Air Pollution and Health: Bridging the Gap from Sources to Health Outcomes: Conference Summary

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ABSTRACT

"Air Pollution and Health: Bridging the Gap from Sources to Health Outcomes," an international specialty conference sponsored by the American Association for Aerosol Research, was held to address key uncertainties in our understanding of adverse health effects related to air pollution and to integrate and disseminate results from recent scientific studies that cut across a range of air pollution-related disciplines. The Conference addressed the science of air pollution and health within a multipollutant framework (herein "multipollutant" refers to gases and particulate matter mass, components, and physical properties), focusing on five key science areas: sources, atmospheric sciences, exposure, dose, and health effects. Eight key policy-relevant science questions integrated across various parts of the five science areas and a ninth question regarding findings that provide policy-relevant insights served as the framework for the meeting. Results synthesized from this Conference provide new evidence, reaffirm past findings, and offer guidance for future research efforts that will continue to incrementally advance the science required for reducing uncertainties in linking sources, air pollutants, human exposure, and health effects. This paper summarizes the Conference findings organized around the science questions.

A number of key points emerged from the Conference findings. First, there is a need for greater focus on multipollutant science and management approaches that include more direct studies of the mixture of pollutants from sources with an emphasis on health studies at ambient concentrations. Further, a number of research groups reaffirmed a need for better understanding of biological mechanisms and apparent associations of various health effects with components of particulate matter (PM), such as elemental carbon (EC), certain organic species, ultrafine particles, and certain trace elements such as Ni, V, and Fe(II), as well as some gaseous pollutants. Although much debate continues in this area, generation of reactive oxygen species induced by these and other species present in air pollution and the resulting oxidative stress and inflammation were reiterated as key pathways leading to respiratory and cardiovascular outcomes.

The Conference also underscored significant advances in understanding the susceptibility of populations, including the role of genetics and epigenetics and the influence of socioeconomic and other confounding factors and their synergistic interactions with air pollutants. Participants also pointed out that short- and long-term intervention episodes that reduce pollution from sources and improve air quality continue to indicate that when pollution decreases so do reported adverse health effects. In the limited number of cases where specific sources or $PM_{2.5}$ species were included in investigations, specific species are often associated with the decrease in effects. Other recent advances for improved exposure estimates for epidemiological studies included using new technologies such as microsensors combined with cell phone and integrated into real-time communications, hybrid air quality modeling such as combined receptor- and emissions-based models, and surface observations used with remote sensing such as satellite data.

KEYWORDS: Sources, pollutants, multipollutant, atmospheric chemistry, exposure, dose, health effects, particulate matter, cardiovascular disease, respiratory disease, mechanisms, susceptibility, vulnerability, confounding, policy.

CONTENTS

REFERENCES

INTRODUCTION

Over the last several decades, a substantial body of evidence has emerged concerning the health effects of air pollutants (Pope and Dockery, 2006; Samet and Krewski, 2007; Anderson, 2009; Russell and Brunekreef, 2009; EPA, 2009a; Brook et al., 2010). Despite some progress in linking air pollution sources to exposures and adverse health effects, significant uncertainties remain regarding causal associations, mechanisms of action, susceptible populations, and confounding (see Rajagopalan and Wolfe, 14SQ5.1 in supplemental material). To address these uncertainties and to guide future research, the international conference "Air Pollution and Health: Bridging the Gap from Sources to Health Outcomes[1]" (hereafter referred to as the Conference) convened air pollution researchers, air quality managers, and policymakers from around the world with a common goal of advancing our understanding of the scientific relationships between air pollutants and health outcomes (http://aaar.2010specialty.org/).

The Conference was based on the National Research Council's (NRC) source-to-health effects paradigm (NRC, 1998), albeit the NRC focused on species in particles less than 2.5 μm in aerodynamic diameter (AD) whereas the larger scope of the Conference included a broader multipollutant framework (here in multipollutant refers to gases and particulate matter mass, components, and physical properties). The Conference focused across five key science areas: sources, atmospheric sciences, exposure, dose, and health effects. Eight policy-relevant science questions (SQs), or guiding themes, and a ninth question regarding findings that provide policy-relevant insights, provided the framework for the Conference (see Table 1). The meeting was designed to appeal to a large interdisciplinary international audience and brought together researchers from across the source-to-health effects paradigm to engage in discussion and rigorous debate regarding the latest information relating adverse health effects of air pollution to emissions sources and atmospheric pollutants. This paper summarizes and synthesizes the Conference findings organized by the nine SQs. The contributing authors (see Table 1) drew information from materials presented at the Conference as well as from supporting published literature, but a comprehensive examination of these topics was not carried out. Conference findings are noted by presentation numbers in the Conference Abstract book, which is provided in the supplemental material. Presentations are not publicly available so specific ones would need to be obtained from the presenting authors.

Following the response to each science questions, authors provide a summary of recent advances as well as a list of research needs that address some of the remaining knowledge gaps in our understanding of air pollution and health.

SQ1. How does our understanding of the health effects of air pollutants (singly or in mixtures) help identify pollutants that can be linked to sources the control of which would provide maximal health benefits? (overarching theme)

Introduction

[1] American Association for Aerosol Research International Specialty Conference, San Diego, CA, March 22-26, 2010.

Identifying air pollution components, physical characteristics, and/or sources that have the greatest impact on human health is critical to reducing risks to public health from air pollution through targeted emissions management strategies. While many experiments have been conducted at high pollutant concentrations and doses, recent use of realistic pollution levels in laboratory and human studies provides a better understanding of the health impact from real-world exposures. To this end, greater emphasis on exposure-response relationships is needed (Mauderly, 12SQ1.3). Recent improvements in the collection of accurate exposure information in epidemiological studies have helped reduce uncertainties in the health associations (Jerrett et al., 16SQ3.4; Jerrett et al., 18A.1; Evans et al., 15SQ3.T3.229; Yap et al., 3SQ2.T5.177). However, the atmosphere is complex and source emissions undergo a wide variety of physical and chemical processing in air and can stay airborne for weeks with transport distances up to several thousand kilometers or more (Seinfeld and Pandis, 1998; Solomon et al., 2008, and references within). Linking source emissions to receptor concentrations by simulating and elucidating the physical and chemical transformations that occur in the atmosphere is an important first step in bridging the gap from sources to health outcomes.

SQ1 can be addressed in two ways: by examining the linkages between (1) pollutants and health effects and (2) sources and health effects. The first group of studies evaluates the health response of a target (e.g., person, population, animal, cell culture) from exposure to specific pollutant(s) that can usually be associated with a specific source (e.g., steel mill) or source type (e.g., diesel engine exhaust, secondary pollutants) through methods such as source apportionment. The second group of studies evaluates the health response of a target from direct exposure to emissions from a specific, known source such as gasoline or diesel engine exhaust from a motor vehicle or emissions from wood or coal burning. Conference findings are presented here for the first approach by looking at health effects associated with particulate matter (PM) mass and its various chemical and physical properties, and gases. The presentation of findings for the second approach explores more direct source-to-health effects associations.

Pollutants and health effects

Particulate matter

Particle sizes of typical focus and concern in health effects studies of air pollution (Solomon and Costa, 2010) include PM_{10}, defined as particles in the size range equal to or less than a nominal[2] 10 μm AD; coarse particles (PMc)[3] in the size range between 2.5 μm and 10 μm AD; fine particles (PMf or $PM_{2.5}$) in the size range less than 2.5 μm AD; and ultrafine particles (UF or $PM_{0.1}$) usually considered less than 0.1 μm AD, but a quasi-ultrafine size (up to 0.18 μm AD) also is considered because of sampling restrictions (Moore et al., 2007; Sioutas et al., 2005). These PM size fractions differ substantially in their composition and biological mechanisms of impact (Gilmour, 14SQ5.2) and appear to elicit different biological responses depending on factors such as location, source impact, age of aerosol, and season (e.g., Godri et al., 13A.4; Gilmour, 14SQ5.2; Duvall et al., 11SQ3.T1.149;

[2] U.S. EPA uses the word "nominal" to encompass the collection efficiency curve's cut point and slope with regard to regulatory particle size distributions (PM_{10}, $PM_{2.5}$, and PMc) in an effort to prevent misinterpretation of the curve as a step function. All uses of size distribution throughout this document, as referenced above, should be considered as "nominal", i.e., not being a step function, whether in reference to a regulatory size range or not.

[3] U.S. EPA's convention for particles in the coarse particle range is $PM_{10-2.5}$, but PMc is used throughout as shorthand.

Gordon et al., 15SQ5.T5.359; Hickey et al., 15SQ5.T5.363; Solomon et al., 2008, and references within; EPA, 2009a).

Exposure to PM is associated with adverse respiratory and cardiovascular effects including premature mortality and morbidity (Brook et al., 2010). However, study results demonstrate that mass concentration does not appear to be a sufficient metric to fully and effectively evaluate the health effects of PM exposure. Size and composition and/or other physical properties, perhaps several in concert, may better reflect the characteristics of particles that are associated with adverse health effects from PM (e.g., Brook et al., 1SQ2.2; Moreno et al., 11SQ3.T1.80; Braniš et al., 11SQ1.T5.170; Henríquez, 15SQ5.T5.274; Debray-García, 15SQ5.T5.271; Dominici et al., 9C.6; Braniš et al., 2010).

Longstanding attempts to identify the relative toxicity of physical and chemical components of particles have not yielded a basis for further refinement of the PM standard, but recent results have pointed toward significant health relevance in air pollution of not only $PM_{2.5}$, but also UF PM and PMc (Hovorka et al., 11SQ1.T1.142; Peltier et al., 11SQ1.T3.159; Debray-García et al., 15SQ5.T5.271; Heo et al., 11SQ1.T2.123; Li, 11SQ1.T5.173; Grinshpun, 11SQ1.T5.310; Wilson, 2C.1). Studies also have been conducted to elucidate the roles of PM components, such as the trace elements V and Ni (e.g., Lippmann and Chen, 11SQ1.T5.163; Chen and Lippmann, 2009), elemental carbon (EC), and organic carbon (OC) (Guskin et al., 11SQ1.T5.366; Dye et al., 15SQ5.T5.287), as well as semivolatile organic components of PM (Verma et al., 11SQ1.T1.144). Research of the complexities of PM exposure suggests a number of related health effects including oxidative stress, which could lead to inflammation and to cardiovascular effects, and adverse respiratory effects, such as asthma (as discussed in SQ5).

PM_{10} and PMc. Identified PM_{10} sources include motor vehicles, road dust, soil, biomass burning, biological components (e.g., pollen, spores), and aged sea salt. A study in Korea (Heo et al., 11SQ1.T2.123) found daily mortality associations with PM_{10} that could be attributed to three local primary sources: motor vehicles, biomass burning, and road dust. An *in-vitro* study (Peltier et al., 11SQ1.T3.159) observed oxidative stress when human respiratory epithelial cells (using BEAS-2B) were exposed to UF, fine, and coarse particles derived from oil combustion and traffic. PMc had the greatest response both immediately and 24 h after exposure compared to the other size fractions studied. The responses, however, were not always consistent with dose, size, or location. In addition, reactive oxygen intermediates for both coarse and fine fractions measured via fluorescent intensity immediately after exposure were negatively correlated with measurements of NF-κB made 24 h after exposure, suggesting different mechanisms depending on location and size or, more likely, chemical composition. Other researchers observed greater reactive oxygen species (ROS) activity in water extracts of coarse PM collected in Lahore, Pakistan, than those of coarse PM collected in Los Angeles, CA, and Denver, CO (Shafer et al., 15SQ5.T5.296). Specific ROS activity appeared to be enhanced in the fine and pseudo-ultrafine PM in comparison with larger particles, especially those from the Los Angeles area. Coarse PM from fireworks caused the greatest ROS response in human pulmonary endothelial and epithelial cells while fine PM induced equal or less ROS production. The smallest response was observed with ultrafine PM associated with pollutants from fireworks (Hickey et al., 15SQ5.T5.361). In a study in Mexico City, inflammatory responses were found with UF and PMf but not with concentrated PMc (Debray-García et al., 15SQ5.T5.271). On the other hand, in a study reported by Gilmour

(14SQ5.2), pulmonary inflammation was more pronounced due to coarse particles relative to fine and UF taken either close to and far from the freeway. Gordon et al. (15SQ5.T5.359) looked at ultracoarse (includes particles greater than 10 μm), coarse, and fine PM collected at different locations (two urban and three rural) in New York State and found higher ROS activity in cells exposed *in-vitro* to PMc relative to fine and UF exposures in the urban areas than in the rural areas (see Figure 1). They also noted higher ROS activity in PMc in winter than in summer.

$PM_{2.5}$. Sources of fine particles include both anthropogenic and natural primary emissions from various combustion processes (e.g., motor vehicles, cooking, fires, various industrial processes) and resuspended agricultural and road dust. Sources also include secondary pollutants such as sulfate, nitrate, and secondary organic aerosol (SOA) formed in air from gaseous precursor emissions from many of the same primary sources (Watson et al., 2008; Solomon et al., 2008). A number of health effects have been associated with $PM_{2.5}$ exposure, including lung cancer incidence and mortality rates (Vinikoor et al., 11SQ1.T5.164; Beelen et al., 2008).

Ambient $PM_{2.5}$ mass concentration has been associated with increased all-cause and cardiovascular mortality (Brook et al., 2010), with cardiovascular morbidity precursors (Devlin, 8SQ6.2), specific cardiovascular morbidity risks such as acute ischemic events (Pope et al., 2006), and increases of arrhythmias in humans (Peters et al., 2001) and mice (Moreno-Vinasco et al., 13A.1). Decreased brachial artery diameter and increased heart rate in a large panel of individuals living in Detroit were associated with personal exposure to ambient $PM_{2.5}$ (Williams et al., 13A.2). Wagner et al. (15SQ5.T5.285) also noted an increase in blood pressure and heart rate variability (HRV) in mice exposed to concentrated $PM_{2.5}$. Further, increased hospital admissions for cardiovascular disease, and for ischemic heart disease in particular, were associated with increases in $PM_{2.5}$ mass at low ambient levels in Denver, CO (Peel et al., 2C.6).

