$ particles/cm$^3$. Evans et al (2010) reported elevated nanoparticles concentrations up to $1.15 \times 10^6$ in a carbon nanofibers (CNFs) production plant, but noted that the concentrations were not due to CNF, but released during thermal treatment of CNFs. Peters et al (2006) reported a large variation in airborne NPs concentrations in a machining and assembly facility in the winter and spring, probably generated through evaporation and subsequent condensation of metalworking fluid components and demonstrated that these ultrafine particles persist in workplace air over long time periods. Peters et al (2009) demonstrated that airborne nanoparticles in a production facility producing nano-lithium titanate are dominated by “incidental” sources (welding or grinding), and that the airborne “engineered” product is predominately composed of particles larger than several hundred nanometers.

Also laser applications may generate NPs. Barcikowski et al (2007) showed that during short-pulse and ultrashort-pulse laser ablation released NPs from the material (laser ablation is an application of a laser for the cleaning and conservation of artworks of different materials like paper, stone, metals, leather). Barcikowski et al (2007) noted that femtosecond laser ablation causes the release of finer particles than nanosecond laser ablation, which may be due to higher energy density. In their study on laser cleaning of paper, they show a dependence on the fibre-size of the paper as cleaning of short-fibre paper generates a higher amount of nanoparticles than cleaning long-fibre paper. Modern laser printers were shown to emit peak NP emission rates of the printers exceeding $7.0 \times 10^8$ s$^{-3}$ (size between 11 and 79 nm) and reaching concentrations to maximum $2.6 \times 10^5$ particles/cm$^3$ (Koivisto et al 2010).

Abrasion of surfaces coated with nano-enabled coatings may generate nanoparticles as well, but it seems to be the use of electrical equipment that dominates the generation of nanoparticles (Kopponen et al 2009; Göhler et al 2010; Wohlleben et al 2011). The studies show the generation of nanoparticles during the sanding process of conventional and nano-enabled coatings. However, no significant difference could be observed between coatings containing and not containing nanoparticle additives. Kopponen et al (2009) note that the hand-held sander was the main source particles with a diameter <50nm. The fraction with larger particles is rather made up from matrix material, which contains the nanoadditives embedded in the coating (Göhler et al 2010). Figure 5 summarizes some of these findings.
Additionally to the PGNPs generated in processes, there are also conventional compounds that contain a fraction of particles at the nano-size that may give rise to emissions of nanoparticles at the workplace. This thesis shows that during paint manufacturing the emission of nanomaterials from conventional components might be significant (chapter 4).

In sum, the background concentration of natural and anthropogenic nanoparticles is variable and in urban environments strongly impacted by traffic exhaust (and exhaust gasses from industrial processes when not properly filtered). It may locally reach high levels. In urban areas with relatively low pollution levels an average background of 10,000 to 20,000 particles/cm³ is common. The concentration of nanoparticles at industrial workplaces generated by heating and combustion processes, by electrical and high-energy (laser) equipment, as well as due to the use of conventional powders with a fraction of nano-sized particulates, may be considerable. It is likely that in many cases, when nanomaterials or nano-enabled products are used, process-generated nanoparticles will dominate the airborne nanoparticles’ number concentration. It is also likely that airborne PGNPs may pollute ‘conventional’ workplaces where no nanomaterials are handled. This indicates the importance of taking nanoparticles into account when carrying out a risk assessment in a conventional workplace where heating or combustion is at stake or where electrical equipment is used. This holds as well for the use of conventional powders. It is advisable for these sources in case of insufficient knowledge or uncertainties to apply a precautionary approach as well, similar to the risk management approach for MNMs.
1.6 Exposure limits for nanomaterials

