PROCEEDINGS OF THE COLLOQUIUM ON PARTICULATE AIR POLLUTION AND HUMAN MORTALITY AND MORBIDITY

(Proceedings of a Colloquium held on January 24-25, 1994)

APPENDIX TO FINAL REPORT

(California Air Resources Board Contract No. 92-341)

Submitted by

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PROCEEDINGS OF THE COLLOQUIUM ON PARTICULATE AIR POLLUTION AND HUMAN MORTALITY AND MORBIDITY

(Appendix to California Air Resources Board Contract No. 92-341 Final Report)

Prepared and Edited by: Robert F. Phalen, Richard C. Mannix, Michael T. Kleinman and Marie C. Tonini.

The material in this document was originally prepared for the Colloquium on Particulate Air Pollution and Human Mortality and Morbidity held on January 24-25, 1994, at the Arnold and Mabel Beckman Center of the National Academies of Sciences and Engineering in Irvine, California. The meeting was sponsored by the California Air Resources Board, with co-sponsorship by the U.S. Environmental Protection Agency, the American Association for Aerosol Research, the Centers for Occupational and Environmental Health at the University of California Irvine and Los Angeles, and the Department of Community and Environmental Medicine, University of California-Irvine.

The included material covers platform and poster papers presented at the Colloquium, as well as session summaries and unsolicited commentaries. However, some of the papers were prepared after the 2-day meeting, and others were revised substantially. Most of the papers and abstracts can be found in two special editions, 7(1) and 7(5) of the peer-reviewed journal Inhalation Toxicology. The material in this document does not contain the revisions that followed peer-review. Therefore, Inhalation Toxicology 7(1) and 7(5), 1995 should be consulted prior to quoting any information herein. This proceedings contains some manuscripts as they were submitted for review. Some must be considered as drafts. Quotation from this document is therefore, discouraged. Copies of this Appendix are available at the cost of printing, handling and mailing. For information, please contact:

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CONTENTS

Poster Session Abstracts

Organizing Committee and Editorial Board Members for Special Issues of Inhalation Toxicology

Colloquium on Particulate Air Pollution and Human Mortality and Morbidity

Dr. David V. Bates, University of British Columbia, Vancouver, Canada
* Dr. Deepak K. Bhalla, University of California, Irvine, California, USA
Dr. Glen R. Cass, California Institute of Technology, Pasadena, California, USA
* Dr. Steven D. Colome, Integrated Environmental Services, Irvine, California, USA
Dr. Timothy R. Gerrity, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA
* Dr. Michael T. Kleinman, University of California, Irvine, California, USA
Dr. Michael D. Lebowitz, University of Arizona, Tucson, Arizona, USA
Dr. Morton Lippmann, New York University, New York, New York, USA
Dr. William J. Mautz, University of California, Irvine, California, USA
Dr. Roger O. McClellan, Chemical Industry Institute of Toxicology, Research Triangle Park, North Carolina, USA
* Dr. Michael S. Perkins, University of California, Irvine, California, USA
* Dr. Robert F. Phalen, University of California, Irvine, California, USA
Dr. C. Arden Pope III, Brigham Young University, Provo, Utah, USA
* Dr. Shankar B. Prasad, South Coast Air Quality Management District, Diamond Bar, California, USA
Dr. Carl M. Shy, University of North Carolina, Chapel Hill, North Carolina, USA
Dr. Mark J. Utell, University of Rochester, Rochester, New York, USA
* Mr. Dane Westerdahl, California Air Resources Board, Sacramento, California, USA
* Dr. James L. Whittenberger, University of California, Irvine, California, USA
Dr. William E. Wilson, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA

* Organizing Committee Members

COLLOQUIUM ON PARTICULATE AIR POLLUTION AND HUMAN MORTALITY AND MORBIDITY

PROGRAM

January 24-25, 1994
Irvine, California

Session S1:	Human Mortality and Morbidity Study Results
Session S2:	Methodology and Reanalysis of Previous Studies
Session S3:	Mechanisms of Particulate Toxicity
Session S4:	Sources, Levels and Characterization of PM10
Poster Session P1:	Human Mortality and Morbidity
Poster Session P2:	Mechanisms of Injury
Poster Session P3:	Air Pollutant Characteristics

Hosted by: The Air Pollution Health Effects Laboratory, Department of Community and Environmental Medicine, UCI, The UC Irvine Center for Occupational and Environmental Health.

COLLOQUIUM PROGRAM

Monday, January 24, 1994

7:00-7:55 BREAKFAST

8:00 Introduction to the Colloquium: Dr. Robert F. Phalen (Colloquium director)

8:05 Description of Evening Sessions: F. Dane Westerdahl (Cal ARB)

8:10 Research Needs Orientation: Dr. Roger O. McClellan (President: CIIT)

Session 1: Human Mortality and Morbidity Study Results **(Papers S1.1 to S1.6)**

Co-Chairs: Dr. Morton Lippmann, Dr. C. Arden Pope III; Monitor: Dr. Michael S. Perkins

8:15 "Review of epidemiological evidence of acute mortality effects of particulate air pollution." Joel Schwartz, Harvard School of Public Health, MA.

"Review of epidemiologic evidence of acute morbidity effects of particulate air pollution." Douglas W. Dockery, Harvard School of Public Health, MA.

"Review of epidemiologic evidence of chronic health effects of particulate air pollution." C. Arden Pope, III, Brigham Young University, UT.

"Long-term exposure to ambient concentrations of particulates and development of chronic disease in a cohort of non-smoking California residents." David E. Abbey, Loma Linda University, CA.

"Associations of ambient PM10 pollution with respiratory symptoms and pulmonary function of children in the Netherlands." Gerard Hoek, Brunekreef, B. and Roemer, W. University of Wageningen, The Netherlands.

"Air pollution and pediatric asthma in Los Angeles." Bart Ostro, Lipsett, M., Mann, J. and Braxton-Owens, H. CAL EPA.

10:45 BREAK

Session 2: Methodology and Reanalysis of Previous Studies **(Papers S2.1 to S2.6)**

Co-Chairs: Dr. Morton Lippmann, Dr. C. Arden Pope III; Monitor: Dr. Michael S. Perkins

11:00 "Daily mortality and exposure to PM10 air pollution, Utah Co., Utah 1985-1992." Joseph L. Lyon and Mori, M. University of Utah Medical Center, UT.

"Particulate air pollution, sulfur and daily mortality: A reanalysis of the Steubenville data." Suresh H. Moolgavkar, Luebeck, E.G., Hall, T.A. and Anderson, E.L. Fred Hutchinson Cancer Research Center, WA.

"Daily mortality analysis by using different regression models in Philadelphia Co." Li, Yuanzhang and Roth, D. Roth Associates, MD.

12:00 LUNCH

1:00 "Los Angeles daily mortality and particulate matter: New results and sensitivity analysis." Patrick L. Kinney, Ito, K. and Thurston, G.D. New York Medical Center, NY.

"Uncertainties in identifying responsible pollutants in observational epidemiology studies." Frederick W. Lipfert. Environmental Consultant, NY.

"Air pollution epidemiology: is the model the message?" George D. Thurston and Kinney, P.L. New York University Medical Center, NY.

2:00 Discussion

3:00 BREAK

Session 3: Mechanisms of Particulate Toxicity **(Papers S3.1 to S3.6)**

Co Chairs: Dr. Mark J. Utell, Dr. Timothy R. Gerrity; Monitor: Dr. Deepak K. Bhalla

3:15 "The clinical perspective." Mark J. Utell. University of Rochester Medical Center, NY.

"Toxicologic evidence for health effects from inhaled particulate pollution." Richard B. Schlesinger, New York University Medical Center, NY.

"Cellular and immunologic injury with PM10 inhalation." Michael T. Kleinman and Bhalla, D.K. University of California, Irvine, CA.

"Surface complexed iron, lung inflammation and hyperreactivity." Daniel L. Costa, Tepper, J.S., Lehmann, J.R., Winsett, D.W. and Ghio, A.J. Duke University, NC.

"Dosimetric issues relating to particulate toxicity." Frederick J. Miller and Gerrity, T.R. Duke University, NC.

"Association of particulate air pollution and acute mortality: Involvement of ultrafine particles?" G. Oberdorster, R. Gelein, N. Corson and P. Mercer, University of Rochester, NY.

5:15 Discussion

6:00 DINNER (Hosted at the Academy)

6:45 POSTERS

7:30 Evening ARB Arranged Session: **(Epidemiological and Biomedical Intrepretations of PM10 Results: Issues and Controversies) Coordinators: Dr. James L. Whittenberger, Dr. Michael D. Lebowitz and F. Dane Westerdahl.**

9:30 ADJOURN FOR DAY 1

Tuesday, January 25, 1994

7:00-7:55 BREAKFAST

Session 4: Sources, Levels and Characterization of PM10 **(Papers S4.1 to S4.9)**

Co-Chairs: Dr. Glen R. Cass; Dr. William E. Wilson; Monitor: Dr. Michael T. Kleinman

8:00 "Variabilities in PM10 concentrations within metropolitan areas and their implications to health effects analyses." Kazuhiko Ito, and Thurston, G.D. New York Medical Center, NY.

"Spatial and temporal variability in the size distribution and acidity of ambient PM10." John D. Spengler, Ozkaynak, H. and Thurston, G.D. New York Medical Center, NY.

"What we know human exposures to acidic sulfate particles." Jed M. Waldman, Koutrakis, P., Allen, G.A., Thurston, G.D., Burton, R.M. and Wilson, W.E. Environ. & Occup. Health Sciences Inst., NJ.

"Labile species in particle-bound water." Wilson, W.E. U.S. EPA, NC.

"Sources and factors influencing personal and indoor exposures to particles and PAHs." John D. Spengler, Harvard School of Public Health, MA.

"Quantifying the contribution of sources of organic aerosols in atmospheric samples." Wolfgang F. Rogge, Hildemann, L.M., Mazurek, M.A., Cass, G.R. and Simoneit, B.R.T. Florida International Unversity, FL.

"Loadings, size distributions and sources of organic compound classes in Los Angeles aerosol." David T. Allen, University of California Los Angeles, CA.

10:20 BREAK

10:40 "Determination of the size distribution and chemical composition of fine particulate semi-volatile organic material in urban environments using diffusion denuder technology." Delbert J. Eatough, Cui, W. and Machir, J. Brigham Young University, UT.

"The effect of variable ambient particle size distributions on the cut point between fine and coarse mass fractions." Dale A. Lundgren, Burton, R.M. and Wilson, W.E. University of Florida, FL.

11:20 Discussion

12:00 LUNCH

SESSION 5: Gaps in Knowledge and Research Needs: Short-term and Long-term.

Session Chair: Dr. Roger O. McClellan. Panel Presentations: Dr. Morton Lippmann, Dr. C. Arden Pope III, Dr. Mark J. Utell, Dr. Timmothy R. Gerrity, Dr. William E. Wilson, Dr. Michael D. Lebowitz, Dr. Glen R. Cass.

1:00 Discussion

2:30 BREAK

2:45 Discussion

4:45 Closing Comments: **Dr. Robert F. Phalen (Colloquium director) and Dr. John R. Holmes (Chief: Cal ARB Research Division).**

5:00 MEETING ADJOURNS

significant associations with all natural cause mortality or incidence of all malignant neoplasms in males. Statistically significant associations were observed between elevated ambient concentrations of one or more particulate pollutants and each of the other disease outcomes. In addition, ozone was significantly associated with increasing severity of asthma, and with the development of asthma in males. Multipollutant analyses indicated that none of the associations between particulate pollutants and disease outcomes were due to correlations with gaseous pollutants studied except possibly for PM2.5 and increasing severity of asthma, which could be due to a correlation with ozone. Observed associations between disease outcomes and PM2.5 or PM10 could be biased towards the null because of increased measurement error due to their indirect methods of estimation.

ASSOCIATIONS OF AMBIENT PM10 POLLUTION WITH RESPIRATORY SYMPTOMS AND PULMONARY FUNCTION OF CHILDREN IN THE NETHERLANDS.

Gerard Hoek, Bert Brunekreef and Willem Roemer. Department of Epidemiology and Public Health, University of Wageningen, P.O. Box 238, 6700 AE Wageningen, the Netherlands.

Between 1987 and 1991 a series of epidemiological studies has been conducted into the acute effects of ambient air pollution on respiratory health of children. In three consecutive winters more than 1000 children (7-11 yrs) living in non-urban communities were studied. General population samples of children were studied with serial pulmonary function measurements (6-10 measurements per child) and an acute respiratory symptoms diary. A panel of children with chronic respiratory symptoms was studied with daily peak flow measurements and an acute respiratory symptoms diary (including medication use). The main exposure variables were the ambient concentration of PM10 and acid aerosol. Concentrations of acid aerosol were very low, 24-hour average PM10 concentrations up to 174 $\mu g/m^3$ have been measured. Higher PM10 concentrations were associated with lower pulmonary function both in the general population samples and the panel population. The associations with PM10 were detected in all three winter periods, whereas associations with SO_2 and NO_2 were found in one winter only, suggesting that particulate matter was the important factor. Only in the panel population a positive association with prevalence of acute respiratory symptoms and medication use was found. Small systematic differences in response between individual children were found.

Daily Mortality and Exposure to PM_{10} Air Pollution, Utah County, Utah 1985-1992

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Previous studies in Utah County have reported an association between exposure to a five day moving average of PM_{10} air pollution and daily mortality from all causes (excluding accidents). We examined this relationship for 1985-1991, using a Poisson regression model to calculate rate ratios (RRs) for place and age at death by exposure to PM_{10} air pollution of 75+ mgm/m^3. The RRs are as follows:

	Location						
	Hospital		Nursing Home		Home+ Other		
AGE	RR	n=	RR	n=	RR	n=	TOTAL
<1	1.15	142	-	1	-	33	1.43
1-59	0.76	284	-	189	1.82	184	1.08
60-74	0.91	734	0.95	161	1.08	324	0.96
75+	1.19	932	1.15	745	0.94	654	1.10
Total	1.03	2092	1.10	936	1.14	1195	1.08

Data on the length of stay for hospitalized patients suggests that about half of those age 65+ who die in a hospital are there longer than five days. Mortality pattern suggests excesses due to PM_{10} exposure may be occurring in hospitalized patients age <1, and those age 75+, in those age 75+ dying in nursing homes, and among those age 1-59 who die at home.

