Int Arch Occup Environ Health (2008) 81:721–726
DOI 10.1007/s00420-007-0245-5

ORIGINAL ARTICLE

Considerations on occupational medical surveillance in employees handling nanoparticles

Michael Nasterlack · Andreas Zober · Christoph Oberlinner

Received: 5 July 2007 / Accepted: 31 August 2007 / Published online: 12 September 2007

Abstract
Objectives The use of engineered nanoparticles not only offers new technical perspectives but also raises questions regarding possible health aspects for producers and users. Nanoparticles may, just by virtue of their size, exert biological effects unrelated to the chemicals they are composed of. These considerations, and results from experimental animal studies suggesting that engineered nanomaterials may pose a health hazard to employees, all underscore the need for preventive measures. In this context, the need for, the feasibility, and the appropriateness of targeted occupational medical surveillance are currently subject to debate.
Methods We compared established concepts for the development of occupational medical surveillance programs to existing knowledge on exposures in workplaces and on health effects of nanomaterials.
Results A variety of potential effect parameters have been proposed for medical surveillance of exposed personnel, such as heart rate variability, blood-clotting parameters, pro-inflammatory cytokines, etc. None of these parameters are specific, most are not validated as individual health risk indicators, and some require sophisticated equipment not routinely available. Against this background, BASF currently puts specific weight on risk assessment and exposure control in workplaces. Particle emissions are primarily avoided by manufacturing in closed systems or using effective extraction systems. Appropriate personal protective equipment has been defined for such operations where an exposure potential cannot be excluded.
Conclusions While there is presently no evidence-based foundation for "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.

Keywords Nanoparticles · Occupational medical surveillance · Risk assessment

M. Nasterlack (✉) · A. Zober · C. Oberlinner
Occupational Medicine and Health Protection Department,
BASF Aktiengesellschaft, 67056 Ludwigshafen, Germany
e-mail: michael.nasterlack@basf.com

Introduction

Human exposure to nanomaterials, i.e., particulate matter with a size of less than 100 nanometers in at least two dimensions, has occurred during the existence of mankind: the main sources being natural or artificial combustion processes. Typical industrial exposures of comparatively recent origin have been, e.g., fumes created through welding and flame cutting processes, exhausts from combustion engines, and others. But also the size distribution of some industrially produced pigments, catalysts, etc. have long comprised the nano range and thus created occupational exposures. Health effects occurring in exposed persons as such have been studied over years, however, typically either under the aspect of general dust exposure or with a focus on potentially substance-related toxic effects depending on the chemical composition of these dusts. Only comparatively recently, with the increasing technical ability to purposefully design and produce nanomaterials of defined chemical composition and geometrical structure, which do not occur in natural environments has the scientific attention

been drawn to potential health effects that are not primarily associated with the chemistry of these materials but related to unique properties associated with the minuscule size and thus enormously large specific surface area of such particles—the subject of nanotoxicology had emerged (Oberdörster et al. 2005).

The increasing growth of nanotechnology in the workplace, and results from experimental animal studies suggesting that engineered nanomaterials may pose a health hazard to employees all underscore the need for preventive measures (Seaton 2006; Schulte et al. 2007). The term prevention comprises all measures directed at minimizing the risk associated with a specific exposure, the early detection through medical surveillance of adverse health effects resulting from such an exposure and the treatment of diseases, if they occur in spite of the aforementioned efforts. Risk reduction can be achieved through appropriate organizational and engineering controls, which are available even for this new technology (NIOSH 2007). The present paper deals with the as yet unresolved question of occupational medical surveillance of employees handling nanomaterials.