In addition, $PM_{2.5}$ is associated with a variety of adverse respiratory effects, which also display relationships with season, location, and $PM_{2.5}$ components. For example, the Children's Air Pollution Asthma Study noted $PM_{2.5}$ exposure associations with increased symptoms and severity of asthma in summer in New York City but not in winter when $PM_{2.5}$ concentrations were lower (Habre et al., 11SQ1.T5.178). As noted in the section on metals below, this difference might be due to the differing composition of $PM_{2.5}$ in summer versus winter or simply due to lower mass concentrations. Another study examined $PM_{2.5}$ effects by season and showed associations between mortality and $PM_{2.5}$ for Detroit, MI, in the warm season and for Seattle, WA, in the cold season. The associations appeared to be with $PM_{2.5}$ from traffic in Detroit, whereas in Seattle they were related to residential oil burning and wood smoke (Zhou et al., 11SQ1.T5.358), each representing major sources in their respective locations and seasons. *In-vitro* studies also showed different associations between markers of inflammation and oxidative stress and $PM_{2.5}$ collected in different seasons as well as with different $PM_{2.5}$ components (Healy et al., 15SQ5.T5.262). Finally, a study of the impact of air pollution mixtures on asthmatic children along the U.S.-Mexican border revealed stronger associations for fine PM compared to coarse PM. These positive associations with increased pulmonary response were observed for pollutant indicators that were related to traffic (Ebelt Sarnat et al., 3SQ3.T5.150).

Ultrafine PM. Ultrafine particles in urban areas are derived primarily from motor vehicles, with some contributions from other combustion sources. Regional nucleation bursts occurring after sunrise on clear, clean days,

including within urban areas, have also been observed (Stanier et al., 2004a, Stanier et al., 2004b) and might result in unexpected health effects on what appears to be clean days or sensitize people for follow-on higher pollution events (Solomon et al., 2008). Ultrafine particles consist of a complex mixture of organic components, EC, and trace elements (Solomon et al., 2008, and references within).

A recent human panel study of an elderly population in Los Angeles, CA, showed that quasi-ultrafine PM, but not other size fractions, was associated with reduced ability to fight oxidative stress, increased vascular inflammation, and increased platelet activation (Delfino et al., 2009). Components of the size fraction associated with these health effects included black carbon and primary organic carbon, but not secondary carbon. All of these health endpoints are important in the pathogenesis of arterial disease (Devlin, 8SQ6.2). An *ex-vivo* animal study more specifically showed increased cardiac ischemia/reperfusion injury following exposure to ambient UF PM by intratracheal instillation (Frasier et al., 15SQ5.T5.266). Further, UF PM collected in Los Angeles produced increased redox activity as measured by dithiothreitol (DTT) assay in a cell-free system and increased macrophage ROS activity (Verma et al., 11.SQ1.T1.144). In Mexico City, UF particle exposures showed increased inflammatory lung responses in rats (Debray-García et al., 15.SQ5.T5.271). In an *in-vitro* study, UF PM induced different inflammatory and oxidative stress responses depending on the driving cycle of the vehicle tested (Li et al., 11SQ1.T5.173).

Particle number concentration. Particle number concentration is a metric of PM that is sometimes used in both epidemiological and toxicological studies. UF PM makes up the majority of particle counts in the size range < 100 nm, so particle number concentration is often used as a surrogate for UF PM mass (especially when PM mass concentration is low). However, the size range represented varies with the instrument employed and can also include particles > 100 nm. The number concentration and size distribution of particle counts in ambient air also depends on the emissions source and age of the particles, with fresh emissions often showing higher numbers at smaller sizes. Then as the emissions age, the median count diameter size becomes larger due to condensation and coagulation, resulting in fewer particles (Seinfeld and Pandis, 1998). Rule et al. (7SQ3.T2.111) found that ambient particle number concentration and particle size distribution differed in four locations across the U.S. and by season; these findings may help explain geospatial differences in health effects found by epidemiological studies.

Emissions from school buses considerably increased particle number and EC concentrations relative to a control site during periods when children were being dropped off at school (Grinshpun et al., 11SQ1.T5.310). A statistically significant association was observed between particle number concentration and the number of school buses, but not with other factors such as automobile commuter traffic. The authors concluded that PM emissions from school buses (including UF diesel particles) significantly contributed to the children's short-term exposure at school. Diesel engine emissions from heavy-duty diesel vehicles were characterized and their potential toxicological relevance was assessed in a study that compared the effects of emission control aftertreatment devices (Hu et al., 5A.5). Aftertreatment devices were efficient in reducing toxic emissions and overall potency of PM emissions in terms of redox activity in spite of a corresponding increase in the total number of particles emitted.

Elemental and organic carbon. Diesel engine emissions are the major source of EC in most urban areas around the world, although residential cooking in developing countries is a constant source of both EC and OC

emissions. Out-of-hospital cardiac arrests in New York City were associated with the traffic-related air pollutants EC and copper (Cu) in the fine PM fraction (Gluskin et al., 11SQ1.T5.366). Parallel findings also were observed by Riediker et al. (2004), who reported cardiovascular effects associated with a "speed change" factor that appeared to represent both braking (marked by Cu) and accelerating diesels. Elevated respiratory symptoms were observed in asthmatic subjects walking along a London street that had high diesel engine emission exposures compared to subjects walking in a nearby park (Utell, 8SQ6.1; McCreanor et al., 2007).

PM with different amounts of EC and OC and smaller amounts of other components (e.g., sulfate) were administered to stressed lung epithelial cells to determine their ability to effectively adapt to additional particle-related oxidative stress (Dye et al., 15SQ5.T5.287). The authors pointed out that cell response was less for carbon black and SRM 2975 (diesel PM) than for an automobile-generated sample of diesel engine exhaust PM, which had a higher OC content, suggesting a role for OC as well as EC.

Day and evening samples were collected at one site in Sao Paulo, Brazil, and analyzed for $PM_{2.5}$ mass, black carbon (BC)[4], and 19 trace elements. Three factors were identified by principal components analysis (PCA): Factor 1 included BC, Ca, Fe, K, Si, Zn, and Ti, which were identified with general traffic. Factor 2 included Ni and Cr and was identified with industry emissions. Factor 3 included V and S characteristic of diesel emissions. Toxicity, measured *in-vitro* as the frequency of micronuclei, was greater in the evening (relative to the morning) when the diesel emission factor was higher, indicating the importance of changes in chemical composition due to changing traffic patterns and atmospheric processing (Martins, 3SQ3.T5.349).

Epidemiological studies that include many $PM_{2.5}$ species—as many as 20 in some studies—consistently found various adverse health associations with BC or EC, and with Ni and V as discussed below, suggesting the importance of sources of these components (Lipfert et al., 5B.5; Grahame and Hidy, 9B.1; Dominici et al., 9C.6). While not numerous, some studies have distinguished between effects of EC and regional air masses without EC. These studies have often reported cardiovascular effects associated with EC but not with regional air masses lacking EC (Schwartz et al., 2005) or with other $PM_{2.5}$ species (Grahame and Hidy, 9B.1; Dominici et al., 9C.6).

Metals. Emerging evidence from both toxicological and epidemiological studies suggests that specific metals, especially vanadium (V) and nickel (Ni), for example, might represent significant cardiovascular mortality and morbidity risks (Cromar et al., 3SQ3.T5.326; Lippmann and Chen, 11SQ1.T5.163; Henríquez et al., 15SQ5.T5.274; Qu et al., 15SQ5.T3.352; Chen and Lippmann, 2009). In California's Central Valley, primarily trace metals in UF PM from motor vehicles and oil combustion (but also PM_{10}, $PM_{2.5}$, nitrate, and sulfate) correlated with ischemic heart disease mortality (Cahill et al., 15SQ5.T3.258). A comparison of women from two cities in China with similar ambient concentrations of PM, but very different concentrations of Ni, showed that women from the city with high Ni had higher markers of systemic inflammation, greater thickness of the carotid artery, and lower levels of a marker of endothelial repair (Qu et al., 15SQ5.T3.352).

Another study collected UF PM at a rural and an urban location in Washington State and analyzed it for trace metals, Fe(II), polycyclic aromatic hydrocarbons (PAHs), and surface functional groups. Fe(II) and anthracene

[4] BC is an optical measurement of dark particles in air similar to, but not the same as, elemental carbon, a measurement obtained by thermal analysis. See Fehsenfeld et al. (2004) for clarification.

from both locations were associated with an initial (0–10 min) decrease in electron transport chain (ETC) activity in the mitochondria, whereas after 20 minutes the association was stronger with the sum of PAHs. Other organic components and trace metals, including total Fe, did not correlate with ETC inhibition (Johansen et al., 15SQ5.T2.256; Faiola et al., 2011).

A study of rats exposed to concentrated ambient particles (CAPs) conducted in Detroit, MI, showed increased heart rate and decreased HRV effects that were associated with a series of trace elements, PM mass, and EC (Wagner et al., 2C.2). An enhanced airway allergic response was associated with V and Pb in CAPs from local industrial sources in allergic rats (Wagner et al., 11SQ1.T5.180). These rats also showed increased inflammatory epithelial responses after an 8-hour exposure to fine CAPs. In another study, extracts of PM samples from two different cities in Chile were instilled in the lungs of rats and showed a correlation between V and Zn and markers of lung injury (Henríquez et al., 15SQ5.T5.274). In a review of CAPs studies (see Tables 2 and 3), Lippmann and Chen (11SQ1.T5.163; Chen and Lippmann, 2009) noted associations between various health endpoints and several metals as well as other components after prolonged exposure to CAPs. Data from a wide range of locations were included in the review.

The Children's Air Pollution Asthma Study investigated the chemical composition of ambient air in two locations in Michigan—Detroit and Grand Rapids—due to different source impacts including the fraction of regional versus local pollution (Habre et al., 11SQ1.T5.178). In this study, metals (Fe, Ni, V, and Zn) were associated with increased symptoms of asthma in children during both summer and winter, whereas associations also were noted with SO_2 and S in the summer and with Cu and Ti in the winter. In the same study, Wagner et al. (11SQ1.T5.180) exposed rats sensitized to ovalbumin (OVA) to CAPs in both cities (~ a 525 $\mu g/m^3$ exposure in both locations for 8 h). Results indicated an enhanced airway allergic response in Detroit following exposure, but an inhibition of the response in Grand Rapids. The enhancement appears related to sulfates, trace elements (Pb and V), and smaller $PM_{2.5}$ particles, while the inhibition was associated with OC and motor vehicle sources. These rats also showed increased inflammatory epithelial responses to fine CAPs.

A study in Los Angeles, CA, examined the redox activity of time-integrated quasi-ultrafine PM (< 180 μm) collected in the morning and afternoon on the campus of the University of Southern California (Verma et al., 11SQ1.T1.144; Verma et al., 2009). The morning PM samples contained primary particles freshly emitted from vehicular sources. In the afternoon, the mixture contained primary and secondary particles. This study monitored many water-soluble metals as well as redox activity (ROS macrophage assay). The authors found higher redox activity in the afternoon, measured by the DTT cell-free assay, associated with products of photochemical aging and with water-soluble organic carbon (WSOC). The ROS activity, on the other hand, while not consistent between morning and afternoon, was highly associated with water-soluble metals (V, Ni, and Cd). They also noted that while measured ROS activity was mostly driven by transition metals, it was possibly amplified by WSOC.

Kleinman and Campbell (14SQ5.3) described studies using CAPs and ambient PM and noted a buildup of Mn in the brain as well as chemical changes in the brain that likely occurred due to these exposures. Several possible mechanisms were described, including one in which Mn disrupts Fe homeostasis in cells and free Fe can produce free radicals via the Fenton reaction (see Figure 2, Zheng and Zhao, 2001).

Finally, residual oil fly ash (ROFA) contains relatively high concentrations of transition metals such as Fe, Ni, and V. Some study results have indicated associations of ROFA with adverse health effects in mice and rats exposed to ROFA with or without varying preexisting conditions (Dreher et al., 2C.3; Carll et al., 3SQ2.T5.48; Delfosse et al., 7SQ6.T5.353; Chen and Lippman, 2009).

Gaseous species

More is known about the health effects of PM species than about their co-emitted gases, such as organic gases emitted by vehicles, as noted in a review by Brook and Wheeler (1SQ2.2). However, evidence also indicates adverse health effects from these co-emitted gases. Results from the Veterans Cohort Study, involving medical data from 1976–2001 for approximately 70,000 individuals, indicated associations between all-cause mortality and several air pollutants, including hazardous air pollutants (HAPs) such as formaldehyde and benzene, EC, traffic-related air quality indicators, and traffic density (e.g., Wyzga et al., 5B.5; Lipfert et al., 2009). Based on these results, the authors concluded that tailpipe emissions of both gases and particles are among the most significant and robust predictors of mortality in the cohort studied, suggesting the importance of a multipollutant approach that includes biologically active gases as well as $PM_{2.5}$ components and/or mixtures related to sources (e.g., diesel engine exhaust). Further, exposing rats to filtered exhaust was found to elicit a greater cardiotoxic effect at similar levels as the unfiltered exhaust, showing that for some effects gases may be as or more important than particulate emissions (Hazari et al., 15SQ5.T5.282). Maejima et al. (2001) found that whole diesel engine exhaust amplified the allergic response to pollen in mice and that 87% of the effect of the diesel exposure remained when particles were filtered from the diesel exhaust. Thus, one of the realities air pollution researchers face is that a pollutant like EC, which represents diesel emissions in major cities, is likely both a cause of health effects in itself because of adsorbed biologically active carbonaceous species on its surface and a marker for co-emitted semivolatile and gaseous pollutants that may have independent health effects and/or synergistic effects.