UNCERTAINTIES IN IDENTIFYING "RESPONSIBLE" POLLUTANTS IN OBSERVATIONAL EPIDEMIOLOGY STUDIES

Frederick W. Lipfert[1] and Ronald E. Wyzga[2]

1. Environmental Consultant, Northport, NY
2. Electric Power Research Institute, Palo Alto, CA

Studies of community air pollution must deal with a complex mixture of substances, for which the available data on concentrations and their distributions vary greatly in completeness and accuracy. The monitoring database available for some pollutants (such as gravimetric particulate measures) far exceeds that available for others (such as carbon monoxide) in terms of spatial and temporal coverage. Little or no reliable routine monitoring data are available on aeroallergens or on particles classified by size and chemistry, for example. In addition, the relationships between outdoor air measurements and personal exposure vary substantially among pollutant species. This paper addresses the concern that the availability and quality of observed data may have limited the validity of the conclusions that can be derived from retrospective studies.

The statistical tool most commonly used to study relationships between air quality and health is multiple regression analysis, for which the validity of conclusions requires conformance with several basic assumptions. The published literature varies in the degree to which this conformance has been observed. We show by data simulation, and by numerical experiments with mortality and air quality data from Philadelphia, that differences in the reliability of exposure estimates among correlated variables can be critical in the selection of the "significant" variables in multiple (joint) regressions. Finally, we consider how nonlinear transformations can affect judgments about the relative importance of the variables considered. While models based on linear pollution relationships may be facile and may be convenient in characterizing effects, we have no assurance that they are in fact correct. Resolution of these issues will require better population-based air quality monitoring data, as well as laboratory studies appropriate to characterizing the nature of the implied biological responses to the mixtures and concentrations that currently comprise community air quality.

This research was supported by the Electric Power Research Institute under RP 3253.

CLINICAL PERSPECTIVE ON RESPIRATORY DISEASE AND THE ROLE OF AIRBORNE PARTICLES.

Mark J. Utell. University of Rochester School of Medicine, Rochester, NY 14642

Particulate matter in the air has been associated with increased respiratory morbidity and mortality. The recent mortality findings are remarkable for the demonstration of an apparent adverse effect of particles in concentration ranges under the present National Ambient Air Quality Standard. This finding warrants consideration in the context of both our understanding of clinical disease and relevant data from toxicologic studies. The elderly and persons with severe chronic lung disease (COPD) would be expected to be particularly at risk; causes of acute cardiopulmonary death might be attributed to pulmonary edema, acute respiratory infection, exacerbation of COPD or perhaps arrhythmias. Yet available toxicologic studies provide few clues in explaining acute mortality at low particle concentrations. Indeed controlled clinical studies with acidic particles at concentrations greater than twenty times ambient fail to produce a pulmonary inflammatory response in healthy individuals; and subjects with COPD, the group at presumably highest risk from the epidemiologic data, show no reduction of lung function with similar acute exposures. Perhaps our understanding of the toxicity of urban particles could be increased by investigations directed at the combined effect of metal ions plus particles, or particles plus oxidants, or even inert particles. The ultrafine fraction is an interesting but untested candidate given the increased toxicity of particles in the nanometer compared to micron size ranges. Thus, despite the epidemiologic observations, from a clinical perspective the pathophysiologic basis for the excess cardiopulmonary deaths remains problematic; until the findings of new toxicologic studies become available, the framework for interpreting the epidemiologic findings will be inadequate.

CELLULAR AND IMMUNOLOGIC INJURY WITH PM10 INHALATION.

M.T. Kleinman, D.K. Bhalla, W.J. Mautz and R.F. Phalen. Department of Community and Environmental Medicine, University of California, Irvine, Irvine, CA 92717-1825.

PM10, or airborne particles less than 10 μm in mass median aerodynamic diameter (MMAD), are associated with adverse effects on human health including chronic lung diseases and mortality, but the mechanisms by which these particles cause or aggravate diseases are not specifically known. PM10 represents a complex mixture, both in terms of size and chemical composition, of aqueous-media soluble and insoluble particles. Furthermore, the ambient aerosol composition varies markedly in different locations and at different times in the same location. To test the effects of PM10 on pulmonary defenses in relation to specific cell targets, barrier-reared Sprague-Dawley rats were exposed to purified air (control), to two important constituents of the fine particle (<1 μm MMAD) fraction of PM10 - ammonium sulfate [SO_4^{-2}] (70 μg m^{-3}, 0.2 μm MMAD) and ammonium nitrate [NO_3^{-1}] (350 μg m^{-3}, 0.6 μm MMAD). Rats were also exposed to an important contributor to the coarse (> 2.5 μm MMAD) mode of PM10 - resuspended road dust (300 and 900 μg m^{-3}, 4.0 μm MMAD). Exposures were 4 hr per day, 4 days per week for 8 weeks. Macrophage-dependent lung defense functions (phagocytosis and respiratory burst activity) were significantly depressed by NO_3^{-1}, SO_4^{-2} and the 900 μg m^{-3} road dust exposures, compared to purified air controls. Lung permeability, as determined from measurements of total protein and albumin concentrations in bronchoalveolar lavage fluid, was significantly greater in rats exposed to SO_4^{-2} and NO_3^{-1}, but not to road dust, when compared to air-exposed controls. Quantitative histopathologic analyses included measurement of alveolar nuclear density, alveolar chord length, alveolar septal thickness and alveolar surface area. These measures showed moderate to substantial changes and, in general, the severity of the responses was in the order of NO_3^{-1} > SO_4^{-2} > road dust, for the concentrations used in these exposures. A count of neutrophils and macrophages in the lung sections did not reveal significant inflammatory activity following the exposures. In summary, this study demonstrated the capability of soluble and insoluble PM10 components to produce pulmonary effects following repeated exposures. Submicron PM10 components changed morphometric characteristics of the lung, depressed macrophage functions related to defenses against respiratory infections, and increased lung permeability, which could exacerbate asthma in sensitive individuals. These findings are therefore consistent with those of epidemiological studies. The study also supports the hypothesis that the fine fraction of PM10 is more toxic than the coarse fraction. (Supported by California ARB Contract No. A933-158).

SURFACE COMPLEXED IRON (Fe^{+3}) ON PARTICLES: ITS ROLE IN THE INDUCTION OF LUNG INFLAMMATION AND HYPERREACTIVITY.

DL Costa, JS Tepper[1], JR Lehmann[1], DW Winsett[1], K. Dreher, and AJ Ghio[2]. USEPA, [1]ManTech Environ. Inc., [2]Duke University, North Carolina

Recent epidemiological studies report a significant relationship between exposure to ambient particles and morbidity, including the exacerbation of asthma. This association exists at particle concentrations not previously thought to pose a health risk, and, to date, has not been linked to specific physicochemical attributes of the particles. We have found that the concentration of surface complexed Fe^{+3} of a variety of environmental particles is associated with the magnitude of particle-induced pulmonary inflammation (cells and injury markers) and the generation of reactive oxygen species *in vitro*. Three particles (Mt. St. Helens dust, ambient particles of Dusseldorf, Ger, and residual oil fly ash), which represented a range of inflammatory potential, were intratracheally instilled (2.5 mg in saline) into 60d old Sprague-Dawley rats. At 96 h post exposure, bronchoconstriction to IV acetylcholine and bronchoalveolar lavage were assessed in anesthetized rats. Both the degree of acute inflammation (PMNs, EOS, LDH, and protein) and bronchoreactivity correlated with the Fe^{+3} loading of the particles as did the genration of TBA reactive products. Interestingly, the residual oil fly ash which had the greatest effect in the animals also recruited significant numbers of eosinophils into the lung. Since the surface Fe^{+3} was paralleled by the degree of acidity of the particle in instillate suspension form, instillations with H_2SO_4 of comparable Ph were assessed using BAL parameters. These were substantially less following acid instillation as compared to the high surface Fe^{+3} particles. Neutralization of the residual oil fly ash instillate enhanced toxicity and resulted in the precipitation of additional particulate material, probably metal oxides and hydrides. It appears that these particles if formed within the lung by *in vivo* neutralization could contribute to the overall toxicity via other mechanisms associated with direct cytotoxicity. The results to date suggest that surface coordinated Fe^{+3} on particles have a significant role in the generation of oxidants and the elicitation of lung toxicity, although other factors may contribute to the response via independent or associated mechanisms. Studies to determine the nature of the oxidant pathways are currently under study. (This abstract does not reflect EPA policy.)

S3.6

ASSOCIATION OF PARTICULATE AIR POLLUTION AND ACUTE MORTALITY: INVOLVEMENT OF ULTRAFINE PARTICLES?

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Recent epidemiological studies show an association between particulate air pollution and acute mortality and morbidity down to ambient particle concentrations below 100 $\mu g/m^3$. Whether this association also implies a causality between acute health effects and particle exposure at these low levels is unclear at this time; no mechanism is known which would explain such dramatic effects of low ambient particle concentrations. Based on results of our past and most recent inhalation studies with ultrafine particles in rats, we propose that such particles, *i.e.*, particles below ~50 nm in diameter, may contribute to the observed increased mortality and morbidity. In the past we have demonstrated that inhalation of highly insoluble particles of low intrinsic toxicity, such as TiO_2, results in significantly increased pulmonary inflammatory responses when their size is in the ultrafine particle range, *i.e.*, ~20 nm in diameter. However, these effects were not of an acute nature and occurred only after prolonged inhalation exposure of the aggregated ultrafine particles at concentrations in the mg/m^3 range. In contrast, in the course of our most recent studies with thermodegradation products of polytetrafluoroethylene (PTFE) we found that freshly generated PTFE fumes containing singlet ultrafine particles (median diameter 26 nm) were highly toxic to rats at inhaled concentrations of 0.7 - 1.0 x 10^6 particles per cm^3, resulting in acute hemorrhagic pulmonary inflammation and death after 10-30 minutes of exposure. We also found that work performance of the rats in a running wheel was severely affected by PTFE fume exposure. These results confirm reports from other laboratories of the highly toxic nature of PTFE fumes which cannot be attributed to gas phase components of these fumes such as HF, carbonylfluoride, or perfluoroisobutylene, or to reactive radicals. The calculated mass concentration of the inhaled ultrafine PTFE particles in our studies was about 64 $\mu g/m^3$, a very low value to cause mortality. Aging of the fumes with concomitant aggregation of the ultrafine particles significantly decreases their toxicity. Since ultrafine particles are always present in the urban atmosphere, we suggest that they play a role in causing acute lung injury in sensitive parts of the population.

VARIABILITIES IN PM10 CONCENTRATIONS WITHIN METROPOLITAN AREAS AND THEIR IMPLICATIONS TO HEALTH EFFECTS ANALYSES

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Recent epidemiological studies have indicated associations between PM10 and mortality/morbidity in various regions in the U.S. However, aside from its possible variability in chemical composition from one region to another, PM10's temporal fluctuations can also vary dramatically from site to site within a metropolitan area. For example, PM10 has been collected at multiple sites in Los Angeles County, CA since 1985. These data show not only site to site differences in the PM10 levels, but also exhibit differences in their baseline PM10 seasonal cycles. This is in contrast to more spatially homogeneous pollutants such as ozone, and therefore presents a special challenge to PM10 exposure assessment for health effects analysis. In this study, all PM10 data from LA and Chicago metropolitan areas during 1985-1990, which have been obtained as part of an ongoing health effects study, are analyzed for their within-city spatial and temporal differences. The sensitivity of various "representative" population exposure estimates (e.g. central site vs. multi-site averages) to these various sites' individual variabilities is discussed. Conclusions are drawn as to the implications of these sensitivity analyses to PM10 health effects model estimates. This research was supported by NIEHS Grant # RO1-ES05711.

S4.4

LABILE SPECIES IN PARTICLE-BOUND WATER

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A number of potentially noxious, water-soluble gases are formed through the photochemical smog process. These include oxidants such as O_3, H_2O_2, and RO_2; acid gases such as SO_2, HCl, HNO_3, HONO, and HCOOH; and organic species such as HCHO, phenol and other polar organic compounds. During inhalation these gaseous species are removed by the wet surfaces of the nose, throat, and upper respiratory system and do not reach the deep lung. However, these species may dissolve in water associated with particles in the air and be transported with the particles into the deep lung. Since a major fraction of the mass of the ambient aerosol is made up of hygroscopic material, the amount of particle-bound water, and thus the amount of noxious material carried to the deep lung in particle-bound water, might be expected to correlate with the total particle mass. Thus it is possible to formulate a hypothesis for a biological effect, due to the noxious material carried to the lung in particle-bound water, which correlates with the total particle mass.

Particles of hygroscopic material such as $(NH_4)_2SO_4$, NH_4HSO_4, NH_4NO_3, and H_2SO_4 form liquid droplets with the amount of liquid water increasing as the relative humidity increases. The gas-phase atmospheric species listed above dissolve in this particle-bound water. Normal analytical techniques do not measure these species which evaporate when the particles dry out during storage, handling, and conditioning. Thus, there is no information on the composition or concentration of the dissolved components which evaporate. In this paper, a photochemical model will be used to calculate the potential concentration of a variety of water-soluble species, an aerosol equilibrium model to determine the amount of particle-bound water, and Henry's Law to determine the amount of these species which might be dissolved in the particle-bound water. The amount of oxidant, acid, or organic species which might be carried to the deep lung in particle-bound water will be compared to that which might reach the deep lung in the gas phase. Methods for testing the hypothesis that noxious gases dissolved in particle-bound water damage the lung will be discussed.

The information in this document has been funded wholly or in part by the U. S. Environmental Protection Agency. It has been subjected to Agency review and approved for publication.