Rationale for occupational medical surveillance

There exist a variety of concepts regarding the development of occupational medical surveillance, which can also be used on a situation with exposure to nanomaterials. Basically, the decision to carry out a targeted occupational medical surveillance requires (1) knowledge about the existence or at least possibility of an exposure to a health hazard, (2) knowledge about specific health effects caused by such an exposure, (3) the availability of tests with a known sensitivity and specificity to detect such health effects in an early, preferably reversible or treatable, stage and (4) establishment to a sufficient degree of the causal relation between exposure and effect. The latter requirement is primarily aimed at avoiding unwarranted fear and anxiety in the tested individual, as well as at the prevention of unnecessary seemingly protective interventions such as restrictions in fitness for duty, which might ultimately lead to job loss and other undesirable social consequences.

Characterization of exposure

There exists no "typical" nanomaterial but a huge variety of particles in the nano size range (Aitken et al. 2006). Important differences between materials involve, for example, size, shape, chemical composition and degree of agglomeration.

Up to now, there is no generally accepted exposure metric. Feasible parameters may be (1) mass concentration, (2) particle number, (3) total particle surface area, (4) particle type including geometry, (5) chemical composition and (6) meaningful contaminants (e.g., metals from catalyst use) (Wittmaack 2007). There is a wide agreement that mass concentration is insufficient to characterize exposure to nanomaterials, and convenient, although not yet widely available, measurement techniques presently exist mainly for particle number. Furthermore, the lack of standardized and uniformly applied measurement methods limits the comparability of measurement results across different companies, sites, plants, or types of workplaces.

Biomonitoring methods, usually the "gold standard" in occupational medicine for quantifying individual exposures, have not been developed for nanomaterials in humans, and it is questionable whether they will be available in the future. Methods applied in animal experiments (e.g., radio-labeling, magnetic tagging) appear not to be an option, and serum levels of the chemical constituents of nanomaterials will usually not provide a sensitive enough outcome metric because of the minute mass concentrations involved in nano-exposures.

While thus a qualitative exposure characterization based on technical use data in a given workplace should be possible, the quantification of workplace measurement results remains a challenge. It has further been demonstrated that measured particle counts do not necessarily represent genuine influences from workplaces, but have to be separated from background exposures which depend on geography, location, weather conditions, behavioral factors, etc. (Kuhlbusch and Fissan 2006). Therefore, as a prerequisite for any study on the effects of nano exposures at the workplace on the health of employees such crude quantitative results have to be expressed as workplace-related *increment of exposure*.

Identification of relevant health end points

Up to now, limited knowledge exists regarding potential health effects of nanoparticles in humans (Gwinn and Vallyathan 2007). It is mostly based on animal experiments with questionable relevance of routes of administration, especially intratracheal instillation of nanoparticle-containing solutions, as well as on cell culture-based in vitro experiments. Inferences were also derived from epidemiological studies on fine dust exposures in workplaces as well as in the general environment (Oberdörster 2001).

Although many of the purported toxicological properties of nanomaterials are attributed to size rather than to chemical composition, it is evident even from the limited available data that the toxic response may vary widely with the type of nanomaterial used (Gojova et al. 2007). If it comes to judging the extent of the size-associated effects of these

materials, and the possible contribution of workplace exposures to the increment of risk as compared to the "background" situation, we may draw back on a wealth of occupational medical experience with "conventional" nano exposures from, e.g., welding fumes, diesel exhaust, flour dust. Nevertheless, a case-by-case assessment of new engineered materials will remain necessary. One of the major challenges in addressing the enormous variability of existing nanomaterials, however, is the lack of appropriate and generally accepted high throughput models (Maynard et al. 2006).

