ECAS 2022

MDPI

Proceeding Paper

Lung dosimetry modelling in nanotoxicology: A critical analysis of the state of the art

Wells Utembe[1,2,3*], Natasha Sanabria[1]

[1] Toxicology and Biochemistry, National Institute for Occupational Health, Johannesburg, South Africa; natashas@nioh.ac.za
[2] Department of Environmental Health, University of Johannesburg, Johannesburg, South Africa
[3] Environmental Health Division, School of Public Health and Family Medicine, University of Cape Town, South Africa
* Correspondence: wellsu@nioh.ac.za or wutembe@cartafrica.org
† Presented at 5th International Electronic Conference on Atmospheric Sciences, 16–31 July 2022; Available online: https://ecas2022.sciforum.net/.

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, as well as 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, as well as 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 Integrated Exposure and Dose Modeling and Analysis System (EDMAS).
Keywords: Lung dosimetry; modelling; inhalation; nanomaterials; nanotoxicology

Academic Editor: *Daniele Contini*
Published: 14 July 2022
Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2022 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

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], cardiovascular disease [6]. Therefore, risk assessment is conducted for ENMs using both *in vitro* and *in vivo* 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. Computer models of dosimetry can supplement or alleviate extensive use of experimental studies. However, the lack of biologically-relevant methods result in many inconsistencies found in nanotoxicological

studies [8-10]. Consequently, 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. Some lung dosimetry models also include retention of deposited ENMs, which depends on the susceptibility of NM to clearance processes that include solubility, ciliary clearance, 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 extra-pulmonary tissues. Following inhalation, ENMs deposit in the respiratory tract via diffusion as they collide with air molecules. 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 physico-chemical 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, empirical (*in vitro*) 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, i.e. deterministic, single-path and stochastic/mechanistic multiple-path 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 is only relevant to the range of the input data and experimental conditions. However, these models do not require specialized computer programs since they comprise of simple mathematical relationships. Stahlhofen, Rudolf [22] found a poor agreement among datasets for thoracic regional deposition but a 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 physico-chemical data, morphometric data and relevant deposition and clearance mechanisms to estimate the dose of NMs deposited and retained in the lung. In simple deterministic models, successive conductive airways in the lower (tracheobronchial region are represented as simple symmetrical structures comprising of 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-'' 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, a stochastic asymmetric lung model was developed Koblinger [23] 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 three external nanoscale dimensions, i.e. NMs 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 of empirical or semi-empirical deposition correlations, computational fluid dynamics (CFD) uses general governing transport equations to predict deposition at a very localized level [29-31]. The disadvantages of CFD include the complexity of the computational models, the required computational time and the required 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 can estimate 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], where the 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, e.g., 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 incorportaed 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 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, e.g. the 1960 version, the 1979 version and the commonly known ICRP66 or the Human Respiratory Tract Model (HRTM) published in 1994 [50]. The ICRP models were derived from experimental deposition data of 1-10 μm particles as well as mathematical expressions for calculating regional deposition in human airways. The three ICRP models use different clearance processes. 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 2 from actual measurements and the ICRP66 consistently overestimated bronchial concentrations [51]. As compared to the MPPD, different deposition rates were obtained uisng the ICRP model for particles less 400nm [52]. Since the ICRP models are semi-empirical, they cannot be applied outside of their 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 matter from the airways results from the 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 a pre-programmed clearance factors such as dissolution rate constants or dissolution rates [53]. A higher prediction of tracheobronchial deposition and a lower pulmonary deposition was 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 on request from the developers. 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 the ICRP66 model and the MPPD model [56]. ExDoM was utilized to assess the exposure to particulate matter-bound metals among landfill workers [57].

The *i*ntegrated 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, gas phase chemical reaction *[58, 59]* The model was evaluated to be in good agreement with results from experimental data as well

as results from other models [59]. However, while the processes that may affect deposition (nucleation, condensation, coagulation and diffusion) are clearly addressed, the processes that affect clearance are not well articulated [60]. 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, Longest [61], Inthavong, Choi [62], Rahimi-Gorji, Gorji [30], Longest, Tian [63], Inthavong, Tu [64], Tian, Hindle [65] 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 were highlighted and discussed.

Author Contributions: "Conceptualization, WU methodology, WU and NS, writing—original draft preparation, WU; writing—review and editing, NS, supervision, NS project administration, NS.; All authors have read and agreed to the published version of the manuscript. Funding: "This research received no external funding. Institutional Review Board Statement: Not applicable. Data Availability Statement: There is no supporting data for this study. Conflicts of Interest: "The authors declare no conflict of interest."