Frame to derive an OEL and a DNEL

Requirements regarding risk management of chemical substances in European Member States are embedded in the legal frame, as defined by the Occupational Safety and Health Framework Directive (OSHD 1989) and the Chemical Agents Directive (CAD 1998). Both directives lay down the employers’ obligation to take the measures necessary for the safety and health protection of the workers, including prevention of occupational risks. The CAD does not refer to nanomaterials as such, but according to legal analysis, the general obligations apply as well to nanomaterials (EC 2008). The CAD (1998) lays down 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. The CAD defines Occupational Exposure Limits (OELs) as a tool to protect workers from chemical risks and states that OELs can be used as a tool for risk assessment. The OEL is defined as the limit of the time-weighted average of the concentration of a chemical agent in the air within the breathing zone of a worker in relation to a specified reference period, generally referring to an 8hrs time-weighted averaged period over a full working week during an entire working life (Arboportaal, nd). Distinguished are in the Netherlands health-based OELs and risk-based OELs, the latter referring to carcinogenic, mutagenic and allergenic substances for which a threshold for an adverse effect cannot be defined. For carcinogenic substances two risk levels have been agreed in the Netherlands: a ‘prohibitive’ risk level corresponding with an additional cancer risk of $>10^{-5}$/ substance/year and a ‘target’ risk level corresponding with an additional cancer risk level of $>10^{-6}$/ substance/year. For inhaled allergenic substances a ‘target risk level’ has been agreed corresponding with an additional risk to become sensitized of 1% ($10^{-3}$/ substance/year) (SER nd). The risk-based OELs are currently under debate in the European Union as an option for a European approach (ETUI 2012). In the Netherlands the employers (c.q. the manufacturer or supplier) have the obligation to derive health-based OELs for the substances they market, while for the risk-based substances, and a few other substances (“without owner”) generated at the workplace the Dutch Ministry of Social Affairs bears the responsibility to derive OELs.

The EU REACH legislation defines DNELs (Derived No-Effect Level) and DMELs (derived minimum-effect level) (REACH 2006). REACH requires manufacturers to derive a health-based DNEL for substances they market in a volume of $>10$ tonnes/year/company (ECHA 2010). The type of hazard data required depends on the market volume (ECHA 2008). REACH prescribes the use of specified assessment factors for derivation of the DNEL, which contrasts the derivation of OELs, which leaves more scope for expert judgment (i.e. by the European Scientific Committee on Occupational Exposure Limits, abbreviated: SCOEL). It has been suggested that this will lead to DNELs, which are generally lower than OELs (Schenk en Johanson 2011). However in practice there are examples of OELs established at a lower level than the registered DNELs (van Broekhuizen 2011a). It has been ar-
It is preferable to harmonize the procedures for deriving OELs and DNELs to avoid confusion (Kalberlah 2007, Schenk and Johanson 2011), but a standardized procedure to derive an OEL from a DNEL is not (yet) agreed. For substances without a threshold effect level REACH proposes to use a DMEL that should follow a risk-based approach (ECHA 2010). To date the methodology to derive a DMEL is under debate in Europe (Püringer 2011) and no DMELs for substances have been derived yet.

OELs and DNELs for nanomaterials

The REACH guidance extends to deriving DNELs for nanomaterials (ECHA 2012a). So far however the registration of DNELs for nanomaterials is exceptional and to the extent that nanoparticulate materials are registered it is not clear whether adequate nanotoxicological data have been used. Illustrative is the registration in the REACH registration dossier in 2012 of carbon black and silica fume as materials for which a nanosize is likely (REACH 2012). Both are known to have primary particles of which a substantial number is likely to be in the nano-range (<100nm) (Kuhlbusch et al 2010; Evonik nd). The particle size of these materials is not published in the REACH registration dossier. Both particulates have an established regulatory limit values in some countries (e.g. GESTIS nd137), but it is not clear whether these take the nano-size into account.

Illustrative is also that the frequently used nanomaterials like TiO2, ZnO, Ag and Al2O3 have not been registered as nanoparticles (REACH 2012). The registered DNEL (inhalation long-term exposure, systemic effects) for these materials is therefore assumed to regard the coarse form. For CeO2 a general worker DNEL-inhalation for long-term exposure with systemic effects is registered, without reference to the particle size. It is not clear whether the published DNEL for CeO2 refers to the nano or the non-nano size, although the identified use for this compound states “Used in industrial polishing - nano cerium dioxide” and “Used as wood protection - nano cerium dioxide”, suggesting the DNEL to refer to the nanosized particulates (ECHA 2011). The nano-application for CeO2 as catalyst in diesel fuel (Ma et al 2011) is however not mentioned in the REACH registration dossier. Table 4 summarizes these findings.

