Final Technical Report

Date of Final Report: August 31, 2006
EPA Grant Number: R827352C016
Center Name: Southern California Particle Center and Supersite (SCPCS)
Center Director: John R. Froines
Title: Particle Dosimetry
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Institution: University of California–Irvine
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Project Period: June 1, 1999–May 31, 2005 (no-cost extension to May 31, 2006)
Period Covered by the Report: June 1, 1999–May 31, 2006
RFA: Airborne Particulate Matter (PM) Centers (1999)
Research Category: Particulate Matter

Topic C: Studies of the Effects of Varying Spatial and Temporal Patterns of Ambient Particulate Matter (PM) and Co-pollutants and Resulting Health Effects with Emphasis on the Role of Atmospheric Chemistry

Objective(s) of the Research Project: The Dosimetry Core had two objectives; it was a service and research core. Dosimetry, or the quantification of deposited and/or uncleared particulate mass, is of importance in both the design and interpretation of the Southern California Particle Center and Supersite's (SCPCS) epidemiology and toxicology studies, and for estimating population exposures using air-monitoring data. Two major aspects of dosimetry are: (1) determining the initial amounts of pollutant deposited on specific sites within the respiratory tract, and (2) determining the fates of deposited material with respect to retention, movement and bioavailability. The Dosimetry Core initiated original research to improve relevant dosimetry models and collaborated with other investigators to improve the design, interpretation and impact of their research.

Achieving these goals required maintaining several important assets, including operational computer codes; an appropriate library and literature data base; a qualified computational technician; and hardware for running codes, printing results and preparing publication-quality figures, tables and charts. The Dosimetry Core also initiated a workshop in order to support and guide Center research and to provide coordination with PM-related dosimetry activities outside of the Center.

Summary of Findings:

Year 1

The Dosimetry Core was active in several areas including:

1. Acquiring and installing dosimetry software that is applicable to adults, children and some laboratory animals (rat, mouse, and ferret)

2. Distributing software and software documentation to Center investigators, and providing tutorials on obtaining and using the output

3. Helping Center postdoctoral researchers Drs. Jacques and Yu refine their research on human dose measurements, and bioavailability modeling

4. Helping doctoral student Mr. Oldham with his thesis research on validation of Computational Fluid Dynamic (CFD) particle deposition models

5. Developing plans for a dosimetry workshop

6. Presenting scientific talks on particulate air pollution, including a dosimetry talk at the University of California-Los Angeles (UCLA) Center's first workshop

The acquired dosimetry software included that generated by 1) the National Council on Radiation Protection and Measurements (NCRP), 2) the International Commission on Radiation Protection (ICRP, the software is LUDEP), 3) the Chemical Industry Institute of Toxicology/National Institute of Public Health and the Environment of the Netherlands (CIIT/RIVM, the software is MPPDep), 4) the University of California Irvine (UCI, based on NCRP software), and 5) Fluent Corporation (the CFD software is called FIDAP). Each software package was tested and is functional. Each package was found to have unique advantages and limitations. The NCRP model includes adults and children of all ages, provides local deposition doses generation-by-generation, and is the most modifiable (in terms of anatomical data input) for research purposes. The ICRP software includes children and women, and it tracks the transport of inhaled particles leaving the lung, but it does not provide local generation-by-generation doses, and it is not easily manipulated to model individuals. The CIIT/RIVM software, MPPDep (Multiple Path Particle Deposition Model), which became available in July 1999, includes adult males and the laboratory rat. MPPDep calculates particle deposition on both a lobe-by-lobe and generation-by-generation basis, inhalability is an option, ventilation and exposure duration can be specified, and it produces publication-quality graphical output. However, MPPDep is not easy to modify to model individual lung anatomies. The University of California, Irvine (UCI) model is an evolving extension of the original NCRP code. We have expanded the code to include hygroscopic aerosols, tobacco smokes and additional species of laboratory animals (rats, mice and ferrets). This model is our main research tool for improving dosimetry models. The FIDAP software is a very-advanced CFD program that runs on our parallel processor. Specialized training is essential for FIDAP users. This package is capable of solving complex-geometry airflow fields and then tracking individual particles through the geometries. FIDAP has been installed, tested and used to solve flow fields in a 3-generation airway branch that exactly matches physiologically-realistic hollow models in our laboratory. We have performed several particle deposition calculations and compared these predictions with actual particle depositions using monodisperse particles in the hollow laboratory models. Initial results were encouraging in that the computed particle depositions matched the observed patterns, thus holding the promise of eventually providing microdosimetric information at specific sites in the respiratory tract. However, the FIDAP code failed to predict the observed total particle deposition as seen in hollow models.