Delfino (9C.2) examined whether markers of primary organic aerosol (POA), SOA, and related pollutant gases are associated differently with airway inflammation versus systemic inflammation. Fractional exhaled NO (F_{eNO}) was used as a marker of large airway inflammation, whereas interleukin-6 (IL-6) was used as a biomarker of systemic inflammation, which is associated with cardiovascular disease risk. Consistent associations of F_{eNO} with ozone (O_3) suggested photochemical reaction products, including gases, may be important in airway inflammation. IL-6 was positively associated with POA markers but not SOA, while the opposite was true for F_{eNO}.

Sources and health effects

Studies that have attempted to link specific emission sources directly to health effects are relatively limited, with perhaps the exception of motor vehicle source studies (see, for example, HEI, 2010). Some intervention studies (see SQ8) have aimed at determining the impact of reducing emissions from a specific source, source type, or a variety of sources, but little information is provided on components and/or specific sources. While source-specific interventions such as the ban on residential use of coal in Dublin in 1990 (Clancy et al., 2002) or a strike closing a steel mill (Frampton et al., 1999), more regional interventions such as for the Beijing Olympic Games (Brunekreef, 6SQ7.1) or even specific human actions such as use of a face mask to decrease exposure to particles (Langrish et al., 2009) can reduce several pollutants at once (e.g., SO_2, NO_2, and particles) from effectively one or more sources.

This suggests that a more targeted control strategy development is needed. To this end, the Conference examined more directly the health effects from three source types in particular—motor vehicles, biomass combustion, and coal burning. The findings for each source are summarized briefly below.

Vehicular emissions

While urban pollutant concentrations vary, recent studies have tried to better characterize motor vehicle emissions and conditions, especially in places with heavy traffic (e.g., Avol et al., 5B.3; Ebelt Sarnat et al., 5B.6; Guarieino et al., 7SQ3.T2.331). In addition, epidemiological and toxicological studies are beginning to more directly address the association between motor vehicle emissions and various health outcomes ranging from premature mortality to various cardiovascular and respiratory morbidity effects (Wagner et al., 2C.2; Hafner et al., 3SQ3.T5.53; Lipfert et al., 5B.5; Grahame and Hidy, 9B.1; Hu et al., 9C.6; Godri et al., 13A.4; Ntziachristos et al., 11SQ1.T5.168; Li et al., 11SQ1.T5.173; Dye et al., 15SQ5.T5.287; Zhou et al., 11SQ1.T5.358; Jalava et al., 15SQ5.T1.253; Øvrevik et al., 15SQ5.T5.277; Hazari et al., 15SQ5.T5.282; Stevens et al., 15SQ5.T5.283; Dye et al., 15SQ5.T5.287; Cho et al., 15SQ5.T5.335; Samet, 2007; HEI, 2010; Grahame and Schlesinger, 2010, and references within; Jalava et al., 2010; Tzamkiozis et al., 2010). In fact, the recent HEI critical review of traffic-related air pollution (Costantini et al., 5B.1; HEI, 2010) concluded that there is "sufficient evidence" to infer a causal role for traffic-related pollution in asthma exacerbation in children and that there is "suggestive evidence" to support a causal relationship between traffic-related air pollution and total and cardiovascular mortality, cardiovascular morbidity, and onset of childhood asthma and other adverse respiratory effects. Another recent review (Grahame and Schlesinger, 2010) reported associations of a series of cardiovascular morbidity and mortality endpoints in the U.S. with motor vehicle emissions (e.g., BC [primarily a diesel emission in the U.S.]). The authors concluded that "there are mechanistic studies supporting a pathophysiological basis for how diesel and/or vehicular emissions could cause such outcomes."

More specifically, a study of exposure to UF particles emitted by a diesel truck found greater vascular inflammatory responses and oxidative stress in human endothelial cells when the truck was operated on a dynamometer using an urban driving schedule rather than in idle mode (Li et al., 11SQ1.T5.173). This demonstrated that particles emitted from the same vehicle, but generated under different operating conditions, can have different potency.

Crouse et al. (5B.7) assessed associations between breast cancer in postmenopausal women and traffic-related air pollutants in Montreal, Quebec, Canada. NO_2 exposure (highest vs. lowest quartile) was associated with a cancer odds ratio of 1.95 (95% confidence interval, 1.14–3.33). The authors noted that family history, benign breast disease, education, and age at menarche are known risk factors for breast cancer and cautioned that NO_2 exposure may be a marker for some other component(s) of air pollution.

The possible health implications of primary and secondary air pollution from motor vehicle exhaust was examined in a tunnel and a laboratory study by Rohr et al. (2C.7). Secondary aerosol ("aging") was generated from the primary emissions by turning on an ultraviolet (UV) light. They found that this aging apparently enhances the toxicity of gases and particles emitted from motor vehicles by increasing oxidative stress and pulmonary inflammation. Preliminary results suggest that aged, photochemically processed vehicular emissions are more toxic than aged coal-fired power plant emissions.

Considerable progress has been made during the last several decades, particularly in California (Ayala, 12SQ1.1), to reduce emissions from automobiles and diesel vehicles, especially emissions of $PM_{2.5}$, CO, SO_2, and NO_x. Progress in reducing health effects may not parallel the mandated reductions, however, because emissions of UF particles, particle number, EC and BC, and specific volatile organic compounds (VOCs) have not been subject to widespread regulation.

Continual evaluation is needed of how new fuels and technologies are changing emissions and their possible impact on health. Initial tests suggest that exhaust from a biodiesel car may be less potent in terms of oxidative potential on a per mass and mileage basis than from the same vehicle using fossil diesel. On the other hand, the pro-inflammatory response on a per mass basis was most potent with biodiesel usage, although results still need to be determined on a mileage basis (Gerlofs-Nijland et al., 11SQ1.T3.157).

Biomass combustion

Respiratory and cardiovascular effects also have been associated with smoke from both residential and large-scale wood and biomass combustion. Some studies used source apportionment approaches to identify biomass combustion sources and relate these sources to observed health effects (Heo et al., 11SQ1.T2.123; Wichers Stanek et al., 11SQ1.T5.166). Another study observed seasonal differences in a time-series analysis examining the effects of sources on cardiovascular mortality in Detroit, MI, and Seattle, WA (Zhou et al., 11SQ1.T5.358). In Detroit, mortality in the winter was associated with combustion sources such as residual oil burning and wood smoke, along with other combustion sources such as traffic, while mortality in summer was associated with motor vehicle emissions.

A major peat wildfire in eastern North Carolina provided an opportunity to examine the relationship of biomass combustion with respiratory and cardiovascular system health effects (Farooqui et al., 11SQ1.T5.181). The study integrated real-time satellite aerosol optical depth (AOD) data with an air quality model to estimate exposures and correlate these data to daily emergency room asthma reports. Preliminary results indicated that exposure to smoke from the peat fire had a significant effect on the respiratory and cardiovascular systems.

A study in Langui, Peru, examined health effects associated with indoor burning of dung used for cooking and heating (Montoya et al., 11SQ1.T3.161). Results indicated a high incidence of respiratory illnesses among all ages of the population. Another indoor air study in houses in rural Pakistan with open wood-burning or non-controlled stoves (i.e., emissions vented to ambient) indicated improvements in respiratory symptoms and eye irritations in women who perform the cooking and their children (Siddiqui et al., 11SQ1.T5.174). An *in-vitro* study examining cellular immunotoxic and genotoxic responses of particles emitted from two different heaters, one with more complete combustion than the other, showed that both induce cell death (Tapanainen et al., 15SQ5.T1.254); however, the heater with more complete combustion appeared to have the least toxic emissions based on the tests performed.

Coal emissions

In North America, coal emissions are mostly from power plants, although some industrial use of coal remains, and have been associated with health effects in some epidemiological studies (Thurston et al., 9C7; Gluskin et al., 11SQ1.T5.366) but not others (Dominici et al., 9C.6; Grahame and Hidy, 9B.1). $PM_{2.5}$ emissions traced to coal-fired

power plants in North America consist almost entirely of SO_2, which forms secondary sulfates in the atmosphere as well as small amounts of oxides of nitrogen (which form nitrates) and trace amounts of coal fly ash. Toxicological studies of simulated coal-plant atmospheres at high concentrations relative to ambient suggest possible health effects from emissions from some power plants but not others (Rohr et al., 2C.7).

In Asia and other countries outside of North America and Europe, uncontrolled residential use of coal occurs widely (e.g., Rohr et al., 2C.7; Heo et al. 11SQ1.T2.123; Hovorka et al., 11SQ1.T1.142; Lippmann, 19SQ9.1). Residential coal use emits large amounts of black smoke/EC and for this reason is widely acknowledged as dangerous (Clancy et al., 2002).

SQ1 Concluding remarks

Recent Advances

Several recent human panel studies with accurate subject exposure to a number of $PM_{2.5}$ species are helping to establish causal associations between pollution components or emissions and their associated health effects. In addition, more than a dozen population-based epidemiological studies have assessed several different health endpoints, using up to 20 $PM_{2.5}$ species in their analyses. Some of these studies have begun to demonstrate that several specific sources and emissions are likely to be quite harmful. A limited number of European studies of human exposure to diesel exhaust have shown increased health risks similar to those found for BC and EC in human panel studies in the U.S. Nevertheless, these recent studies must be repeated using different atmospheres to solidify the associations.

Knowledge Gaps/Research Needs

Despite significant advancements in relating pollution components to specific health outcomes, a number of gaps remain in this research area:

- Few studies have been published that provide firm evidence of causal relationships between components or emissions and their associated health effects to help guide policymakers and regulators in making better-informed decisions regarding emissions reductions.
- A lack of detailed, highly time-resolved air quality data and an insufficient understanding of atmospheric chemistry make it difficult to carry out adequately detailed source apportionment (see SQ2 and SQ3).
- A parallel deficiency exists in human panel studies of susceptible people (e.g., Schwartz et al., 2005; Delfino et al., 2009) exposed to ambient air in different airsheds dominated by different sources.
- The potency of air pollutants for one biological effect or health outcome may not hold for other effects or outcomes (Mauderly, 12SQ1.3).
- Additional population-based epidemiological and human panel studies are needed that have accurate exposure information and also include many relevant PM species and properties and other pollutants.
- Apart from the many studies of diesel engine exhaust, few toxicological studies have focused on specific sources (Grahame and Schlesinger, 2007).
- Obtain more accurate air quality data and atmospheric chemistry information with both higher spatial resolution to better understand, for example, pollutant concentrations in microenvironments and an individual's personal exposures and temporal frequency to better understand acute and chronic exposures.

- Improved atmospheric sciences information needs to be tied to specific cardiovascular and respiratory health endpoints through toxicological and human panel studies and population-based epidemiological studies.
- More accurate actual exposure information (i.e., ambient or personal versus CAPs or high-dose toxicological experiments) to a variety of PM species and sources also is crucial to reduce uncertainty in epidemiological studies.
- For population-based epidemiology, serious thought should be given to using concentrations of several different pollutants modeled to areas near the subjects' homes and assessing how risk estimates of the different pollutants change rather than using concentrations from central monitors to express exposure across a wide area.

SQ2. How reliable are methods (measurements and models) and approaches (epidemiological and toxicological) for studying and quantifying the links between air pollutants (species and/or sources) and adverse health effects?

Introduction

A wide range of methods and approaches are used in research that spans the source-to-health effects continuum (NRC, 1998). Over the last 40 years, considerable progress has been made in better understanding this source-to-outcome paradigm, but significant uncertainty remains regarding the reliability of these methods and approaches to fully assess the effects of air pollution on human health. Measurements and models, along with information about toxicity, susceptible populations, confounding errors, etc., need to be interpreted collectively via the weight-of-evidence approach to provide guidance as to what sources or source mixes should be controlled to achieve the greatest reduction in health risks from air pollution. Characterizing the uncertainties and limitations of these data and approaches is central to obtaining this goal. The reliability of methods and approaches for linking sources with health effects was discussed including uncertainty in measurement methods, air quality models and modeling approaches, and atmospheric chemistry, as well as various approaches to exposure assessment and epidemiology and how they influence study design and uncertainty.

Measurement Methods

Uncertainties in measurements, estimated exposure concentrations, and source contributions affect the characterization and quantification of source-to-health relationships (Russell et al., 1SQ2.1; Sheppard et al., 6SQ7.3; Hemann et al., 9A.6). Two types of measurement errors are typically described with regard to estimating exposure: (1) instrument errors, related to collection and analysis for estimating concentrations at a point in space and time, and (2) distance errors, related to estimating individual or population exposures of pollutant concentrations at one or more locations away from the monitors. The repeatability of measurements of typically measured pollutants (e.g., ozone, nitrogen dioxide, carbon monoxide, sulfur dioxide, $PM_{2.5}$ mass, $PM_{2.5}$ metals, elemental and organic carbon) in routine monitoring networks has provided a wealth of knowledge of pollutant characteristics. Nevertheless, uncertainty exists regarding the extent to which the right compounds are being measured in terms of both relevancy to health and measuring what is actually in the air since the measurement itself (collection and analysis methods)

can bias the measured concentration and composition (Russell et al., 1SQ2.1; Fehsenfeld et al., 2004). This section focuses on the latter issue.

Major chemical components

Differences in analytical methods, sampling artifacts, and measurement time scales can influence health impact assessments of the chemical components of air pollution and increase uncertainty in exposure and health assessments and source attribution (Oakes et al., 3SQ2.T1.6). Most routine analytical methods for the typically measured component gases and components of $PM_{2.5}$ have well-defined uncertainty due to the availability of standards, referenced to Standard Reference Materials (SRMs). One exception, however, is for the measurement of OC and EC on quartz-fiber filters where SRMs are not available yet several analytical methods are used routinely. Thermal-optical analysis (TOA) approaches are among the most widely used (Flanagan et al., 3SQ2.T2.22; Maimone et al., 2011). OC and EC determined by these approaches are operationally defined and depend on the analysis protocol (e.g., thermal ramp, pyrolysis correction approach) as described in the literature (e.g., Fehsenfeld et al., 2004; Chow et al., 2007, Chow et al., 2010; Solomon et al., 2008, and references within). Differences among the two most commonly used TOA methods for OC are usually in the range 10–20%, but EC can differ by up to a factor of 2 or more due to the optical correction approach or thermal protocol employed. An equally large error can occur when converting measurements of only carbon (e.g., TOA) into total organic carbon mass or carbonaceous material by accounting for unmeasured components such as bound oxygen, hydrogen, and associated water. The appropriate conversion is sensitive to location (urban or rural), season, and influence of sources such as smoke and bioaerosols and has been shown to vary from 1.2 to 2.2 (Flanagan et al., 3SQ2.T2.22; Turpin and Lim, 2001).

