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Authors
Darquenne, Chantal
Hoover, Mark D
Phalen, Robert F

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Review

Inhaled aerosol dosimetry: Some current research needs

Chantal Darquenne [a,*], Mark D. Hoover [b], Robert F. Phalen [c]

[a] Department of Medicine, University of California, San Diego, CA 92093-0623, USA
[b] Respiratory Health Division, National Institute for Occupational Safety and Health, Morgantown, VA 26505-2888, USA
[c] Department of Medicine, Center for Occupational and Environmental Health, University of California, Irvine, CA 92617-1830, USA

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ABSTRACT

After the presentation of 60 papers at the conference "Advancing Aerosol Dosimetry Research" (October 24–25, 2014 in Irvine, CA, USA), attendees submitted written descriptions of needed research. About 40 research needs were submitted. The suggestions fell into six broad categories: 1) Access to detailed anatomic data; 2) Access to subject-specific aerosol deposition datasets; 3) Improving current inhaled aerosol deposition models; 4) Some current experimental data needs and hot topics; 5) Linking exposure and deposition modeling to health endpoints; and 6) Developing guidelines for appropriate validation of dosimetry and risk assessment models. Summaries of suggestions are provided here as an update on research needs related to inhaled aerosol dosimetry modeling. Taken together, the recommendations support the overarching need for increased collaborations between dose modelers and those that use the models for risk assessments, aerosol medicine applications, design of toxicology experiments, and extrapolation across species. This paper is only a snapshot in time of perceived research needs from the conference attendees; it does not carry the approval of any agency or other group that plans research priorities or that funds research.

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* Corresponding author.

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1. Introduction

A diverse assortment of scientists active in inhaled dosimetry related research assembled for a two-day topical conference ("Advancing Aerosol Dosimetry Research") on October 24 and 25, 2014 in Irvine, CA that featured 60 papers. The attendees identified their specialties and/or interests to include: toxicology, physiology, anatomy, engineering, physics, industrial hygiene, occupational medicine, aerosol science, fluid dynamics, epidemiology, environmental science, and computer modeling. After the papers were presented and discussed, attendees were invited to provide written descriptions of "needed research".

Like many other fields of research, a point has been reached where major advances in inhaled aerosol dose modeling will only be achieved with an interdisciplinary approach that includes modelers, experimentalists, physiologists, risk assessors, occupational scientists and clinicians. The meeting participants provided about 40 suggestions of current needs in aerosol dosimetry research. An edited summary of these suggestions is provided here as an update to those made at the first conference, "Frontiers in Aerosol Dosimetry Research" that was also held in Irvine, CA on October 24 and 25, 2005 (Phalen & Hoover, 2006) The contributions are a snapshot in time, and not the product of any agency or group that develops and/or funds aerosol dosimetry-related research.

2. Access to detailed anatomic data

Modelers expressed the need for wider access to detailed anatomical data on the mammalian respiratory tract including the extra-thoracic airways, the conducting airways and the alveolar region. Such datasets are not only needed for the human, but also for several animal species commonly used in toxicology studies. It was suggested that a data repository archive that could be freely accessed by modelers should be created. Such a repository will require new funding for its creation and maintenance.

Beyond anatomical data that are undoubtedly necessary inputs to any lung modeling effort, an accurate description of the biomechanical properties of the lung is also essential, including the alveolar region of the lung, so that realistic cyclic expansion and contraction of the lung units as breathing proceeds can be incorporated in the models (Asgharian, Price, & Oberdorster, 2006). So far, most studies of the alveolar region have assumed rigid structures or isotropic expansion of alveolar space, although there is a broad appreciation and some evidence in the literature that this may not be appropriate (Balashazy, Hofmann, Farkas, & Madas, 2008; Darquenne, Harrington, & Prisk, 2009; Lee & Lee, 2003).

