ERA-NET SIINN
Safe **I**mplementation of **I**nnovative
Nanoscience and **N**anotechnology

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Knowledge Gaps 2
Identification of knowledge gaps on the correlation between epidemiological health reports and possible safety and handling of nanomaterials (deliverable updates in months 24 and 36)

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1. Epidemiologic studies and the effects of ambient MNMs.

Epidemiologic research is a preplanned study that collects adequate information and samples regarding exposure to hazards, health outcomes, and other relevant variables defined in advance. The goals of analytic epidemiology are to characterize the relationship between exposure and outcome, often focusing on dose response. Epidemiologic research is the means of confirming or refuting purported associations between hazards and health outcomes. On the other hand, the impact of anthropogenic processes results in unprecedented increase of the engineered or manufactured nanomaterials (MNMs) particle concentration, often by one or two orders of magnitude above their natural concentrations. The most significant are the various outdoor anthropogenic combustion sources, including vehicles (and other forms of transport), as well as industrial and power plants, all utilizing fossil fuels. Another significant combustion source is biomass burning, including controlled and uncontrolled forest and savannah fires. There are also indoor combustion sources such as stoves and heaters utilizing fossil fuels and biomass, as well as tobacco smoking. Therefore epidemiological long-term and time-series studies investigating the association between MNMs exposure and health effects are largely needed. Despite long-term health effects of MNMs have not been published to date, studies in air-polluted areas with higher concentration of microparticles ($PM_{2.5}$ and PM_{10}) have indicated that there is a correlation between microparticles and long-term health problems, mainly mortality due to cardiopulmonary causes [1], lung cancer [2, 3] and ischemic heart diseases [2], suggesting that MNMs may also potentially contribute.

One of the components that may be responsible for the observed health effects related to proximity to motorized traffic is MNMs because of the documented toxicity [4-5]. A recent expert panel confirmed the potential adverse health effects of MNMs [6-7]. In the documentation for the expert panel, the near-roadway studies were used to derive the potential long-term health effects of MNMs, based upon the large concentration contrast near major roads [6]. Most studies of MNMs near major roads were conducted close to motorways with up to 300,000 motorized vehicles per 24-h [5, 8-14] have shown a large contrast with a rapid decrease in particle number concentration (PNC) with increasing distance from the motorway.

Epidemiological long-term and time-series studies investigating the association between particle exposure and health effects are largely based on a single monitoring site located somewhere in an urban background. Hence, a central exposure assessment issue is to learn how well particle concentrations are represented in a wider urban area if measured at one single centrally located site. Studies in urban areas have shown that spatial variability for $PM_{2.5}$ and PM_{10} is generally small and temporal correlation measured at different sites is high [15]. Hence, there is a consensus in the scientific community that a background station measuring $PM_{2.5}$ and PM_{10} mass concentrations could

be regarded as representative for larger urban areas. In contrast, exposure assessment for NMs is still in its initial stage compared to exposure assessment for fine particles $PM_{2.5}$ and PM_{10} [16-17]. Compared to microparticles, MNMs have shorter atmospheric lifetimes and are transported over shorter distances, so that they are less evenly distributed over a city area. Their atmospheric lifetimes are in the order of hours and can be even shorter in the vicinity of local particle sources with higher MNMs concentrations [16]. With growing distance from the particle source, both atmospheric dilution and coagulation play an important role in the rapid PNC decrease. Kulmala et al. [18] indicated that after nucleation, typical particle growth rates in mid-latitudes, depending on temperature and availability of condensable vapours, are in the range from 1 to 20 nm/h (increase in physical diameter).

2. MNMs air measurement techniques and the problem of data interpretation.

The majority of the published studies reporting on particle number and number size distribution applied electrostatic classifiers (EC) and condensation particle counters (CPC) methods most commonly based on electrostatic classifiers operating in combination with particle counters as differential/scanning mobility particle sizers (DMPS or SMPS, respectively) [19] can provide information on particles with size below 100 mm. This is possible if the instrumental method enables measurements of particle number size distribution, usually in a broader range, from which the sections of data encompassing MNMs is extracted.