DETERMINATION OF THE SIZE DISTRIBUTION AND CHEMICAL COMPOSITION OF FINE PARTICULATE SEMI-VOLATILE ORGANIC MATERIAL IN URBAN ENVIRONMENTS USING DIFFUSION DENUDER TECHNOLOGY

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Collection of particles on a filter results in underestimation of particulate organic compounds due to losses of the particulate semi-volatile organic material during sample collection, i.e. a "negative sampling artifact." This artifact results in the loss of about half of the particulate organic material during sampling. These semi-volatile organic compounds lost from particles can be correctly measured using a multi-component, multi-channel diffusion denuder sampling system. A multi-system, multichannel, high volume diffusion denuder sampler has been used for the determination of the particle size distribution and chemical composition of semi-volatile organic compounds in fine particles in three urban environments, Provo UT, Los Angeles CA and Philadelphia PA. Organic compounds lost from the particles included paraffinic and olefinic compounds, aromatic compounds, aromatic acids, and, organic acids and esters. Underestimation of the composition of semi-volatile organic compounds in particles is a function of molecular weight, chemical compound class and particle size. The majority of the organic compounds in urban particles in fine particles 0.8 to 2.5 μm in size are semi-volatile organic compounds lost from the particles during sampling onto a filter. About half of the organic compounds in particles 0.4 to 0.8 μm in size are lost from the particles during sampling. The majority of carbonaceous material in particles smaller than 0.4 μm is not lost from the particles during sampling. The results obtained using the diffusion denuder sampling system indicate that the fine particulate organic constituents to which an urban population is exposed have not been well characterized or quantified in previous studies.

THE RELATIONSHIP OF URGENT HOSPITAL ADMISSIONS FOR RESPIRATORY ILLNESSES TO AIR POLLUTION LEVELS IN MONTREAL

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The relationship between the number of daily urgent hospital admissions to 31 hospitals for respiratory illnesses and ambient air pollution in Montreal, Canada was investigated for warm periods between 1984 and 1988. Time series regression models controlled for seasonality, day of week, autocorrelation, temperature, and relative humidity. For July-August periods, all respiratory admissions were positively associated to the 8-hour maximal average for ozone 4 days prior to the admission day ($p < 0.01$), but this was confounded by temperature. High intercorrelations between ozone, particulates and temperature, plus low levels of ozone (90% < 60 ppb), may explain this finding. Asthma admissions in May-October periods increased by 2.7% over mean levels for each 12 $\mu g/m^3$ increase in estimated PM_{10} levels 3 days prior to the admission day (95% confidence interval, 0.1 to 4.8%). In July-August periods, admissions for respiratory illnesses excluding asthma were 9.6% higher (95% confidence interval, 0.5 to 18.7%) when estimated SO_4^{2-} had exceeded 8.1 $\mu g/m^3$ 4 days prior to the admission day compared to days when SO_4^{2-} was at or below this level. There were no significant findings for nonrespiratory admissions after controlling for weather. The effects found were at levels below the U.S. National Ambient Air Quality Standards for PM_{10} of 150 $\mu g/m^3$, but are nevertheless relevant to public health, since hospital admissions are expected to be accompanied by considerably more frequent occurrences of less serious outcomes. The present findings suggest that particulate air pollution during photochemically active periods, is related to respiratory morbidity in Montreal.

P1.5

RESPIRATORY HEALTH STATUS OF ELEMENTARY SCHOOL CHILDREN RESIDING IN TEPLICE CZECH REPUBLIC.

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Northern Bohemia in the Czech Republic has among the highest levels of particulates and sulfur dioxide (SO_2) in Europe. The annual averages of both PM_{10} and SO_2 in the highly polluted northern Bohemian district of Teplice (TEP) are typically near 100 $\mu g/m^3$, but levels are much greater in the winter when emissions are high and temperature inversions occur. For example, this past February, the monthly average PM_{10} and SO_2 were well above 200 $\mu g/m^3$ with some 24-hr averages in excess of 800 $\mu g/m^3$. For comparison, the annual PM_{10} AND SO_2 averages in the cleaner southern Bohemian district of Prachatice (PRA) are about 30 $\mu g/m^3$. We previously observed lower pulmonary function and a greater prevalence of respiratory symptoms in 8th grade children living in TEP as compared with children living in PRA. The primary purpose of this study was to ascertain if similar differences were discernable for younger children living in TEP and PRA. A second purpose was to determine if additional decrements in pulmonary function result from exposure during the winter pollution season in TEP. Respiratory questionnaire responses were obtained and forced expiratory spirometry was measured in 2nd, 5th and 8th grade students in both districts. Respiratory symptoms (cough, phlegm, wheeze) were significantly more prevalent in all three grades in TEP than in PRA ($P<0.01$). The prevalence of chronic bronchitis for TEP children, all grades combined, was more than twice that of PRA children ($P<0.01$). Spirometry was initially measured in October 1992 following a 6 month period of perhaps the cleanest air in TEP in a decade. Height-adjusted FVC and FEV_1 were significantly lower in both boys and girls in all three grades in TEP than in PRA ($P<0.01$). District differences for both questionnaire responses and pulmonary function were still significant when controlling for gender, age, allergies, home smoking incidence, pets, private home/apartment residency or heating/cooking fuels. We repeated spirometry measurements in March 1993 following the winter pollution season. In TEP, no differences were observed between FVC and FEV_1 measured in October and March, suggesting that these children had chronically depressed lung function. No differences across times were observed in PRA, indicating our measurements were reliable. Our findings show a definite difference in the respiratory health status between children living in the two districts which may be due to the high levels of particulate and/or SO_2 that are present in TEP.

P1.8

SHORT-TERM AIR POLLUTION EXPOSURES AND LUNG FUNCTION CHANGES IN SCHOOLCHILDREN FROM THREE SOUTHERN CALIFORNIA COMMUNITIES OF CONTRASTING AIR QUALITY

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Experimental Design and Methods. This study addresses the question whether short-term (hourly or daily) air pollution changes in metropolitan Los Angeles cause short-term lung function or symptom changes in schoolchildren. Any such effects might be important to public health in themselves, or might be important confounders in studies of air pollution's longer-term health effects. During the 1992-93 school year we studied 269 children aged 8-11 from 3 elementary schools in 3 different communities -- Rubidoux (inland semirural, with high oxidant and high particulate but low strong-acid pollution), Upland (inland urban, high in oxidant, particulate, and strong acid), and Torrance (coastal urban, with moderate levels of primary pollutants but relatively low in oxidant). Each child underwent lung function and symptom evaluation mornings and afternoons Monday through Thursday, and again on Friday morning, during one school week each in fall, winter, and spring. Two different subgroups of children were studied in two successive weeks at each school, for a total of 6 weeks testing each season. Children were given activity diaries for each testing day, and filled out brief questionnaires summarizing their recent outdoor and indoor physical activity during each health testing session. Questionnaires concerning children's respiratory health history were submitted to parents. In all, 250 children provided health data for all 3 seasons and 240 provided parents' questionnaire data, but only 15 had complete daily test results. Most missing data reflected school holidays or trips, rather than illness absences. Concurrently with health testing, ozone (O_3), nitrogen dioxide (NO_2), and respirable particulate (PM) concentrations (24-hour averages) were measured inside and outside the school, using passive sampling badges for gases and miniature cyclone samplers for PM. Cyclones collected particulates of approximately 5 μm diameter and smaller. Personal environments of selected students (different ones each day) were monitored similarly, to determine how closely typical personal exposures tracked the pollutant concentrations measured at the school. On two days each week, strong acids and ionic components of PM were characterized using portable annular denuder samplers. Ozone was measured inside and outside the school on alternate days with an ultraviolet photometric monitor.

Preliminary Results of Air Monitoring. During testing weeks, outdoor PM was highest in Rubidoux while O_3 and NO_2 were highest in Upland (see table). Pollutant concentrations were usually lower inside schools than outdoors. Indoor/outdoor concentration ratios in Rubidoux averaged near 0.9 for PM, 0.25 for O_3, and 0.2 for NO_2, while the other two schools averaged near 1.6 for PM, 0.6 for O_3, and 0.5 for NO_2. Rubidoux's lower ratios may reflect more air conditioning and higher outdoor PM levels. (Ratios decreased as outdoor PM concentrations increased.) Personal PM exposures were generally higher than outdoor or indoor concentrations at schools; overall average 24-hr PM levels (in $\mu g/m^3$) were 40 personal, 26 outdoors, and 21 indoors. Personal NO_2 exposures averaged slightly below outdoor concentrations. Personal O_3 exposure concentrations averaged about one-fourth of outdoor concentrations; these measurements showed substantial variation probably due to wind velocity effects. When all 3 communities/3 seasons were considered, average personal exposure concentrations correlated with concentrations of the same pollutant measured at the school or the nearest air monitoring station ($r = 0.5$ to 0.8). Concentrations of different pollutants usually were less highly correlated. Accordingly, statistical analyses of health vs. air quality used monitoring data from nearest stations for O_3 and NO_2, used data from outside schools for PM, and treated each pollutant's effect independently.

P1.9

SEPARATING THE EFFECTS OF TEMPERATURE AND SEASON ON DAILY MORTALITY FROM THOSE OF AIR POLLUTION IN LONDON: 1965-1972

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Most analyses of the large data base of daily mortality and indices of pollution in London, England for 1958-1972 have dealt with the confounding influence of ambient temperature and/or season by using empirical adjustment models in the determination of the regression coefficients for the pollutants. The conclusions about the influence of the measured pollutants (SO_2, BS, and H_2SO_4) on mortality have varied due, at least in part, to the selection of the form of the temperature/season adjustment model. We have taken an alternate approach to separate the influences of temperature, season, and ambient pollutant levels on daily mortality. In each season, the majority of days fall within one or two temperature ranges, within which the daily death rates also fall within narrow ranges. Within these restricted temperature and mortality ranges, there are similar and highly significant associations between the daily concentrations of H_2SO_4 and daily mortality that are not confounded by temperature or seasonal variations. By contrast, the associations between Black Smoke and mortality in these restricted ranges are much weaker or absent.
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STATISTICAL METHODS FOR ASSESSING ASSOCIATION BETWEEN DAILY MORTALITY AND PARTICULATE AIR POLLUTION

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Recently several studies have shown an association between daily mortality and particulate air pollution. Statistical methods used in these studies were Poisson regression models in which parameter estimates and corresponding standard errors were obtained using generalized estimating equations (GEE). GEE was originally described by Liang and Zeger (Biometrika 1986;73:13-22) in the context of longitudinal data analysis. Since the structure of data for evaluating an association between daily mortality and particulate air pollution differ greatly from that of data for which the GEE method was originally intended, there are concerns regarding the appropriateness of the GEE method used in recent studies and the conclusions regarding health effects of particulate air pollution.

In this presentation we will review Poisson regression models for correlated data and examine the appropriateness of the GEE method for the analysis of daily mortality and air pollution. The results of the simulation study will be presented. The simulation study suggests that a type I error rate (i.e., declaring statistical significance when in fact there is no effect) of the GEE method is much higher than the conventional 5% when applied to time-series data. We will discuss possible alternative statistical methods for assessing an association between daily mortality and particulate air pollution.

ASSOCIATIONS BETWEEN DAILY MORTALITY, OZONE AND PARTICULATE AIR POLLUTION IN TORONTO, CANADA

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Recent time-series studies have reported associations between daily mortality and various measurements of airborne particulates, including TSP, PM_{10} and coefficient of haze (COH). However, only a few studies (Kinney & Ozkaynak, *Environ. Res* 54; 99-120, 1991 and Kinney & Ozkaynak, *Am. Rev. Resp. Dis.* 145;A95, 1992) have reported an association between daily mortality and previous day hourly-maximum oxidant levels in major urban areas like Los Angeles and New York City. We have recently gathered and analyzed an extensive aerometric particulate data base from Toronto, Canada, over a 19-year period, from 1972-1990. These data were combined to provide total and cause-specific daily mortality counts for multiple age groups, available through a health data base maintained by Statistics Canada. The daily aerometric time-series records, which included pollution data on TSP, SO_4, COH, O_3, SO_2, CO and NO_2, were obtained from sixteen air monitoring stations from five boroughs of Toronto. Meteorological and visibility data were obtained from Pearson Airport, in Toronto. We conducted multiple regression analyses of mortality on the pollution and meteorological variables after detrending the mortality and pollution series to control for seasonal variations in the data. A model which included temperature, relative humidity, same day maximum one-hour O_3 and either same day TSP or estimated PM_{10} explained approximately 2% of the variation in the detrended daily mortality. Regression slopes (ß) for PM_{10}, TSP, and ozone were $ß_{TSP}$ = 0.011 deaths/$\mu g/m^3$ ($p<0.001$), $ß_{PM10}$ = 0.022 deaths/$\mu g/m^3$ ($p<0.001$), and $ß_{O3}$ = 0.017 deaths/ppb ($p<0.01$), respectively. The estimated contribution of each pollutant to daily mortality at the mean pollution levels were 2.3% for either PM_{10} or TSP and 1.5% for ozone. The total estimated contribution of particles and ozone to daily mortality was about 4%. This analysis however could not distinguish the estimated mortality effects of TSP from those associated with exposures to PM_{10}. The findings from this analysis are consistent with results from previous epidemiologic investigations conducted for other U.S. metropolitan areas.

HUMAN MORTALITY, AIR POLLUTION, AND UNEMPLOYMENT IN SOUTHERN CALIFORNIA

by

Joseph E. Haring, Ph.D., Pasadena Research Institute with the assistance of E. S. Vataru, California Institute of Technology

Abstract

Background. Environmental regulations in the United States are based on the presumption that human mortality is adversely affected by air pollution. Many rules are castin terms of risks of death per million population. Recent studies published in the New England Journal of Medicine and elsewhere have reported associations between air pollution and mortality rates. These studies have not yet persuaded the medical profession to accept a causal relation between smog and human mortality. A new study of 30 cities by Merva and Fowles asserts that mortality is more tightly correlated with unemployment than with air pollution.

Methods. In this study we estimated the effects of air pollution on mortality in Southern California, defined as Los Angeles, Orange, San Bernardino and Riverside Counties, while controlling for unemployment. Similarly, we estimated the effects of unemployment on mortality, while controlling for air pollution.

Results. Mortality rates in Southern California were most strongly associated with unemployment. After adjusting for unemployment, we observed statistically significant and robust associations between air pollution and mortality.

Conclusions. Although there are numerous other factors worthy of separate study, these results suggest that both unemployment and air pollution contribute to excess mortality in Southern California.