Measurements of PM can include both the loss of collected components through volatilization (negative sampling artifacts) and the gain of gas-phase components absorbed or adsorbed onto the filter or collected sample (positive sampling artifacts). Negative artifacts can affect the Federal Reference Method for $PM_{2.5}$ mass due to loss of semivolatile components during sampling (Hering and Cass, 1999; Fehsenfeld et al., 2004). Measured OC concentrations are impacted by positive sampling artifacts when gas-phase carbon compounds absorb or adsorb at active sites on the quartz-fiber filter used to collect PM. This results in an overestimation of OC and adsorbed compounds if not properly adjusted (Brook and Wheeler, 1SQ2.2), although accurate adjustment methods have not been determined as yet (Maimone et al., 2011). The overestimation can be significant, approaching 100% or more of the actual ambient OC, depending on sampling flow rate, temperature, and gas-phase organic carbon species concentrations.

Continuous measurements of gaseous pollutants and integrated filter-based measurements of both PM mass and some components are found to be reliable and represent our reference standards for comparison of new methods such as new continuous PM methods (Fehsenfeld et al., 2004; Solomon and Sioutas, 2008). A study conducted in Atlanta, GA, for example, showed transient increases in water-soluble iron, a potential inducer of oxidative stress, which could not be detected in integrated filter samples (Oakes et al., 3SQ2.T1.6). Continuous measurements can be less prone to sampling artifacts relative to many routine time-integrated filter-based measurement methods (Solomon and Sioutas, 2008). They also can provide increased information on sources and potential acute health impacts of significant recent interest to the health effects community (EPA, 2008a; Lippmann, 2009) by capturing

short-term (1 h or less) pollutant events that are not possible to be observed with longer (e.g., 24 h) monitoring periods (Saarikoski et al., 2B.6; Solomon and Sioutas, 2008; Wexler and Johnston, 2008).

Redox characterization

A growing body of research suggests that health impacts associated with exposure to air pollutants results, in part, from the oxidative properties of the compounds present. In response, a recent research thrust has been to develop and apply measurement methods to characterize redox properties of ambient aerosols for use as a metric of exposure (Godri et al., 3SQ2.T3.36; Simpson et al., 3SQ3.T5.369). Various assays used to measure PM redox activity can lead to different results (Verma et al., 2009). Also, it is not clear from the current state of the science which approach(es) is most likely to be predictive of adverse health effects.

Satellite measurements

Use of satellite measurement retrieval is rapidly increasing (Hoff and Christopher, 2009; Gupta et al., 2006). These data can reduce spatial information gaps and help identify potential biases in estimates of exposure (Lee et al., 3SQ2.T3.33; Kumar et al., 3SQ2.T3.313; Kumar et al., 2011). At present, health-related studies employing satellite data have focused on NO_2 and $PM_{2.5}$, the latter estimated from AOD measurements with an uncertainty in estimating $PM_{2.5}$ of approximately 30% in the most careful studies (Hoff and Christopher, 2009). Satellites also can provide information on physical and chemical aerosol characteristics, as mentioned below, but these data have not been used in health studies.

The improved spatial and temporal characterization offered by satellite data can be used in epidemiological studies to reduce exposure misclassification. A pilot study (Huff et al., 3SQ2.T5.49; Kumar et al., 2011) successfully applied satellite AOD as a surrogate for $PM_{2.5}$ along with $PM_{2.5}$ data to obtain more representative estimates of surface $PM_{2.5}$ than was obtained by using either AOD or $PM_{2.5}$ data alone. The combined data set was used as a predictor of acute myocardial infarctions and asthma emergency room visits. Results suggest that satellite data also may provide a cost-effective way of assessing subject-specific exposures to some gases and PM mass (Lee et al., 3SQ2.T3.33). The utility of satellite-based aerosol measurements, however, is influenced by three important factors: (1) spatial resolution at which data are retrieved, (2) spatial-temporal intervals within which the data are aggregated, and (3) nature and types of aerosol sources (Kumar et al., 3SQ2.T3.313). Application of these methods is in its early stages and some data gaps have been observed in individual retrievals due to interference from clouds and variations in surface characteristics. A major limitation for use in health studies is that PM-related satellite retrievals are typically linked to mass estimated from AOD, with little compositional information, as well as AOD being a column measurement that then needs to be related to $PM_{2.5}$ at the surface. Future research will involve determining how best to integrate satellite retrievals (column measurements) with measurements from air quality networks (point in space) and modeling activities.

Air Quality Modeling

Air quality models serve multiple purposes in exploring the relationships between air pollutants and health effects. One important application is extending observations spatially to reduce exposure errors and uncertainties that arise from the limited spatial coverage of current routine monitoring networks, especially given concerns that air pollution data from central monitors may provide inaccurate exposure estimates due to varying levels of air pollutants at

spatial scales much finer than those captured by the central monitors. The success of modeling in improving exposure estimates appears to be species (and location) dependent. Modeled sulfate concentrations, for example, generally agree within uncertainties with ambient measurements, but EC and $PM_{2.5}$ do not (Hu et al., 9B.6). In general, secondary pollutants (e.g., sulfate) have less spatial variation than primary pollutants (Turner and Allen, 2008; Solomon et al., 2008). Models also are used to identify specific sources of air pollutants (e.g., Lobo et al., 9D.4; Vette et al., 11SQ1.T3.158; Russell, 2008) either at specific locations or spatially. Such information can be used to identify health-source impact associations directly or to provide additional information on the composition of pollutants (e.g., Baek et al., 3SQ3.T5.64; Ebelt Sarnat et al., 5B.6). Further, air quality models play a key role in identifying the most efficient and cost-effective strategies for reducing source emissions and protecting human health and welfare, thus serving an important management function (e.g., EPA, 2009a). Recently, models also are being used to identify potential impacts of climate change on air quality and health (Winner et al., 18B.1).

Models also are important for integrating impacts of multiple species since in reality people are exposed to mixtures of gases and particles of widely varying size and composition (Brauer, 12SQ1.2). Yet, interpretation and integration of results for many pollutants is complicated. While multipollutant models are being used more, colinearity of pollutants is still an issue resulting in unreliable effect estimates (Hamilton et al., 13B.2). Uncertainty also results since current two-pollutant or multipollutant models ignore possible synergistic effects of pollutants and are less complex in design compared to the various single-pollutant models (Suh, 16SQ3.3). Despite these issues, two-pollutant models have greatly improved our understanding of single-pollutant health effects as well as confounding factors. Alternatively source proximity studies (e.g., traffic, wood smoke) have been suggested to account for whole mixtures, with a focus on identifying sources that contribute most to health-relevant exposures (Brauer, 12SQ1.2).

Air quality models can be divided roughly into emissions-based and empirical models. Emissions-based models track atmospheric transport and transformation of pollutants from sources to receptors; empirical models are based on analysis of observations. Each of these modeling approaches has significant advantages and limitations, but can be used together (either separately with merged interpretive results or in a hybrid modeling scenario) to reduce uncertainty in model predictions (Russell, 2008).

Emissions-based models

Emissions-based air quality models have been used extensively for estimating source contributions at receptor sites and for developing pollutant control strategies (Russell, 2008), but have been less frequently applied in health studies. Loss of temporal resolution can be a problem with these types of models and can take significant computational and human resources to apply them over an extended time period (Russell et al., 1SQ2.1). The loss of temporal detail arises from the lack of temporal variation in model inputs. An additional bias in emissions-based models is that formation of SOA is not captured (Morris et al., 2006; Pun et al., 2003). Although new approaches include information on the evolution of organic carbon volatility, which appears to address this bias (Murphy et al. 5C.1; Pandis, 16SQ3.1), obtaining agreement between measurement data and modeling estimates is still a challenge.

Murphy et al. (5C.1) developed an improved organic carbon module for the chemical transport model known as Particulate Matter Comprehensive Air Quality Model with extensions (PMCAMx-2008) that incorporates

the latest smog chamber results including an explicit gas-phase chemical aging mechanism. The model performed well for predicting inorganic and organic aerosol mass when compared to ambient observations in cities as well as rural locations in both the U.S. (all seasons in 2001) and European domains.

Empirical models

Empirical models include both receptor and regression modeling approaches. A number of air pollution health effects studies have used receptor models such as Positive Matrix Factorization (PMF) and Chemical Mass Balance (CMB), both EPA-approved models. In the last 5–8 years, a suite of new receptor models has emerged (see, for example, discussions in Watson et al., 2008; Solomon et al., 2008). While past studies have found similarities in source-health outcome relationships when various approaches are applied to the same chemical data sets (Sarnat et al., 2008; Thurston et al., 2005), those methods have limited ability to identify some sources, particularly when the sources are small and/or have similar temporal trends in air quality impact or emissions composition relative to other sources (Watson et al., 2002). Using PMF, the largest errors in daily contributions were observed in scenarios where at least two of the three simulated factors related to source contributions were moderately to highly correlated (Habre et al., 3SQ2.T1.5). This is an important finding because similar source correlations occur naturally and may lead to errors in predicting average and daily contributions in source apportionment studies. The use of chemical composition data with high temporal resolution can potentially reduce the uncertainty in source impact estimates (Buset et al., 2006, Lanz et al., 2006; Watson et al., 2008).

Land-use regression (LUR), an emerging empirical modeling approach, is being used to address the limited spatial coverage found in routine air quality monitoring networks. This approach uses auxiliary data on a city's physical characteristics to estimate pollutant levels in relation to local activities (Levy et al., 3SQ2.T3.37; Chen et al., 3SQ2.T3.38; Johnson et al., 9B.5; Levy, 15SQ3.T3.230; Crouse et al., 2009). Not only do these models increase spatial detail, they can integrate filter-based and continuous surface data as well as satellite observations. Applications have demonstrated good agreement between measured and modeled benzene and organic compounds, although NO_2 is more challenging (Levy et al., 3SQ2.T3.37; Chen et al., 3SQ2.T3.38; Johnson et al., 9B.5). LUR models also have provided estimates of long-term averages of pollutants, such as NO_2 at a high spatial resolution (Levy et al., 3SQ2.T3.37), but modeling errors still cause uncertainty in exposure classification (Chen et al., 3SQ2.T3.38). Additionally, results are limited by the number of monitoring sites (Levy, 15SQ3.T3.230).

Modeling uncertainty and limitations

While most modeling results have significant uncertainties, the level of uncertainty is difficult to quantify because measurements of source impacts are generally not available. At present, source apportionment methods have a 25–40% uncertainty (Russell et al., 1SQ2.1) and depend on the model and input data used (Solomon et al., 2008). The 25–40% modeling uncertainty is significantly greater than uncertainties in observations for most routinely measured species in national or other research networks (Fehsenfeld et al., 2004; Chow et al., 2008), but is more equivalent with results for carbonaceous components (OC, EC, and organic carbon species). This raises the question of whether it might be better to use concentrations observed directly in epidemiological analyses and then identify the sources after developing health relationships with the individual components (Russell et al., 1SQ2.1).

Given the uncertainties with both empirical and emissions-based models, a recent trend is to integrate the two approaches into hybrid models. Torotrella et al. (3SQ2.T1.3), for example, quantified the source contribution of PM from a coal power station to the surrounding area by combining a numerical dispersion model (CALPUFF), detailed chemical data and a receptor model (EPA CMB 8.2), and morphological-chemical recognition data (scanning electron microscopy–energy-dispersive X-ray spectroscopy analysis). Other approaches are briefly noted by Russell (2008).

A major limitation of current air quality models is the need for accurate information on source emissions, particularly composition. Recent studies have obtained chemical speciation information for mobile source emissions and urban atmospheres that potentially can be used for source apportionment (Saarikoski et al., 2B.6; Shafer et al., 3SQ2.T1.2; Bilonick et al., 3SQ2.T3.354; Hand et al., 5C.5). A major challenge is to capture emissions in a way that mimics their release into the atmosphere (e.g., Robinson et al., 2007). Emissions from many sources (e.g., automobiles, utilities) are changing dramatically in both lower emission levels and altered composition, which presents further analytical measurement challenges, particularly for identifying trace organic carbon compounds.

Atmospheric Chemistry

A greater understanding of atmospheric chemistry, especially the transformation of organic carbon species in air that occurs between the source and receptor, is needed to increase the reliability of air quality assessment methods. Organic aerosol is prevalent and is influenced by photochemistry (Hildebrandt et al., 13D.4; Asaawuku et al., 13D.5), that is, volatile species undergo chemical reactions in air (aging) to less volatile species that may form particles directly or condense onto existing particles (Seinfeld and Pandis, 1998). Consideration of the instability of organic tracer species as well as the formation of secondary air pollutants is critical in assessing the composition of the air pollution mixture and source impacts (Matsunaga and Ziemann, 3SQ2.T2.14; Aimanant and Ziemann, 3SQ2.T2.25; Murphy and Pandis, 5C.1; Canagaratna et al., 5C.2; Zhao et al., 7SQ3.T2.324; Hildebrandt et al., 13D.4; Robinson et al., 2007). Understanding these atmospheric processes is important for understanding population exposure (Brook and Wheeler, 1SQ2.2; Pandis, 16SQ3.1). In addition, the sampling devices themselves, as well as the sample collection, can influence (i.e., result in sampling artifacts) the chemistry of the collected PM, as noted earlier, which is important when using these data for toxicological studies or assays to assess, for example, the oxidative potential of PM (Godri et al., 3SQ2.T3.36; Saarikoski et al., 2B.6).

