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INHALED PARTICLE DOSIMETRY: Session Commentary

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The Third Colloquium on Particulate Matter and Human Health addressed the roles that inhaled particle dosimetry plays in understanding the potential health risks of human populations exposed to particulate air pollution. Nineteen papers, including posters, were presented that addressed particle deposition and clearance in both humans and laboratory animals. The effects of age, gender, and illness were addressed, as well as ultrafine particles and correlations between particle deposits and tissue pathology. The papers and related discussions also illuminated some important gaps in knowledge, such as the accuracy of dosimetry predictions for individuals; the underrepresentation of susceptible populations; the movement of deposited particles to nonlung tissues and organs; and the accuracy of extrapolations across species. Although current dosimetric information is useful for understanding the effects of particulate air pollution, several unsolved problems remain.

It is well understood in toxicology that "the dose makes the poison" (Paracelsus, 16th century), and inhaled particles are no exception. The session question addressed by 16 posters, 3 platform papers, and a general discussion at the Third Colloquium on Particulate Matter (PM) and Human Health (Durham, NC, June 6–8, 1999) was: What improvements in dosimetry and extrapolation modeling will provide for better evaluation of human health effects and risk assessment? Plenary speaker Joachim Heyder emphasized the power of aerosol dosimetry when applied to individuals, as opposed to groups. Heyder observed that in aerosol inhalation studies with dogs, those animals that responded were those with the greatest doses. Heyder recommended a focus on "individual dosimetry," because individual responses are most often the crux of toxicological problems. Plenary speaker Frederick Miller chose to focus on three fundamental uncertainties relating to PM dosimetry. First, the particle property (or properties) most closely tied to potential adverse health outcomes has (have) not been identified: Candidates include particle number, surface area, volume and mass. Second, regional doses within the respiratory tract are still poorly understood. Third, the important adverse effects of inhaled particles have not been well elucidated. From the observations of these speakers it is clear that dosimetry has much to offer, and that it faces substantial challenges in relation to the question addressed by the session.

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RECENT FINDINGS

Aside from the major advances over the past 50 years in understanding the phenomena of inhaled particle deposition and clearance, some recent achievements were presented at the colloquium. (Authors of papers are given in parentheses.) Three papers addressed airways disease. Two modeling papers indicated that airflow-obstructed lungs can be expected to have increased particle deposition as well as increased heterogeneity of deposits within the respiratory tract (T. B. Martonen, R. A. Segal, and C. S. Kim; and J. S. Brown, D. Crawford-Brown, and W. D. Bennett). Experiments with inhaled radiolabeled 5-μm mass median aerodynamic diameter particles in patients with obstructive airways disease indicated that in comparison to healthy controls, the patients, in fact, exhibited increased deposition, and that poorly ventilated regions had both the highest deposition and the fastest clearance (J. S. Brown, K. L. Zeman, and W. D. Bennett).

Three papers addressed residual particles in autopsy lungs. Examination of 43 (of a collection of 117) autopsy lungs (Hispanic males 16–73 yr of age from California) for pathologic changes and particle deposits indicated that fibrosis, muscle hypertrophy, and inflammation (especially in the proximal respiratory bronchioles) were positively correlated with indices of mineral dust retention (M. G. Menache, K. E. Pinkerton, F. H. Y. Green, E. B. Bahne, and M. B. Schenker). Total particle content (minerals and carbon) measured in digested autopsy lungs from Mexico City and Vancouver residents correlated positively with 3-yr mean PM10 levels in the two cities; PM10 was higher in Mexico City, as was lung particle loading (M. Brauer, B. Stevens, S. Vedal, C. Avila-Casado, T. I. Fortoul, and A. Churg). Similarly, mineral analyses of particles recovered from dogs and people in Mexico City produced correlations between elemental composition of particles from lungs and those in fugitive dust and fly ash particles, indicating the promise of eventually linking specific sources to lung burdens (J. Gallagher, J. Inmon, G. L. Calderon, F. Blanchard, R. Kellogg, J. Scott, L. Stettler, J. Lewtas, A. Levine, and A. K. Prahalad).

Ultrafine (UF, diameter 0.1 μm and less) particles were studied in inhalation experiments with both rats and humans. In rats, inhaled ultrafine radioactive Ag particles indicated that silver was dissolved in blood, but that focal accumulations (of grains in autoradiograms) were seen in lung and liver (G. L. Finch, K. J. Nikula, E. B. Barr, J. C. Seagrave, M. B. Snipes, C. H. Hobbs, and J. L. Mauderly). Whether or not the accumulations were formed in the rats livers after transport or transported there as intact particles is an important issue. In human studies, UF particles of 0.04 μm diameter had greater deposition efficiencies in females ($n = 11$) than in males ($n = 11$), but larger UF particles (0.08 and 0.10 μm diameter) had similar gender-related deposition; UF particles of 0.06 μm diameter had marginally greater deposition in females (P. A. Jaques and C. S. Kim). Doses per unit airway surface area was greatest in large airways for UF (and fine and coarse) particles in both men and women; women tended to have greater deposition efficiencies of UF (and coarse) par-

ticles than did men (C. S. Kim, S. C. Hu, P. Jaques, J. Ding, and P. DeWitt; S. C. Hu and C. S. Kim).