VARIABILITY OF PARTICLE DEPOSITION WITH AGE IN ADULTS WITH NORMAL LUNG FUNCTION.

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Recent epidemiological studies suggest increased morbidity among the elderly and very young associated with particulate air pollution. We are currently investigating the variability in fractional deposition (DF) of inhaled particles in subjects with normal lung function aged 8 - 70. To date we have measured DF in thirty five (35) subjects with normal pulmonary function ranging in age from 18 - 60. Each subject inhaled 2μm monodisperse, carnauba wax particles while following a breathing pattern previously determined by respiratory inductance plethysmography in that subject (i.e. that subject's spontaneous pattern at rest). Breath by breath DF (ratio of particles not exhaled /total particles inhaled) was determined by photometry /pneumotach at the mouth. We have found no variability of DF with age (r=.02), mean DF = .28+/-.07 (ages 18-40) and .27+/-.05 (ages 41-60). The mean tidal volumes (Vt) and breathing periods (T) for the two groups were also not different, Vt=372 ml and T=3.57 sec for the young adults (n=18) and Vt=436 ml and T=3.53 sec in the older group (n=17). Multiple regression analysis shows that among all subjects the variability in DF is best predicted by variability in the breathing period (T) associated with the pattern used to breathe the particles, the ratio FRC/TLC (resting lung volume to total lung capacity), and specific airway resistance (sRaw). Greater DF occurs for increasing T, decreasing FRC/TLC, and increasing sRaw. We are presently studying subjects over age 60 both with and without (> 30 pack years smoking history) normal lung function and will conclude by studying children age 8-18. Information derived from this study should prove useful in determining age-relative risks that may be associated with the inhalation of pollutant particles in ambient air. Supported by USEPA Cooperative Agreement CR812738. This is an abstract of a proposed presentation and does not necessarily reflect EPA policy.

ACIDIC AEROSOLS: EFFECTS ON ALVEOLAR MACROPHAGE FUNCTION AND OZONE RESPONSIVENESS IN HUMANS. M.W. Frampton, P.E. Morrow, M.J. Utell. University of Rochester School of Medicine, Rochester, NY

Particulate matter in the atmosphere has been associated with increased respiratory morbidity and mortality. Sulfuric acid aerosols, the predominant particulate species in many industrialized areas, may act directly by impairing host defenses, or indirectly by potentiating effects of other pollutants such as ozone. To examine direct effects of acidic aerosols, we exposed 7 healthy nonsmoking volunteers to aerosols of either H_2SO_4 or NaCl, 1000 $\mu g/m^3$ for 3 hours, with intermittent exercise. Lung function was measured, and bronchoalveolar lavage was performed 1 hour after exposure. There were no significant changes in lung function. The proportion of cells recovered were similar following NaCl and H_2SO_4 exposure, indicating the absence of an airway inflammatory response. Release of superoxide anion by alveolar macrophages (AM) stimulated with opsonized zymosan decreased following H_2SO_4 exposure (NaCl, 3.49±0.25 nmol; H_2SO_4, 3.01±0.28 nmol, $p<0.06$). Similar findings have been observed in rabbits exposed in an identical manner. To determine whether H_2SO_4 aerosols potentiate airway function responses to ozone in asthmatic subjects, 30 allergic asthmatic subjects underwent 3-hour exposures to 100 $\mu g/m^3$ H_2SO_4 and NaCl (control) aerosols (in random order), followed 24 hours later by 3-hour exposures to ozone (0.08, 0.12, or 0.18 ppm). Analyses revealed evidence for direct effects of ozone on lung function, and for interactions between aerosol and ozone exposure both immediately after ($p=0.005$) and 4 hours after ($p=0.030$) exposure. There were no significant effects of exposures on symptoms. These studies suggest that exposure to H_2SO_4 at 1000 $\mu g/m^3$ may alter AM release of superoxide anion in healthy volunteers, and exposure to 100 $\mu g/m^3$ may enhance responses to ozone exposure in asthmatic subjects.

P2.6

ASSESSMENT OF LOCAL DEPOSITION OF INHALED PARTICLES IN HUMAN LUNGS

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Deposition site and dose of inhaled particles within the lung are key determinants in risk assessment of particulate pollutants. Traditionally, particle deposition in the lung is measured from the entire lung and regional deposition information within the lung is deduced from other indirect measurements such as radioaerosol clearance. In the present study, we developed a method that can measure regional deposition of inhaled particles within the lung in situ using serial bolus delivery technique. A small bolus (40 ml half width) of monodisperse aerosols (1, 3 and 5 μm dia.) was delivered sequentially to a specific volumetric depth of the lung (Vp = 100-400 ml with a 50 ml increment) in 22 healthy subjects (11 male and 11 female). The subject inhaled the bolus via a laser aerosol photometer (25 ml dead volume) with a constant flow rate (Q = 150, 250 and 500 ml/s) and exhaled with the same flow rate without a pause to the residual volume: the inspiratory volume was 500 ml from the FRC in all tests. Deposition efficiency (DE) of and deposition fraction (DF) in local regions as well as total deposition fraction (TDF) of the lung were obtained. The results were compared with existing experimental data. It was found that TDF values agreed well with existing human data. However, regional DF was not consistent with conventional data. The results also show that TDF is consistently greater in female than male regardless of particle size and flow rate used. The increase was particularly prominent in the shallow but not in the deeper volumetric regions of the lung. The results also suggest that local or regional enhancement of deposition occurs in healthy subject and that the local enhancement may have significant health consequences in patients with lung disease. *This is an abstract of a proposed presentation and does not necessarily reflect EPA policy.*

P2.7

THE DEVELOPMENT OF AN AMBIENT PARTICLE CONCENTRATOR (FOR HUMAN AND ANIMAL INHALATION EXPOSURE STUDIES).

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A number of studies have underlined the importance of the acute and chronic effects of ambient particles on respiratory health. Because fine particles are capable of penetrating deeply into the respiratory system, most of the health studies have focused on the inhalable portion of the particle size spectrum. Previous studies to examine exposure/response relationships between particle exposure and adverse respiratory effects have been based on artificial preparations, or collected and resuspended ambient particles, rather than the natural material found in ambient air. Artificial particles may not be representative and collected particles may be difficult to redisperse. In addition, the chemical characteristics of ambient particles may change upon resuspension.

A new technique has been developed to enable us to generate ambient particle concentrations at desired levels up to 1-2 mg/m^3 at flow rates in the range of 5-25 liters/minute. By using a dilution system, the concentration of other pollutants, temperature and relative humidity can be controlled. This approach makes it possible to use ambient particles for inhalation studies and it also allows for control of potential confounding factors. This technique employs two slit-nozzle virtual impactors connected in series, each of them operating with a 0.15 μm 50% cutpoint. The virtual impactors were characterized separately in terms of their cutpoints and interstage losses. Ambient aerosol containing particles in the size range 0.15-2.50 μm can be concentrated in two steps. as it is drawn through the virtual impactors. The sampling flow rates are 1 m^3/minute and 100 liters/minute in the first and second virtual impactors, respectively. The concentrated aerosol can be supplied to a human or animal exposure chamber with a peristaltic pump that minimizes interstage particle losses.

PARTICLE INSTILLATION IN HUMAN LUNGS: A METHOD FOR MEASURING LUNG RESPONSE TO INERT PARTICLES

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Recent epidemiologic studies suggest that changes in morbidity and mortality may be associated with fluctuations in the 24-hour average concentration of suspended ambient respirable particulate matter. Possible mechanisms for such effect remain obscure. We have used bronchoalveolar lavage (BAL) to study the response of the human lung to intrabronchial instillation of suspended "inert" particles. Twenty ml sterile physiologic saline solution (PSS) containing 3 to 30 x 10^7 iron oxide particles (Fe_2O_3, 2.5 μm physical diameter) were instilled into the lingula of healthy non-smoking volunteers (n=17) via bronchoscopy. The suspensions were free of endotoxin (Limulus amebocyte lysate assay, Endotect, ICN Biomedical). As a control, 20 ml PSS (without particles) was instilled into a segment of the right middle lobe. We quantified the total cells, percent of several cell types and cells containing particles recovered by BAL from both segments at one to 91 days post-instillation (PI). Returns from an initial 20 ml lavage provided a "bronchial" fraction. Returns from 5 x 50 ml subsequent aliquots were pooled to provide an "alveolar" fraction. At one day PI (n=6), the mean number of cells recovered from the lingula was increased in both the bronchial (20.6 x 10^5 cells) and alveolar (19.7 x 10^7 cells) fractions compared to the control (6.7 x 10^5 cells and 2.7 x 10^7, respectively). Neutrophils represented 53% of bronchial fraction cells and 31% of alveolar fraction cells from the lingula, but only 29.0 and 1.6% respectively from the control lobe. Mononuclear cells also were increased in the lingular lavageate. These changes had completely regressed by 4 days PI (n=2). Total AM containing at least one particle diminished only slightly from 6.1 x 10^6 at one day to 4.4 x 10^6 at 91 days, however, the proportion of particle-laden AM increased from 5.8% to 21.7%. These findings indicate that "inert," insoluble particles remain sequestered in AM for extended periods and that such particles may cause a transient acute inflammatory response whose genesis is under study. This response may be relevant to exploring mechanisms that might underlie health effects of exposure to ambient respirable particulate matter. [Supported by USEPA Cooperative Agreement CR817643. This is an abstract of a proposed presentation and does not necessarily reflect EPA policy].

RAT - HUMAN DIFFERENCES IN MACROPHAGE OXIDANT PRODUCTION BY POLLUTANT PARTICLES. Q. Rahman[1], J. Norwood[2], G. Oberdorster[3] and G. Hatch[2]. [1]Indus. Tox. Res. Center, Lucknow, India; [2] H.E.R.L., U.S. E.P.A., Res. Tri. Park, NC., [3]Univ. of Rochester School of Med., Rochester, N.Y.

Macrophages and inflammatory cells generate active oxygen species in the process of killing and degrading microorganisms. Air pollutant particles may be ingested by macrophages and stimulate the same mechanisms to produce a long-term oxidative burden to the lung if particles are not degraded. We are comparing rat and human alveolar macrophages (AM) in their oxidative response to inhaled particles through the use of luminol chemiluminescence (CL) and oxygen-18 labeling. The same particles that are being tested in a 90 day inhalation study in rats (carbon black, amorphous and crystalline silica, ultrafine TiO_2, asbestos) are added to AM *in vitro* in the presence of media containing luminol and a catalase inhibitor. Direct CL (thought to be due mostly to O_2- production) is measured, a peroxidase is added to quantify H_2O_2 released from cells, then LDH release is measured as a cytotoxicity marker. Results to date suggest that rat AM respond differently than human AM in the following ways. 1) They have a lower (~2 fold) basal and particle-stimulated CL than human AM, 2) they produce less H_2O_2 (either basal or particle-induced), and 3) they have a different spectrum of response to the same particles. For example, ultrafine TiO_2 is an active stimulant of rat but not human AM while the reverse is true of crocidolite asbestos. In both species, O_2- CL is generally increased by particles while H_2O_2 release is often greatest in "unstimulated" cells. These preliminary results suggest that humans may be more susceptible than rats to inhaled particles because human AM have a more active oxidative burst than rat AM. (This abstract does not reflect E.P.A. policy).

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RISK ASSESSMENT OF INHALED PARTICLES: INTEGRATING TIME-ACTIVITY PATTERNS WITH RESPIRATORY TRACT PARTICLE DEPOSITION MODELS

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Evaluating the risks associated with chronic exposure to toxic air pollutants due to inhalation and aerosol particles requires a quantitative estimate of the actual mass depositing in various regions of the respiratory tract. Although sophisticated mathematical models are available to predict particle deposition in the major regions of the respiratory tract, these models are generally limited to predicting deposition of particles of known size and specific ventilation rates. Risk assessment professionals who use these models must make simplifying assumptions about "typical" particle sizes and "average" ventilation rates (e.g. m^3/day expressed as l/min flow rates). However, particle deposition in the lung changes dramatically at different ventilation rates, and average values do not necessarily predict average deposition fractions or regional deposition patterns. Our research examines the validity of making such simplifying assumptions.

Recently-available studies of human daily activity patterns which provide estimates of the fraction of time different U.S. subpopulations spend in activities with markedly different ventilation rates from resting to heavy exertion were used to estimate daily time-activity distributions. Activity-specific ventilation rates throughout a typical day for persons of specific age groups were then used instead of average daily ventilation rates to calculate aerosol deposition. Representative indoor and outdoor mass median aerosol diameters taken from published literature sources were used to define exposure concentrations throughout the day. Using the Yeh and Schum (1980) predictive aerosol deposition model, the daily deposition rates in the different regions of the respiratory tract are compared for the following individual exposure scenarios: indoor and outdoor workers in low and high activity occupations, and adult and child non-workers in a residential setting who are exposed to ambient air particles. The fractional contribution of different daily activity patterns to the total daily dose is presented, and the integrated daily dose is compared to predictions using "average" ventilation rates.

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P2.12

THE ORONASAL AIRWAYS: THE DEFINER AND IGNORED RESPIRATORY ZONE OF THE PM-10 REGULATORY CONVENTION.

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The particle penetration properties of the nasal and oral airways are the defining feature of the PM-10 convention. This definition implicitly assumes that only particles able to penetrate these airways can produce particle-associated health effects. Though not stated explicitly, this definition implies that no health effects resulting from exposure to particles are associated with these airways.

Some particles within the PM-10 envelope are deposited in the nasal and oral airways, as well as particles outside of the envelope (except for non-inhalable particles). Evidence for health effects of particles deposited in the oronasal (ON) airways is scant, primarily because most epidemiological and clinical studies have focused on the intrathoracic airways.

With improved techniques for detecting physiological changes and/or acute/chronic health effects in the ON airways, the role of these airways in providing data for regulation and control of particle exposure need further examination. Surveys of the incidence of nasal diseases indicate evidence for increasing occurrence of allergy, rhinitis and sinus infection in urban dwellers; these studies suggest that further investigation of the factors relating particle exposure to nasal disease are needed. There is evidence for variability of ON particle deposition efficiency whose relationship to health effects has not been studied.