3. Access to subject-specific aerosol deposition datasets

The need for additional experimental studies of aerosol deposition was noted by many meeting participants. In recent years, there has been a substantial development of sophisticated individual subject-specific computational fluid dynamics (CFD) models of aerosol transport and deposition in human lungs (Rostami, 2009). However, independent experimental validation of predictions from these new models is sparse. Because of the lack of subject-specific data, most validations used averaged in vivo data from the literature. As considerable inter-subject variability exists both in airway geometry and in deposition data, validating models with averaged in-vivo data is not optimal. The validation process could be significantly improved if subject-specific aerosol deposition data could be published along with the anatomical data and relevant physiological parameters from which these computational models were developed.

Similarly, there have been very few recent aerosol deposition studies in the animal models commonly used for toxicological studies. There is also a need for more realistic animal inhalation exposures in exposure systems in which the exposure dose is validated (e.g. Oldham, Phalen, & Budiman, 2009). Some participants also felt that many of the existing datasets of aerosol deposition in animals are outdated and that studies using newer exposure technologies that also monitor breathing parameters should be performed. Indeed, there is a need for more accurate physiological input data for various animal species. Examples of such physiologic variables are functional residual capacity, breathing frequency, and tidal volume for the exposure scenario being modeled. Allometric equations for anatomical and physiological parameters as functions of individual body mass for mice, rats, dogs and humans are provided in a review by Lindstedt and Schaeffer (2002). Such allometric equations are useful for modeling, as body mass is an important variable that modifies an individual's pulmonary function and other relevant parameters. Although representative, these values do not represent a "single' value for a given animal/individual but rather a default value that can be used when direct measurements are lacking.

4. Improving current inhaled aerosol deposition models

The current computational models fall into two main types; traditional, that use simplified airway models (e.g., MPPD – Asgharian, Hofmann, & Bergman, 2001; ICRP, 1994; NCRP, 1997), and computational fluid dynamics (CFD) models that can use realistic airway structures (e.g., from scanning data in living subjects). Both approaches need improvement.

Beyond the evident need for accurate anatomical data to develop the lung models and the access to experimental data to validate numerical predictions, several other issues are in need of more attention. Those identified by the meeting participants included 1) the effects of aerosol inhalability and route of inhalation (e.g., nasal vs oral inhalation) on aerosol deposition predictions, 2) the effects of the physical characteristics of the aerosol (e.g., solid vs. aqueous particles, volatile particle components, particle shapes, nano-sizes, etc.) on their fate, and 3) the interaction of aqueous/soluble particles with wetted surfaces.

Unlike simplified conventional compartmental and one-dimensional (1D) mechanistic models that typically describe the entire lung, the more recent three-dimensional (3D) computational fluid dynamics (CFD)-based models only include a specific region of the lung (for example Darquenne, Harrington, & Prisk, 2009; Darquenne, van Ertbruggen, & Prisk, 2011; Longest, Tian, Li, Son, & Hindle, 2012; Ma & Darquenne, 2011; Ma & Lutchen, 2009; Sznitman, Helmsch, Wildhaber, Tsuda, & Rosgen, 2009). This is because of limitations in reconstruction of smaller airways due to the lack of image resolution and because CFD models are typically more costly in terms of computational power than the conventional models, which makes the development of a 3D model of the entire respiratory tract airway unrealistic. Accordingly, there is a need for developing new multiscale strategies to link varied models that apply to different regions of the body (e.g. lung, blood, and other compartments). It should be noted that such effort has been initiated recently by a few groups of investigators (e.g., Corley et al., 2012; Oakes et al., 2014).

Most existing models of aerosol dosimetry provide information only on the physical process of aerosol transport and deposition in static anatomical airway data. It was noted that models could be significantly improved if they would also consider the effects of physiological phenomena on particle inhalation and post-deposition events. One major improvement could come from better coupling between CFD modeling and physiologically based pharmacokinetic (PBPK) models to not only predict aerosol deposition sites but also the subsequent effects of particle clearance, metabolism, distribution, and elimination.