Table 4  DNELs (inhalation long-term exposure systemic effects) of some “parent” materials for nanomaterials, as published in the REACH register, compared with OELs

<table>
<thead>
<tr>
<th>Name substance</th>
<th>CAS nr</th>
<th>DNEL (1) mg/m³</th>
<th>OEL mg/m³</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiO2, Titanium dioxide</td>
<td>13463-67-7</td>
<td>10</td>
<td>10</td>
<td>DNEL for coarse TiO2; not for nano-TiO2. OEL is ACGIH for coarse TiO2.</td>
</tr>
<tr>
<td>Ag Silver</td>
<td>74440-22-4</td>
<td>0.1</td>
<td>-</td>
<td>Not registered for nano-Ag</td>
</tr>
<tr>
<td>ZnO, Zinc oxide</td>
<td>1314-13-2</td>
<td>5</td>
<td>5</td>
<td>Not registered for nano-ZnO. OEL is Dutch OEL for ZnO-smoke</td>
</tr>
<tr>
<td>Al2O3, Alumina oxide</td>
<td>1344-28-1</td>
<td>15.63</td>
<td>-</td>
<td>DNEL Local effects, not nano</td>
</tr>
<tr>
<td>Graphite</td>
<td>7782-42-5</td>
<td>1.2</td>
<td>2</td>
<td>DNEL Local effects. OEL is ACGIH value (excl. fiber forms of graphite)</td>
</tr>
<tr>
<td>CB, Carbon Black</td>
<td>1333-86-4</td>
<td>2</td>
<td>3.5</td>
<td>DNEL for systemic as well as local effects. OEL is ACGIH value</td>
</tr>
<tr>
<td>SiO2, amorphous, smoke</td>
<td>60676-85-0</td>
<td>0.3</td>
<td></td>
<td>German OEL for the respirable fraction.</td>
</tr>
<tr>
<td>SiO2, Silica fume</td>
<td>69012-64-2</td>
<td>0.3</td>
<td></td>
<td>DNEL only registered for local effects</td>
</tr>
<tr>
<td>CeO2, Cerium dioxide</td>
<td>1306-38-3</td>
<td>3</td>
<td>-</td>
<td>REACH registry explicitly mentions nano-applications</td>
</tr>
</tbody>
</table>

(1) DNEL-inhalation for workers with long-term exposure systemic effects
For a few specific nanomaterials the industry and research have advised an OEL or a DNEL. These are summarized in table S. Bayer (Pauluhn 2009), Nanocyl (2009) and NIOSH (2010) proposed OELs for multiwall carbon nanotubes (MWCNTs). DNELs were calculated in an experimental study by Stone et al (2009) applying the DNEL methodology with the prescribed assessment factors to MWCNTs, fullerenes, Ag and TiO₂ (see table 5).