P2.13

ESTABLISHING AN EPIDEMIOLOGICAL CONTEXT FOR THE ASSOCIATION OF MORTALITY WITH EXPOSURE TO PARTICULATE MATTER

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Recent epidemiologic studies consistently show an association of daily mortality with short-term elevations in ambient exposure to particulate matter (PM). An association of long-term mortality rates with PM exposure has also been observed. These findings simultaneously raise concern as to severity of the effect and skepticism as to its biologic plausibility. Though mortality studies should continue, they are not likely by themselves to eliminate all doubt. Instead, they should be accompanied by a vigorous program of experimental studies to investigate mechanisms by which PM-sulfur oxide (SO_x) exposure might cause mortality, atmospheric chemistry studies to further determine the specific components of the ambient PM-SO_x mixture and epidemiologic studies to determine whether PM-associated mortality occurs in a plausible, coherent biomedical context. In addition to mortality, epidemiologic studies should further address morbidity, and physiologic change in domestic and international settings. Important epidemiologic issues, requiring further investigation, include the following: apparent discrepancies between exposure-morbidity and exposure-mortality lag times; the strength with which lung function decrements predict mortality; the degree of irreversibility of childhood lung function decrements; and the international, inter-ethnic consistency of PM-related findings. If PM exposure indeed causes excess mortality, we would expect stable PM-related lung function decrements to occur in the same exposed populations. Current evidence strongly suggests that lung function decrements predict premature respiratory and cardiovascular mortality, even after adjustment for smoking. Thus, in our view, demonstration of stable PM-SO_x-related decrements in lung function would greatly enhance the credibility of the mortality findings. Available evidence suggests that short-term changes in PM-SO_x exposure produce short-term changes in lung function. Interim evidence from China also suggests that PM-SO_x exposure retards lung function growth in children. However, it is not yet clear whether long-term PM-SO_x exposure produces long-term stable decrements in lung function. This issue should be investigated until resolution is achieved.

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SPATIAL VARIATION IN FINE AND COARSE PARTICLE MASS WITHIN METROPOLITAN PHILADELPHIA

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Particle mass concentrations ($PM_{2.5}$ and PM_{10}) were measured in metropolitan Philadelphia during the summer of 1992, as part of a large effort to characterize acid aerosol concentrations within urban environments. Sampling was performed simultaneously at seven sites located within metropolitan Philadelphia and at a rural site approximately 18 miles from the city center. Sites were selected based on their population density and on their relative locations within Philadelphia. particle sampling was performed on alternate days, with sampling conducted over 24-h periods beginning at 8 am. All samples were collected using 10 $L \cdot min^{-1}$ Harvard Impactors.

In this paper, we examine and compare the spatial variation in fine ($d_a<2.5$ μm) and coarse ($2.5<d_a<10$ μm) particle mass concentrations. The effects of population density, traffic, location, wind direction, and other factors that may influence their spatial variation are discussed. Statistical analyses will be performed using Pearson correlation coefficients, as well as one-way analysis of variance (ANOVA) and univariate and multivariate regression procedures. This information will help epidemiologists understand how well, or poorly, measurements of fine, coarse, and PM_{10} aerosols collected from a single urban monitoring site are able to characterize particle concentrations within an urban area.

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P3.5

TEMPORAL AND SPATIAL VARIATIONS OF PM_{10} AND ITS SOURCES IN THE SOUTH COAST AIR BASIN

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Statistical associations have been observed between human mortality and fine and sulfate particles. However, significant gaps in our knowledge exist in explaining the observed health effects based on results from controlled exposure studies. It is possible that the causative agent is a species that is correlated with particulate matter, but not measured by routine sampling of atmospheric aerosols. Free radicals, such as hydroxyl radicals. are responsible for the formation of fine and sulfate particles. They are also known to be damaging to lung tissue, as well as playing a role in the pathogenesis of a wide variety of disease states, including inflammation and cancer. These observations suggest that radicals may be at least partly responsible for adverse health effects, and that fine particle mass could serve as a marker for free radical dosage. Applying receptor models to time-series aerosol data to determine the temporal variations of source contributions may provide additional insight regarding mixtures of species that cause a disproportionate fraction of the health effects.

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WHY CORRECT PM10 MEASUREMENTS FOR PRESSURE?

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The objective of airborne particulate sampling is to provide an estimate of airborne concentration, human exposure, and ultimately dose; the estimated dose is based on particulate mass per unit volume of air and the total volume of air inhaled over a given time.

Human response to changes in altitude have been extensively studied. For data associated with acclimatized individuals living in Denver, Colorado (1580 meters) the range of arterial blood gases have been measured to be Po_2: 65 - 75 mmHg and Pco_2: 34 - 38 mmHg.[1] Evidence further indicates that if Pco_2 is kept below 40 mmHg, the alveolar Po_2 can be reduced to approximately 50 mmHg before an increase in ventilation occurs.[2] Thus, no appreciable increase in respiration minute-volume would be expected to occur among acclimatized individuals at common U.S. urban elevations.

Given this physiological data it appears erroneous to assume that at elevations associated with any major U.S. metropolitan area, humans would receive different doses of PM10 over a 24 hour exposure given equal mass per unit volume concentrations (unadjusted for temperature and pressure). Because EPA exposure regulations for PM10 are expressed in units of mass per unit volume (ug/m^3) they should not require temperature or elevation corrections for comparison of sampling results to standards.

In 40 CFR 50, Appendix J - Reference Method for the Determination of Particulate Matter as PM10 in the Atmosphere, Section 11 - Calculations, the instructions are to calculate the average flow rate over the sampling period and then correct to EPA reference conditions (Q_{std}).

$$Q_{std} = Q_a \times (P_{av}/T_{av})(T_{std}/P_{av})$$

where:

Q_{std} = average flow rate at EPA reference conditions, std m^3/min;

Q_a = average flow rate at ambient conditions;

P_{av} = average barometric pressure during the sampling period or average barometric pressure for the sampling site, kPa (or mmHg);

T_{av} = average ambient temperature during the sampling period or seasonal average ambient temperature for sampling site, K;

T_{std} = standard temperature, defined as 298K;

P_{std} = standard pressure, defined as 101.3 kPa (or 760 mmHg).

P3.11

PM_{10}, FINE PARTICLE, AND NITRIC ACID CONCENTRATIONS IN CALIFORNIA DURING 1988-89

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The concentrations of acidic gases and particles were measured at ten sites throughout the state of California between October 6, 1988, and September 25, 1989, as part of the California Acid Deposition Monitoring Program (CADMP). Seven of these sampling sites represented urban areas (South Coast Air Basin, San Francisco Bay Area, Bakersfield, Santa Barbara, and Sacramento) and three represented forested areas (Sequoia, Yosemite, and Redwood National Parks). Twelve-hour daytime and nighttime measurements were taken on filters using standard PM_{10} inlets and Teflon-coated fine-particle inlets. The denuder-difference method with absorbing nylon filters was used to obtain nitric acid concentrations. Other measured concentrations included particulate mass, sulfate, nitrate, chloride, ammonium; water-soluble sodium, magnesium, potassium, and calcium; and gaseous ammonia, sulfur dioxide, and nitrogen dioxide.

The twenty-four hour average federal PM_{10} standard of 150 $\mu g/m^3$ was exceeded at the Bakersfield, Central Los Angeles, and Azusa sites. The highest fine particle mass concentrations did not always correspond to the highest PM_{10} concentrations at any of the sites. PM_{10} mass concentrations were generally highest for nighttime samples. The maximum 12-hour nitric acid concentration of 37 $\mu g/m^3$ was measured during summer at the Azusa site in downtown Los Angeles. Maximum daytime nitric acid concentrations were less than 3 $\mu g/m^3$ at the rural sites.

COMMENTARY:

SUMMARY OF THE COLLOQUIUM ON PARTICULATE AIR POLLUTION AND HUMAN MORTALITY AND MORBIDITY; IRVINE CALIFORNIA; Jan 24 & 25th 1994

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SUMMARY OF THE COLLOQUIUM ON PARTICULATE AIR POLLUTION AND HUMAN MORTALITY AND MORBIDITY; IRVINE CALIFORNIA; Jan 24 & 25th 1994

INTRODUCTION:

This colloquium, which attracted over 200 participants, heard 6 papers on epidemiology; 6 papers commenting on epidemiological methods; 5 papers on possible mechanisms of particle toxicity; and 9 papers on sources, levels and composition of particles less than 10 microns in size (PM10). In addition, there were 15 posters on epidemiology, 13 posters on mechanisms of lung injury, and 11 posters on air pollution characterization.

On the way to Orange County, I wrote down ten questions which I hoped would be answered by the colloquium. I propose to summarize the proceedings by examining what appear to me to be the best answers available.

1. Are the associations between PM10 and mortality in time series studies, robust?

The associations have been shown in 16 different locations on three continents. New data were presented at the colloquium from Chicago indicating a stronger association than in Philadelphia. This association was shown in four different model analyses. It is clear that differing ways of handling seasonality and weather effects can exert

a major influence on the outcome of these calculations; but in general similar conclusions are reached when different de-trending models are used. Although re-analyses of data from Steubenville were presented showing that a positive association was dependent on which population was included, and which aerometric data were used, these criticisms did not undermine the aggregate of the larger datasets. The relationships between exposure data and outcomes would be influenced by errors in the measured pollutants, and no account had been taken of these. Nevertheless, the associations demonstrated must, on the whole, be considered to be robust.

2. Can any common confounder be suggested?

Although in any individual study it is possible to suggest that SO2, or aerosol acidity, or ozone might also have influenced mortality, the locations in which the PM10 relationship has been shown to hold contain some with no SO2, some with no acidity, and others with minimal ozone. No confounder common to all the studies can be suggested. The longitudinal 6 cities study indicates that the increased risk of mortality with higher levels of PM10 is responsible for overall reduced survival (thus the time-series relationship cannot be dismissed as attributable to an acceleration of death by a short interval of 48 hours or so). New data from an analysis of an American Cancer Society dataset supports the conclusion from the 6 city study that

increased PM10 may be associated with an increased risk of lung cancer. In these studies, increased sulfate concentrations appear to be important; but as sulfates are a common component of PM10 in the summer, they cannot be regarded as a confounder. Nevertheless, it was clear that in individual studies, logistic regression methods were not easy to apply in separating the effects of different pollutants; or of pollutants in relation to weather patterns.

3. Why is cardiovascular mortality related to PM10?

Although speculative mechanisms can be proposed, there is currently no convincing explanation of this. The clarification of this relationship represents an important research priority.

4. Is there convincing evidence of other adverse effects of PM10?

PM10 levels have been shown to influence hospital admissions from acute respiratory disease; and in Toronto in the summer it was shown that although PM10 is significantly associated with such admissions, coarse particle mass (TSP minus PM10) was not. PM10 has also been shown to influence asthma emergency visits, and to be associated with increased medication use in asthmatics. It also affects peak flow rate performance in normal children. A detailed comparison of data in which other measurements of particulate pollution

were converted to presumed PM10 values, showed that other indices of adverse effects, such as increased respiratory symptoms, were consistent with these. In the Czech Republic, in regions where the mean monthly average PM10 values exceed 200 micrograms/m3, there is an increased prevalence of chronic bronchitis in children, and an increase in postneonatal mortality. In an adult nonsmoking cohort in California, recruited prospectively, PM10 levels were associated with an increased risk of development of airway obstructive disease.

The answer to this question must therefore be affirmative. Nevertheless, there were difficulties in interpreting some of the outcome data; it was suggested that RSV infections in children might have a cyclical pattern which would confound hospital admission data; and that the role of other pollutants such as SO2 was difficult to exclude in single studies.

5. If consistency, temporality, and coherence criteria are met, is an understanding of mechanisms in this case necessary for a conclusion of causality?

Different people will make different judgements on this question. There was no time to explore the reasons for different answers (this would have required statements of inherent or acquired bias, for which there was no time). There seemed little doubt that most would have agreed that the present status of the findings indicated, beyond

question, that the reasons for the epidemiological data must be actively sought.

6. How does the composition of PM10 particles vary in different places or at different times?

There was a great deal of information on this question. In summertime, the aerosol (both sulfate and nitrate) components were important; in other areas, the particle composition indicated that woodsmoke was important; in some places with high traffic density, a third of the fine particles were organic compounds; cigarette smoke had been identified as present in ambient fine particles, and leaf surface abrasion products could also be detected in some areas. Particles larger than one micron in size were generally formed by abrasion, and particles from 0.1 to 1.0 microns were usually formed by growth. We were reminded that 1 micron particles would last for 300 days in the atmosphere, and could travel thousands of miles; that 10 micron particles would last for one day, and might travel as far as seven hundred miles; and that 70 micron particles would only travel 7 miles. Dozens of hydrocarbons can be identified with fine particles, and up to 35% of volatile organic species could be lost during sampling. There seemed little doubt that there would be bound to be differences in composition of "PM10" in the same place in different seasons, and between different places.

7. Might the active particles be 1 micron or less in size?

There appear to be at least four reasons for suspecting that this is the case:

a) the higher penetration rates into small airways of smaller particles;

b) the fact that 1 micron particles would have similar indoor and outdoor concentrations; hence the cardiac invalid sitting indoors might get the same exposure as if he or she were outdoors. Also the intercorrelations between different monitors in the same region are higher for smaller particles, indicating that the population of a large area (such as greater Philadelphia) would be more uniformly exposed to smaller particles;

c) the observation of enhanced toxicity with very small particles (see paragraph 8 below).

d) the limited personal sampling data indicates that personal PM10 exposures were often 50% higher than outdoor and indoor concentrations.

Dosimetric comparisons of exercising humans and sedentary rats indicated that deposition of some sized particles within small airways might be greater in man than in small animals. Nonuniform ventilation of the lung (as is usual in cases of COPD) might lead to "overloading" of the well ventilated parts, with a consequently much enhanced effect.

8. What do we know of the effects of 10 micron and smaller

research centres in 10 countries has been launched. This will involve panels of children, and daily PM10 measurements will be made. The results of this study will be followed with great interest, as will the ongoing study of children's health in 12 Southern California communities.

