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Lung Dosimetry Modelling in Nanotoxicology: A Critical Analysis of the State of the Art †

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Abstract: The estimation of the dose of inhaled nanomaterials is of fundamental importance in occupational and environmental health. Indeed, the toxicology and risk assessment of inhaled NMs depends on deposition rates in various parts of the lung, coupled with clearance/retention rates that depend on processes such as physical removal by ciliary clearance, macrophage-mediated clearance and lymphatic clearance, together with dissolution and disintegration. A number of lung dosimetry models have been designed to estimate the deposition and retention of inhaled particles, including empirical models, deterministic models, stochastic statistical models and mechanistic multiple-path models. Various assumptions are used in these models, including use of a symmetrical or asymmetrical lung, which affects the performance of these models. This study presents the most recent developments of in vivo dosimetry in nanotoxicology, with a focus on the design and modelling approach, and the required input data used, together with verification and validation status of the model. Widely implemented models in nanotoxicology were identified and analyzed, i.e., the Multiple Path Particle Dosimetry (MPPD) model, International Commission on Radiological Protection (ICRP) models, the National Council on Radiation Protection and Measurement (NCRP) model, the Exposure Dose Model (ExDoM) and the Integrated Exposure and Dose Modeling and Analysis System (EDMAS).

Keywords: lung dosimetry; modelling; inhalation; nanomaterials; nanotoxicology

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1. Introduction

Engineered NMs (ENMs) possess unique chemical, physical and biological properties only exhibited at the nanoscale (less than 100 nanometres) and not in bulk. Consequently, these materials have many applications in cosmetics, food, pesticides, medicines, electronics, clothes, construction materials, etc. However, there are concerns over toxicological risks to workers, consumers and the environment. ENMs have been linked with an array of toxicological effects including inflammation [1,2], DNA damage [3–5] and cardiovascular disease [6]. Therefore, risk assessment is conducted for ENMs using in vitro, in vivo and in silico methods.

Dosimetry measures or estimates the internal dose of a substance in individuals/populations to provide a link between an external exposure and a biological response [7]. Laboratory animals are often used in inhalation toxicological and pharmacological studies, where the dose–response analysis is important to estimate the ENMs that are actually deposited in the lungs of these species and humans. Lack of biologically relevant methods results in many inconsistencies found in nanotoxicological studies [8–10]. Computer models of dosimetry

can supplement or alleviate extensive use of experimental studies. In this regard, a number of lung dosimetry models have been developed to estimate the fraction of particles of a given size, shape and density that is deposited in a region of the respiratory tract. However, the dose of ENMs in a particular site of the lung also depends on the clearance kinetics of the NM. Therefore, some lung dosimetry models also include retention of deposited ENMs, which depends on the susceptibility of NM to clearance processes that include solubility and ciliary, macrophage-mediated and lymphatic clearance. This study presents the most recent developments of lung dosimetry in nanotoxicology.

2. Lung Dosimetry Modelling of Nanomaterials

One must assess deposition of ENMs in the respiratory system, their subsequent fate, and exposure to extrapulmonary tissues. Following inhalation, ENMs deposit in the respiratory tract via diffusion as they collide with air molecules and airway walls. Important mechanisms in the deposition of larger particles (e.g., inertial impaction, gravitational settling and interception) do not contribute significantly to inhaled ENM deposition [11]. The significance of each mechanism depends on particle characteristics, location in the lung and breathing rates.

Lung deposition models require information on lung morphometry/physiology, airflow patterns, and physicochemical characteristics of the particles. Morphometric measurements have been conducted in various animals including humans [12–15], dogs [16,17] rats [17,18] and hamsters [17]. In addition, physical representations of the lung have been developed from materials such as silicone rubber [19,20] and acrylic (Veroclear) [21]. These morphometric measurements and cast replicas have been invaluable in the development of many lung dosimetry models, that include deterministic, single-path and multiple path, as well as stochastic/mechanistic models.

Empirical models are based on equations that are derived from experimental data. Models developed from this "top-down" approach have a limited scope since the empirical data are only relevant to the range of the input data and experimental conditions. However, these models do not require specialized computer programs since they comprise simple mathematical relationships. Stahlhofen et al. [22] found poor agreement among datasets for thoracic regional deposition but good agreement between extrathoracic deposition data, for both oral and nasal breathing, and for total deposition.

