NANOTOXICOLOGY

CHARACTERIZATION, DOSING AND HEALTH EFFECTS

EDITED BY

NANCY A. MONTEIRO-RIVIERE

North Carolina State University
Raleigh, North Carolina, USA

C. LANG TRAN

Institute of Occupational Medicine
Edinburgh, UK

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Estimating Nanoparticle Dose in Humans: Issues and Challenges

Eileen D. Kuempel

National Institute for Occupational Safety and Health, Cincinnati, Ohio, U.S.A.

OVERVIEW

Quantitative estimation of internal dose is a key step in the risk assessment of nanoparticles. Lung dosimetry models describe the deposition and clearance of inhaled particles in the respiratory tract, but these models have not been fully validated for the disposition of nanoparticles, which may include translocation beyond the respiratory tract. The current models and methods will be discussed, along with the data needs and challenges to validate and extend these models to better estimate nanoparticle dose.

INTRODUCTION

Workers historically have been among those in the human population most likely to be exposed to hazardous substances. With new technologies comes the potential for worker exposures to new substances such as nanoparticles.* Of particular concern to understanding the health risk to workers are the limited data available to evaluate the potential toxicity of new engineered nanoparticles and the lack of standardized methods for measuring and characterizing exposures to nanoparticles in the workplace (2). In addition, the potential for exposure outside the workplace exists when nanoparticles

*The term "nanoparticle" refers here to any nanometer-sized structure with at least one dimension <100 nm, including spherical, fibrous, or other shapes; nanoparticle refers to the primary structure, but aggregates or agglomerates of nanoparticles also occur (1).

are released into the environmental (either by disposal or intentional use in environmental remediation) or used in consumer products (such as cosmetics or sunscreens). The existing scientific literature on the physical and biological factors influencing particle and fiber toxicity in animals and humans provides information and data to develop interim risk estimates and health protection strategies. These studies indicate that the particle characteristics (including size, shape, and chemical composition), the internal dose in the respiratory tract, and the fate and persistence of the particles in the body are key factors influencing the risk of developing adverse health effects (2–5).

Workers may be exposed to nanoparticles by various routes including inhalation, ingestion, and dermal exposure. Inhalation exposure to various airborne particles and fibers continues to be associated with increased morbidity and mortality from work-related lung diseases (6). Nanoparticles may become airborne during production and use, particularly when present in dry powders or liquid sprays (2). This chapter focuses on airborne nanoparticle exposures and the estimation of internal nanoparticle dose in workers.

BIOMATHEMATICAL LUNG MODELS

To estimate the risk of disease in humans exposed to nanoparticles, it is necessary to understand the relationship between the external exposure and the internal dose. Biomathematical models are used to quantitatively describe the physical and physiological factors that influence the uptake and retention of substances in the body, as well as the biological responses to a given dose. Biomathematical models that describe the exposure-dose relationship are variously called dosimetric, toxicokinetic, or physiologically-based pharmacokinetic (PBPK) models, while those that describe the dose-response relationship are called toxicodynamic or pharmacodynamic models.

Biomathematical models have applications in both experimental design and risk assessment. In experimental studies, biomathematical models may be used to generate and test hypotheses of biological mechanisms. For example, by evaluating whether a dosimetric model validated for respirable particles also adequately describes the disposition of nanoparticles, hypotheses about the factors influencing the deposition and retention of particles of various characteristics can be evaluated. Biomathematical models are also used to estimate doses for toxicological study. For example, a lung dosimetry model can be used to estimate the airborne particle concentration that will result in a target dose in the lungs over a given duration of exposure. In quantitative risk assessment, validated biomathematical models are used to: (1) provide estimates of the biologically-effective

dose; (2) extrapolate exposure, dose, and response data from one species to another, from one dose to another, or from one route of exposure to another; and (3) describe the sources of variability in the factors that influence internal dose in a population. Obtaining the data required to calibrate and validate biomathematical models can be facilitated by collaboration among experimenters and modelers and by consideration of quantitative modeling needs in the experimental design.