There was a dinner at the meeting; but it had to be eaten so hurriedly if the posters were to be viewed that it could not be described as a banquet. Had it been a banquet, one could have identified some ghosts at it. Leonardo da Vinci who wrote "dust causes damage" alongside a drawing of the lung; Siméon-Denis Poisson, who dropped out of medical school and in 1837 wrote a book with the title: "Researches on the Probability of Opinions" which dealt with the distribution of infrequent events; David Hume, the Scots philosopher who pondered the problem of causal inferences from associations; and Sir Austen Bradford Hill who discussed causal inference in environmental epidemiology, and who warned us (with foresight?) that we could not demand knowledge of biological mechanisms. In the wings there would have been, on one side, a number of epidemiologists and biostatisticians who do not believe that air pollution causes significant adverse health effects, accompanied by those under contract to press the same view; and on the other, a growing number of investigators whose work supports a contrary judgement. Although it would have been tactless to point them out, Lave & Seskin would unquestionably have

been present. Perhaps it was fortunate that there wasn't a banquet.

As evidence accumulates that exposures to criteria pollutants such as PM, ozone, and lead at concentrations well below the current standards are associated with adverse health effects, the absence of monitoring data in non-exceedence areas becomes a critical limitation in our ability to assess health risks for such pollutants in the exceedingly large populations at risk. Future criteria document evaluations will be hampered by these gaps in PM data.

Summary of Knowledge Gaps

There are important knowledge gaps in all the major component areas of investigation, i.e.: 1) selection and implementation of exposure assessment protocols; 2) selection and application of epidemiological models and methods; and 3) identifying mechanisms and temporal patterns of biological responses to PM exposures and combinations of PM and gaseous exposures. Some preliminary assessments of the extent and significance of the gaps in these areas follow:

1) Exposure Assessment Protocols: The most critical limitations to improvements in defining exposure-response relationships lie, in my view, in the much greater current limitations of the art of exposure assessment. Within the area of PM exposure assessment, there are a number of specific areas where further investigations are needed. These include:

a) Retrospective Exposure Assessment. The needs in this area include improvements in models for constructing indices of personal exposure distributions based on: 1) network monitoring data; 2) geographic variations within regional airsheds; 3) indoor-outdoor ratios; 4) outdoor activity patterns; 5) residential histories; 6) in-transit exposures; etc.

b) Prospective Measurements of Temporal Patterns of PM Exposures. The separation of the acute effects of PM from those of continously monitored concentrations of gases such as ozone will not be successfully accomplished until the nature of the temporal variation of PM is better known. Ideally, continuous direct-reading PM monitors are needed at more of the network monitoring sites.

c) Analyses of More PM Components. The analysis of PM filters for sulfate, nitrate and ammonium ions, combined with some site-specific calibration studies, would permit reasonable and adequate estimation of aerosol H^+ exposures, one of the most likely causal factors for PM-related health effects. In some cases, this is possible on archived network filters, as well as in prospective sample collection and analysis.

2) Epidemiological Models and Methods: Refinements in this area are clearly needed, and are discussed in greater detail in the summary prepared by Dr. Arden Pope.

3) Biological Response to PM Exposure: As advances occur in fundamental understandings of disease processes related to PM exposures, it should be possible to identify causal exposure factors and their biological averaging times, and this knowledge should be used to guide the selection and implementation of more relevant exposure assessment and health outcome selection protocols.

PARTICULATE AIR POLLUTION AND HUMAN HEALTH: ASSESSMENT OF THE EPIDEMIOLOGY

Abbreviated title:

PARTICULATE POLLUTION AND HEALTH

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PARTICULATE AIR POLLUTION AND HUMAN HEALTH: ASSESSMENT OF THE EPIDEMIOLOGY

The number of epidemiologic studies that report health effects associated with particulate air pollution has grown dramatically since the late 1980's. The epidemiology sessions of the Colloquium on Particulate Air Pollution and Human Mortality and Morbidity, provided an excellent opportunity to review, discuss, debate, and evaluate much of this recent research. Because of the breadth of studies presented and opinions expressed, my assessment of these sessions will not attempt to review or summarize the presentations or discussions in detail. This assessment will briefly outline the evidence of human health effects of particulate air pollution from various types of epidemiologic studies. Based on the presentations and discussion at the colloquium, I will also briefly outline the various ways that this evidence is being interpreted and discuss the main questions that remain unanswered.

EPIDEMIOLOGIC OBSERVATIONS

Early episodic studies. Early studies focused on severe air pollution episodes and observed large increases in cardio-pulmonary disease mortality associated with extremely elevated concentration of particulate and/or sulfur oxide air pollution. Although the biological mechanisms involved were poorly understood, there remained little disagreement that, at very high levels, ambient air pollution can contribute to increased respiratory illness and early cardio-pulmonary mortality.

Population-based cross-sectional mortality studies. Population-based (ecologic) cross-sectional studies evaluated the spatial distribution of mortality and air pollution. These

critical of specific studies. Others suggested or implied that the consistency and coherency of the studies was being overstated. Nearly all of the participants recognized that the epidemiologic results would be more appreciable if the biological mechanisms involved were better understood. However, few participants seemed willing to attribute the observed associations between particulate air pollution and various measures of cardio-pulmonary disease strictly to chance.

Causal interpretation. Many colloquium participants recognized that the epidemiological studies provide substantial evidence implicating respirable particulate air pollution as a risk factor for cardio-pulmonary disease--even at levels common to many U.S. cities. For given health endpoints, reasonable consistency was observed across different researchers, study areas, and study designs. The studies also suggest a coherence or cascade of associations across various health endpoints. This consistency and coherency of epidemiologic results strengthens the implication that particulate air pollution likely plays a causal role in contributing to cardio-pulmonary disease.

Methodological Bias. It was suggested that observed air pollution health effects were due, at least in part, to systematic methodological or modeling bias. Such an explanation for these effects is lacking because of the wide range of research designs, analytical approaches, and statistical modeling techniques that have been used. Furthermore, many of the studies evaluated the sensitivity of their results and found them to be not very sensitive to different modeling approaches.

Confounding. The observed associations between human health and particulate air pollution from the epidemiological studies may be due to confounding of another uncontrolled risk factor that is correlated with both exposure and disease. For example, confounding may occur in an individual daily time-series study because of inadequate control

of seasonal factors, epidemics, other long wavelength trends, or weather variables. The time-series studies taken together, however, provide little evidence that the observed effects were due to confounding by weather or related factors. Almost all of the studies tried to control for weather factors. Similar pollution effects were estimated in warm and cold climates, dry and humid locations, and locations where particulate concentrations peak in the summer and areas with winter peaks.

Chronic exposure studies that evaluated spatial distributions of mortality and air pollution also observed associations between cardio-pulmonary health and particulate pollution. Important potential confounders in these studies such as unaccounted for differences in smoking, socio-economic, or demographic variables, are not potential confounders in daily time-series studies because such factors do not change daily in correlation with air pollution. Therefore, to be consistent with the overall epidemiologic results, a potential confounder must be associated across both time and space. Furthermore, it must be much more correlated with cardio-pulmonary disease than with other disease.

The most likely potential confounder, would be another pollutant or combination of pollutants that are highly correlated with fine particulates. Two potential confounding pollutants are sulfur dioxide and ozone. Similar particulate pollution effects, however, are observed in locations where ozone and sulfur dioxide levels are low and not correlated with particles.

RESEARCH NEEDS

Future research should continue to refine the methodological approaches and modeling techniques used, to deal with potential confounders within specific studies, and to evaluate confounding by cross-study evaluations. Care must be taken to conduct well-designed

statistical modeling with well-defined hypotheses. For example in the time-series studies, temporal correlations between various pollutants and weather variables assures that including enough variables in the model will at least partially obscure possible pollution effects. Good statistical modeling requires an understanding of the implications of this multicollinearity, judicious selection of variables included in the models, and adequate sensitivity analysis. Even with good modeling, multicollinearity problems are endemic in these studies. Data from a single epidemiologic study cannot conclusively demonstrate that observed particulate air pollution effects are not due to confounding by weather variables. The most important evidence will continue to be the consistency and coherency of the pollution effects across many studies areas, various study designs, and different health endpoints.

Specific issues that need to be addressed by future research include: 1) an understanding of the biological mechanisms that are involved, 2) relationships between ambient air pollution as monitored at central monitoring sites with personal exposures to air pollution, 3) determination of an adequate index of particulate pollution for use in assessing health risks and for use in pollution control public policies, 4) understanding the relationships between and relative importance of chronic versus acute exposures, 5) defining susceptible populations, 6) refining estimates of the magnitude of the effect for different health endpoints, 7) understanding interactions between particulate air pollution and other risk factors including infectious agents, and 8) designing pollution control strategies and strategies for susceptible populations to mitigate the health consequences of pollution. Obviously epidemiologic studies alone cannot adequately address these issues. Continued contributions from toxicology, exposure assessment, and other disciplines will be required.

SESSION SUMMARY
MECHANISMS OF PARTICULATE TOXICITY

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Introduction

The first two sessions of this meeting focused on studies methodologies related to the potential association between particulate matter concentration and human morbidity and mortality. Despite some of the striking findings from many epidemiologic studies demonstrating associations between very low levels of ambient particulates and excess mortality (both daily as well long-term) and morbidity (Dockery et al., 1994; Schwartz, 1994), nagging questions about the biological plausibility of these responses persist. Though one could press the argument that the establishment of biological plausibility is not necessary to prove causation, the need for biologically plausible explanations for the observations is important. At present the epidemiologic studies indicate that associations exist between health outcomes and ambient concentrations of particulate matter less than 10 μm in diameter (PM10). Furthermore, the concentrations at which effects are thought to occur are below the current PM10 standard. From a public health and regulatory perspective

it is extremely important to know what component(s) of PM10 is the causative agent. Attempts to isolate a causative agent are wrapped up in questions of biological plausibility.

The third session addressed the issue of the biological plausibility of increased morbidity and morbidity. Presentations in this session can be broken down into three categories: dosimetric plausibility, toxicologic plausibility, and clinical plausibility. We will discuss the presentations in this order since it provides a logical way of approaching the overall issue of biologic plausibility. In each case we will consider general issues surrounding each category and integrate into the discussion the pertinent presentations.

DOSIMETRY

Particle dosimetry in the respiratory tract is an excellent starting point for discussions of biological plausibility for it can address key issues from a perspective independent of precise particle composition. These issues include: (1) animal to human dosimetric extrapolation; (2) the influence of compromised lungs in altering regional lung dose; (3) the proper particle dose metric, i.e. particle mass vs. particle number vs. particle surface area; and (4) lung defense against inhaled particles.

The paper of Miller et al in this session raised questions relating to all four of these issues. Dr. Miller showed that there can be considerable differences in intrathoracic particle deposition and distribution between humans and non-primate animal species, and that these differences can arise both because of differences in intrathoracic deposition efficiency and because of differences in particle inhalability. Indeed Dr. Miller made a very strong argument that if coarse mode particles were responsible for effects in humans then the likelihood of seeing effects in rats at comparable concentrations would be small based entirely on considerations of the relatively small fraction of ambient particles that can penetrate into the breathing zone of the rat and subsequently into the intrathoracic airways. Dr. Miller also showed that when different ventilatory regions of the lung are compromised (such as in pre-exiting COPD) with respect to their ventilatory capacity, those regions of the lung that are still healthy can receive a disproportionately high dose of particles placing those remaining healthy regions at even greater risk and thus further compromising the lung's

reserve capacity. With respect to questions of the actual dose metric, Dr. Miller's presentation illustrated some very important points. The common dose metric that is considered for particles is based on mass. However, if particle mass concentration is fixed particle number concentration increases as the inverse cube of particle diameter. Thus, Dr. Miller showed that a dose metric based on particle number could lead to very high fine and ultrafine particle numbers in alveoli when compared with the same particle mass in the coarse mode. Furthermore, when he compared predicted particle numbers in alveoli of rats to predicted particle numbers in alveoli of humans for the same mass exposure concentration he showed a much greater number of fine and ultrafine particles in human alveoli than in rat alveoli. This observation could account for the lack of effects observed in some animal toxicology experiments conducted at near real-world particle mass concentrations. Lastly, Dr. Miller postulated that the high numbers of fine and ultrafine particles delivered to alveoli might lead to a condition of "overload" of alveolar macrophages, and that this "overload" condition is based on particle number rather than mass as has been previously hypothesized by Morrow (1992).

Dr. Miller concluded overall that from a dosimetric perspective fine and ultrafine particles seemed much more likely than coarse mode particles to be a causal factor in particulate related human health effects. However, it should be pointed out that the lifetime of ultrafine particles in the atmosphere is very short, thus ultrafines do not constitute a large fraction of the ambient aerosol. Therefore, dosimetric arguements must be weighed in the context of the actual ambient concentrations of particles.

TOXICOLOGY

There were four presentations that addressed biological plausibility from the mechanistic standpoint using animal toxicology studies. These presentations examined a wide range of particles and effects, though specifically focusing on acute effects. The types of particles discussed, and for which data were presented, included: sulfate and nitrate aerosols, sulfuric acid-coated ultrafine metallic particles, real-world particles with surface complexed iron (Fe^{+3}), road dust (uncharacterized), ultrafine teflon particles, and diesel particles.

these radicals elicit acute lung toxicity.