Choosing the exposure approach

Each person's exposure is unique, and specific exposure estimates and the assumptions to obtain them vary considerably. Health researchers can obtain individual exposure estimates by modeling the effect of various exposure determinants (e.g., time-space activity) or by manipulating a subject's exposure in a controlled laboratory setting. In choosing a research approach, it is critical to recognize how the assumptions that account for exposure errors or lack of specific exposure information can impact the associations found in the health analyses (e.g., Goldman et al., 15SQ3.T3.221) and/or how they can limit the extent to which identified associations provide definitive information on the emissions sources or pollutants that are most harmful. Furthermore, different pollutants can impact different health endpoints, and a subject's susceptibility (see SQ6) can impact their response. Both of

these factors make it difficult to prove that a given source is the most "harmful" and thus should be a top priority for policymakers to implement emission reductions.

A range of complementary study designs, each based on different assumptions, are used to assess the relative impacts of one source versus another for a selected health outcome. Epidemiological study designs generally include retrospective population or cohort studies (e.g., Sarnat et al., 5B.6; Clougherty et al., 5B.7; Tucho et al., 13B.1), prospective cohorts (e.g., Avol et al., 5B.3; Williams et al., 7SQ6.T5.133; Gale et al., 9C.3), prospective panels (e.g., Delfino et al., 9C.2; van Ryswyk et al., 9D.1; Williams et al., 13A.2; Volckens et al., 15SQ3.T3.249), and controlled exposure studies (Urch et al., 11SQ4.T4.336; Jeon et al., 3SQ2.T3.26; Anderson et al., 15SQ5.T5.284). The level of detail needed to characterize exposure increases across this spectrum of epidemiological study designs. A variety of toxicological approaches can then be used to study the plausibility and underlying causality of associations identified by epidemiological research.

Epidemiology

Air quality standards are mostly driven by exposure concentration–response functions (CRFs) derived from epidemiological studies (Brook and Wheeler, 1SQ2.2; WHO, 2005), which require available and accurate pollutant exposure and health data. Exposure assessment for epidemiology should be designed based on the type of health effects to be evaluated, such as acute versus chronic or effects, in relation to emissions sources (Sheppard et al., 6SQ7.3; Kim et al., 2009, Brauer, 2010). To distinguish the effects of different PM size fractions or other pollutants or the role of source emissions, CRFs should be constructed for each PM constituent and size fraction, for each gas, and for synergistic and antagonistic interactions among pollutant components (Brook and Wheeler, 1SQ2.2).

In addition, linking sources and specific air pollution components to observed health effects depends on the pollutants measured with the result that epidemiological studies will likely fail to find associations with the causal air pollution component(s) if those components are not measured. In these cases, associations will be found with whatever limited species are monitored (Graham and Hidy, 9B.1). However, progress has been made in monitoring PM components for use in epidemiological studies.

The major uncertainties in epidemiology are exposure misclassification (Peters and von Klot, 1SQ2.4) and confounding factors (see SQ7). The latter includes both individual and aggregate factors such as smoking, occupation, education, prior ill health, physiological factors, and co-pollutants (Yap et al., 3SQ2.T5.177). These uncertainties can be reduced by integrating economic models, traffic models, and emission projection models into the population exposure model (Brook and Wheeler, 1SQ2.2; Ebelt Sarnat, 5B.6).

Epidemiological studies have suggested the existence of certain susceptible groups in the general population, although individuals cannot easily be identified. Many factors have been shown to result in increased susceptibility (Sacks et al., 5D.1; Joubert et al., 5D.3; Green et al., 5D.6; also see SQ6). However, the extent of susceptibility among the population and how it varies temporally and spatially is not well known and thus increases uncertainty in epidemiological studies. Just as CRFs are ideally desired for individual PM constituents and for gases, CRFs by susceptibility class (Brook and Wheeler, 1SQ2.2) would enable more accurate risk and benefit calculations. This level of detail, however, in both susceptibility and pollutant types, requires considerably more research and understanding (Cetta et al., 11SQ1.T5.348).

Retrospective studies. Retrospective studies use existing air quality and health data to examine associations between air pollution exposure and health effects within a large population, typically assuming that observed ambient measurements from routine monitoring sites are representative of the population exposure (Ito et al., 2C.5; Peel et al., 2C.6). Thus, they are particularly useful for deriving CRFs to aid in development of policy. Advantages include a large sample size, such as multiple years and/or consideration of a large population (e.g., an entire large city) and existing data usually compiled for other purposes (e.g., administrative tracking of health care statistics). A disadvantage is that individual exposures are not available so exposure estimates are based on a limited number of outdoor central monitors, as used by Ito et al. (2C.5) and Peel et al (2C.6), for example. Consequently, when data collected at multiple monitoring sites are compared for their relative health effects, their differential measurement errors are important to consider (Flanagan et al., 3SQ2.T2.22; Bilonick et al., 3SQ2.T3.354; Goldman et al., 15SQ3.T3.221). In addition to the mismatch between the location and the spatial resolution of air pollution measurements and health data, the time people spend in various microenvironments (Van Ryswyk et al., 9D.1) also can bias exposure estimates and, consequently, risk evaluation.

Some measures can be taken, however, to help adjust for systematic bias. Exposure estimates from monitoring sites can potentially be refined based on some broad assumptions such as using the most proximate monitor to the reporting hospitals (Ebelt Sarnat et al., 5B6; Broadwin et al., 3SQ2.T3.30; Kumar et al., 3SQ2.T3.312) if subjects' addresses are not known, adjusting for spatial/geographic differences (e.g., use of air conditioning by Janssen et al., 2002), or using estimates of outdoor penetration indoors (Ebelt Sarnat, 5B.6; Lunden et al., 9B.2; Van Ryswyk et al., 9D.1; Hodas et al., 3SQ2.T3.32; Wallace et al., 3SQ2.T3.35). Nonetheless, it remains difficult to rely on retrospective epidemiological studies to identify which sources are most harmful due to the lack of individual-level exposure assignments, the potential for covariation among the range of exposure variables (e.g., different pollutants or source factors), and differences in exposure errors and the disparity in health and exposure data used among the various studies. How these issues impact results among studies conducted worldwide can best be answered through studies that have sufficient information regarding the population or the subjects to improve exposure precision, such as cohort or panel studies.

Cohort studies. As mentioned above, cohort studies obtain more exposure information about the study population than retrospective studies, for example, focusing on a specific source, such as a cohort of daily commuters (Sarnat et al., 15SQ5.T3.259). Subject addresses also can be identified, which represents a significant step forward in exposure assignment. Cohort studies typically include measuring a range of covariates that can be adjusted to reduce confounding as well as study-specific air quality data. The number of physical and empirical models that resolve spatial patterns in exposure is growing rapidly (e.g., Johnson et al., 9B.5; Richmond-Bryant et al., 7SQ3.T2.85; Baek et al., 3SQ3.T5.64; Huff et al., 3SQ2.T5.49; Lee et al., 3SQ2.T2.24; Jiang et al., 15SQ3.T3.355). Unfortunately, these models have so far only been developed for a limited number of pollutants (e.g., NO_2) or are less reliable for certain pollutants (e.g., SOA, toxics). Uncertainties remain between the pollutants that these models predict with some confidence and the sources they represent (Wheeler et al., 7SQ3.T2.116; Levy et al., 3SQ2.T3.37). Exposure models that consider spatial patterns as well as individual time-activity patterns are available (Burke et al., 2001). While information on the latter is rarely available for retrospective cohorts, some

newer prospective cohorts are collecting time-activity information to allow for greater exposure precision (Subbarao et al., 2009).

Panel studies. Panel studies also obtain more exposure information than retrospective studies and can be designed to target a specific exposure of interest, such as exposure to traffic (e.g., Padhi et al., 5B.4; Ruiz et al., 11SQ1.T1.351), and often include personal exposure measurements, which are more feasible in panel studies (e.g., Williams et al., 13A.2; Wallace et al., 2D.1). However, panel studies are often limited to measurements that can be obtained with personal monitoring equipment (Teng et al., 3SQ2.T3.39) or equipment placed indoors at subjects' homes and therefore comprise a smaller number of participants. One of the more effective panel study designs involves all participants residing at the same location (e.g., retirement home). In this case, it is more feasible to collect a wide range of exposure variables, including detailed composition and source contribution information (Delfino et al., 9C.2; Dubowsky et al., 2006; Delfino et al., 2008), because measurements are generally only needed at this one location. Nevertheless, participant exposures still represent a mixture of pollutants and sources, and any covariation among the exposure variables makes it difficult to be certain which source or pollutant type is most responsible for the observed effects.

Controlled exposure studies. Uncertainties related to the assumptions made in deciding what exposure to assign to a subject or population cannot be determined directly from multipollutant exposure studies. Even in controlled exposure situations, such as a chamber (Walsh et al., 3SQ2.T3.27) or a location-specific panel study (Padhi et al., 5B.4; Ruiz et al., 11SQ1.T1.351; Sarnat et al., 15SQ5.T3.259; Zangari et al., 15SQ5.T3.341), individuals usually inhale a mixture of pollutants, so it is unclear which components or properties contribute most to the observed responses (Eiguren-Fernandez et al., 7SQ3.T2.82; Kirrane et al., 13B.6; Sarnat et al., 15SQ5.T3.259). The true exposure and full range of health outcomes occurring in a study population is rarely, if ever, known or well understood. Mixtures from a given source (e.g., diesel) can be tested, however.

Statistical simulation studies are used to estimate exposure errors (Habre et al., 3SQ2.T1.5; Özkaynak et al., 2009), or sensitivity analyses within specific health studies can show how the associations change with different exposure assignments (Saarikoski et al., 5B.6; Kumar, 3SQ2.T3.312), such as source apportionment factors (Baek et al., 3SQ3.T5.64; Pachon et al., 9A.1) and exposure time windows or lag structures (Wilson, 2C.1). While these sensitivity analyses often provide new insight, they can also lead to a different set of relationships among pollutants and outcomes that frequently differ among studies. Consistencies in findings among studies that employ similar or different approaches, however, increase confidence among researchers that a particular exposure-effect link exists and points toward potential mechanisms. Objective criteria for linking specific exposure with health outcomes based on a range of study approaches could be developed in the future, but until then, as noted earlier, a weight-of-evidence approach and careful scientific assessment remains the current path forward.

Toxicology

Linking pollutants to health effects also is achieved through toxicological studies that can provide information on mechanisms relating exposure to health effects (see SQ5). A basic requirement in toxicological studies is that an accurate estimate of the dose (i.e., amount or other property of a pollutant that affects a biological target) be known (see SQ4). However, air pollution is a complex mixture that varies in time and space, making simulations of its

804 characteristics under laboratory conditions very difficult, if not impossible (Cassee, 1SQ2.3). For example, while
805 regulated gaseous pollutants can be generated as single-component atmospheres (or mixtures), PM requires other
806 techniques.
807 Particle concentrator technologies are used to increase concentrations of local ambient PM fractions
808 (usually fine and ultrafine) in inhalation chambers for both human clinical and animal studies (Cassee, 1SQ2.3;
809 Walsh et al., 3SQ2.T3.27; Clougherty et al., 5D.6; Mills et al., 2008). An improved concentrator system to
810 aerosolize higher concentrations of coarse particles over extended periods of time (100 $\mu g/m^3$ for almost 7 h) for
811 inhalation chamber studies has been developed to study the relationship of soil dust and human health effects
812 (Ashbaugh, 3SQ2.T3.314). Mobile facilities also have been developed and implemented to allow measurements
813 close to an emission source of interest (Cassee, 1SQ2.3; Freney et al., 2006), such as road traffic. Still, the small
814 number of observations and the lack of repeatability due to the variability of outdoor PM mixtures often limits these
815 controlled exposure studies. The variability of outdoor PM mixtures poses a particular problem when trying to
816 demonstrate causal relationships, especially which PM size fraction(s) or components are responsible for specific
817 health effects.
818 Toxicological studies, on the other hand, can be used to more thoroughly evaluate biological mechanisms,
819 including effects on the cardiovascular system and the brain after both short-term and long-term exposures (Walsh et
820 al., 3SQ2.T3.27; Kleinman and Campbell, 14SQ5.3; Chen and Lippmann, 15SQ5.T5.261; Gerlofs-Nijland et al.,
821 2010). Recent research has included, for example, a comparison of UF, PMf, and PMc effects in rodent models
822 (Debray-García et al., 15SQ5.T5.271) and studies that found a negative impact of ambient PM on atherosclerosis,
823 heart rate, HRV, and other health endpoints (Chen and Lippmann, 15SQ5.T5.261; Lippmann and Chen, 2009).
824 Animal toxicological studies also can provide insight into factors (e.g., confounders) that influence the
825 impact (e.g., chronic stress) of air pollution. Specific amounts of collected PM can be administered to animals by
826 using the so-called intratracheal instillation technique (Cassee, 1SQ2.3; Plummer et al., 3SQ2.T4.40). Although this
827 approach has limitations (e.g., dose given all at once rather then gradually as in inhalation studies), it demonstrates
828 that PM toxicity depends not only on the dose and composition but also on the animal species (e.g., rat, mouse, dog)
829 or strain (Phalen et al., 10SQ4.1; Plummer et al., 3SQ2.T4.40; Phalen et al., 2010). However, animal models are not
830 the most representative due to differences between humans and animals, and human studies are best to characterize
831 human health effects from air pollution (Cassee, 1SQ2.3; Clougherty et al., 5D.6). One human clinical study had
832 volunteers wear an efficient face mask during exposure to filtered or unfiltered diluted diesel exhaust or outdoor air
833 pollution (Cassee, 1SQ2.3). This study suggested that the particulate-phase component of the air pollution mixture
834 was responsible for causing acute increases in blood pressure, arterial stiffness, and reduced HRV. These findings
835 also are confirmed in animal studies in which collected PM and ROFA, which is rich in the transition metals Fe, Ni,
836 and V, have been used, resulting in a number of changes in biomarkers related to cardiovascular health outcomes in
837 rats with preexisting spontaneously hypertensive heart failure (Carll et al., 3SQ2.T5.48).
838 Various studies have focused on the use of *in-vitro* cell systems to assess either biological mechanisms or
839 the relative toxicity of the PM properties tested (Cassee, 1SQ2.3). *In-vitro* studies are limited, however, by the
840 simplicity of the system. The respiratory tract in particular is quite complex, and the lung with its many interacting

cell types cannot easily be mimicked. Co-cultured lung cells (macrophages, epithelial cells, and dendritic cells) have been used in experiments and modeled in 3D, which at least partially accounts for cellular interplay (Gehr et al., 10SQ4.3). Stereological systems also allow the study of particle movement in cell cultures and have provided supporting evidence that small (e.g., UF) insoluble particles can translocate from the lungs across biological barriers and accumulate in other organs of the body (Gehr et al., 10SQ4.3).