Current biomathematical models pertaining to particles and fibers generally focus on particle deposition and/or clearance and retention processes (7–2), although some models in rats quantitatively describe the relationships between exposure, dose, and markers of adverse biological responses (11,12). For poorly-soluble particles and fibers, these models are typically limited to the respiratory tract; yet data from animal studies indicate that additional paths need to be considered to accurately estimate nanoparticle dose in humans. To the extent that particles are soluble, uptake of their elemental constituents into the blood from the lungs or gut may also determine their systemic distribution and potential toxicity (e.g., soluble forms of various metals such as manganese, nickel, or chromium). For poorly-soluble nanoparticles, additional pathways beyond the lungs include nerve axon transport to the brain (13) and entry into the blood circulation and transport to nonpulmonary organs (14,15). Intra-cellular organelles (e.g., mitochondria) in the lungs and other organs may also be target sites for nanoparticles (16,17). Models to estimate nanoparticle dose by non-inhalation routes of exposures, such as dermal (18, see Chapter 9), may also be required to adequately describe nanoparticle dose in humans.

Deposition of Nanoparticles in Human Lungs

Particle size is a key factor determining whether and in what location inhaled particles are likely to deposit in the respiratory tract. Human studies using radiolabeled particles have shown that the total fraction of particles depositing in the respiratory tract increases to greater than 90% as particle size decreases into the nanoparticle size range (1–100 nm) (7). The fractional deposition of nanoparticles in the alveolar and tracheobronchial regions can be several times higher than that for larger respirable particles.[†] Total nanoparticle deposition increases with exercise (19) and among individuals with chronic obstructive lung disease or asthma (20). Nanoparticle deposition in exercising individuals was shown to be underpredicted by several human lung deposition models (21). Current human lung models have had limited evaluation of the deposition of the smallest

[†]The term respirable refers to particles that are capable of depositing in the alveolar (gas-exchange) region of the lungs (7).

nanoparticles (e.g., <10 nm) (9) and of charged particles including nanoparticle sizes (22).

Clearance and Retention of Nanoparticles in Human Lungs

Limited human data are available on the clearance and retention of inhaled particles and fibers. Recent studies have measured the short-term retention of nanoparticles based on low dose, short-term exposure to radiolabeled carbon nanoparticles ("Technegas"; ~25–100 MBq dose achieved in a few breaths). Most of the deposited nanoparticles remained in the lungs up to two days following exposure, although the measured amount varied (~65% at 24 hours (20); 95% at six hours (23); 99% at 46 hours (24)). These studies did not find evidence for the rapid translocation of nanoparticles to the blood circulation or accumulation in the liver, as had been reported earlier (25). The findings of the Nemmar et al. study (25) may have been influenced by the instability of the radiolabel-nanoparticle complex (20,24).

Long-term clearance and retention data of nanoparticles in humans are not available. For larger, respirable particles (~1–5 μm), the long-term retention half-time in humans is on the order of months to years (7). Human studies of retained particle dose are rare, and coal miners have been the most studied. One study of coal miners found black pigment in liver and spleen tissues, and the amount of pigment was associated with both lung disease severity and years worked in coal mining (although no pigment-related pathology was observed in these nonpulmonary organs) (26). This study suggests that both lifetime cumulative exposure and lung disease status can influence the translocation of particles into the blood circulation—even for larger (micrometer size) coal particles. Another possible route by which particles can enter the blood circulation is via the digestive tract (e.g., from ingestion of particles following mucociliary clearance from the lungs). Particle characteristics (e.g., surface reactivity) can also influence the disposition of inhaled particles. Tran and Buchanan (27) showed that respirable quartz, which is cytotoxic, was cleared less effectively from coal miners' lungs and was transported more readily to the lung-associated lymph nodes than was coal dust, which has relatively low inherent toxicity.