CLINICAL

When considering the issue of biological plausibility, the ultimate issue is whether the putative health effects of low levels of particulate exposure are reasonable from a clinical perspective, are consistent with other observed effects of air pollutants on humans, and are consistent with toxicological investigations using animal models. The most perplexing observation is that of excess daily mortality associated with 24-hour average particulate concentrations as low as 50 $\mu g/m^3$. Although there is general agreement about the plausibility of a causal relationship between particulate exposure and the excess mortality observed in the London smog episodes where particulate concentrations reached as high as 4000 $\mu g/m^3$, Dr. Mark Utell raised serious concerns about such a causal relationship existing down to concentrations as low as 50 $\mu g/m^3$. Since individuals at risk for mortality from particles would be expected to be indoors, the contribution of ambient particles would be further reduced recognizing that 100% penetration from the outside is highly unlikely. In his presentation, he pointed out that persons apparently at risk to the effects of particulate matter are the elderly and persons with severe obstructive lung disease. Their causes of death would most likely be due to pulmonary edema, acute respiratory infection, exacerbation of COPD or arrhythmias. Dr. Utell argues that toxicologic and controlled human exposure studies provide scant support for such phenomena occurring as a result of ambient particulate exposures as low as 50 $\mu g/m^3$. In individuals with COPD with an average FEV_1 of approximately 50% predicted, the group reasonably assumed at highest risk from the epidemiologic data, no reductions in lung function occurred with two-hour exposures to approximately 85 $\mu g/m^3$ H_2SO_4 aerosols with intermittent exercise (Morrow et al., 1994). In a recent study, inhalation of sulfuric acid aerosols at 1000 $\mu g/m^3$ for three hours by healthy volunteers without lung disease followed by lavage 18 hours later did not cause an influx of inflammatory cells into the alveolar space nor evidence for alterations in antimicrobial defenses (Frampton et al., 1992). Dr. Utell contends that the epiphenomena associated with potential fatal clinical states as pulmonary edema with heart failure are so complex and variable that minor events such as a slight increase in pollution could not possibly account for the event of death. He does suggest, however, that more

studies of the effects of ultrafine particles or metal complexed particles are needed in light of the data from studies such as reported in this session by Dr. Oberdörster.

COMMENT

The papers presented in this session provide a diverse perspective on the issue of biological plausibility. Several old and several new issues were raised. The issue of dose metric as it relates to a focus on a particular size cut for a standard, as well as for future toxicologic and clinical investigation is very important. It seems clear that coarse mode particles are not capable of producing loadings in the alveolar spaces that one could reasonably associate with potential toxicity. However, fine and ultrafine particles are capable, at low mass concentrations, of leading to significant particle numbers being deposited in alveolar spaces. If one postulates a mechanism by which the lung responds to particle number, then particle number, and consequently fine and ultrafine particles, may be very important. This is made even more compelling when one considers that since most exposure to air pollutants occurs indoors, then there must be significant penetration of particulates indoors. It seems only reasonable that the fine fraction, or possibly some ultrafine fraction, could achieve such a penetration.

The animal toxicologic studies provided some new insights. The investigation of surface-complexed Fe^{+3} presents one of the very few studies with particulates that is grounded on a mechanistic base. This research presents a very compelling model linking a specific component of real-world particulate matter with frank inflammatory effects in animals. It is important that this work be pursued in a setting whereby animals are exposed by inhalation as opposed to instillation. A key question that needs to be pursued is the question of exposure of populations to particulate matter with surface-complexed Fe^{+3}. If this, or other transition metals, is the causative agent, then it should be present in all of the urban areas that show an association between particulate matter, and morbidity and mortality. The geographic independence of the epidemiological findings would suggest that transition metal concentrations should be tightly linked to particulate mass concentrations.

The study of the effects of short-term exposure to an ultrafine teflon aerosol provides powerful evidence of the potential for particle number or surface area playing a role in particle-mediated toxicity. Because of the dramatic effects observed, including death of otherwise healthy animals, it is essential that this research be replicated with absolute assurance that animals are not

being exposed to HF or other radicals, and are just being exposed to teflon particles.

Animal studies with sulfate and nitrate aerosols have generally shown very unremarkable effects at ambient or near ambient concentrations. However, some caution has to be used before dismissing these aerosols out of hand. First, sulfuric acid aerosols do alter mucociliary clearance, increase airway responsiveness, and induce secretory cell hyperplasia. Furthermore, acid aerosols have been demonstrated to have immunosuppressive effects via alterations in macrophage activity. Although these effects are not dramatic, it is not altogether clear what effects might occur in appropriate animal models of human disease such as COPD and pulmonary hypertension. For example, seemingly trivial effects of sulfuric acid aerosol on mucociliary clearance in normal humans could have significant impacts in compromised lungs where mucus inspissation and plugging of small airways occurs. Further reason to not dismiss acidic aerosols is provided by the poster presentation of Lippmann et al at this colloquium demonstrating that by analyzing London mortality data by season, the association with particulate matter disappears leaving an association with aerosol acidity.

Finally, our tools for studying lung injury have become increasingly sophisticated during the past decade. Novel approaches provide opportunities to identify mechanisms of injury including characterization of the role of mediators, the identification of new neurotransmitters, and an understanding of the subtleties of immune suppression. Such techniques could uncover mechanisms by which particles alone or complexed with metals could provoke pulmonary edema, arhythmia, or exacerbation of severe obstructive airways disease. Clearly the development of an animal model of chronic lung disease could provide important insights.

Because of the low concentrations of particulate matter now associated with excess morbidity and mortality a concerted effort must be made to unravel the toxicological processes potentially responsible for these effects. These efforts should be conducted in tandem with de novo epidemiologic studies and reanalyses of old studies. Epidemiologic investigations need to proceed to both ensure that potential confounders have not been overlooked and to potentially narrow the field of toxicologic investigation. The latter can be accomplished by study designs contrasting population responses to different ambient particle composition. Studies of biological plausibility and mechanisms should utilize both animal models and human clinical studies, and in vivo and in vitro test methods. Coordination of approaches among different laboratories will be vital to ensure the generation of a data base that is coherent and usable for the development of reasonable mechanistic models. The ultimate question of the causal relation between very low level particulate concentration and excess daily mortality based on clinical plausibility is serious.

The biological plausibility of significant exposure-response relationships presented and published was discussed as issues of appropriate and accurate exposure measurements as well as the patho-physiological nature of the results. Interpretations too often depend on data from stationary monitors when individuals' exposures are not reflected by such measurements. Further, the size and species of the particulate should be critical aspects of the exposure measurements, especially as different particles produce different physiological and pathological responses.

It was pointed out that immuno-histochemical techniques have shown effects in different aged animals (primarily starting early in life), though most of the effects are functional and not anatomical. It was pointed out that different species have different temporal effects post retention (and there can be species differences in the temporal effects). As with gases, and in conjunction with the different reactive species of both, one has to focus on the effects that occur in the different regions of the lung and the outcomes therefrom. This discussion was illustrated by examples of effects of smoking, a highly reactive mix of gas and small particles. This discussion lead to the comparison of long-term high-exposure tobacco smoke effects on morbidity and mortality compared to the extrapolated effects related to small short-term increases in ambient PM10, which would imply that the latter extrapolations are much too large.

Further, one has to look more closely at effects in those (especially the elderly) with existing cardio-pulmonary diseases; it would be likely that some small shortening of life (or increased morbidity and disability) could occur under the circumstances described in earlier presentations of major associations.

It was concluded that one needed epidemiological studies that utilized appropriate monitors (re: simplicity, reliability, and quality of data) for personal exposure assessments within designed studies that focused on the dose-response nature of the PM effects. These new study designs should have the ability to explore non-linear threshold models, especially of morbidity.

Sources, Atmospheric Levels and Characterization of Airborne Particulate Matter

Comments presented at the Symposium on Particulate Air Pollution--Associations with and Mechanisms for Human Mortality and Morbidity, January 1994, Irvine CA

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Sources, Atmospheric Levels and Characterization of Airborne Particulate Matter

Introduction

A knowledge of the physical and chemical character of particulate air pollutants is necessary to the design of laboratory-based toxicological studies and field-based epidemiological studies of air pollution health effects. The purpose of the present working paper is to outline areas in which advances in source emissions measurements, atmospheric measurements, and atmospheric models could be sought that would improve our ability to inform health scientists of the character and origin of pollutant loadings in the atmosphere.

Emissions from Sources

A complete characterization of the particulate matter emissions from sources must begin with source sampling methods that achieve an accurate separation between gas-phase and particle-phase emissions from each source. Dilution source sampling systems are presently available that seek to cool hot exhaust gases to ambient temperature before sampling, thus causing those materials that are in the vapor phase at high temperatures (but that will enter the particle phase upon cooling in the plume downwind of the source) to in fact enter the particle phase within the sampler before sample collection. Additional research is needed to avoid sampling artifacts during source sample collection, perhaps through the use of diffusion denuder systems that preserve the gas/particle phase separation at the point where the source samples are collected on filters at the end of a dilution tunnel.

Conventional source sampling systems presently exist that can be used to measure the size distribution of particulate matter emissions in size ranges above about 1 μm particle diameter through collection in a sequence of cyclone separators. Greater size resolution for particles smaller than 1 μm is needed, both to study the likely transport properties of very small particles (e.g. in support of lung deposition calculations), to support air quality modeling studies of the condensational growth of secondary aerosols (e.g. sulfates and nitrates) onto the primary particles that are emitted directly from sources, and to answer questions raised at the present conference about the possible importance of ultrafine aerosols. Such high resolution size distribution measurements

can be made by sampling from dilution tunnels using electrical aerosol analyzers or cascade impactors.

The bulk chemical composition of the particulate matter emissions has been measured from many sources, but generally only over a broad range of particle sizes (e.g. all particles < 10 μm diameter; all particles < 2.5 μm diameter). If cascade impactors were used to measure the size distribution of the submicron-size primary particles emitted at sources, then the impactor samples could be analyzed to determine the details of particle chemical composition as a function of particle size.

Comprehensive emission inventories have been developed in many parts of the United States for use in summarizing the relative importance of various sources of PM_{10}. Similar emission inventories for smaller particle sizes would be useful in identifying the relative importance of the various sources of easily respirable fine particles and even ultrafine particles.

Analyses of source samples and atmospheric samples both show that there are hundreds of organic plus inorganic compounds emitted as particulate matter from air pollution sources. Indeed, there are far more compounds than there are major types of air pollution sources (e.g. automobiles, boilers, etc.). Rather than conducting toxicological studies on a nearly endless number of pure compounds, it may be both more efficient and effective to subject whole source effluents from real sources to toxicological examination. This has been done with diesel exhausts; the approach could be generalized to examine the remaining sources.

Characterization of Atmospheric Samples

The status and needs for characterization of atmospheric samples generally parallel those just discussed for source samples. The goal should be to seek low-artifact sampling methods that achieve a correct separation between the gas and particle phases, and that provide information on the details of the size distribution and chemical composition of the submicron fraction of the ambient particle complex. Diffusion denuder methods for low artifact ambient sampling exist within the research community. These methods should be adapted to the needs of the governmental routine air monitoring networks. Likewise, cascade impactor systems are in the use within the research community for particle size and composition determination, but the large routinely-collected ambient data sets based on impactor measurements that would be needed to

characterize entire airsheds generally do not yet exist. Opportunities exist to greatly improve the particle size and chemical resolution of governmental routine air monitoring networks.

Secondary aerosol sulfates are often formed by heterogeneous chemical reaction within liquid water droplets in the atmosphere. While large amounts of data on water-soluble pollutants exist, surprisingly little information is available on the concentration of aerosol phase water itself. Measurement methods should be sought that directly measure the water content of airborne particles such that the formation and transport of water-soluble pollutants can be better understood.

Research opportunities also exist at the interface between aerosol characterization studies and health effects studies. Air pollutant levels in the United States generally are low enough that the high particle concentrations often needed for accelerated toxicological studies cannot be obtained by directly exposing test animals to ambient air. Instead, idealized (and possibly over-simplified) artificial aerosols are used. From work discussed at the present conference, it appears that aerosol concentrators can be built that could be used to increase real atmospheric particle concentrations to levels that would be useful in laboratory toxicology studies. Application of such methods should be pursued in the near future.

Finally, epidemiological studies have been conducted that seek associations between airborne particle mass concentrations or sulfate concentrations and various health indicators. The largest contributor to the fine particle burden in cities is usually carbonaceous aerosol, but carbon particle concentrations are seldom measured directly. An attempt should be made to co-ordinate ambient particle characterization studies with epidemiological studies such that an epidemiological assessment of the hazard due to exposure to airborne carbonaceous particles can be achieved.

Connecting Emissions to Air Quality

Computer-based air quality models provide an analytical tool for connecting knowledge of air pollutant source characteristics to predicted ambient concentrations and population exposures. Several needs can be identified for research into air quality modeling methods for particulate matter.

At present, model components have been developed that can track the transport of particles from sources, the production of low vapor pressure materials by chemical reaction in the atmosphere, growth of airborne particles by condensation and coagulation, and the dry deposition of particles at the earth's surface. Many investigators are presently in the process of integrating descriptions of each of these steps into complete models for the effect of particle-phase plus gas-phase pollutant emissions on particulate air quality. Such complete models seek to be able to predict the size distribution and chemical composition of the ambient particle complex directly from data on meteorological conditions and source emissions. There is a need for better input data for these models, particularly better information on the size and composition of the initial particle emissions at the source, and a need to support thorough testing of model predictions against atmospheric aerosol data sets.

Many of the worst air pollutant-related health disasters have occurred when high levels of SO_2 and particulate matter accumulated in fogs. Development and testing of detailed fog chemistry models designed to help illuminate the effect of emissions sources on the composition of fog droplets should be encouraged.

Specialized air quality models designed to assess source contributions to toxic and hazardous particulate organic compounds should be developed. A key component of such a model development effort is the acquisition of comparable data on both source emissions and ambient concentrations of the target compounds sufficient to thoroughly test air quality model performance.

Most of the air quality models presently being developed that contain a highly accurate description of particle size and chemical composition are episodic models designed to examine high concentration events on an hour-by-hour basis over the period of a few days. Models suited to predicting long-term average effects of emissions on particulate air quality for secondary aerosol species over periods of years or longer should be developed as they will be needed to study issues related to chronic health effects.

AEROSOL EXPOSURE, PHYSICS AND CHEMISTRY - SUMMARY OF KNOWLEDGE

Comments presented at the Symposium on Particulate Air Pollution - Associations with, and Mechanisms for, Human Mortality and Morbidity, January 1994, Irvine, CA

by

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AEROSOL EXPOSURE, PHYSICS AND CHEMISTRY

SUMMARY OF KNOWLEDGE

Exposure. In several areas where comparisons have been made, including the South Coast Air Basin (Los Angeles) and Philadelphia (summer of 1992), fine mass, and especially sulfate and nitrate, appear to dominate the variability in PM10 (Particulate Matter with diameter < 10μm). This might also be true for TSP (Total Suspended Particulate Matter). Fine particulate matter, and especially the sulfate component, tends to be regional in nature; therefore, one sampler may give a fine-particle concentration measurement which is representative of an entire metropolitan area. Fine particulate matter effectively penetrates into homes so indoor exposure to outdoor particles will be related to the outdoor particle concentration.