References

1. Gojova, A., et al., *Induction of inflammation in vascular endothelial cells by metal oxide nanoparticles: effect of particle composition.* Environmental health perspectives, 2007: p. 403-409.
2. Park, M.V.D.Z., et al., *The effect of particle size on the cytotoxicity, inflammation, developmental toxicity and genotoxicity of silver nanoparticles.* Biomaterials, 2011. **32**(36): p. 9810-9817.
3. Auffan, M., et al., *CeO2 nanoparticles induce DNA damage towards human dermal fibroblasts in vitro.* Nanotoxicology, 2009. **3**(2): p. 161-171.
4. Hackenberg, S., et al., *Silver nanoparticles: Evaluation of DNA damage, toxicity and functional impairment in human mesenchymal stem cells.* Toxicology Letters, 2011. **201**(1): p. 27-33.
5. Trouiller, B., et al., *Titanium dioxide nanoparticles induce DNA damage and genetic instability in vivo in mice.* Cancer research, 2009. **69**(22): p. 8784-8789.
6. Helfenstein, M., et al., *Effects of combustion-derived ultrafine particles and manufactured nanoparticles on heart cells in vitro.* Toxicology, 2008. **253**(1–3): p. 70-78.
7. Kuempel, E., et al., *Lung dosimetry and risk assessment of nanoparticles: evaluating and extending current models in rats and humans.* Inhalation toxicology, 2006. **18**(10): p. 717-724.
8. Cohen, J.M., G.M. DeLoid, and P. Demokritou, *A critical review of in vitro dosimetry for engineered nanomaterials.* Nanomedicine, 2015. **10**(19): p. 3015-3032.
9. Sayes, C.M., et al., *Comparative Pulmonary Toxicity Assessments of C60 Water Suspensions in Rats: Few Differences in Fullerene Toxicity in Vivo in Contrast to in Vitro Profiles.* Nano Letters, 2007. **7**(8): p. 2399-2406.
10. Sayes, C.M., K.L. Reed, and D.B. Warheit, *Assessing toxicity of fine and nanoparticles: comparing in vitro measurements to in vivo pulmonary toxicity profiles.* Toxicological Sciences, 2007. **97**(1): p. 163-180.
11. Oberdörster, G., E. Oberdörster, and J. Oberdörster, *Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles.* Environmental health perspectives, 2005. **113**(7): p. 823-839.
12. Weibel, E.R., A.F. Cournand, and D.W. Richards, *Morphometry of the human lung*. Vol. 1. 1963: Springer.
13. Horsfield, K. and G. Cumming, *Morphology of the bronchial tree in man.* Journal of applied physiology, 1968. **24**(3): p. 373-383.