Translocation of Nanoparticles in Rats

Studies in rats have shown that nanoparticles can enter the blood circulation and translocate to nonpulmonary organs. This translocation appears to be influenced by the particle dose; particle size; and chemical composition. Oberdörster et al. (14) showed significant accumulation of ^{13}C nanoparticles in the liver of rats within 18 and 24 hours of inhalation. At the higher dose of 180 $\mu g/m^3$, increased ^{13}C was detected in the rat liver within 0.5 hour of

exposure, but not until 18 hour at the 80 $\mu g/m^3$ dose. In contrast to ^{13}C nanoparticles, iridium nanoparticles had very low translocation from the lungs (15). The ^{192}Ir in the blood was close to the level of detection and had very low accumulation in other organs (<1%); yet, the fraction of the 15-nm nanoparticles translocating to other organs was nearly 10 times greater than that for the 80-nm particles—indicating that smaller nanoparticles are more easily transported from the lungs (15). Geiser et al. (17) observed the rapid translocation of titanium dioxide nanoparticles from the lungs in rats; within one hour after inhalation, 24% of the nanoparticles were observed within and beyond the epithelial cell barrier of the lungs, including within blood capillaries and red blood cells.

Limited data are available on the long-term clearance and retention of nanoparticles in rat lungs. Semmler et al. (28) reported similar long-term retention of iridium nanoparticles compared to micrometer-size particles. Kuempel et al. (29) found that the long-term retained lung burdens of ultrafine and fine titanium dioxide, carbon black, and diesel exhaust particles in rats were similar to those predicted from several rat lung dosimetry models. While these studies suggest that the long-term clearance of respirable particles may be similar for micrometer- and nanometer-size particles, they do not explain the systemic translocation observed in short-term studies of nanoparticles (14,15) or the potential role of particle characteristics in addition to size.

Biological Mechanisms of Nanoparticle Disposition

Our understanding of the mechanisms of particle clearance and retention comes largely from animal studies. Nanoparticles have been shown to be less effectively phagocytized by alveolar macrophages than larger respirable particles (30,31). Nanoparticles are also taken up and retained in the lung interstitium to a greater extent (32–34). If the epithelium is damaged, such as by pulmonary inflammation, particles can more easily penetrate the lung epithelial barrier (35). A possible mechanism for the adverse cardiovascular events associated with increased particulate air pollution in human studies (36) may be related (either directly or indirectly) to combustion-derived nanoparticles through inflammatory and prothrombic processes (4).

Nanoparticles that deposit in the nasal region in rats have been shown to translocate to the brain via olfactory and trigeminal nerve axons (13,37) and have been associated with inflammation in specific brain regions (37). Nanoparticles have also been shown to localize in or near cell organelles, including mitochondria and nuclei, and have been associated with oxidative stress and cell damage (16,17). The extent these pathways and processes may occur in humans exposed to nanoparticles is not known.

Use of Lung Dosimetry Models in Risk Assessment

Several chronic inhalation studies of nanoparticles (poorly-soluble ultrafine particles) in rats provide quantitative dose-response data that can be used to develop initial risk estimates for nanoparticles. The steps to using animal inhalation bioassay data in developing quantitative risk estimates include (29):

1. Select the animal model, dose metric, and disease response.
2. Analyze the dose-response relationship (e.g., statistical model) and estimate the internal dose associated with a specified risk of disease (target dose).
3. Extrapolate the target dose from animals to humans (e.g., normalize on lung mass or lung surface area)—assuming equal response to equivalent doses (if no data otherwise).
4. Determine the human-equivalent airborne exposure concentration and duration associated with the target lung dose (e.g., using a human lung dosimetry model).