Novel exposure systems have been developed and include magnetic delivery of particles to cell cultures (Abid and Kennedy, 3SQ2.T3.28) or air-liquid interface exposure systems (Cassee, 1SQ2.3). Recently, the oxidative potential of particles (but potentially also of gases) has been suggested as a useful measure to predict adverse human health effects related to air pollution exposure (Jedynska et al., 3SQ3.T5.52; Tasat et al., 3SQ3.T5.55; Simpson et al., 3SQ3.T5.369; Van Winkle et al., 5D.2; Cheung et al., 11SQ1.T1.143; Peltier et al., 11SQ1.T3.159; Gordi et al., 13A.4; Shafer et al., 15SQ5.T5.296; Cho et al., 15SQ5.T5.335; Van Winkle et al., 2010). Although this indicator has been applied in various settings and has suggested a role for both metals and semivolatile organic carbon compounds in inducing oxidative stress, further evidence needs to be collected to elucidate the biological relevance of oxidative potential for predicting human health effects.

Table 4 summarizes the advantages and limitations of the various experimental approaches available in toxicology to better link exposure to air pollutants and health effects.

SQ2 Concluding remarks

Recent Advances

Linking air pollutants and their related sources to adverse health outcomes requires more accurate characterization of pollutant concentrations as well as use of methods and approaches that can quantify these relationships. A number of historical methods that have been thoroughly evaluated are quite reliable (typically excellent precision) for measuring the routine pollutant gases and the major and some minor particulate matter species (e.g., ions, metals, total carbon) (Chow, 2005; Solomon et al., 2001; Fehsenfeld et al., 2004; Chow et al., 2008). The measurements obtained from those instruments, however, often are not sufficient to provide information on the spatial and temporal variations of pollutants as well as on levels of specific organic and inorganic species that may be of particular interest to health researchers (e.g., ROS) or to quantify source impacts. Nevertheless, routine monitoring networks have provided reliable data sets for epidemiological studies, and various modeling approaches are being used successfully to overcome some of the spatial and temporal limitations of such data, including better integration of air quality and epidemiological models and use of satellite data using hybrid approaches. The growing body of information becoming available from application of new measurement techniques, including aerosol mass spectrometers and on-line water-soluble carbon analyzers, is providing information that is rapidly improving approaches for estimating secondary organic carbon formation. A range of epidemiological approaches exist and more confidence in source/pollutant and health effects associations are obtained when several studies converge on similar results. Toxicology, although somewhat limited by interspecies and *in-vitro* extrapolations to humans and the difficulties of simulating real-world exposures under controlled conditions, offers a variety of approaches for studying the plausibility and underlying causality of associations identified by epidemiological research. This

research affords insight into the biological mechanisms of human health effects due to air pollution (see SQ5) that can lead to development of preventive or avoidance measures.

Knowledge Gaps/Research Needs

The reliability of methods (measurements and models) and approaches (epidemiological and toxicological) has improved significantly in many cases, but many uncertainties remain that need to be better quantified to improve links between air pollutants and health effects and these include:

- Uncertainty exists regarding the extent to which the right compounds are being measured in terms of both relevancy to health and measuring what is actually in the air since the measurement itself (collection and analysis methods) can bias the measured concentration and composition.
    - Through the inlet SRMs need to be developed that challenge the measurement process from sampler inlet while in the field through laboratory analysis.
    - Significant uncertainties remain in field and laboratory measurements of organic and elemental carbon and organic species, especially the semi-volatile organic species. The latter limits identifying potential health effects of this important class of compounds, as well as the effects associated with directly emitted primary organic carbon and their sources.
    - Continuous PM speciation methods require additional scientific and operational evaluation prior to implementation in routine monitoring networks.
    - Comparison of methods to measure the redox activity (oxidation potential) of PM and the components that generate ROS are needed since different methods provide different results, likely since they are not actually measuring the same properties. As well, additional evidence needs to be obtained to elucidate the biological relevance of oxidative potential for predicting human health effects.
- Model results do not agree and their uncertainties are not well characterized, so the choice of approach for use in exposure assessment is not straightforward.
    - Significantly improved emissions estimates, especially for speciated PM, are needed across a variety of sources to improve the accuracy of emissions-based modeling results.
- A weight-of-evidence approach, integrating results from measurements and models and from different modeling approaches across the source-to-health effects continuum is needed to provide guidance as to the most effective and efficient reduction strategies to achieve the greatest reduction in health risks from air pollution.
    - Continued development of hybrid modeling approaches (emissions- and empirically-based) and combining measurement and models will reduce uncertainty in model predictions and exposure estimates, i.e., reduce exposure misclassification.
- Linking air pollutants and their related sources to adverse health outcomes requires more accurate characterization of pollutant concentrations as well as use of methods and approaches that can quantify these relationships.

- Uncertainties in air pollution – health effects associations can be reduced by integrating economic models, traffic models, and emission projection models into the population exposure model.

SQ3. How do relevant pollutant properties vary in space and time from sources and in ambient air, and what are the implications of these variations for population exposure?

Introduction

Air pollutant concentrations and characteristics can vary considerably in space and time depending on the emissions, meteorology, and air chemistry (Seinfeld and Pandis, 1998; Solomon et al., 2008). These factors drive intra- and inter-urban concentration variability (Turner and Allen, 2008; Allen and Turner, 2008) and in combination with indoor exposures and activity patterns produce widely varying human exposures (NRC, 1991). Different pollutants and pollutant components also may have different spatial and temporal patterns; for example, secondary pollutants may vary little over a large geographical area and over several days, whereas primary pollutants may vary significantly over and during the same space and time (Turner and Allen, 2008; Allen and Turner, 2008; Demerjian and Mohnen, 2008). These factors, along with the complexity of the multipollutant mix, bring considerable uncertainty to estimates of outdoor human exposure, often referred to as measurement error (see SQ2). Additional uncertainty occurs because most of the exposed population spends a vast majority of time indoors and is not directly exposed to the ambient atmosphere.

A number of studies presented at the Conference described how PM mass and components varied in space and time and the importance of those characteristics in assessing exposure from specific sources, the need for a multipollutant science-based approach and regulations, and how uncertainty in population exposure estimates results from the use of one or a few fixed-location monitoring sites. The continued development of improved instrumentation has allowed more highly time and/or spatially resolved measurements to be made, including the individual exposure level (Jerrett, 16SQ3.4). This increased density of observations permits better characterization of spatial/temporal patterns of concentration. In addition, improved models have been developed to provide spatial/temporal concentration estimates as well as improved understanding of indoor/outdoor concentration relationships.

Pollution characterization

Measurements

New measurement approaches have been used to better characterize the spatial variability of air pollution across major cities. In New York City, for example, Clougherty et al. (9A.2) collected two-week integrated samples at 150 street-level sites for $PM_{2.5}$, trace metals, EC, ozone, NO_x, and SO_2. Within-season temporal variability accounted for a larger portion of $PM_{2.5}$ variability (~ 60%) than for EC, NO_2, or SO_2 (16–35%). Spatial variability in $PM_{2.5}$, EC, and SO_2 were predicted from oil burning and building density, based on multiple factor analysis methods and LUR. $PM_{2.5}$ and EC also were estimated from diesel and local traffic. NO_2 was estimated by built space and traffic. Different spatial patterns for Ni and V observable in this large, spatially distributed urban data set point to different sources, and the authors suggest the possibility of disentangling their potential health effects in future analyses. Similar results were obtained using a less dense network of integrated samplers (Peltier and Lippmann, 2010).

Massoli et al. (5A.2) studied emissions from motor vehicles and their impact on adjacent neighborhoods using a combination of two mobile monitoring vans (Schwab et al., 7SQ3.T2.101) and a fixed site. They found significant differences between the upwind and downwind sides of the highway with strong CO_2, NO, BC, and particle number concentration gradients downwind of the Long Island Expressway (pollution decreased a factor of 2–3 within 150 m). These results are similar to those found by Zhu et al. (2004) in Los Angeles, CA.

Another detailed near-roadway study of elemental composition in different size fractions found that coarse lead was enriched near a U.S. highway (either 20 or 275 m from the highway) relative to a control site, but UF lead was enriched away from the highway, suggesting different sources for the different size fractions (Baldauf et al., 15SQ3.T3.192). Concentrations of most other elements measured, excluding K, Mg, and Ni, which were not enriched in any size fraction relative to the control site, were enriched in one or two of the three size fractions whereas, Ba, Ca, and Fe were abundant in all three size fractions (UF, PMf, and PMc) near the freeway.

A number of other studies have explored the near-road and on-road environment (Kozawa et al., 2B.1; Hudda et al., 5A.1; Kimbrough et al., 15SQ3.T3.200; Kimbrough et al., 15SQ3.T3.201). UF particles, particulate carbon, and nitrogen oxides, all pollutants with identified motor vehicle sources, had the highest correlations with proximity to roads (Kozawa et al., 2B.1; Hudda et al., 5A.1; Massoli et al., 5A.2; Schwab et al., 7SQ3.T2.101; Kimbrough et al., 15SQ3.T3.200; Kimbrough et al., 15SQ3.T3.201; Baldauf et al., 15SQ3.T3.192). It is unclear, however, from a variety of studies (Wagner et al., 2C.2; Ito et al., 2C.5; Peel et al., 2C.6; Cheung et al., 11SQ1.T1.143; Verma et al., 11SQ1.T1.144) which components of motor vehicle exhaust are associated with health effects. For example, it remains uncertain whether UF PM or EC (i.e., particles associated with motor vehicle emissions) is a causal component; if elevated concentrations of certain pollutant gas mixtures, e.g., NO_2 and CO, are driving the effects; or if the adverse health effects are due to the entire multipollutant mix (Lipfert et al., 5B.5).

The Detroit Exposure and Aerosol Research Study (DEARS) (Vette et al., 11SQ1.T3.158; http://www.epa.gov/dears/) measured and modeled concentrations of traffic-related air pollutants (e.g., BC, NO_x, CO, and particle counts) indoors and outdoors of asthmatic children's homes in Detroit, MI. Cardiovascular effects arising from exposure to traffic emissions also are being assessed (Williams et al., 13A.2). These data provide input for individual exposure estimates to be related to observed respiratory system and cardiovascular outcomes.

Attention to identification of localized elevated concentrations from sources, or "hot spots," is likely to increase. Cahill et al. (11SQ3.T1.197, 2011), for example, report a cancer cluster in an area heavily affected by a railroad yard in California. Sulfur, very fine metals, and soot, as well as coarse particles from polluted soil and a series of PAH species, were measured upwind and downwind of the rail yard day and night. Very fine (90–260 nm) and UF particles and chemical components associated with diesel exhaust had downwind/upwind ratios exceeding 2. Optical absorption and NO_2 had even higher ratios. PMc had high concentrations of diesel-associated trace metals, petroleum-derived *n*-alkanes, and PAH species including benzo[a]pyrene. Hamilton et al. (13B.2) used air quality modeling (MM5 and CMAQ) to simulate hourly values for five criteria pollutants and 16 HAPs over a 90-day period in 2000 in Harris County, TX. A linear mixed-effects regression model was used to estimate the resulting health effects. Geospatial techniques were used to map the predicted hospital admission rates to identify potential

hot spots for further examination. Preliminary findings suggested significant spatial differences associated with differences in meteorological and pollutant values in the predicted admission rates across the modeled grid.

Multipollutant exposure

While investigators have long recognized the complexities of air pollution resulting from source emissions and chemical reactions in the atmosphere (e.g., Seinfeld and Pandis, 1998), regulations continue to be written in terms of single-pollutant "indicators" for the effects of such mixtures. Recent reviews (e.g., Demerjian et al., 4SQ8.2; NRC, 2004a; Hidy and Pennell, 2010; Mauderly et al., 2010) propose that regulations based on an integrated multipollutant paradigm are important to improve public health from exposure to pollutant mixtures. Risk assessment will require extended epidemiological and toxicological studies aimed at characterizing the effects of mixtures in terms of identified constituents resolved over space and time (Brauer, 12SQ1.2). Cohort (e.g., Lipfert et al., 5B.5) and toxicological studies (e.g., Mauderly, 12SQ1.3) are now beginning to include complex real-world mixtures associated with health outcomes.

Particles are probably the most complex components of multipollutant mixtures, with characterization complicated by their sources, formation mechanisms, and the semivolatile nature of some constituents (Robinson et al., 13D.5; Donahue et al., 13D.1; Kreidenweis et al., 11SQ3.T1.202). The bulk composition of PM mass is becoming increasingly well documented with application of new measurement methods using, for example, particle mass spectrometry (Canagaratna et al., 2007; Sullivan and Prather, 2005) and near real-time, continuous chemical speciation methods (Solomon and Sioutas, 2008; Wexler and Johnston, 2008). Increased attention on UF and coarse particle composition also is prompting development of new ways to characterize PM exposure and has led to the question of whether mass concentration by size is the appropriate effects-related metric.