There exist several hundred published papers from in vitro assays on the biological behavior and effects of nanomaterials. The studies were targeted, e.g., on cell viability, phagocytotic behavior, signaling pathways, markers of inflammation, increased oxidative stress and other endpoints. Specific attention has been devoted to the question of skin penetration, with ambiguous results for different particle types and skin models (Baroli et al. 2007; Cross et al. 2007; Rouse et al. 2007; Gamer et al. 2006; Vogt et al. 2006). It is widely accepted that in vitro assays may serve as high throughput screening instruments and help to elucidate underlying mechanisms and principles of pathogenetic processes in toxicology; however, they rarely provide results which can be extrapolated to intact organisms, let alone human beings, in a straightforward manner (Wörle-Knirsch et al. 2006). A recent ECETOC workshop concluded that in the ongoing process of hazard identification, in vitro screening strategies have to be developed to assess the possible reactivity, biomarkers of inflammation and cellular uptake of nanoparticles; however, this process has to be validated using in vivo techniques (Warheit et al. 2007).

Animal studies have demonstrated unspecific inflammatory reactions as a potential cause for pulmonary fibrogenesis and cardiovascular effects. Tumorigenic effects have only been observed in rats, and might be related to overload conditions (Borm et al. 2006). No dose–response relations can be derived from these experiments for the time being. As a particular potential cause for concern the ability of nanoparticles has been mentioned to travel via blood stream or the olfactory pathway to the brain and to other organs (Oberdörster et al. 2004; Garnett and Kallinteri 2006). This consideration, however, would not only apply for engineered nanoparticles but also for the ones from conventional occupational and environmental sources, and thus not address a new phenomenon. The pathophysiological significance of such particle redistribution remains to be elucidated.

Epidemiological data specifically derived from nanoparticle-exposed humans are currently not available (NIOSH 2007). The applicability of research results from environmental epidemiology on airborne pollutants to nano exposures in the workplace is doubtful for several reasons. Firstly, environmental exposures tend to be more complex than workplace exposures. While they do comprise exposure to nano-sized particles, there are other factors like SO_2, NO_X and even traffic-related noise exposures that constitute a highly complex exposure situation where—even in the presence of measurable effects—the causal agent, let alone a group of interacting agents, cannot not easily be identified. Secondly, in most environmental epidemiologic studies the target groups showing effects related to particulate matter were children, sickly or elderly people; thus, susceptible subgroups that are not relevant to a major extent in work environments. Thirdly, environmental studies which did not explicitly take nanoparticles into account produce similar results like the ones quoted as supporting nanoparticles-induced health effects in humans (e.g., Yeatts et al. 2007).

In the absence of specific human data, the extensive experience with welders and flame cutters which has been gained over the past seven or eight decades may come closest to what may be a model to estimate the potential health effects of engineered nanoparticles. Welding produces fumes containing high numbers of partly ionized, partly oxidized, sometimes highly reactive metallic particles in the nano-size range, along with irritant and toxic gases like, e.g., ozone, carbon monoxide and nitrogen oxides (Zober 1981; Blättler 1998; Wieners et al. 2000; Antonini 2003). In a comprehensive overview, which addressed respiratory, dermal, central nervous system (CNS), carcinogenic and reproductive effects of welding exposures, a relative paucity of findings becomes evident (Antonini 2003). Decrements in lung function have been observed in small numbers of heavily exposed welders, infrequent cases of interstitial fibrosis have been attributed to improper workplace ventilation or mixed dust exposure, and CNS and reproductive findings have mostly been absent or inconsistent or attributed to other welding-related exposures such as radiant heat. A clear relationship between lung cancer and welding fumes has never been established. Consequently, the IARC classified welding fumes and gases as "possibly carcinogenic", with limited evidence in humans and inadequate evidence in experimental animals (IARC 1990).

While this experience derived from welding can of course not serve to dismiss health concerns related to engineered nanoparticles, it may to some extent help to put too far-reaching concerns into perspective.