If, rather than employing instrumentation for particle size distribution measurement, only a particle counter is used, the outcome of the measurement is the total particle number concentration in the detection size range of the instrument. There are two important implications of this to the interpretation of this value as a measure of MNMs particles. Firstly, this means that the outcomes of the measurements are not specifically MNMs concentrations, unless specific inlets are used which restrict the range of particles entering the detecting arm of the instrument. While it is true that in most typical environments PNC is dominated by MNMs particles, which is, thus, usually a good approximation of the total PNC, it is important to keep in mind that these are not the same, that there are environments where there are significant particle modes outside the MNMs range and therefore the two concentrations (MNMs and total number) differ significantly. Secondly, and even more significantly, the condensation particle counters often detect particles in the range extending to lower sizes than the window set by the DMPS/SMPS. This means that the counters are capable of detecting particles in the earlier stages of nucleation, and the presence of the nucleation mode which is below the size detection limit set by the DMPS/SMPS. Therefore in most situations, the counters would detect more particles than the DMPS/SMPS, and significantly more in the environments where a nucleation mode is frequently present. The above points are important when comparing PNC

reported in different papers and when specifically considering MNMs. Since different studies use different sets of instrumentation and investigate a different size range window, comparison of the total particle number concentrations reported should be conducted with caution [20].

3. Safety and Handling of NNMs

Applications of nanotechnology have been described for the construction (e.g. for cement, wet mortar and concrete, paints, and coatings, insulation materials, glass and infra-structural materials), food, cosmetics, powders industries [21].

Risk assessment models using available animal and worker data paint a concerning picture of workplace exposures to MNMs that may approach toxic levels despite being at the limit of detection with current technology.

Five criterion actions are presented by P. A. Schulte et al. [22] that should be practiced by decision–makers at the business and societal levels—if nanotechnology is to be developed responsibly. These include (1) anticipate, identify, and track potentially hazardous nanomaterials in the workplace; (2) assess workers' exposures to nanomaterials; (3) assess and communicate hazards and risks to workers; (4) manage occupational safety and health risks; and (5) foster the safe development of nanotechnology and realization of its societal and commercial benefits.

Those procedures also require medical surveillance, exposure registries, and epidemiological studies. Summarized results from epidemiological studies on health effects of fine and ultrafine particles applied to workplaces exposed to engineered nanoparticles reveal that those studies in occupational settings seem mandated, for adequate worker protection, but face several challenges, including exposure quantification and adequate confounder characterization [23]. Therefore inclusion of individual measurements of ultrafine particles in future studies will allow exploiting the full scale of temporal-spatial variation of both ambient and engineered nanoparticles.

Published exposure measurements of airborne concentrations of CNTs, or total carbon in work areas producing or using CNTs, indicate the potential for workers to be exposed to levels of CNTs associated with granulomatous inflammation, lipoproteinosis, and early-stage, persistent pulmonary fibrosis in animal studies. Workplace exposures to airborne concentrations of approximately 7 to 35 mg/m3 CNT over 5.6 years were estimated to be equivalent to the lowest observed adverse effect levels in the two currently published rat subchronic inhalation studies [24,25]. These limited exposure data in workers indicate the potential for workers to be exposed at airborne concentrations of CNTs exceeding the 8-hour limit of quantification (7 $\mu g/m^3$) of the measurement method [26], which is associated with more than 10% excess risk of early-stage adverse lung effects based on the animal data. However, the steps in estimating occupational risks from animal dose–response data

have many uncertainties. For example in the case of occupational aerosols, such as airborne CNTs, the animal dose–response data are extrapolated to predict risk in workers if exposed up to a full (45-year) working lifetime. This requires estimation of the human lung dose corresponding to a critical (adverse) effect or absence of effect in the animal. The animal lung dose (measured or estimated) is extrapolated to humans using data on factors that influence species-specific lung dose (particle size-specific regional deposition in the lungs, breathing rates, exposure scenario). In the absence of other data, it is assumed that, at an equivalent dose, the human and animal response is equal. The work-place exposure scenario (concentration and duration) that would result in the human-equivalent lung dose is estimated using a human lung dosimetry model. Currently, these models have not been evaluated for CNTs [27]. In addition, there is a critical need for more data on worker breathing zone concentrations of CNTs, including in workers who are using products containing CNTs or the structurally-similar Carbon nano fibers. A current effort in this regard is the national surveillance program in France which initially will monitor workers exposed to CNTs and titanium dioxide [28].