Therefore, even though we would not expect one sampler to give a representative measure of coarse particles for a metropolitan area, TSP or PM10 may, as well as PM2.5, provide a measurement of the variability of fine particle mass that could be used as a surrogate for population exposure to fine mass. This approximation should be best for cities where sulfate is the major PM component. It may not hold for very large and diverse metropolitan centers such as Los Angeles or New York, or for cities with high ammonium nitrate, especially if the nitrate concentration pattern is

and be carried with the particles into the deep lung. Water-soluble gases in polluted air include oxidants such as O_3, H_2O_2, and organic peroxides; acid gases such as SO_2, HCl, HNO_3, HONO, and formic acid; and polar organic species such as formaldehyde. Some of these species may have biological effects, but current techniques do not measure particle-bound water or the species dissolved in it.

Cut-Point. Particulate matter is naturally divided into fine particles (nuclei mode plus accumulation mode) and coarse mode particles, based on different sources and different chemical composition. In determining exposure to particulate matter for use in epidemiological and other research studies, it would be desirable to collect fine and coarse particles separately. Measurements of particle size distribution indicate a concentration minimum between the fine and coarse modes in the size range between 1.0 and 2.5μm. However, it is not clear whether 1.0μm, 2.5μm, or somewhere in between would be the best cut-point to separate fine and coarse particles.

If a significant amount of coarse mode mass is found in the 1.0 to 2.5μm size range, PM2.5 mass measurements may not be an accurate measurement of fine particle mass. It is not known how much coarse particulate matter really exists in the atmosphere with diameters between 1.0 and 2.5μm. The material observed between 1.0-2.5μm could be an artifact due to particle bounce in impactors, a lack of sharpness of the particle size separation by impactors or

cyclones, or break up of aggregates of smaller particles in the sampler inlet. However, material observed in this size range could be real. The efficiency of many particle control devices decreases with particle size, allowing much greater emissions of the small-size tail of the coarse mode. Particles in this size range (1.0-2.5μm) also have a much longer atmospheric lifetime than larger particles. Both of these factors could lead to more particles in this size range in ambient air than would be predicted from the size distribution of freshly-generated, uncontrolled coarse mode aerosols.

The potential health effects of particles in this size range are important since the efficiency of lung deposition is high in this size range and a significant fraction of the number and surface area of coarse mode particles will be contributed by particles in this size range. Coagulation and condensation processes rarely grow fine particles above 1.0μm. However, evaporation of fog droplets, formed in highly polluted air, can form fine particles with a small amount of the accumulation mode mass above 1.0μm. Therefore, further analysis is needed before the best cut point for separating fine and coarse particle mass can be determined.

These comments have been reviewed in accordance with the United States Environmental Protection Agency's peer and administrative review policy and approved for publication.

PM10 RESEARCH NEEDS

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ABSTRACT

The Colloquium on Particulate Air Pollution and Human Mortality and Morbidity held in Irvine, CA, January, 1994, had scientific sessions on I. Epidemiologic Findings; II. Epidemiologic Methods; III. Mechanisms of Toxicity; and IV. Sources, Levels and Characterization of PM10. After each platform session the scientists in attendance contributed written suggestions for additional needed research. The suggestions, totaling over 100, are condensed and summarized here. These suggestions demonstrate a perceived need for additional data to supplement existing studies, plus the need for a considerable amount of additional basic research in many areas relating to the issue of the effects of PM10 on human health.

INTRODUCTION

On January 24 & 25, 1994, over 200 scientists participated in a Colloquium on Particulate Air Pollution and Human Mortality and Morbidity. The specialties of these participants included epidemiology, biostatistics, pulmonary medicine, occupational medicine, toxicology, physiology, cell biology, risk assessment, receptor modeling, source modeling, atmospheric chemistry, aerosol science, chemical engineering, and public health. The participants offered over 100 written suggestions for additional research related to each of the following platform sessions: I. Epidemiological Findings; II. Epidemiologic Methods; III. Mechanisms of Toxicity; and IV. Sources, Levels and Characterization of PM10. Many of the suggestions were similar enough to be combined, and all of them have been edited or paraphrased for the sake of consistency and clarity. These suggestions for research were not officially discussed at the Colloquium due to time constraints. In addition, they do not carry the imprimatur of any funding agency or regulatory agency. Rather, they are a encapsulation of the perceived needs for research as expressed by a large and diverse group of scientists who are actively involved with many aspects of the problem of understanding and dealing with the impact of particulate air pollution on the health of human populations. The suggestions are organized below in accordance with the Colloquium sessions. The most frequently mentioned suggestions are listed first, for emphasis.

5. Special sensitive populations that deserve additional study emphasis include the elderly, persons with advanced COPD (chronic obstructive pulmonary disease), young children, asthmatics, users of medications that might modify responses to air pollutants, individuals with significant cardiovascular disease, and those who live near monitoring stations (where exposure is more precisely known). Those specific segments of the population actually dying from low levels of particulate air pollutants still must be identified.

6. More study is needed on the effects of weather-related variables, especially in cities or rural areas that have very low levels of anthropogenic air pollution. This could include areas that have been successful in air pollution mitigation efforts.

7. Additional longitudinal studies are needed. Especially important are those that include better exposure assessments, including personal exposures.

8. Case-control studies are needed that compare those people dying on low-pollution days and on high-pollution days.

9. Occupationally-exposed populations, working in environments in which concentrations of specific particulate air pollutants are elevated, should be studied and analyzed for information that might help to understand environmental exposures.

10. A centralized collection of generally-accepted data sets should be established, so that a methodological "shoot-out" could be performed on these data sets. There is still confusion about the facts themselves (actual air concentrations, death rates etc.).

11. A full risk assessment analysis should be performed for each identifiable major

component of PM10, and risks should be compared with those from non-PM10 hazards.

12. Existing epidemiological studies should be re-examined and integrated in a meta-analysis that takes into account differences in methodology, as well as differences in exposure to air pollutants.

13. Studies are needed that explore possible synergy among air pollutants.

14. The temporal associations, including time-lags between exposure and effects (1 day, 2 day, etc.) and short-term vs. long-term effects, should be investigated more thoroughly.

15. Lung function studies should be included in epidemiological investigations in order to clearly separate effects on large airways from those on small airways.

16. The nature of dose-response relationships for mortality and morbidity should be examined more thoroughly.

17. New, affordable, continuous, direct-reading air monitors should be developed and made available for epidemiological studies.

18. Reports of increased non-lung cancer rates in women exposed to high levels of air-pollutants should be followed up.

EPIDEMIOLOGIC METHODS (SESSION II)

Varied epidemiologic methods have been used by various investigators to generate their findings. Many suggestions related to the research tools were offered.

1. The exposure aspects of the exposure-response models require special attention. Improved models are needed so that personal exposures, including consideration of activity patterns and exposure locations, can be studied. Models should be refined to allow better evaluation of temporal variations in exposure, as well as variations in chemical species and physical forms of the pollutants. Just using particle mass estimates from a few scattered sampling sites is too crude for health-related studies.

2. An environmentally-realistic synthetic data base should be defined and used to examine the sensitivities, differences, and uncertainties inherent in the various modeling approaches.

3. A modeling "shoot-out" (as recommended in relation to Session I) is needed to better understand subtle differences in the currently-used methods.

4. Uncertainty analysis methodology should undergo improvement, especially in relation to estimation of exposure.

5. Models should include methods for estimating the reductions in life expectancy due to exposure to PM10 components, as opposed to just mortality, so that the societal costs of elevated death rates could be better estimated.

6. The available monitoring data bases and methodology should be improved to include at least daily monitoring of particulate material in cities, better measures of common personal exposures, and improved characterizations of hospital-related exposures.

7. Improvements in statistical software are needed, especially regarding those packages that would help epidemiologists who are not thoroughly trained in statistical methodology.

8. The problem of autocorrelation in time-series data requires additional study.

MECHANISMS OF TOXICITY (SESSION III)

Three general types of studies, human clinical, laboratory animal, and in-vitro toxicological, comprise the bulk of investigations relating to inhalation toxicology. The in-vitro toxicological studies are often subdivided into categories relating to isolated organs, tissue cultures, cell cultures, and biochemical processes. Because of the unique exposure route characteristics of particle inhalation, contaminant metabolism, and of lung diseases, most inhalation toxicology studies have been conducted with whole animals. However, research suggestions covered each of the above types of studies.

1. In addition to greater use of existing animal models that are available, new animal models must be developed for the compromised human. These include models for the following: various types of active pulmonary infections; chronic asthma; COPD; emphysema; cancer (a transgenic animal model is needed); cardiovascular diseases; and fibrotic diseases.

2. Ultrafine singlet and aggregated particles, especially those smaller than 0.1 μm in diameter, must be studied with respect to their fates when inhaled, their inflammatory potentials, and their direct toxicity to various cells present in the lung. These studies should include several physical forms and chemical compositions of particles, including metal and metal-coated otherwise inert particles. (Note: Many investigators question the existence of a truly inert particle with respect to potential toxicity when inhaled.)

3. Toxicologic studies should be conducted to focus on some additional objectives, including: identification of thresholds for effects; dose-response relationships; more realistic dust sizes (especially sub-micrometer in diameter), lower dust concentrations; and chronic exposures.

4. More information is needed regarding the dosimetry of inhaled particles within the respiratory tract. Studies that shed light on where individual pollutants deposit may help identify how animal species, age and body size modulate toxicity. Comparative studies are also needed to aid in extrapolations from animals to humans. Dosimetry studies should include diseased animal models, and diseased humans.

5. Greater focus is needed on the issue of biological plausibility for particles causing human deaths. Such studies should explore cardiovascular, cardiopulmonary, neurological and immunological etiologies at the whole-animal, tissue, cellular and biochemical levels.

6. Toxicologic studies are needed that: lead to validated in-vitro models for cellular injury in various lung regions; identify cyto-toxic, geno-toxic and fibro-toxic mechanisms; and identify molecular mechanisms that could lead to acute mortality.

7. Greater focus on quantitative small airways pathology is needed, especially regarding

comparative phenomena in chronically-exposed humans vs commonly-used animal models.

8. Studies are needed that directly compare human and laboratory animal macrophage-related phenomena; both toxicologic and mechanistic studies are required.

9. Additional biomarkers of exposures and of effects are needed so that exposure-response relationships can be improved for individual components of PM10.

10. Additional information is needed on the dosimetry and effects of aqueous aerosol particles that carry dissolved gases and vapors into the respiratory tract.

11. Iron-coated (especially ionic Fe) particle generation systems should be developed, and used in inhalation studies. Similar considerations apply to fine particles of other transition metals.

SOURCES, LEVELS AND CHARACTERIZATION OF PM10 (SESSION IV)

As this session proceeded at the Colloquium, it became apparent that it covered a large and complex area. The suggestions for research covered diverse topics and ranged from the very basic to the highly applied.

1. Basic studies are needed on the composition of, and reactions among, metastable species in the atmosphere. Such transient species, most of which may not yet be identified, escape "filter" analyses, and may, in fact, be the culprit(s) in human mortality and morbidity. Particulate mass (as we now understand it) may be only a surrogate problem.

2. Particulate mass must be speciated both with respect to composition, and for primary particles, emission sources. Such categories might include: combustion products from

various fuels; silicates; carbon; pollen; molds; agricultural; industrial; free radicals; atmospheric reaction products (especially with ozone); various organic fractions; etc. Measurements that are gravimetrically-based are too crude to allow for interpretation of health effects or for planning mitigation.

3. The organic fraction of PM10 requires more study regarding its chemistry in aqueous media, exposure factors for human populations, indoor and outdoor compositions, size characteristics, transformations on filters, and losses in sampling devices.

4. More information is needed on size distributions of the various chemical species in PM10. This is especially true for those particles smaller than 2.5 μm in diameter, as they exist in ambient air in significant numbers.

5. Aqueous aerosol droplets require more study, especially related to their prevalence, reactions within them and their absorption of and liberation of pollutant gases and vapors.

6. More data are needed on variations, chemical, spatial and temporal, in outdoor and indoor aerosols. This need includes gathering more data from those cities already studied by epidemiologists.

7. Improvements are needed in several types of instruments, including: those sensitive to new species of pollutants; continuous reading instruments; those that separate particles from gases and vapors; and those that provide more and better information on size distributions.

8. The particle-size fractions and compositions in California should be better studied and better monitored so that epidemiological comparisons with eastern areas of the U.S. can be facilitated.

9. Episodes of air pollution should be more intensively characterized and studied at several diverse locations.

10. Methods for generating more realistic aerosols for laboratory studies are needed. This includes use of aerosol concentrators. The need applies to human exposures, laboratory animal studies and atmospheric chemistry investigations.

11. Gas-to-particle conversions should be more thoroughly studied and modeled.

12. More thorough weather studies are needed. Better weather data will improve understanding of the effects of weather-related variables on air pollution itself, as well as understanding of the effects of weather on health.

13. Sulfate, nitrate and acidity should be better characterized in those cities that have already been studied by epidemiologists.

14. Studies are needed to define the pollutant mixtures that will result from the widespread use of proposed "alternative" fuels.

CONCLUDING REMARKS

This exercise in soliciting suggestions for research on PM10 from a group of actively-engaged scientists is valuable to the extent that it actually improves the efficiency and payoff of future research efforts. Everyone who plans, conducts or supports research might benefit from contemplating, weighing and discussing these suggestions. In addition, the exercise allows us to make some immediate observations. Most striking is the realization that scientists perceived that we currently have only a meager and unsatisfactory knowledge of

the topic that stimulated the Colloquium – the relationship of particulate environmental air pollution to human mortality and morbidity. In many areas methodological limitations appear to be the major problem that blocks our progress. It is clear that a considerable amount of work still needs to be done. It is also apparent that particulate mass is perceived to be far to crude a measure for linking specific air pollutants to human health. However, one can't help but be optimistic at the clarity of the message contained in the suggestions regarding the next logical steps. Also, a remarkable similarity in research needs across specialties is seen. Perhaps in a few years, or decades, several completion checks could be entered beside items in the lists presented above. This will be the case only if the will and the means exist to mount a substantial, concerted, and sustained research effort.

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