14. Shang, Y., et al., *Detailed computational analysis of flow dynamics in an extended respiratory airway model.* Clinical biomechanics, 2019. **61**: p. 105-111.
15. Yeh, H.-C. and G. Schum, *Models of human lung airways and their application to inhaled particle deposition.* Bulletin of mathematical biology, 1980. **42**(3): p. 461-480.
16. Horsfield, K. and G. Cumming, *Morphology of the bronchial tree in the dog.* Respiration Physiology, 1976. **26**(2): p. 173-182.
17. Raabe, O., *Tracheobronchial geometry-human, dog, rat, hamster.* Lovelace Foundation for Medical Education and Research. Report number LF-53., 1976.
18. Yeh, H., G. Schum, and M. Duggan, *Anatomic models of the tracheobronchial and pulmonary regions of the rat.* The anatomical record, 1979. **195**(3): p. 483-492.
19. Cheng, Y.-S., Y. Zhou, and B.T. Chen, *Particle deposition in a cast of human oral airways.* Aerosol Science & Technology, 1999. **31**(4): p. 286-300.
20. Zhou, Y. and Y.-S. Cheng, *Particle deposition in a cast of human tracheobronchial airways.* Aerosol Science and Technology, 2005. **39**(6): p. 492-500.
21. Nordlund, M., et al., *Multicomponent aerosol particle deposition in a realistic cast of the human upper respiratory tract.* Inhalation toxicology, 2017. **29**(3): p. 113-125.
22. Stahlhofen, W., G. Rudolf, and A. James, *Intercomparison of experimental regional aerosol deposition data.* Journal of Aerosol Medicine, 1989. **2**(3): p. 285-308.
23. Koblinger, L., *Analysis of human lung morphometric data for stochastic aerosol deposition calculations.* Physics in Medicine & Biology, 1985. **30**(6): p. 541.
24. Hofmann, W., *Regional deposition: deposition models.* Journal of Aerosol Medicine and Pulmonary Drug Delivery, 2020. **33**(5): p. 239-248.
25. Hofmann, W., R. Winkler-Heil, and I. Balásházy, *The effect of morphological variability on surface deposition densities of inhaled particles in human bronchial and acinar airways.* Inhalation toxicology, 2006. **18**(10): p. 809-819.
26. Martonen, T.B., J.A. Rosati, and K.K. Isaacs, *Modeling deposition of inhaled particles.* Aerosols handbook, 2005.
27. Mitsakou, C., C. Helmis, and C. Housiadas, *Eulerian modelling of lung deposition with sectional representation of aerosol dynamics.* Journal of Aerosol Science, 2005. **36**(1): p. 75-94.
28. Rostami, A.A., *Computational Modeling of Aerosol Deposition in Respiratory Tract: A Review.* Inhalation Toxicology, 2009. **21**(4): p. 262-290.
29. Longest, P.W. and L.T. Holbrook, *In silico models of aerosol delivery to the respiratory tract—development and applications.* Advanced drug delivery reviews, 2012. **64**(4): p. 296-311.
30. Rahimi-Gorji, M., T.B. Gorji, and M. Gorji-Bandpy, *Details of regional particle deposition and airflow structures in a realistic model of human tracheobronchial airways: two-phase flow simulation.* Computers in biology and medicine, 2016. **74**: p. 1-17.
31. Kolanjiyil, A.V. and C. Kleinstreuer, *Computationally efficient analysis of particle transport and deposition in a human whole-lung-airway model. Part I: Theory and model validation.* Computers in Biology and Medicine, 2016. **79**: p. 193-204.
32. Lejon, C. *Lung Deposition Models for Exposure and Risk assessment*. 2019 5 April 2019]; Available from: file:///C:/Users/WellsU/Downloads/FOIR4753.pdf.
33. Oberdörster, G., *Lung dosimetry: pulmonary clearance of inhaled particles.* Aerosol science and technology, 1993. **18**(3): p. 279-289.
34. Snipes, M., B. Boecker, and R. McClellan, *Retention of monodisperse or polydisperse aluminosilicate particles inhaled by dogs, rats, and mice.* Toxicology and applied pharmacology, 1983. **69**(3): p. 345-362.
35. Anjilvel, S. and B. Asgharian, *A multiple-path model of particle deposition in the rat lung.* Toxicological Sciences, 1995. **28**(1): p. 41-50.