Deterministic lung models use "bottom-up" approaches to integrate physicochemical data, morphometric data and relevant deposition and clearance mechanisms to estimate the dose of NMs deposited and retained in the lung. These models can range from models based on relatively simple mathematical calculations to mathematically complex (multiple-path) models with lung structures that are constructed from actual airway measurements (Asgharian et al., 2001). In simple deterministic models, successive conductive airways in the lower tracheobronchial region are represented as simple symmetrical structures comprising a set of straight cylindrical tubes, or bifurcating Y-shaped units, with branching at fixed angles into distal tubes [23], while the alveoli are approximated by truncated spheres. Each airway receives identical deposition fractions since the inhaled airflow and particles are equally distributed among all airways in a given generation. In these symmetric deterministic models, each inhaled particle follows the same path and the models are referred to as "single-path" or "typical-path" models [24]. Such deterministic symmetric lung models do not take into consideration the asymmetric branching patterns of airways that lead to inter-individual variability of particle deposition among humans [25]. Therefore, there have been efforts to develop mechanistic and stochastic lung dosimetry models to obtain more realistic and reliable results. For example, Koblinger [23] developed a stochastic asymmetric lung model by statistically analyzing data, i.e., the frequency distributions and correlations among several bronchial and bronchiolar airway parameters such as airway diameters, lengths, branching and gravity angles. While simple deterministic models use a single path that defines average lung conditions, stochastic models do not assign the morphometric parameters but are allowed to vary in a random manner, and thereby take

into consideration the asymmetric branching of airways that leads to inter-individual variability among humans [26]. The lung morphometric parameters are described by statistical distributions using probabilistic or Monte Carlo techniques to account for variations in lung asymmetry and trajectory [27].

Computational modelling of the deposition of nano-objects with at least one external nanoscale dimension, i.e., ENMs in the respiratory tract involves formulation of mathematical equations describing physical and chemical processes, specification of the initial and boundary conditions, and determinations of the solutions of equations for the specified geometry [28]. Without the need for empirical or semi-empirical deposition correlations, computational fluid dynamics (CFD) uses general governing transport equations to predict deposition at a greatly localized level [29–31]. The disadvantages of CFD include the complexity of the computational models, the required computational time and the necessary computer software, hardware and expertise.

Computational approaches either use Eulerian concepts, involving the tracking of an ensemble or concentration of particles, or Lagrangian modelling concepts, where single particles are tracked. The former approach is more suitable for high concentrations of smaller particles, while the latter is preferable for fewer and larger particles [32].

Lung dosimetry of inhaled ENMs also includes clearance, which depends on the region where the ENMs are deposited and the retention characteristics of the specific ENMs. Clearance mechanisms in the lung include mucociliary transportation, phagocytosis by pulmonary alveolar macrophages and dissolution followed by absorption into the systemic circulation through diffusional and pinocytotic processes. In the conducting airways, the main clearance mechanism for insoluble particles is the mucociliary escalator, where mucus created via ciliary beating constantly flows [33]. In the upper generation airways, coughing appears to be an effective removal mechanism for deposited ENMs. In the alveolar region, insoluble ENMs are cleared by alveolar macrophages. However, alveolar macrophage-mediated clearance processes among mammalian species differ significantly [34].

3. Lung Dosimetry Models Widely Implemented in Nanotoxicology

Models have been developed to estimate the in vivo deposition and retention (clearance) of inhaled particles. The Multiple Path Particle Dosimetry (MPPD) model is a suite of 10 asymmetric, structurally different stochastic multiple-path models for the estimation of the deposition and clearance of inhaled monodisperse and polydisperse particles (0.01–20 μm) in various respiratory zones of humans [35,36] as a function of particle concentrations, breathing patterns, airway regions and generation number [37]. Clearance mechanisms include mucociliary transportation, phagocytosis by pulmonary alveolar macrophages and dissolution (followed by absorption into the systemic circulation). Recent versions of the MPPD model can be implemented for ENMs with fast dissolution rates [38].