Availability of suitable medical tests

The potentially relevant health end points ascribed to engineered nanoparticles (cardiovascular, pulmonary, inflammatory) are unspecific, have a high prevalence in the general population, and share multiple non-occupational

risk factors. The very few existing studies with experimental short-term human exposure to nanomaterials have failed to demonstrate reproducible health outcomes suitable for occupational medical surveillance (Beckett et al. 2005; Scharrer et al. 2007). Nevertheless, on the basis of findings in experimental animals a variety of potential effect parameters have been proposed for medical surveillance of nano-exposed employees, such as heart rate variability, blood-clotting parameters, pro-inflammatory cytokines, etc. None of these parameters are specific, most are not validated as individual health risk indicators, and some require sophisticated equipment not routinely available. Other tests like, e.g., ECG, chest X-ray and pulmonary function are well-established diagnostic tools for the assessment of symptomatic persons or high-risk populations with a known or expected typical pattern of findings. No such pattern is known with regard to nanoparticles; thus, no individualized interpretation of results would be possible.

Arguments pro and contra "nano-specific" medical surveillance

While our considerations so far dealt with the *feasibility* of medical surveillance, also the *appropriateness* of conducting medical surveillance can be judged according to established criteria referenced, e.g., by Borak et al. (2006): (1) burden of suffering, (2) accuracy and reliability of the examination method, (3) effectiveness of early detection, (4) harms of screening and (5) benefits outweighing harms.

The first criterion requires that the health condition to be averted must be sufficiently common in the surveyed population and pose a substantial threat to health to justify routine screening. While this is certainly true in the general population for some of the health end points discussed in the context of nanotoxicology, the utter lack of knowledge regarding the population attributable risk, if existing, associated with occupational nano exposures precludes any conclusions on this point.

The second criterion refers to the availability of tests with established and sufficient sensitivity, specificity and positive predictive value for the outcome of interest. As we have already pointed out such data is currently lacking.

The third criterion implies that screening is justified only if finding the condition in an earlier stage leads to a better health outcome than if screening was not performed. This may be the case for some of the conditions discussed in the given context, e.g., early diagnosis of a cardiovascular disease may elicit a surgical intervention to prevent a myocardial infarction from occurring. This is, however, a general medical consideration that applies with or without exposure to nanomaterials. In the context of occupational medical surveillance this criterion further implies workplace interventions can be conceived that can mitigate or even remove a work-related causal factor and thus improve the health prospect of the affected individual.

This points directly to the limitations imposed by the fourth criterion, potential harms caused by the screening (Schulte and Salamanca-Buentello 2007). These harms include adverse effects of the tests themselves, e.g., chest radiographs are associated with a certain, albeit small, risk of inducing a malignancy through ionizing radiation (Konietzko et al. 2001). This known small risk has to be put into perspective against the unknown and unpredictable benefit of searching for results that no one can even describe for the time being. These harms also include the stigmatizing and distressing effects of false-positive tests followed by unnecessary further invasive procedures and eventually treatment.

The fifth and last criterion, whether benefits outweigh harms, can obviously not be judged on the basis of existing knowledge.

Taken together, we conclude that there is currently no basis for targeted "nano-specific" occupational medical surveillance.

Current concepts for the safe handling of nanomaterials

The substance-related health risk at a given workplace is commonly defined as hazard (specific for a given substance) times magnitude of exposure. It is obvious that in the absence of sufficient hazard information the outcome of this equation cannot simply be assumed to be zero. Against this background, BASF currently puts specific weight on exposure control in workplaces. At workplaces in research and production where nanoparticles are handled, risk assessments have been conducted through monitoring of exposures using state-of-the-art methods. For the safe handling of nanoparticles BASF has established specific working procedures, which are summarized in a respective guideline (BASF 2004). Particle emissions at the workplace are primarily avoided by manufacturing in closed systems or by using effective extraction systems. Appropriate personal protective equipment (PPE) has been defined for such operations where an exposure potential cannot be excluded.

As a consequence of the above considerations, workers handling nanomaterials are not subjected to any unusual medical surveillance. Instead, routine practices related, e.g., to respirator use or shift work are employed in accordance with current legal requirements, best practice and BASF policy.