36. Demokritou, P., et al., *An in vivo and in vitro toxicological characterisation of realistic nanoscale CeO2 inhalation exposures.* Nanotoxicology, 2013. **7**(8): p. 1338-1350.
37. ARA. *Multiple-Path Particle Dosimetry Model (MPPD v 2.11)*. 2017 03 May 2022]; Available from: https://www.ara.com/products/multiple-path-particle-dosimetry-model-mppd-v-211,.
38. Miller, F.J., et al., *Improvements and additions to the multiple path particle dosimetry model.* Journal of Aerosol Science, 2016. **99**: p. 14-26.
39. Cassee, F.R., et al., *Particle size-dependent total mass deposition in lungs determines inhalation toxicity of cadmium chloride aerosols in rats. Application of a multiple path dosimetry model.* Archives of toxicology, 2002. **76**(5): p. 277-286.
40. Ling, M.-P., et al., *Assessing the potential exposure risk and control for airborne titanium dioxide and carbon black nanoparticles in the workplace.* Environmental Science and Pollution Research, 2011. **18**(6): p. 877-889.
41. Patterson, R.F., et al., *Particle deposition in respiratory tracts of school-aged children.* Aerosol and Air Quality Research, 2014. **14**(1): p. 64-73.
42. Ji, J.H. and I.J. Yu, *Estimation of human equivalent exposure from rat inhalation toxicity study of silver nanoparticles using multi-path particle dosimetry model.* Toxicology Research, 2012. **1**(3): p. 206-210.
43. Chio, C.-P. and C.-M. Liao, *Assessment of atmospheric ultrafine carbon particle-induced human health risk based on surface area dosimetry.* Atmospheric Environment, 2008. **42**(37): p. 8575-8584.
44. Martins, L.D., et al., *Potential health impact of ultrafine particles under clean and polluted urban atmospheric conditions: a model-based study.* Air Quality, Atmosphere & Health, 2010. **3**(1): p. 29-39.
45. Asgharian, B., *A model of deposition of hygroscopic particles in the human lung.* Aerosol science and technology, 2004. **38**(9): p. 938-947.
46. Romeo, D., B. Nowack, and P. Wick, *Combined in vitro-in vivo dosimetry enables the extrapolation of in vitro doses to human exposure levels: A proof of concept based on a meta-analysis of in vitro and in vivo titanium dioxide toxicity data.* NanoImpact, 2022. **25**: p. 100376.
47. Tsiros, P., et al., *Towards an in silico integrated approach for testing and assessment of nanomaterials: from predicted indoor air concentrations to lung dose and biodistribution.* Environmental Science: Nano, 2022. **9**(4): p. 1282-1297.
48. Romeo, D., et al., *An integrated pathway based on in vitro data for the human hazard assessment of nanomaterials.* Environment International, 2020. **137**: p. 105505.
49. Yao, W., D.L. Gallagher, and A.M. Dietrich, *Risks to children from inhalation of aerosolized aqueous manganese emitted from ultrasonic humidifiers can be greater than for corresponding ingestion.* Water Research, 2021. **207**: p. 117760.
50. Boecker, B.B., *Comparison of old and new ICRP models for respiratory tract dosimetry.* Radiation Protection Dosimetry, 1995. **60**(4): p. 331-336.
51. Harley, N., I. Fisenne, and E. Robbins, *Attempted validation of ICRP 30 and ICRP 66 respiratory models.* Radiation protection dosimetry, 2012. **152**(1-3): p. 14-17.
52. Hammer, T., H. Fissan, and J. Wang, *Determination of the delivered dose of nanoparticles in the trachea-bronchial and alveolar regions of the lung.* NanoImpact, 2019. **14**: p. 100162.
53. Chang, I., et al., *Software for the draft NCRP respiratory tract dosimetry model.* Radiation Protection Dosimetry, 1991. **38**(1-3): p. 193-199.
54. Yeh, H.-C., et al., *Comparisons of calculated respiratory tract deposition of particles based on the proposed NCRP model and the new ICRP66 model.* Aerosol Science and Technology, 1996. **25**(2): p. 134-140.
55. Hoover, D. *An Overview of National Council on Radiation Protection and Measurements Report No. 176 on Radiation Safety Aspects of Nanotechnology*. 2017 27 May 2022]; Available from: https://orau.org/ihos/downloads/tech-topics/workersafety/2017/Hoover_2017-08-29pt1.pdf.

56. Aleksandropoulou, V. and M. Lazaridis, *Development and application of a model (ExDoM) for calculating the respiratory tract dose and retention of particles under variable exposure conditions.* Air Quality, Atmosphere & Health, 2013. **6**(1): p. 13-26.
57. Chalvatzaki, E., V. Aleksandropoulou, and M. Lazaridis, *A case study of landfill workers exposure and dose to particulate matter-bound metals.* Water, Air, & Soil Pollution, 2014. **225**(1): p. 1-19.
58. Georgopoulos, P.G., et al., *Integrated Exposure and Dose Modeling and Analysis System. 1. Formulation and Testing of Microenvironmental and Pharmacokinetic Components.* Environmental Science & Technology, 1997. **31**(1): p. 17-27.
59. Lazaridis, M., et al., *Integrated exposure and dose modeling and analysis system. 3. Deposition of inhaled particles in the human respiratory tract.* Environmental science & technology, 2001. **35**(18): p. 3727-3734.
60. Georgopoulos, P.G., et al., *Integrated exposure and dose modeling and analysis system. 1. Formulation and testing of microenvironmental and pharmacokinetic components.* Environmental science & technology, 1996. **31**(1): p. 17-27.
61. Tian, G., et al., *Development of a stochastic individual path (SIP) model for predicting the tracheobronchial deposition of pharmaceutical aerosols: Effects of transient inhalation and sampling the airways.* Journal of Aerosol Science, 2011. **42**(11): p. 781-799.
62. Inthavong, K., et al., *Micron particle deposition in a tracheobronchial airway model under different breathing conditions.* Medical engineering & physics, 2010. **32**(10): p. 1198-1212.
63. Longest, P.W., et al., *Validating Whole-Airway CFD Predictions of DPI Aerosol Deposition at Multiple Flow Rates.* J Aerosol Med Pulm Drug Deliv, 2016. **29**(6): p. 461-481.
64. Inthavong, K., et al., *Effects of airway obstruction induced by asthma attack on particle deposition.* Journal of Aerosol Science, 2010. **41**(6): p. 587-601.
65. Tian, G., et al., *Validating CFD Predictions of Pharmaceutical Aerosol Deposition with In Vivo Data.* Pharm Res, 2015. **32**(10): p. 3170-87.