Collaborations with Center Investigators. Dr. Peter Jacques, who was involved in human clinical exposures, worked with us to plan measurements of particle deposited dose in individual subjects during exposures to concentrated ambient particles (CAPs). If this could be achieved, the responses of individuals can be correlated with their measured total, and calculated regional particle depositions. In addition, Dr. Rong Chun Yu worked with us to define his research on the bioavailability of organics absorbed in or adsorbed on inhaled F. We helped to define a generic "atmosphere to target tissue" research model that could then be applied to specific cases, such as organic-coated diesel exhaust particles.

Our involvement in Mr. Oldham's doctoral research on CFD modeling helped him to focus on particles of importance in urban air pollution in the 1 to 10 μm aerodynamic diameter size range. Because CFD models are the only ones capable of computing individual particle deposition locations, as opposed to "smeared" doses, they may be able to explain differences between normal and susceptible subpopulations, if such differences are due to anatomical abnormalities that produce hot spots of particle deposition. Mr. Oldham also worked on converting clinical MRI (Magnetic Resonance Imaging) scans on individuals into forms that can be input into FIDAP for flow solutions and particle deposition calculations. If this effort is successful it will be especially useful for evaluating particle deposition in the upper airways of children and adults with respiratory diseases.

Year 2

The following lists some of the Year 2 accomplishments:

1. Plans were made with Dr. Kleinman for performing a respiratory-tract morphometric and dosimetric study on the Balb/c freeway-study mice. A preliminary protocol and study design were developed.

2. All dosimetry software was maintained in a current and functional state. This included renewal of the CFD software and installation of upgrades. Extraction of hourly wind, temperature, dew point and visibility data for 13 weather stations in the L.A. Basin was added as a new capability.

3. Plans for an international conference on particulate material were initiated. The American Association for Aerosol Research (AAAR) took the organizational lead, and the U.S. Environmental Protection Agency (EPA) contributed start-up funds. The Dosimetry Core was centrally involved in directing this important conference, the fourth in a series started in 1994.

4. Our graduate student, Mr. Oldham completed the experimental portion of his doctoral research on CFD model validation for PM deposition and began writing his thesis. The Science To Achieve Results (STAR) grant will be acknowledged in journal publications derived from his thesis. It appears that the CFD approach is promising for defining local regions in airways that have high particle depositions. The computed patterns of deposition predicted for 1, 3 and 10 μm aerodynamic diameter particles were consistent with his

laboratory experiments. Mr. Oldham shifted his main focus to conducting the rodent exposure "freeway study" with Drs. Kleinman and Sioutas.

5. At every opportunity, dosimetry discussions occurred between the Dosimetry Core and other SCPCS investigators. Topics included considering body size factors as dose modifiers in the "children's study," performing Balb/c lung morphometry, defining the air-to-lung PM transfer coefficient for mice in exposure cages used in the freeway study, and upgrading the wind data during exposures of mice to CAPs.

Year 3

The following list highlights our accomplishments:

1. The lung morphometry on the Balb/C freeway study mice was completed. This involved making about 2 dozen in-situ lung casts, selecting 3 casts from ovalbumin sensitized mice and 3 casts from normal mice for detailed morphometric measurements, performing the measurements, and using them to calculate particle deposition efficiencies. In addition, 20 casts were subjected to measurements of a few airways in order to determine the extent to which variations in casting volume influenced the cast airway sizes. The results were interesting. First, the ovalbumin sensitization did not significantly alter airway dimensions. This means that sensitization is not expected to change the deposition of particles in the freeway study, provided that sensitization does not significantly alter breathing patterns during exposure to CAPs. Second, variations in casting volume (which are unavoidable due to the tiny cast volumes used in mice) did not significantly change the sizes of airways. Third, the morphometric measurements of the Balb/C mice tracheobronchial trees were significantly different from those obtained by us previously on $B6C3F_1$ mice. This is a novel finding that implies the strain of mouse will significantly influence its deposition dose in an inhalation study. In past dosimetry work, "a mouse was a mouse," but in the future, the mouse type/strain will also be seen as an important piece of dosimetry information. These findings were significant enough to trigger a paper.

2. Our doctoral student, Michael Oldham, completed his program. His research involved validation of a CFD particle deposition model by comparing predictions to bench-top particle depositions in hollow airway models. The thesis, "Comparison of CFD Predictions and Experimental Results for Local Particle Deposition Patterns in Idealized Human Airways," supports the use of high concentrations of PM in Dr. Nel's SCPCS research project.