Recommendations and conclusions

While there is no evidence-based foundation for targeted "nano-specific" occupational medical screening, general

medical screening with methods aimed at some of the health outcomes under discussion can be performed, especially if they are of high relevance in the general population. Such screening should be devised weighing the risk to benefit ratio for the tests in consideration, keeping in mind the risks associated with untargeted medical surveillance. Where such a program is newly adopted, it should be communicated to the stakeholders that all examination outcomes whatsoever will have no consequences regarding employability, liability, etc.

The results of such general medical examinations can provide a basis for future epidemiologic studies. Given the high incidence of the suspected end points in the general population, it will take a long time and a large number of "truly" exposed persons to achieve enough statistical power to detect workplace-related effects. Nevertheless, gathering of health information in such cohorts might lead to the detection of rare but specific health outcomes, if ever they exist. Therefore, the establishment of exposure registries to enable the conduct of large-scale multi-centric prospective epidemiologic studies is recommended.

Acknowledgment The authors are occupational physicians employed by BASF Aktiengesellschaft, Germany, which produces and uses materials in the nano-size range. The authors declare that they have no other competing interest in the subject.

References

Aitken RJ, Chaudhry MQ, Boxall ABA, Hull M (2006) Manufacture and use of nanomaterials: current status in the UK and global trends. Occup Med 56:300–306

Antonini JM (2003) Health effects of welding. Crit Rev Toxicol 33:61–103

Baroli B, Ennas MG, Loffredo F, Isola M, Pinna R, Lopez-Quintela MA (2007) Penetration of metallic nanoparticles in human full-thickness skin. J Invest Dermatol 127:1701–1712

BASF (2004) Guide to safe manufacture and for activities involving nanoparticles in the workplace. http://corporate.basf.com/en/sustainability/dialog/nanotechnologie/mitarbeiter.htm?id=dipTAAfbhbcp-lj. Last accessed 26 June 2007

Beckett WS, Chalupa DF, Pauly-Brown A, Speers DM, Stewart JC, Frampton MW, Utell MJ, Huang LS, Cox C, Zareba W, Oberdörster G (2005) Comparing inhaled ultrafine versus fine zinc oxide particles in healthy adults: a human inhalation study. Am J Respir Crit Care Med 171:1129–1135

Blättler MA (1998) Schadstoffexposition beim Schweißen. Sichere Arbeit, pp 25–29

Borak J, Woolf SH, Fields CA (2006) Use of beryllium lymphocyte proliferation testing for screening of asymptomatic individuals: an evidence-based assessment. J Occup Environ Med 48:937–947

Borm PJA, Robbins D, Haubold S, Kuhlbusch T, Fissan H, Donaldson K, Schins R, Stone V, Kreyling W, Lademann J, Krutmann J., Warheit D, Oberdörster E (2006) The potential risks of nanomaterials: a review carried out for ECETOC. Part Fibre Toxicol 3. doi:10.1186/1743-8977-3-11

Cross SE, Innes B, Roberts MS, Tsuzuki T, Robertson TA, McCormick P (2007) Human skin penetration of sunscreen nanoparticles: in-vitro assessment of a novel micronized zinc oxide formulation. Skin Pharmacol Physiol 20:148–154

Gamer AO, Leibold E, van Ravenzwaay B (2006) The in vitro absorption of microfine zinc oxide and titanium dioxide through porcine skin. Toxicol In Vitro 20:301–307

Garnett MC, Kallinteri P (2006) Nanomedicines and nanotoxicology: some physiological principles. Occup Med 56:307–311

Gojova A, Guo B, Kota RS, Rutledge JC, Kennedy IM, Barakat AI (2007) Induction of inflammation in vascular endothelial cells by metal oxide nanoparticles: effect of particle composition. Environ Health Perspect 115:403–409

Gwinn MR, Vallyathan V (2007) Nanoparticles: health effects—pros and cons. Environ Health Perspect 115:1818–1825