This approach is illustrated in Fig. 1. It has been used in quantitative risk assessment of occupational exposure to poorly-soluble particles (ultrafine or fine titanium dioxide, ultrafine carbon black, diesel exhaust particulate) (29). Two current human lung dosimetry models (8,9) were used to estimate the working lifetime exposure associated with the lung doses identified in the rat dose-response modeling. Although all the particles analyzed are considered to be poorly-soluble with low inherent toxicity (38), the rat-based lung cancer risk estimates were higher for the ultrafine particles compared to the same airborne mass concentration of fine particles (29). This finding reflects the greater pulmonary inflammation and lung tumor response that have been observed in rats exposed to nanoparticles compared to an equal mass of larger particles of similar composition. Other dose metrics including particle surface area (39,40) or particle size and volume (41) have been shown to better predict these adverse responses to either nanoparticles or larger respirable particles in the rat lungs.

ISSUES AND CHALLENGES TO NANOPARTICLE DOSE ESTIMATION IN HUMANS

In the absence of human data, animal models are often used in risk assessment (as described above). One of the major challenges in using animal data is extrapolating from animals to humans. It is often not clear to what extent observed differences in dose and response are due to qualitative versus quantitative differences across species. For example, rat studies have shown that nanoparticles can translocate from the lungs to the blood circulation and other organs (14,15,17), while most of the human studies of

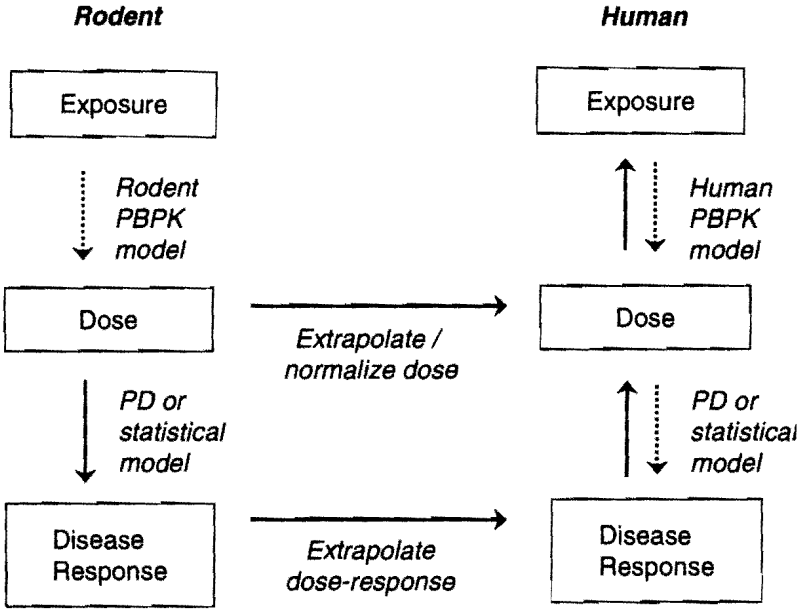

Figure 1 Schema for using rodent exposure-dose-response data and biomathematical models in risk assessment of nanoparticles. The steps are as follows: The internal dose associated with an adverse effect is estimated from rodent data using a dose-response model. The target dose is extrapolated to humans by normalization (e.g., equivalent dose per unit of tissue mass, volume, or surface area). The rodent dose-response relationship is also extrapolated to humans, typically by assuming equal response to an equivalent dose in both species if no other data are available. A human PBPK or dosimetry model is used to estimate the exposure scenarios (concentration and duration) that are expected to lead to the target dose in a given population (by age, exercise level, breathing pattern, etc.). Alternatively, if human exposure data are available, then the internal dose can be predicted and evaluated with the dose-response model in rodents (or humans, if available) to estimate the associated disease risk. Also, if a rodent study does not include internal dose data, a relevant PBPK model could be used to estimate it. *Abbreviations*: PBPK, physiologically-based pharmacokinetic model (also called dosimetry model); PD, pharmacodynamic model.

short-term exposure to carbon nanoparticles have not (20,23,24). From these studies alone it is not possible to determine whether the differences are qualitative (e.g., nanoparticles do not translocate across human lung epithelium into the blood, but do so in rats); quantitative (e.g., translocation is dose-dependent and the doses in humans were too low or of too short a duration to detect an effect); or some combination (e.g., various translocation processes exist and operate to different extents across species). A challenge for dosimetry modeling of nanoparticles is to determine what physical and biological factors allow nanoparticles to translocate beyond the lungs (e.g., by blood circulation or axonal transport) and at what rates in humans and animals, since these pathways and processes are not considered in the current particle and fiber lung dosimetry models.