Except from the contamination through the inhalation route, direct contact exposure could also be harmful. Measurements on laboratory protective gloves revealed that they were contaminated with MNMs indicate thus the consideration of dermal contact as a potentially important exposure route [29]. In order to prevent dermal exposure, the efficiencies of protective clothes and gloves with respect to MNMs' penetration also have to be evaluated. Only a few studies have assessed MNMs' penetration through protective clothing. Huang et al. [30] study on protective clothing performance with regard to NaCl particle penetration has been performed in the size range of 10–1000 nm. The results indicate that woven fabrics behave almost the same as fibrous filters with a maximum penetrating particle size between 100 and 500. The maximum penetration was between 50 and 80%. In the study of Golanski et al. [31] different types of protective clothing, woven, and non-woven, were tested through diffusion method with Pt and TiO2 nanoaerosols. The efficiencies of cotton, polyester and high density polyethylene were investigated. Cotton and polyester present almost the same efficiency when tested with TiO_2 and Pt particles with mean geometric diameter around 10 nm. Non-woven fabrics (air-tight materials) are more efficient against Pt and TiO_2 nanoparticles centered around 10 nm than woven cotton and polyester. This is consistent with observations [32] made for graphite nanoparticles with mean geometric diameter ranging between 40 and 80 nm. Gloves made of three different materials i.e., nitrile, latex, and neoprene were also tested with TiO_2 and Pt nanoparticles in static conditions with mean geometric diameter around 10 nm and were found very efficient [31]. No nanoparticle penetration through the gloves was observed during exposure of a few minutes.

Given the growing use of MNMs and so many unknowns about their potential health effects and as it is almost certain this growth will outpace epidemiological studies, there are

arguments that instead of waiting for these reports, it is imperative to develop effective methods for assessing health risks associated with MNMs exposure [33]. An active approach would be to take precaution now so that the people at higher risk can be properly protected. This is particularly important for the health surveillance and monitoring of workers who may be exposed to MNMs in the occupational setting. One of the strategies for preventing serious nanotoxicity from happening is to identify early biological events associated with exposure to harmful MNMs and then use that information for prevention. This can be achieved through biomarker studies in MNMS target organs/tissues or preferably in the biological fluid [33]. A "biomarker" is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [34]." Therefore, the role of biomarkers in assessing the health effects of MNMS is to link exposure to the disease outcomes by providing mechanistic indicators that are associated with early adverse effects of NNMs. Although it is expected that it may take a long period of time to develop a panel of biomarkers that can be used as indicators of exposure-specific disease outcomes, identification of early biological responses related to injury pathways, based on our knowledge in air pollution research, would be a good starting point.

Finally, a major tool for prevention of occupational disease from exposure to specific agents is the use of occupational exposure limits (OELs). OELs for MNMs would be useful in reducing the health risk to workers exposed to MNMs by providing risk managers and health professionals with a quantitative health basis for assessing the effectiveness of risk management practices (e.g., use of engineering controls).

4. Knowledge gaps

i. *Lack of reliable NNMs dispersion models*. [35]. Land-use regression (LUR) is increasingly used to develop empirical models for the long-term average concentration of outdoor air pollution [36]. LUR models have been developed for NO2, NOx, VOC, and to a lesser extent $PM_{2.5}$ and soot or elemental carbon [36]. LUR models require monitoring data for typically between 20 and 80 locations in a reasonably confined study area to establish the spatial variability of ambient concentrations. These data however are currently not readily available for MNMs.

ii. *Lack of standard set of protocols for in vitro and in vivo toxicity*. There are challenges particularly the validation of *in vitro* tests with appropriate predictive power for *in vivo* effects in whole organisms [37]. Cells in culture do not experience the range of pathogenic effects that are likely to

be observed *in vivo* which are partly related to issues of translocation, toxicokinetics and coordinated tissue responses. The latter is the most under-researched area in toxicology.

