

Aerosol Dosimetry Research Needs

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The October 2005 Frontiers in Aerosol Dosimetry Research Conference brought together 95 experts representing 53 organizations from 12 different countries to discuss the state of the art in estimating internal doses from inhaled aerosol particles and gases. About one-third of the conference participants were from universities, one-third from commercial firms, and one-third from government/national laboratories, consulting firms, and other entities. At the end of the 2-day meeting, which was held at the Beckman Center of the National Academies on the University of California, Irvine, campus, attendees were invited to submit written suggestions for high-priority research. More than 50 suggested projects were submitted and the suggestions have been grouped into 32 specific topics covering four broad categories. An edited summary of the suggestions is provided here, starting with those topics most often noted. These suggestions are simply a snapshot of the priorities of individual scientists, and do not carry the approval of any regulatory or funding agency.

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DEVELOPMENT AND VALIDATION OF DOSIMETRY MODELS

Although existing aerosol deposition models are impressive in their mathematical elegance and ability to provide useful dose predictions, many suggestions were offered that related to their improvement:

1. Scrutinize past and present particle deposition, retention, and clearance models to identify needs for improvement and a logical sequence for developing and validating new models.
2. Study the fundamental theories of particle deposition (including phenomena such as evaporation and bulk behavior) and evaluate the alternative approaches for their ability to explain observations.
3. Analyze the basic phenomena responsible for the deposition of inhaled particles (including factors such as flow instability and particle dynamics), especially for the submicrometer, noninertial regime.
4. Ascertain what is known and what is unknown regarding obtaining correct dose assessments (not just particle deposition predictions), including any special retention or clearance issues for nanoparticles.
5. Improve physical simulations of particle deposition in the respiratory tract to provide more realistic physiological conditions. Such simulations should include modeling all regions of the respiratory tract in an integrated fashion, from the nares to distal alveoli, instead of focusing on isolated regions.
6. Establish a scientific basis for determining the relative importance of model parameters and how the key model parameters and models can be validated.
7. Develop better physical (hollow) models of all of the airways and establish experimental designs and protocols for their validation with respect to in vivo particle inhalation.
8. Validate the predictions of lobar particle deposition models.

9. Improve particle deposition models for the alveolus, including anatomical, physiological, mechanical and functional factors.
10. Establish a common database for the purpose of making the results of various particle deposition models accessible.
11. Facilitate better coordination of efforts of groups using various particle deposition approaches in order to define the scope of needed improvements and to facilitate joint research activities.

These suggestions indicate concerns for the adequacy of current approaches to modeling inhaled particle deposition. The needed improvements include clear identification of what advances are needed, how to proceed, and how to validate the models. To make major advances, enhanced communication (and coordination) among several specialties, including theoretical aerosol physics, fluid dynamics, anatomy, and physiology will be required.

UNDERSTANDING NANOPARTICLES AND COMPLEX AEROSOLS

Particle deposition models have been, and still are, primarily focused on smooth, rigid, solid, spherical micrometer size particles, but such ideal particles seldom occur outside the laboratory. Nonideal aerosols include nanoparticles (with one or more dimension smaller than $0.1 \mu\text{m}$), fiber-like particles, agglomerates, and particles in combination with gases (other than those found in clean air). Several suggestions were offered related to nonideal aerosols and aerosol systems and the need to better define the overall research needs:

1. Improve the understanding of nanoparticle formation, transport and deposition/retention in the respiratory tract.
2. Better define the leaching/dissolution/absorption characteristics and translocation out of the lung of deposited nanoparticles.
3. Obtain in vivo data on the translocation of nanoparticles from the lung to the rest of the body, especially to the cardiovascular system.
4. Facilitate experimental measurements of the dose and toxicity (including cardiovascular and other effects) of inhaled combustion products (which are frequently in the nanoparticle size range).
5. Improve the understanding of cigarette smoke particles (including those from nontraditional cigarettes, such as mentholated) to define the effects of electrical charges and particle size distributions on deposition and ill effects (especially cancer).
6. Better understand pharmaceutical aerosol drug delivery. Include studies of microdosimetry (localized depositions) for inhaled antibiotics, proteins, and liposome/vesicle delivery systems.
7. Improve the understanding of particle-gas mixture behavior, in terms of both physical interactions and biological effects.