**Table 5** OELs and DNELs as proposed by industry and by research groups

<table>
<thead>
<tr>
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<th>OEL/DNEL</th>
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<tr>
<td>MWCNT (Baytubes)</td>
<td>8-hr TWA (6)</td>
<td>50, 7.1x10⁵ - 3.2x10⁷</td>
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<td>MWCNT (10-20nm/5-15μm) (1)</td>
<td>Short-term inhalation (8)</td>
<td>201, 4.1x10⁵ - 5.1x10⁵ Stone et al 2009</td>
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<td></td>
<td>Chronic inhalation</td>
<td>33.5, 7.1x10⁵ - 8.5x10⁵ Stone et al 2009</td>
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<tr>
<td>MWCNT (10-20nm/5-15μm) (2)</td>
<td>Short-term inhalation (8)</td>
<td>4, 8.5x10⁵ - 1.0x10⁶ Stone et al 2009</td>
</tr>
<tr>
<td></td>
<td>Chronic inhalation</td>
<td>0.67, 1.4x10⁵ - 1.7x10⁵ Stone et al 2009</td>
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<tr>
<td>MWCNT (Nanocyl)</td>
<td>8-hr TWA</td>
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<td>CNT (SWCNT and MWCNT)</td>
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<td>44.4, 2.9x10³ Stone et al 2009</td>
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<td>Ag (18-19nm)</td>
<td>DNEL-lung scenario1 (3)</td>
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<td>TiO₂ (21nm)</td>
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<td>17, 8.3 x 10³ Stone et al 2009</td>
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<td>TiO₂ (10-100nm) (REL) (4)</td>
<td>10hr/day, 40hr/week</td>
<td>300, 4.5x10⁻³ – 4.5x10⁷ NIOSH 2011</td>
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<td>TiO₂P₂₅ (primary size 21nm)</td>
<td>TWA 8h/d, 5d/w</td>
<td>1200, 6.5x10⁻⁷ NEDO-1 2009</td>
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</table>

(1) Based on a NOAEC for pulmonary effects of 5mg/m³ (for 6 hours)  
(2) Based on a LOAEC for systemic effects: 0.3 mg/m³ (for 6 hours)  
(3) Extrapolating the LOAEC to a NAEC using an extrapolation factor of 3 (scenario 1) and 10 (scenario 2)  
(4) REL = Recommended Exposure Limit  
(5) The number of particles/cm³ was calculated assuming that the particles have a spherical form, and CNTs have a cylindrical form.  
(6) TWA = Time weighted average  
(7) 8hr- TWA, 40-hour/ week, 50 weeks /year, for 45 years  
(8) An inhalation period of 15-minutes, unless otherwise specified

The differences in the values for MWCNT suggest that different toxicological concepts and sample characteristics may lead to a different limit value. Pauluhn (2009) assumes that assemblages of MWCNT lead to volumetric lung overload, which triggers a sustained pulmonary inflammation. Stone et al (2009) suppose immune effects to be the critical effect and derive a significantly lower DNEL. Stone et al (2009) emphasize that there might be substantial differences in the potential of different CNTs to induce toxic effects or even tumors, depending on the form and properties of the carbon nanotubes. Stone et al. (2009) suggest that evaluations will have to be made on a case-by-case basis. NIOSH (2010) based their proposal for a recommended exposure limit (REL) regarding multiwall carbon nanotubes on the limit of quantitation (LOQ) of NIOSH Method 5040, currently the recommended analytical method for measuring airborne CNT. The LOQ for the NIOSH method 5040 is 7 μg/m³. NIOSH (2010) stated that an excess risk of adverse lung effects is predicted below this level and therefore advised to reduce airborne concentrations of CNT and CNF as low as possible below the REL. It is not clear how the manufacturer Nanocyl derived its proposal for an OEL for their MWCNTs but their proposal (Nanocyl 2009) is in line with the NIOSH advice.
NIOSH (2011) proposed an OEL for nano-TiO\textsubscript{2} based on toxicological data and used the US threshold limit value (TLV) for coarse TiO\textsubscript{2} (of 1.5 mg/m\textsuperscript{3}) as reference. The NIOSH proposal is higher than the DNEL proposed by Stone et al (2009), which reflects the strict use of specified safety factors as prescribed in the DNEL-methodology. The higher OEL for TiO\textsubscript{2} as proposed by Shinothara et al (NEDO-1 2009) might be caused by a higher density of the TiO\textsubscript{2} studied by Shinothara et al. 2009.