Body size will affect both airway size and specific ventilation (volume of air breathed per unit of body mass); thus, age-related effects on particle dosimetry can be expected. Studies of 2-μm-diameter particle deposition in subjects aged 7 to 35 yr found that children had a higher rate of particle deposition normalized to lung surface area than did adults and adolescents. The investigators attributed the difference to increased specific ventilation in relation to lung size, instead of differences in age or body height (W. D. Bennett and K. L. Zeman). In a modeling study comparing the deposition of 1-μm aerodynamic diameter particles in a 22-mo old versus an adult, the infant had a predicted 38% relative increase in deposition (C. J. Musante and T. B. Martonen).

A multiple-path (airway) particle deposition model for rats and humans was used to indicate significant differences in particle deposition among the lobes for both species; the model also indicated that UF particle deposition was high, but confined to relatively few acini (R. Subramaniam, J. I. Freijer, B. Asgharian, F. J. Miller, F. R. Cassee, L. van Bree, and P. J. A. Rombout). The computational model was used successfully in predicting the deposition of inhaled cadmium chloride particles of various sizes in experimentally-exposed rats. The rats lungs were also evaluated toxicologically, and preliminary results failed to show a particle size effect on biochemical changes as determined by analysis of bronchoalveolar lavage samples (F. R. Cassee, A. J. F. Boere, L. van Bree, P. H. B. Fokkens and J. I. Freijer). Clearance of insoluble radioactive sulfur colloid particles deposited directly into the bronchi (via bronchoscope and breathhold) of anesthetized dogs ($n = 5$) was studied. Sublobar segments differed in initial clearance rates of the particles, but clearance appeared to be complete in all of the studied regions by 24h (W. M. Foster, K. Macri, S. McCulloch, T. Myers, and A. N. Freed). Finally, airflow patterns in a transparent replica of the human nasal cavity were examined using a particle laser velocimetry technique: The complex geometry produced very complex flow patterns having regions of flow separation, reverse flows, and stagnation (J. T. Kelly, L. M. Hopkins, A. S. Wexler, and A. K. Prasad).

The papers just described clearly do not represent all of the research activity in particle dosimetry, but they illustrate the types of studies that are being conducted in response to the questions surrounding particulate air pollution; these papers should be considered to be only samples of current relevant research. On the other hand, each of the papers made one or more useful contributions to the understanding of inhaled particle dosimetry.

UNCERTAINTIES

The papers just described, along with similar research in the literature, not only represent recent advances in understanding the dosimetry of inhaled particles, but they also show that gaps in knowledge tend to overwhelm

what is known. A complete analysis of dosimetry-related uncertainties is not feasible, so a sampling will have to suffice. For the purposes of understanding particulate air pollution, uncertainties exist with respect to the following issues:

- Particle deposition and clearance requires much more study in diseased/abnormal humans and laboratory animals. The diseases and conditions of interest are numerous and include asthma, upper and lower respiratory tract infections, sleep apnea, emphysema, fibrosis, respiratory tract cancer, edema, and congenital abnormalities of the airways. The currently used laboratory animal models of diseased humans represent a special challenge for dosimetry as such models are not only varied, but they are often produced by unusual and extreme treatments. Species differences in structure and function further complicate comparative dosimetry considerations.
- Particle clearance and translocation to sites beyond the airway surfaces requires more emphasis. Where and why insoluble particles accumulate and how diseases/abnormalities influence those processes is a large area for investigation. This is an especially crucial topic for ultrafine particles, as they may have significant access to subepithelial tissues in the respiratory tract, and they may translocate intact to organs such as the heart, blood vasculature, brain, kidney, and liver. Accumulation of insoluble particles in such locations may have adverse consequences that are relevant to particulate air pollution. Conversely, knowledge of which accumulations are benign is also important.
- Although some dosimetry information is available related to differences in body size and gender, this knowledge is incomplete, especially in relation to particle clearance, accumulation, and potential transport to nonlung tissues. This issue is compounded by possible differences in the effects of disease conditions in the very young and the very old compared to typical adults. The extent to which nonanatomical gender differences (such as hormonal and immunological) influence dosimetry is important for study.
- Correlating particle dosimetry and toxicologic responses is an area that has just begun to be investigated. The relevant characteristics of particles, such as number, surface, volume, and mass that produce adverse responses, is a part of this issue, as is the significance of prior exposures (which may produce tolerance or sensitization).
- Species differences in dosimetry and their implications for understanding human risks require more study. Clearly, a large fraction of our knowledge of the effects of particulate air pollution must come from laboratory animal studies. Both confident extrapolations and understanding mechanisms of action require additional dosimetry research.
- How well dosimetry models work for individuals is largely unknown. There is a need to validate all aspects of dosimetry, including regional deposition and clearance phenomena, for individual people and laboratory animals. Techniques for such studies are available, but they have yet to be adequately exploited.

- Realistic air pollution, which includes complex particles and particle/gas mixtures, requires study. The real world is more complex than what has been examined in dosimetry investigations. Real aerosols include particles that are hygroscopic, contain organic and inorganic components, and have properties that may significantly modify breathing patterns and airway structure. Real-world activities involve unusual breathing patterns as well as costressors (thermal and emotional, for example) that may alter the dosimetry and effects of inhaled particles.

As expected, the uncertainties related to dosimetry are substantial, and clearly not all can be investigated thoroughly. Therefore, judgment, careful planning, and increased interactions across relevant disciplines will all be essential if dosimetry research is to make important contributions in the near term. The time for such contributions is at hand, because there is currently an appreciation for the importance of dosimetry in providing for a better evaluation of the human health effects of particulate air pollution.