8. Advance the basic understanding of nonspherical particle dynamics.

BIOLOGICAL AND HEALTH-RELATED ISSUES

There is a widespread belief that the current understanding of basic biological phenomena and health-related information has not been adequately considered in aerosol dosimetry models. Aspects of this issue include incorporating epidemiology and toxicology data into models, and defining the appropriate dose metrics (such as particle composition, mass, surface area, count, or bioavailability) to use in models. In addition, the physical and chemical interactions of particles with airway fluids and cells have not been adequately addressed by modelers. Suggested research needs were:

1. Improve the utilization of dose-response information in dosimetry models, which will lead to better definitions of what should be modeled and to what accuracy. Both human and laboratory animal data should be considered.
2. Incorporate epidemiology findings and mechanistic toxicology results into the design of dosimetry models.
3. Explore the concepts of homeostasis and essential biological functions more fully so that they can inform dosimetric model advances.
4. Better define the relevant dose metrics associated with important biological responses.
5. Improve the understanding of individual susceptibility, which is modified both by genetic and environmental factors, as well as age and gender.
6. Improve particle clearance models in order to include (a) mucus transport (especially local aspects), and (b) partition coefficients for aerosol components in mucus, surfactant, and lung cells; include applications for pharmaceutical aerosols and nanoparticles.
7. Examine the local chemical reactions associated with particles (and particle-gas combinations) in the respiratory-tract environment.
8. Quantify the effect of various disease states on airway structure and airflow dynamics.
9. Perform dosimetry reconstructions on older studies (especially for nanoparticle inhalation) to increase the understanding of relevant biological doses and dose metrics (such as particle surface area and projected area).

OTHER RESEARCH PRIORITIES

Several suggestions identifying research needs pointed to other problems that may require additional attention:

1. Develop better tools for measuring particle deposits in living subjects. Such tools include the use of radiotracers, quantum dots (nanocrystals on the order of one or a few nanometers in size that emit easily detectable photons), and magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET),

and single-photon emission computed tomography (SPECT) technologies.

2. Expand dosimetry modeling efforts to include biodefense-related aerosols, including chemical, biological, and nuclear agents.
3. Expand dosimetry modeling to include gravitational and other conditions relevant to aerosols that may be encountered in the exploration of space. These problems are of special interest to the National Aeronautics and Space Administration and include dusts related to manned missions to the Moon and Mars and exposures in microgravity environments. Both theoretical and experimental approaches are needed.
4. Include dosimetry efforts related to the exposure of specific individuals. Consideration of an individual's anatomy, ventilation, and particles present in the breathing zone (as opposed to just the local environment) of an individual will be required. This research will be facilitated by the ability to apply sophisticated computational fluid dynamics (CFD) techniques integrated with quantitative biometric information.

CONCLUSIONS

Given the variety of these suggestions from participants in the Frontiers in Aerosol Dosimetry Conference, it is likely that larger, more diverse groups of individuals interested in advancing the science of aerosol respiratory dosimetry would identify even more high-priority research topics.

Although it is clear that particle dosimetry models have undergone remarkable development and sophistication, it is also clear that there is a need and an opportunity to make major

advances. Responding to the foregoing research needs and priorities will not be an easy task. Most current dosimetry modeling is performed by individuals or small groups (often with a single specialization) who attend their own specialty meetings and read their own journals. The resulting "intellectual isolation" of individual and small-group dynamics can prevent major conceptual advances. Enlarging the intellectual scope of particle dosimetry modeling will require major efforts aimed at enhancing communications and facilitating collaborations with a variety of other disciplines. Conferences such as this one, with a focus on broad dosimetry issues, are just one part of the solution.

Among the greatest needs is to define just what "dose" is relevant to a specific biological process or endpoint. Only calculating the number or mass of particles that initially deposits in a region of the respiratory tract must eventually give way to much more sophisticated computations. Another related key significant need is to define the biological events that are important enough to warrant modeling. Validation of dosimetry models is a continuing problem, one that will require the development of criteria and consensus on what validation vis-à-vis particle dosimetry means. Validation approaches may differ, depending on the type of model and the quality and quantity of available data. The emergence of new technologies (such as nanotechnology) and new frontiers (such as space exploration) points out gaps in our knowledge and limitations in our current approaches. Again, improved cross-disciplinary interactions and improved coordination and strategic planning are important needs, as is the availability of research funding.