3. A dosimetry workshop was held at UCLA on October 26, 2001. The workshop served to bring several SCPCS investigators together to integrate their knowledge on Dosimetric issues related to several of the Center's themes. Presentations by Drs. Sioutas, Cho, Hinds, Phalen, Yu and Nel were followed by focused discussions. A significant result from the workshop was that the elevated PM concentrations used in Dr. Nel's in-vitro research could be supported as being realistic representations of local doses in human lung regions during actual exposures in the L.A. Basin as defined by Dr. Hinds' research. This result is a useful scientific advance, and it also strengthens future publications of Dr. Nel. The workshop also had some implications for the SCPCS epidemiology research in that the importance of

understanding "individual" exposures was emphasized. The workshop results were used to contribute to the plans for seeking renewal of the STAR Grant program.

4. A transfer coefficient study was started with nine mice being exposed to 1 μm diameter fluorescent tracer particles in the freeway study animal exposure system. The purpose was to quantify deposition in the mice under exposure conditions. Additional tracer particle sizes were planned for Year 4.

Year 4

We contributed heavily to the freeway study, including helping with logistics, conducting exposures, performing bioassays, and characterizing the exposure system's delivery of air pollutants to the mice. Support was provided to Dr. Harkema's group (from Michigan State University) by helping with lung casting of the Brown Norway rat. We also helped neurotoxicologist, Dr. Campbell of UCI to get neurotoxicity data on mice exposed in the freeway study. With respect to research, we worked on how mouse variety can significantly affect the deposition of inhaled particles.

Year 5

This grant year was productive in several ways. The objectives included publication of research results, continuing support of the "freeway study" and preparation and measurement of rodent lung casts in order to produce data on particle doses in toxicology studies. The Dr. Nel paper for which we provided dosimetry-related contributions was published (Li N, Hao M, Phalen RF, Hinds WC, Nel AE. Particulate air pollutants and asthma: a paradigm for the role of oxidative stress in PM-induced adverse health effects. *Clinical Immunology* 2003;109:250-265). In support of the Freeway Studies, we worked on the performance of the mouse exposure system that is supplied with air pollutants by the particle concentrator.

During Year 5 the Dosimetry Core continued to support the freeway studies by assisting during exposures, endpoint acquisition and data analysis.

The preparation and morphometric analysis of lung casts continued throughout the year. Ten rat lungs were cast and stored for measurement, and large-airway morphometry was conducted on casts made in Brown Norway Rats. We concluded that this rat, which is widely used in PM studies, appears to have normal (for rats) large airway structure. Arrangements were discussed with the CIIT Centers for Health Research for incorporating our rodent lung measurements into their widely used dosimetry software MPPD1.

Year 6

The final year focused on publications and presentations.

Conclusions

1. The aerosol dosimetry software packages (LUDEP and MPPD) in current use that predict inhaled particle deposition efficiencies are both useful for predicting human doses. Although

each program gives slightly different values for similar inputs, the differences are within the range of values expected in human populations. Because MPPD1 (the latest version) is free (from the CIIT website), user-friendly and includes adults, children and rats, it is recommended for use in the Center. However, LUDEP is also very acceptable.

2. CFD approaches to solving inhaled particle deposition problems have great promise in that individual differences and micro deposition patterns can be addressed. Although such approaches are not adequately validated for use in epidemiology research, they are useful for designing in-vitro particle toxicology studies.

3. Our morphometry and particle deposition calculations indicate that different mouse strains/varieties can receive different particle doses, even when exposed to the same air pollutant. Thus, dosimetry information in one mouse strain does not necessarily apply to another strain.

4. Ovalbumin sensitization of Balb/C mice did not significantly change airway dimensions, which simplifies interpretation of particle studies in which sensitized and non-sensitized animals are compared.

5. Sophisticated dosimetry calculations support the use of relatively large particle doses in in-vitro studies, if particle deposition hot-spots in the lung are believed to relate to effects.

6. Whole-body aerosol exposures of mice can provide for efficient inhalation of CAPs. However, careful design and testing of exposure cages is required.

7. The current state of modeling inhaled particle deposition in children is strong. Predictions using computer software models are consistent with clinical-setting measurements.

8. Concentrated airborne particulate matter exposures appear to be capable of increasing inflammatory endpoints in the brains of Balb/C mice (Campbell, et al., 2005).

References:

Campbell A, Oldham M, Becaria A, Bondy SC, Meacher D, Sioutas C, Misra C, Mendez LB, Kleinman M. Particulate matter in polluted air may increase biomarkers of inflammation in mouse brain. *NeuroToxicology* 2005;26(1):133-140.

Li N, Hao M, Phalen RF, Hinds WC, Nel AE. Particulate air pollutants and asthma: a paradigm for the role of oxidative stress in PM-induced adverse health effects. *Clinical Immunology* 2003;109:250-265.

Supplemental Keywords: NA

Relevant Web Sites: http://www.scpcs.ucla.edu