A generic approach for the derivation of DNELs for manufactured nanomaterials was proposed by Pauluhn (2010), based on the evidence that repeated rat inhalation exposure studies suggest that the particle displacement volume is the most prominent unifying denominator linking the pulmonary retained dose with toxicity (the overload hypothesis). He calculates a volume-based generic concentration of 0.54 \( \mu \text{g} \text{PM}_{\text{resp}}/\text{m}^3 \) (\( \text{PM}_{\text{resp}} \) = respiratory particulate matter) to represent a defensible OEL. Related mass concentrations can be calculated by multiplication of the volume concentration with the agglomerate density: \( C_m = 0.54 \mu \text{g} \text{PM}_{\text{resp}}/\text{m}^3 \times \rho \), where \( C_m \) is the mass-based concentration and \( \rho \) is the PM-agglomerate density. Calculating DNELs with this algorithm gives rise to DNELs with a similar magnitude as the DNEL for (coarse) parent for materials. The “Pauluhn-approach” has been scrutinized by the RIVM (2012), and it was concluded that the overload hypothesis cannot be seen as representative for the critical effect of nanomaterials. In chapter 4 of this thesis the approach suggested by Pauluhn (2010) will be compared with other generic approaches.

**OELs and DNELs for nanomaterials and a precautionary approach**

So far neither within the Dutch nor within the European legal frameworks OELs or DNELs for nanomaterials have been derived on the basis of nanotoxicological data. As shown above, only for a limited number of nanomaterials specific OELs or DNELs have been proposed.

An important hurdle to the derivation of health-based OELs and DNELs for nanomaterials is the insufficiency of hazard data. Additionally there is the need to adapt the metrics used for OELs (and DNELs) to the characteristics of nanomaterials: metrics such as particles’ surface area concentration (cm\textsuperscript{2}/m\textsuperscript{3}) and number concentration (number/m\textsuperscript{3}) may well be a better metric for risk assessment than mass (Abbott et al 2010, Ashberger et al 2010, Ramachandran et al 2012). Also the characteristics of the airborne nanoparticles should be considered, which might be strongly influenced by the assemblies formed. In this context ECHA (the European Agency administering REACH) notes that the particles’ toxicity as-produced, as-exposed or as-interacted may differ (ECHA 2012b). There are also knowledge gaps in particle toxicology and the study of particle-induced carcinogenesis to decide whether for certain nanomaterials a health-based or a risk-based OEL should be advisable or that even another approach is preferable (Shvedova et al 2010).

For risk assessment of nanomaterials (including the derivation of OELs and DNELs) a case-by-case approach is advocated, similar to chemical substances (ECHA 2012a). But even for the most frequently used (and studied) nanomaterials like nano-TiO\textsubscript{2} and carbon nanotubes (CNT) the available toxicological data are limited and the advised risk levels may vary due to different methods and assumptions used to derive the OELs (Kuempel et al 2012) and possibly due to differences in characteristics of the nanomaterials studied as well (see table 5).
As explained in section 1.4 in such cases an option is to invoke the precautionary principle and to derive precaution-based limit values.

A problem with the derivation of precaution-based limit values is that the legal system defines its frame for risk assessment to a health-based or risk-based approach and does not include a precaution-based approach for setting OELs. Also it might be argued that precaution-based limit values cannot guarantee to protect the health of workers. However, it is clear that a lack of hazard data does not release the employer from the obligation to provide a safe workplace. In view thereof, as will be further elaborated in chapter 2 the precautionary approach to the use of nanomaterials may be operationalized by the converting the REACH principle no data no market into the principle no data no exposure. This might in principle be guaranteed by full containment of the process in operation, but workplace experience suggests that even such systems cannot guarantee that substances are not released. Filling, cleaning and maintenance operations, leakages or accidents may release nanoparticles in the workplace (Reijnders 2012). It may also be argued that when no explicit choice is made for an exposure limit, the implicit choice is made to regard the current exposure level as acceptable. Against this background the Dutch Social and Economic Council (SER) concluded that precaution-based nano reference values were needed to provisionally fill this gap due to the absence of OELs and DNELs and advised the Minister of Social Affairs to accept this approach (SER 2012).

Precautionary generic approaches to standard setting
The approach based on nano reference values is one of the proposed precautionary generic approaches to standard setting. The first of these generic approaches was proposed by the British Standards Institute (BSI 2007). BSI (2007) proposed a generic hazard-banding concept for limit values based on the assumption that the hazard potential of the nanoparticle is greater than the hazard potential of a large particle. BSI applied the principle of ‘standard setting in analogy’ and acknowledged that this assumption would not be valid in all cases. BSI stated that although the levels relate to existing OELs for bulk materials, they are intended as pragmatic guidance levels only and should not be assumed to be safe workplace exposure limits.