iii) *Quantitative data on toxicological effects of nanoparticles* are still scarce even at the single organism level. Ecotoxicological information on nanoparticles is required at several levels (single organisms, simplified communities and whole ecosystems) for risk assessment and regulatory purposes.

iv) Lack of *in situ* studies about the *fate of nanosize materials and their impact on animals and other communities*.

v). For epidemiological time-series studies two aspects are important, namely *the temporal correlation of concentrations measured at different sites in the same city and the difference in absolute levels of concentrations measured at different sites in the city.* The concentrations of MNMs are not monitored for regulatory purposes, so additional air-monitoring systems are needed to characterize outdoor concentrations of MNMs. The use of a single monitoring station may not provide an accurate approximation of the actual human exposure to MNMs over the whole urban area. In epidemiological studies assessing adverse health effects from long-term UFP exposure, multiple monitoring sites covering the spatial variability will be required to obtain accurate exposure/risk coefficients. [13,38,39]. A thoughtful selection of the measurement sites have to be considered as there is high variability within an urban area although reasonable correlations over time have been observed for MNMs when measured at urban background stations.

vi). The size of particles depends on the multiplicity of *sources and processes which lead to their formation,* and therefore, on the material from which the particles were formed, with the complex scientific knowledge behind these processes still containing many significant gaps.

vii). Although basic technologies exist, personal, easy-to-use monitors to measure the particle number, surface area, or mass concentration of NM aerosols are not yet available. *The measurement of MNMs exposure lacks standard methods or validated metrics* related to the high costs of MNMs monitoring equipment. Major questions remain on how to reliably differentiate emitted and ubiquitous background MNMs [40].

viii). *Measurements of CNT airborne characteristics* are needed to determine the extent to which CNT particle size and morphology may influence lung deposition and retention, after accounting for aerodynamic diameter. It would be useful to know how the characteristics of CNT materials in the workplace *compare with those in the animal studies,* and to have sufficient data to link those

characteristics to the hazardous properties of the CNTs in order to prevent adverse health effects in workers [27].

ix). *Biomarker studies for ENM toxicity are currently at their early stage.* The ideal biomarkers for assessing environmental and occupational exposures should be able to provide strong mechanistic, molecular, or biochemical basis for the diseases, be exposure specific, reflect early adverse health effects, have clinical relevance, and easy to use. Although we are not able to identify the biomarkers that meet all these criteria at this time, our experience in biomarker research for the incidental or ambient MNMs, can be used to facilitate this process due to some similarities between ambient NMs and certain MNMs. One of the injury mechanisms that are common to ambient NMs and certain MNMS is the induction of oxidative stress and inflammatory responses by particles [33].

x)**.** Cellular interactions with certain nanomaterials may not introduce any new pathological conditions, but one cannot ignore *novel mechanisms of injury that require special tools, assays and approaches to assess their toxicity [37]*.

xi)**.** *Controlling effectively airborne exposures to MNMs in the workplace is difficult in the absence of OELs.* At present, there are practically no OELs specific to nanomaterials that have been adopted or promulgated by authoritative standards and guidance organizations. The vast heterogeneity of NNMs limits the number of specific OELs that are likely to be developed in the near future, but OELs could be developed more expeditiously for NNMs by applying dose–response data generated from animal studies for specific nanoparticles across categories of NNMs with similar properties and modes of action [41].

xii). *There is lack of registries and medical surveillance of NNMs workers* [42]. Registries are useful tools for conducting surveillance of new or perceived hazards since they provide documentation of who is working with which materials, when and where in the facility exposures are occurring. Establishing a registry of workers exposed to NNMs across workplaces, and perhaps across countries, will greatly aid in conducting subsequent epidemiologic studies [43].

xiii). *There is a need for research on what factors and parameters influence the effectiveness of engineering controls and personal protective equipment* [44]. Filtration data for monodisperse nanoscale particles suggest air-purifying respirators provide expected levels of filtration protection against nanoparticles [45]. However, small amount of data exist on the effectiveness of gloves and clothing to protect against exposures to MNMs [29-32].

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