Additional challenges to estimating nanoparticle dose relate to both general model validation issues and nanoparticle-specific issues (Table 1). Many biomathematical models of particle and fiber deposition and clearance have been developed in rodents and humans; however, before such models are extended to nanoparticle-specific processes, evaluation of the model structure and validation is needed. Harmonization of the various respiratory tract models and features would help to reduce uncertainties pertaining to model structure. A major limitation in any of these investigations is the sparse human data. New tools and techniques are promising to provide alternative approaches to obtaining useful data. For example the use of human lung casts with simulated air flow allows measurement of fiber deposition fractions (42), a technique which could be applied to nanoparticles of varying size and shape. New applications of labeling techniques to nanoparticles (e.g., using gold-label or quantum dots) are also promising for detecting and quantifying nanoparticles dose in the body in experimental animal studies (43). In vivo and in vitro studies can also provide the scientific basis for determining the appropriate dose metric (e.g., particle mass, number, surface area) (39) to predict exposure, dose, and response relationships for nanoparticles in animals and humans. Collaboration among biomathematical modelers and experimental scientists is critical to identifying and filling data gaps for improved model development and prediction of nanoparticle dose in humans. As with any biomathematical modeling, additional challenges include determining the sensitivity of the model predictions to alternative assumptions and parameter values, and accounting for population variability in key parameter values (44).

The development and validation of human lung dosimetry models for nanoparticles would provide an improved tool for risk assessment, by reducing uncertainty in estimating what exposures are likely—or unlikely—

Table 1 Challenges and Data Needs for Estimating Nanoparticle Dose in Humans

Validation of Current Lung Models	Extension of Models for Nanoparticles
Harmonize the various respiratory tract models	Include pathways for particle translocation beyond the lungs
Validate model predictions by particle size and type	Identify uptake by routes other than inhalation
Evaluate and validate extrapolation methods from animals to humans	Determine appropriate particle dose metric (e.g., surface area, mass, number)
Perform sensitivity analysis of model parameter values	Determine role of nanoparticle shape and agglomeration
Include population variability in key parameters and pathways	Identify target tissues for nanoparticle disposition
	Determine association between internal dose and adverse biological responses

to result in internal doses associated with adverse effects. Questions remain concerning the adequacy of current lung dosimetry models to adequately describe the inhalation and retention of nanoparticles. It is also not known what exposures to nanoparticles occur in workers and whether the exposures present a health concern. Given these uncertainties, research is needed to fill the key data gaps to improve the risk estimates in workers, consumers, and the environment. In the meantime, strategies are needed to minimize nanoparticle exposures in workers producing or using these materials (including engineering controls, work practices, and personal protective equipment) (1,45,46).

CONCLUSIONS

Dose estimation is an important element in evaluating the potential toxicity of nanoparticles and estimating the risk of exposure. The extent to which current models and methods accurately predict the internal dose of nanoparticles from occupational or environmental exposures is not fully understood. Compared to larger particles, inhaled nanoparticles may translocate within the body much more readily. They may enter previously unrecognized pathways (e.g., olfactory nerve transport to the brain) and retention sites in cells (e.g., mitochondria). Ingestion and dermal pathways are potential routes of exposure to nanoparticles but have had limited study. Studies to date suggest that the traditional focus on the lungs as the primary route of exposure and target organ of inhaled particles will need to be expanded to consider all the possible pathways and organs that may receive nanoparticle doses. New experimental methods for tracking and measuring nanoparticles dose in vivo provide potential tools for obtaining quantitative dose data that are essential for dosimetry model validation and refinement.

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