IFA (Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung) (IFA 2009 and updated in 2012) further developed the precautionary, generic hazard-banding concept assuming that the particles’ surface triggers the potential effects and can be characterized by the size and the density of the nanomaterials. IFA proposed to use the particles’ number concentration required to attain a mass concentration of 0,1 mg/m³ for particles in the size range up to 100nm. In doing so, IFA referred to a number of existing and proposed exposure limits for particles, which IFA thought to be relevant, such as the NIOSH proposal for nano-TiO₂ (NIOSH 2011) and the German risk limits for respirable biopersistent granular toner particles (BAUA 2010). To derive benchmark levels for granular nanoparticles with a sphere-like shape, and normalized at a diameter of 100nm, IFA calculated the number of particles/cm³ that correspond to a mass concentration of 0,1 mg/m³ (see Chapter 7, table 2 at page 158). These calculations lead to two risk bands for insoluble granular nanoparticles: one for nanomaterials with a density <6.000kg/m³ and one with a density >6.000kg/m³. Consequently, for granular nanoparticles with a smaller
diameter the mass-based benchmark level is stricter: for nanoparticles with a 50 nm diameter a factor 8, and with a 20 nm diameter a factor 125. For carbon nanotubes (CNTs) for which no manufacturer’s declaration is available stating that the CNTs do not exhibit asbestos-like properties, IFA proposed a provisional fibre concentration of 10,000 fibres/m³, based upon the German exposure risk ratio for asbestos (BAUA 2008). In view of the Dutch limit value for asbestos, which was recently further reduced, the benchmark for such CNTs might even have to be set at a lower level (SER 2011). IFA advised to use a low-risk band for soluble nanomaterials similar to the OEL for the coarse (or molecular) form. RIVM evaluated the usefulness of the BSI and IFA concepts (Dekker et al 2010) and concluded that the benchmark levels suggested by IFA can be used as provisional and pragmatic nano reference values (NRV) to reduce the workers’ exposure to nanomaterials. Dekker et al. (2010) emphasized that the NRVs, as presented here, are not health-based and proposed to use the NRVs in the Netherlands.

Hesterberg et al (2010) proposed to use diesel exhaust particulates (DEP) as a generic model to suggest limits for toxic effects of nanoparticles. The International Agency for Research on Cancer (IARC) classified diesel engine exhaust as carcinogenic to humans (Group 1), based on sufficient evidence that exposure is associated with an increased risk for lung cancer (Benbrahim-Tallaa et al 2012). Hesterberg et al (2010) state that DEP, as a complex mixture of ultrafine and coarse particles and a variety of gaseous components of toxicological relevance (e.g. nitrogen oxides, carbon monoxide, aldehydes), may bear similarities to e.g. fullerenes, carbon-based nanotubes and to sphere-shaped primary particles, whereas their physical structure (i.e., agglomerates of spherical primary particles) bears similarities to others that also have a strong tendency to agglomerate (e.g., titanium dioxides and other metal oxides). Typical size distributions for DEP were found for primary particles in the range of 15-40nm, and for agglomerates in the range of 60-100nm (Burtscher 2005). Hesterberg et al (2010) suggested a NOEL (no-observed effect level) for cardio-vascular effects for DEP at an exposure level between of 100 μg/m³ PM1 (3 × 10^4 particles/cm³) and 200 μg/m³ PM1.5 (5 × 10^4 particles/cm³). These levels are in the same order of magnitude as the proposed levels for NRVs for biopersistent granular nanomaterials.

In sum: it is highly questionable whether in the near future sufficient health-based OELs and/or DNELs will become available to support employers to fulfill their legal duty of providing a safe workplace. Precaution-based nano reference values (NRVs) may fill the gap created by the absence of health-based OELs and/or DNELs, but must be workable and acceptable. This is an important topic in the following chapters
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