Carbon compounds

The complex nature of carbonaceous components of PM perhaps represents the biggest challenge in exposure measurement. The presence of hundreds if not thousands of nonvolatile and semivolatile organic carbon compounds in particles of partially known toxicity represents a complexity insufficiently addressed in exposure science (e.g., Mauderly and Chow, 2008). Measurement uncertainty introduced by sampling artifacts, volatility of particles at the source, the evidence of large biogenic contributions, and particle aging including time-dependent component volatility add complexity to characterizing exposure to organic carbon (e.g., Maimone et al., 2011; Donahue et al., 13D.1; Hildebrandt et al., 13D.4; Pandis, 16SQ3.1). Still, the relative importance of organic carbon components needs to be balanced against the increased concern for the apparent role of EC exposure and health impacts (e.g., Grahame and Hidy, 9B.1; Avol et al., 5B.3). Although EC is consistently much lower in concentration compared with OC, EC appears to have a potentially stronger link with health response than the organic carbon fraction. However, as noted in SQ1, EC, which is associated with incomplete fuel combustion and motor vehicle exhaust, is in a complex mixture, and other co-emitted components (e.g., OC, V, sulfur) may contribute to the observed health associations (Dye et al., 15SQ5.T5.287; Martins et al., 3SQ3.T5.349).

Indoor–outdoor relationships

Hodas et al. (3SQ2.T3.32) have examined chemical-species-specific penetration of ambient particles into the indoor environment. Estimated air exchange rates (AERs) obtained using the Lawrence Berkeley National Laboratory

(LBNL) infiltration model were used along with size-specific particle penetration coefficients and deposition loss rates to provide inputs for the indoor–outdoor particle mass balance equation to calculate indoor concentrations of outdoor-generated $PM_{2.5}$. Kioumourtzoglou and Suh (11SQ1.T1.147) examined the contribution of outdoor sources to indoor $PM_{2.5}$ using sulfur as a tracer and the relationship of these sources to markers of respiratory system inflammation. They also explored species-specific indoor–outdoor relationships and found that only indoor concentrations of sulfate had a significant correlation with outdoor values. BC, calcium, lead, zinc, and bromine correlated well with sulfur but with wide confidence intervals, suggesting substantial spatial variability in their outdoor levels. Using PMF on the indoor composition data, Kioumourtzoglou and Suh (11SQ1.T1.147) identified six sources: secondary $PM_{2.5}$ (10%), motor vehicles (28%), sea salt (5%), burning oil (4%), crystal dust (15%), and resuspended dirt particles (~ 1%).

Population exposure

Population exposure depends on areal density of emissions and resulting ambient concentrations in space and time as determined by measurements, modeling, or both. Improved spatio-temporal detail is needed to obtain accurate population exposures, but, in general, it is not practical to deploy a large number of monitors in many different locations over extended time periods, even using 120 passive monitors as done by Clougherty et al. (9A.2). A number of efforts are in progress that use a variety of measurement and modeling methods to provide both spatially and temporally resolved exposures.

Recent efforts have used satellite measurements of AOD to estimate fine particle concentrations (Liu et al., 2007a, 2007b, 2009a, 2009b; also see SQ2). Van Donkelaar et al. (9B.3) have developed a relatively coarse resolution (10 km by 10 km) global climatology for $PM_{2.5}$ for 2001–2006 by combining AOD from two satellite instruments (MODIS and MISR) with modeled aerosol properties derived from a large-scale chemical transport model (GEOS-CHEM). Liu et al. (2009a) also suggested that sulfate particle concentrations can be modeled using satellite data. Other physical and chemical aerosol characteristics, size distribution, and types of particles by source (e.g., biomass burning, urban, maritime, desert dust) can be identified qualitatively from the wavelength dependence of AOD (Kaskaoutis et al., 2007, and references within).

Pakbin et al. (2B.3) measured PMc at 10 sites across Los Angeles, CA: six (urban core) within 15 km of the University of Southern California (USC), one approximately 30 km to the south of USC, two in the eastern part of the basin in Riverside (75 km east of USC), and one located outside the basin in the southern San Joaquin Valley. The study showed relatively strong correlations between sites in close proximity ($r > 0.80$), but weak correlations between the urban center and distant sites. The monthly coefficients of determination (CODs), with most median values > 0.2, indicate modest heterogeneity overall, but the CODs calculated between the urban core site pairs were homogeneous. These observations confirm that differences in coarse particle sources and sinks within this urban region should be considered when calculating exposures.

LUR models continue to be developed to estimate past exposure. For example, LUR models examined wintertime spatial variability in several pollutants using GIS-based source indicators (e.g., traffic, building density). In a study by Chen et al. (3SQ2.T3.38), fine spatial scale NO_2 concentrations were modeled across Montreal, Quebec, Canada, using LUR and three different extrapolation methods to estimate historical exposure to traffic-

related air pollution. Results indicated that annual concentrations of NO_2 decreased by 50% between 1985 and 2006. The reductions were not spatially homogeneous, with the highest decline occurring in downtown areas (~ 75%). These exposure estimates were then related to breast cancer incidence, and only the improved LUR model results yielded a statistically significant odds ratio for this Montreal population.

Baldauf et al. (15SQ3.T3.192) summarized a number of near-road pollution gradient studies and the modeling tools available to assess population exposure in a downwind area. Differences in PAH and metal concentrations were observed near versus far from the roadway. Field measurements also indicated the potential role of noise barriers and vegetation in mitigating downwind pollutant concentrations. While barriers can reduce concentrations downwind, they may lead to elevated concentrations on the roads themselves. Vegetation may provide enhanced mitigation without increasing on-road concentrations.

Improved population exposure measures can be obtained at the intraurban level by combining monitoring data with dispersion/chemical transport models and exposure factors as illustrated for Atlanta (Sarnat et al., 5B.6). Six exposure approaches were compared: (1) central site (CS) monitoring data, (2) spatially interpolated (SI) multiple-site monitoring data, (3) Community Multiscale Air Quality (CMAQ) model outputs, (4) American Meteorological Society/EPA Regulatory Model (AERMOD) outputs, (5) CMAQ-AERMOD hybrid and blended model outputs, and (6) spatial and temporal surrogates of AERs. Preliminary analyses for each exposure metric showed that finer spatial resolution in ambient concentrations and incorporation of exposure factors into the analyses yielded different estimates of pollutant exposures compared to using only CS ambient monitoring data, particularly for spatially variable primary air pollutants. Incorporating spatially resolved metrics into epidemiological results also will likely yield different results than those obtained using just CS data.

Population exposures can be developed effectively from individual exposures and the time-activity patterns that produce those exposures. Obtaining high time resolution individual exposure data reduces uncertainty in exposure estimates for epidemiological studies. In that regard, Jerrett (16SQ3.4) described the concept of a "time-geography of exposure" in which a measurement system coupled with a global positioning system would permit mapping of concentrations and the resulting exposure. He described several miniature sensors, including ones that measured NO_x, ozone, CO, T, and RH, combined with position (http://www.citizensensing.org). Health data such as blood pressure, heart rate, and breathing rate also can be obtained simultaneously with additional sensors. Current communication devices employing Wi-Fi allow near real-time transfer of data to scientists and allow individuals to obtain real-time access to pollution data (e.g., air quality index, traffic reports) for adjusting schedules and paths to minimize pollutant exposures.

Changes in health effects with changing exposures

An increasingly important facet of air quality management is the documentation of changes in exposure with pollution reduction followed by changes in health effects (accountability, van Erp et al., 4SQ8.1; HEI, 2003; Demerjian, 4SQ8.2; also see SQ8). Tracing changes in exposure, with ambient concentrations as a surrogate, to changes in health response is difficult, especially when multiple sources are reduced at once or the reductions occur over long time periods. Only a few studies have attempted to trace such changes for particles (e.g., Shinodaet al., 2A.6; Pope, 4SQ8.4; Laden et al., 2006). Results from accountability studies are described in SQ8.

SQ3 Concluding remarks

Recent Advances

Continued development of instrumentation that provides more highly time and/or spatially resolved measurements, including at the individual exposure level, allows better characterization of spatial and temporal patterns of concentration. In addition, better models have been developed to provide spatial/temporal concentration estimates as well as an improved understanding of indoor–outdoor concentration relationships. New information about pollutant mixtures and on- and near-road and downwind population exposures from motor vehicles has provided an improved knowledge of human exposure to gradients in airborne pollutants. This includes geographically extensive characterization of the spatial and temporal differences in PM and its composition as well as gas-phase components, including precursor and oxidant species. Spatial distributions of exposures can be estimated using combined ground and satellite data for some species, and chemical transport and multiple spatial scale models.

Knowledge Gaps/Research Needs

The Conference identified a number of important gaps in knowledge and areas that warrant further study:

- An issue that still needs greater elucidation is the comparative importance of indoor relative to outdoor exposure to ambient aerosol mixtures. While measurements and methods are improving, current information remains uncertain for interpreting epidemiological findings. Without resolution of the importance of indoor versus outdoor exposure with regard to eliciting health effects, debate about the impact of exposure measurement error on the epidemiologic associations is likely to continue.
- Studies in different cities and climates would help to provide data for generalizing population exposures, including indoor-outdoor activity patterns.
- Extended investigation is needed of gradients in pollutant mixtures across population centers, including near sources and areas of different population density.
- Broadened measurements of air chemistry should include not only regulated species for compliance, but also groups of compounds suspected to be hazardous to humans.

SQ4. What advances have been made in understanding the relationships between exposure, both spatially and temporally, and estimates of dose that tie to health outcomes?

Introduction

Dosimetry provides essential information that links sources of air pollutants to their deposition and fates in exposed subjects. A key feature of dosimetry is quantification at every step from the emissions source, through environmental transport, to inhalation, and finally to distribution at target sites within the body. Thus, dosimetry has a broad scope, ranging from meteorology to molecular biology with an emphasis on mathematical modeling (Phalen et al., 10SQ4.1; Phalen et al., 2010).

Dosimetric models are used for several purposes including modeling dose-response relationships, linking source contributions to dose, identifying potentially susceptible human subgroups, and extrapolating laboratory results to human populations. Mathematical models that predict individual deposition doses of air pollutants are commonly used to estimate doses in epidemiology and toxicology studies and in risk assessments. Such models

typically use input data on pollutant physical characteristics, subje1ct breathing patterns, biological characteristics, and exposure times (ICRP, 1994; NCRP, 1997; Kane et al., 2010). Output data include inhaled pollutant total deposition, regional deposition in various portions of the respiratory tract, and sometimes pollutant clearance and internal translocation data. Mathematical dosimetry models also are useful for designing and interpreting animal studies.

A basic requirement in toxicological studies is the need to know the dose or amount of pollutant of interest or property (metric) that affects a biological target. The dose delivered can be known accurately, such as in *in-vitro* experiments or by using *in-vivo* intratracheal instillation or a bolus injection. In inhalation experiments, the dose typically is estimated mathematically based on a range of modeling approaches or more simple equations that are derived empirically (ICRP, 1994, 1995; Alexander et al., 2008; Finlay and Martin, 2008; Kleinstreuer and Zhang, 2010).

The National Research Council (NRC, 2004b) has commented on research progress and uncertainties with respect to particle dosimetry. The uncertainties and knowledge gaps that were identified in the most recent report included the following:

1. potential differences in fractional and regional deposition between older subjects and younger adults;
2. translocation of inhaled deposited particles to non-respiratory-tract sites;
3. effects of gender, age, and abnormal respiratory-tract characteristics on particle clearance;
4. gaps in knowledge on the deposition of specific particle fractions, "especially ultrafine particles"; and
5. information on dosimetry for laboratory animal models of human diseases.

Nearly all of these gaps, plus additional dosimetric topics such as advances in particle dosimetry and reduced uncertainty in results, were addressed at the Conference and are touched on below, as well as described in more detail by EPA (2009a) and Phalen et al. (10SQ4.1 and 2010), and literature cited within these publications.

Dosimetry scales

Dosimetry can be organized by scale, from macroscopic to microscopic (Solomon et al. 2011) as well as microenvironmental. Examples of each scale are given below.

Macroscopic scale

The macroscopic parameter *iF*, the intake fraction, was defined by Bennett (10SQ4.2) as "the incremental intake of a pollutant, summed over all exposed individuals, and occurring at any time, released from a specified source or source class, per unit of pollutant emitted." Thus, *iF* is a transfer coefficient that describes the efficiency with which an emitted pollutant ends up being inhaled. Lobscheid et al. (11SQ4.T3.208) described modeling studies in which *iF* was combined with a chemical-specific effect factor (*EF*) to estimate the health impacts of gasoline and alternative transportation fuels. Such an evaluation is necessary to predict the health impacts of substituting emerging fuels for gasoline. Preliminary modeling data indicated that a 10% biofuel substitution could avoid the loss of up to 20,000 disability-adjusted life years annually in the U.S. A concept similar to *iF*, the surface area deposition index (*SADI*) was applied to jet aircraft engine emissions by Lobo et al. (9D.4). The *SADI* is the surface area of the particulate emissions that deposit in the human respiratory tract per kilogram of fuel burned. Measurements downwind of the

Atlanta International Airport indicated that there were no statistically significant differences in the SADI for different jet-engine designs.

Microscopic scale

At the microscopic level of dosimetry-related phenomena, Gehr et al. (10SQ4.3) suggested the potential roles of a newly appreciated cell type found in the tracheobronchial tree, namely, the dendritic cell. Such cells have processes that reach from the basement membrane to the airway lumen (see Figure 3) and may thus participate in antigen recognition, presentation to other immune-system cells, and pollutant sequestration in the airway epithelium. Additional research is required to elucidate the significant potential roles of dendritic cells in respiratory-tract responses to inhaled air pollutants.