The MPPD has undergone verification and validation. For example, two rodent studies indicated good agreement between experimentally determined deposition values and those predicted [35,39]. The model was made publicly available and used widely to predict the lung deposition and retention of various ENMs [40–44]. A hygroscopic particle growth model was incorporated into the MPPD model for the prediction of the deposition of hygroscopic particles [45]. The MPPD model has been combined to extrapolate air concentrations corresponding to the in vitro doses to human exposure levels [46]. The MPPD model has also been linked with the PBPK model to assess biodistribution of ENMs [47–49].

The International Commission of Radiological Protection (ICRP) developed semi-empirical lung dosimetry models for inhaled radioactive particles for adult Caucasian males. Various versions of the model exist, including the 1960 version, the 1979 version and the commonly known ICRP66 or the Human Respiratory Tract Model (HRTM) that was published in 1994 [50]. The ICRP models were derived from experimental deposition data for 1–10 μm particles and mathematical expressions for calculating regional deposition in human airways. The three ICRP models use different clearance processes. For example,

while the 1959 model does not include any dissolution or absorption to the systemic circulation, the 1994 model includes dissolution and absorption into the systemic circulation [50]. In a validation study, the ICRP model was shown to be within a factor of two from actual measurements, and the ICRP66 consistently overestimated bronchial concentrations [51]. As compared to the MPPD, different deposition rates were obtained using the ICRP model for particles less than 400 nm [52]. Since the ICRP models are semi-empirical, they cannot be applied outside the scope of adult Caucasian males.

The National Council on Radiation Protection and Measurements (NCRP) developed a mechanistic lung dosimetry model to address the ICRP shortfalls. Clearance of particles from the airways results from mechanical processes (e.g., transport of intact particles) and absorptive processes (e.g., dissolution and transport) [53]. Each region is assigned an effective clearance rate, which is based on a first-order differential equation that assumes that the rate of clearance is proportional to the amount radioactive material present. The model software requires the name of the substance, which is then linked to pre-programmed clearance factors such as dissolution rate constants or dissolution rates [53]. A higher prediction of tracheobronchial deposition and a lower pulmonary deposition were reported by the NCRP models than the ICRP 1994 [54]. The NCRP noted the needs for the inclusion of ENMs that reach the systemic circulation, which are expected to have different uptake, distribution and retention characteristics compared to soluble radionuclides for which the model was designed [55]. The model also needs to be updated to include accumulation of ENMs in secondary organs following translocation.

Since the MPPD, ICRP and NCRP models can only be utilized to calculate deposition and clearance from constant exposure, the Exposure Dose Model (ExDoM) was developed to enable estimation of deposition and clearance resulting from variable continuous exposure conditions [56]. The model operates on Windows computers and is available from the developers by request. EXDoM utilizes semi-empirical approaches similar to the ICRP models and can be utilized to calculate clearance for soluble as well as relatively insoluble particles. The deposition module of the model was successfully validated against experimentally derived values as well as against results from the ICRP66 and MPPD models [56]. ExDoM was utilized to assess the exposure to particulate matter-bound metals among landfill workers [57].

The integrated Exposure and Dose Modeling and Analysis System (EDMAS) was also developed to address the inherent shortcomings of the MPPD, ICRP and NCRP models. However, while ExDoM deals with variable continuous exposure conditions, EDMAS has the capacity to address time-dependent changes in particle size and composition resulting from nucleation, condensation, coagulation and gas phase chemical reaction [58,59]. The model was evaluated and shown to be in good agreement with results from experimental data and results from other models [59]. However, while the processes that may affect deposition and time-resolved particle characteristics (nucleation, condensation, coagulation and diffusion) are clearly addressed by Georgopoulos et al. [58] and Lazaridis et al. [59], the processes that affect clearance are not well articulated. One disadvantage of the model is that, as a mechanistic model, it requires many physiology parameters.

In addition to the models discussed in the previous paragraphs, there is need to assess the applicability of models designed for microparticles, such as those by Tian et al. [60], Inthavong et al. [61], Rahimi-Gorji et al. [30], Longest et al. [62], Inthavong et al. [63], Tian et al. [64] and Kolanjiyil and Kleinstreuer [31], to NMs. Unfortunately, the availability of some these models in computer-executable software is not certain.

In summary, different in vivo dosimetry models have different designs, structures, underlying assumptions and capacities to estimate the dose of inhaled ENMs. These models have been integrated with other models, where the merits and drawbacks are highlighted and discussed.

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