IARC (1990) Chromium, nickel and welding. In: WHO (ed) IARC monographs on the evaluation of carcinogenic risks to humans, Geneva, vol 49, pp 447–525

Konietzko N, Jung H, Hering KG, Schmidt T (2001) Das Strahlenrisiko bei Röntgenuntersuchungen des Thorax. Pneumologie 55:57–71

Kuhlbusch TA, Fissan H (2006) Particle characteristics in the reactor and pelletizing areas of carbon black production. J Occup Environ Hyg 3:558–567

Maynard A, Aitken RJ, Butz T, Colvin V, Donaldson K, Oberdörster G, Philbert MA, Ryan J, Seaton A, Stone V, Tinkle SS, Tran L, Walker NJ, Warheit D (2006) Safe handling of nanotechnology. Nature 444:267–269

NIOSH, National Institute for Occupational Safety and Health (2007) Progress toward safe nanotechnology in the workplace. DHHS (NIOSH) Publication No. 2007-123

Oberdörster G (2001) Pulmonary effects of inhaled ultrafine particles. Int Arch Occup Environ Health 74:1–8

Oberdörster G, Oberdörster E, Oberdörster J (2005) Nanotoxicology—an emerging discipline involving studies of ultrafine particles. Environ Health Perspect 113:823–839

Oberdörster G, Sharp Z, Atudorei V, Elder A, Gelein R, Kreyling W, Cox C (2004) Translocation of inhaled ultrafine particles to the brain. Inhal Toxicol 16:437–445

Rouse JG, Yang J, Ryman-Rasmussen JP, Barron AR, Monteiro-Riviere NA (2007) Effects of mechanical flexion on the penetration of fullerene amino acid-derivatized peptide nanoparticles through skin. Nano Lett 7:155–160

Scharrer E, Hessel H, Kronseder A, Guth W, Rolinski B, Jörres RA, Radon K, Schierl R, Angerer P, Nowak D (2007) Heart rate variability, hemostatic and acute inflammatory blood parameters in healthy adults after short-term exposure to welding fume. Int Arch Occup Environ Health 80:265–272

Schulte PA, Salamanca-Buentello F (2007) Ethical and scientific issues of nanotechnology in the workplace. Environ Health Perspect 115:5–12

Seaton A (2006) Nanotechnology and the occupational physician. Occup Med 56:312–316

Vogt A, Combadiere B, Hadam S, Stieler KM, Lademann J, Schaefer H, Autran B, Sterry W, Blume-Peytavi U (2006) 40 nm, but not 750 or 1,500 nm, nanoparticles enter epidermal CD1a+ cells after transcutaneous application on human skin. J Invest Dermatol 126:1316–1322

Warheit DB, Borm PJ, Hennes C, Lademann J (2007) Testing strategies to establish the safety of nanomaterials: conclusions of an ECETOC workshop. Inhal Toxicol 19:631–643

Wieners D, Latza U, Baur X (2000) Inhalative Belastungen durch Schweißverfahren. Zbl Arbeitsmed 50:38–44

Wittmaack K (2007) In search of the most relevant parameter for quantifying lung inflammatory response to nanoparticle exposure: particle number, surface area, or what? Environ Health Perspect 115:187–194

Wörle-Knirsch JM, Pulskamp K, Krug HF (2006) Oops they did it again! Carbon nanotubes hoax scientists in viability assays. Nano Lett 6:1261–1268

Yeatts K, Svendsen E, Creason J, Alexis N, Herbst M, Scott J, Kupper L, Williams R, Neas L, Cascio W, Devlin RB, Peden DB (2007) Coarse particulate matter (PM2.5-10) affects heart rate variability, blood lipids, and circulating eosinophils in adults with asthma. Environ Health Perspect 115:709–714

Zober A (1981) Symptoms and findings at the bronchopulmonary system of electric arc welders. Zbl Bakt Hyg 173:92–119