Finally, there is a need to assess how much model detail is required to answer a specific question at hand. While the access to ever improved anatomical and physiological data allow for the development of increasingly more elaborate models (although at the cost of increased computational power and time), the field might benefit from a thorough assessment of the most important features needed to provide predictions that are accurate enough to bring improved insights to risk assessors, clinicians and epidemiologists.

5. Some current experimental data needs and hot topics

Despite decades of research on aerosol exposure and its effects on human health, there are yet numerous gaps in knowledge that need to be filled. For example, the fate of varied nanoparticles following their deposition in the respiratory tract is still poorly understood (Oberdorster, Stone, & Donaldson, 2007). How are these deposited particles cleared post deposition and where do they travel and eventually end up? The topic of particle clearance and transformation, crucial for risk assessment, was not well represented at the conference. This highlights the need for creating more opportunities for researchers in parallel fields to interact and collaborate.

For ethical reasons, most of the toxicological studies are performed in animals. Results from these studies then need to be extrapolated to human scenarios in an attempt to estimate human health risks. This is a non-trivial task that was pointed out by some participants as still being performed in a rudimentary fashion. Better extrapolation strategies are needed and should be developed.

Inhalability (i.e., particle aspiration- or inhalation-efficiency) is still poorly understood, with current human models strictly applying only to the average worker exposed to low wind speeds. Studies in other environmental conditions, laboratory animals, children, and other human populations are needed. Results from inhalability studies are also badly needed as inputs to computational models to provide more realistic exposure predictions for a wider group of subjects and exposure scenarios.

Finally, the recent development of e-cigarettes brings with it several unknowns in terms of potential toxic effects. More research is required on e-cigarette emissions, their deposition in the respiratory tract regions, and their potential toxicities.

6. Linking exposure and deposition modeling to health endpoints

Exposure scientists, modelers, clinicians and toxicologists have historically worked in separate “worlds”, with relatively few interactions. Such interactions are not only important but also required for a critical evaluation of how exposure-informed hazard assessment and hazard-informed exposure assessment can lead to modeling that improves our understanding of the health impacts from particulate matter exposure. In particular, there is a need for better linking epidemiological, toxicological and modeling studies to improve the tools available for risk assessment of various aerosol exposures. Improvements in medical aerosol applications require collaborations between modelers and clinicians. Some participants suggested the need for identifying and linking specific particle “metrics” (i.e., properties that determine the biological effects) to specific health-related outcomes. Such metrics are needed by modelers in order for their efforts to be more applicable to real-world problems.

7. Developing guidelines for appropriate validation of dosimetry and risk assessment models

There is currently no gold standard approach to validate models of aerosol deposition or models of risk assessment. The field would benefit from the formulation of guidelines for researchers, regulators and physicians for reliable risk assessments. The guidelines should consider clear and likely different requirements for acute, sub-acute and chronic exposures.

8. Conclusions

Most of the recommendations provided by the meeting participants strongly suggest the need for more interdisciplinary research from the disciplines of environmental exposure and toxicology, medicine, and modeling, not only to improve our understanding of the adverse health impacts of particulate matter exposure but also to develop new practices in medicine and applied physiology. Progress in aerosol dosimetry modeling itself depends on input from those who apply the models to their problems. Although much progress has been made since the 2005 conference, new challenges, and research opportunities have arisen. All of the participants who filled out the research needs form also indicated (in response to a question) that a similar follow-on conference with even more disciplines represented was needed.

For additional recent reviews that also cover needed research see Frolich and Salar-Behzadi (2014), Hofmann (2011), Phalen, Mendez, and Oldham (2010), Rostami (2009), and Wang (2011).

Declaration

The authors' declare that they have no conflicts of interest. Also, the authors of this paper are solely responsible for its content, and this content does not necessarily represent the views or policies of their respective organizations.

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