Microenvironmental scale

Microenvironmental dosimetry refers to the doses received in specific environments such as homes, schools, vehicles, and outdoors. Time-activity patterns, along with microenvironment contaminant levels, are used to estimate the daily personal doses received by subjects that move from one microenvironment to another. Van Ryswyk et al. (9D.1) measured the personal $PM_{2.5}$ exposures of asthmatic children living in Windsor, Ontario, Canada, and found that the amounts of time spent indoors and in transit (~ 70% and 3% of the daily total, respectively) were similar in winter and summer. However, exposure times in school and outdoors differed in winter (school in session) and summer (school not in session). Considering both exposure concentrations and exercise levels, the $PM_{2.5}$ dose rates were approximately 2:1 during transit compared to being at rest at home (in both winter and summer), but the impact of the higher dose rate was offset by the small amount of time spent in transit. Dose rates also were elevated approximately twofold during home cooking compared to non-cooking exposures and sedentary activity. Lee et al. (9D.2) studied time-activity patterns in Koreans and found that times spent indoors (~ 15 hours per day) were shorter than those in the U.S. and that Koreans also stayed outdoors considerably longer in the evening than Americans. Valente et al. (9D.7) studied exposures of asthmatic children in Portugal to $PM_{10,}$ O_3, NO_x, and BTEX (benzene, toluene, ethylbenzene, and xylenes—a group of volatile organic carbon compounds associated with petroleum products such as gasoline) based on questionnaires and air-modeling simulations. They found that differences in physical activity were a significant factor in explaining differences in asthma severity. The increased dose received during high ventilation states was a more significant dosimetric exposure factor than was seasonal variation in air quality. This result is not surprising as even moderate exercise can easily double or even quadruple the ventilation rate (ICRP, 1994).

Effects of age and gender on aerosol deposition

Kim et al. (9D.5) performed extensive aerosol deposition studies on healthy men and women in the age ranges of 24–39 years and 61–98 years at various ventilation states. Subjects breathed aerosols in the size range 0.04–5 μm AD. The overall objective was to gather data for developing and validating a comprehensive aerosol dosimetry model that would apply to both genders under a broad range of ages, breathing patterns, and aerosol sizes (NRC items 1, 3, and 4). Although age did not significantly alter particle deposition for a given ventilation, the subject's gender had small effects, with differences observed in where particles deposited and how quickly they were cleared. For example, deposition varied between average men and average women, in part because women on average have

smaller airways in the extrathoracic and tracheobronchial regions of the lung, which can shift deposition proximally. This shift resulted in reduced deposition in the alveolar region and more rapid clearance in women because a higher fraction of particles were deposited in the upper respiratory tract. The question of whether or not body size in adult men and women explained the particle deposition differences is still unanswered. Breathing patterns, ventilation rates, and disease played more important roles in the distribution of lung dose than did age or gender in healthy adults.

Animal model dosimetry

Animal models (here referring to the actual animal and not mathematical models) are critical at this time to understanding deposition and clearance within the respiratory tract across a range of possible susceptible populations as well as healthy subjects (Phalen et al., 2008). However, while methods have been proposed for extrapolation from laboratory animals to humans (Jarabek et al., 2005; Brown et al., 2005), the translation from animals to humans remains an area of significant uncertainty (Méndez et al., 9D.3; Phalen et al., 10SQ4.1; Méndez et al., 2010; Phalen et al., 2010).

Mice have become primary animal models in air pollution studies due to the availability of genetically defined strains (Phalen et al., 2008; Phalen and Méndez, 2009). Such strains are useful for research related to susceptible human subpopulations. Reviews by Méndez and Phalen (9D.3) and Méndez et al. (2010) report the current status of modeling particle deposition in mice (NRC item 5). They found that different strains (and even variants within a strain) can have significantly different respiratory tract anatomies and ventilation parameters. Although the mathematical models used for rats and humans are available for application to mice, the anatomical and physiological database required for input to these models is still inadequate for many important strains. Incorporating even a few of the emerging murine disease models into dosimetric calculations is a significant current challenge.

Overview of new developments in particle dosimetry

An overview of significant recent advancements in aerosol dosimetry was presented by Phalen et al. (10SQ4.1, 2010). Emphasis was on new developments that are particularly relevant to epidemiological and toxicological studies and include the emergence of ultrafine size (i.e., diameter < 0.1 μm) as a category of current interest in air pollution (NRC item 4). New research indicates that surface properties (e.g., surface area) or number counts may be more appropriate metrics of UF particles than mass. Ultrafine particles, as well as some slightly larger ones, have been observed to have direct access to the brain via the olfactory nerves (Phalen et al., 10SQ4.1; Oberdörster et al., 2004; Kreyling et al., 2006; Oberdörster et al., 2009; EPA, 2009a; Oberdörster, 2010; Phalen et al., 2010). These nerves penetrate the cribriform bony plate that separates the nasal cavity from the brain. Although the toxicological significance of this translocation is not yet understood, it may eventually be shown to play a role in central nervous system disorders. This internal exposure route (NRC item 2) is an important area for future research.

Another recently appreciated phenomenon (included in NRC item 3) is the existence of regions of the lung that receive very high particle deposition doses in relation to surrounding tissues (Meyer et al., 2003; Phalen et al., 2008, 2010; Scheuch et al., 2008; EPA, 2009a; Kleinstreuer and Zhang, 2010). The general uneven airflow patterns seen in diseased respiratory tracts (e.g., viral inflammation to more severe chronic obstructive pulmonary disease)

and places of enhanced particle deposition, referred to as "hot spots," are areas of ongoing and new research (Phalen et al., 10SQ4.1, 2010). Hot spots, which also are observed in healthy subjects and occur mainly at airway bifurcations, most certainly have toxicological significance. Noteworthy are local airway surface-specific particle deposition doses that are 1,000 or more times greater than average surrounding tissue doses. Such hot spots have implications for both dosing in *in-vitro* studies and toxicological considerations for susceptible individuals. Such high local doses could explain how small total doses might have large biological impacts.

Traditional concepts of the rate of clearance of deposited particles from the tracheobronchial airways have been challenged over the last decade (NRC items 3 and 4) (Phalen et al., 10SQ4.1, 2010). Specifically, the longstanding view that intact (undissolved) particles deposited on human tracheobronchial airways are completely cleared by mucociliary action within 24 hours is certainly wrong in many cases. Disease states, including transient viral infections, have been known for some time to inhibit normal mucociliary clearance for up to 8 weeks postinfection. This clearance failure is usually overcome by the health-preserving cough reflex. There is current debate on the rates of particle clearance from tracheobronchial airways in normal healthy lungs. The International Commission on Radiological Protection (ICRP) dosimetry model software (LUDEP) has particle clearance rates in healthy bronchi that are considerably slower than 24 hours (ICRP, 1994). Recent studies have challenged the model's slow bronchial clearance rate in healthy lungs (Bailey et al., 2007), and users of the ICRP software should be cautious when selecting the clearance rates for dosimetric calculations.

SQ4 Concluding remarks

Recent Advances

Recent advances in dosimetry have shed new light on individual and subpopulation internal exposures, challenged the idea that all laboratory mouse strains have similar deposition efficiencies for inhaled pollutants, and added the mammalian brain to the list of organs that may be exposed to inhaled ultrafine particles. Evidence is building regarding slow bronchial clearance of insoluble particles from the respiratory track. Dosimetric differences among persons with healthy and diseased lungs are supportive of the observed differences in the susceptibility of some subgroups to air pollutants. Also see Phalen et al. (2010) for additional details.

Knowledge Gaps/Research Needs

The recent advances in air pollution dosimetry both narrow the uncertainties described by the NRC committee (NRC, 2004b) and open new questions that require answers and areas that deserve further investigation:

- It appears that age alone likely is not a factor that influences susceptibility to air pollution in healthy adults, although gender might be.
- Differences among "animal models" and extrapolation of mouse models to humans presents a challenge due to the anatomic and physiologic differences among mouse strains: it appears that multiple dosimetric mouse models will be required.
- The health implications of the nose-to-brain translocation of ultrafine particles present a new challenge in dosimetry and toxicology.
- Near-term research is recommended on:

- the effects of respiratory-tract diseases on the initial distribution of inhaled air pollutants within the lung;
- the respiratory tract anatomy and physiology of emerging rodent models employed to simulate compromised humans; and
- the characteristics of particles that might increase their olfactory pathway transport to the brain.

SQ5. Are patterns emerging that relate component(s) of air pollution and/or source types to mechanisms? What is the status of identifying and measuring biomarkers of exposure and/or adverse health effects from air pollution?

Introduction

Important insights about the pathogenesis of air pollution components were presented at the Conference. While the theme of the Conference was multipollutant exposure, most of the studies related to this question focused on the effects of particles rather than of gaseous pollutants or interactions among different air pollutants. Since particle composition is quite variable, depending on source and atmospheric processing (see SQ1), a considerable number of studies focused on the role of particle composition. Mechanisms that were investigated included oxidative stress and inflammation, impaired function of the cardiovascular and respiratory systems, and changes in immune responses. Biomarkers of exposure also were discussed.

Effects of particles on oxidative stress and inflammation in lung cells

Results of a number of studies presented at the Conference suggested that pollutants that induce oxidative stress and resulting inflammation are a likely mechanism by which PM causes adverse effects. Various trace metals, for example, have been associated with inducing oxidative stress in cells of the respiratory system. *In-vitro* exposure of human lung epithelial cells to ambient fine particles sampled in different seasons and locations (city center, urban background, and rural sites) in Cork, Ireland, showed that heterogeneous mixtures of metals with oxidizing potential, along with inorganic ions that control acidity, elicited different responses in terms of the release of substances that mediate the inflammatory process (IL-6, IL-8, and TNF-alpha) and the production of intracellular ROS (Healy et al., 15SQ5.T5.262). Results suggested that ROS generation was essentially induced by trace metals (Fe, Mn, and Cu in particular), mostly from anthropogenic sources, and that PM in rural locations (higher concentrations of ions) has less potential for generating ROS than in urban locations. Uribe et al. (15SQ5.T5.289) found that human cultured epithelial cells exhibited more pronounced oxidative stress when incubated with particles collected in the Mexico City subway system compared with particles sampled at ground level; the authors attributed these findings to higher metal content in the subway system particles. A study by Shafer et al. (15SQ5.296), which used a macrophage-based *in-vitro* protocol exposed to particles sampled in different locations (Los Angeles, CA, Denver, CO, and Lahore, Pakistan), indicated a significant role of transition metals in generating ROS with significant differences among the locations. Statistical modeling identified a small subset of metals (Mn, Fe, Ni, and Co) as potentially associated with ROS activity. Maciejczyk et al. (15SQ5.T1.362, 2010) reported that metals, mainly Mn, Fe, Ni, and Pb, were associated with a higher expression of transcription factors involved in the genesis of an inflammatory response in mice exposed to concentrated ambient particles. Using a cell-free solution, Shen et al. (15SQ5.T2.255) also provided

evidence that transitional metals—Fe and Cu in particular—present in particles may be involved in the generation of potent biological oxidants, possibly through the Fenton reaction occurring within recruited inflammatory cells (neutrophils and macrophages). Johansen et al. (15SQ5.T2.256) further showed that the oxidation state of transition metals may be an important determinant of oxidative stress as Fe(II) in UF PM appeared to be more related to mitochondrial toxicity than total iron content.

A detailed study by Cho et al. (15SQ5.T5.335) demonstrated that different fractions of diesel exhaust particles can potentially induce different levels of oxidative stress through two distinct exposure pathways: Particle-bound material, generated during heating of the diesel fuel, primarily remains within in the lung lining once deposited and directly interacts and damages pulmonary cells. Soluble components of oxygen-transferring materials and electrophiles (such as transition metals), on the other hand, can cause local damage as well as cross the cell membrane of pulmonary epithelial cells as individual molecular species and thus translocate elsewhere in the body and possibly cause damage to other target organs or systems. Despite the wide variations in particle composition, evidence suggests that secretion of cytokines by lung epithelial cells exposed *in-vitro* to particles of different sources is apparently regulated by common cell-signaling pathways. These findings indicate that particle-mediated injury may follow common pathogenic mechanisms. The *in-vitro* studies of Øvrevik et al. (15SQ5.T5.277) demonstrated that effects due to particle exposure can be highly dependent on the activation of the endothelial growth factor receptor, a common pathway of inflammatory regulation.

Tasat et al. (3SQ3.T5.55) also noted oxidative stress as one of the mechanisms responsible for adverse respiratory effects due to ambient PM from downtown Buenos Aires, a city with high population density and traffic counts. Also, redox activity was highly correlated ($r = 0.93$) with antioxidant levels in nasal lavage in women (ages 30–40) exposed to biomass smoke during cooking (Padhi et al., 15SQ5.T3.342). The influence of size and composition in determining particle-dependent pulmonary inflammation indicated a more intense inflammatory response in rats receiving ultrafine and fine particles in comparison with coarse particles (Debray-García et al., 15SQ5.T5.271).

Studies in rats (Henríquez et al., 15SQ5.274) demonstrated that changes in markers of pulmonary injury (lactate dehydrogenase, total protein, and infiltration of cells) induced by instilled ambient particles were correlated with some transition metals, especially V and Zn, but not with total PM mass. These responses are important because they are indicators of recruitment and activation of inflammatory cells in the alveolar environment and an increase in the permeability of the alveolar-capillary barrier. An important observation regarding chronic exposure to particles on pulmonary tissues was made by Lee at al. (15SQ5.T5.260), who found that relatively long-term exposures (from 7 days to 26 days postnatal at 8 h/day, 5 days/week) of rats to ambient particles can interfere with airway branching patterns, mostly in distal airways.

Air pollutant effects on the cardiovascular system

Studies of cardiovascular effects of air pollution addressed heart rhythm disturbance, myocardial ischemia, and endothelial dysfunction. Moreno-Vinascol et al. (13A.1) explored the role of carotid body sensitivity in the pathogenesis of ventricular arrhythmias. The carotid body, a neuroepithelial structure located close to the bifurcation of the common carotid artery, is primarily a sensor of arterial oxygen partial pressure, but it also may affect cardiac

rhythm. Genetically engineered mice with severe cardiomyopathy exposed intratracheally to ambient PM exhibited higher levels of pulmonary and systemic markers of inflammation in comparison with normal animals, as well as increased carotid body sensitivity. Heightened carotid body function was associated with reduced HRV and marked increases in premature ventricular contractions, nonsustained ventricular tachycardia, and idioventricular rhythms. These findings support the concept that chronic heart failure primes the lung, carotid body, and left ventricle for an exaggerated response to particles that can increase the risk of fatal arrhythmias. Enhanced susceptibility to alterations in heart rhythm also was demonstrated in spontaneously hypertensive rats after a single exposure to diesel exhaust (Hazari et al., 15SQ5.T5.282). In an investigation of the role of oxidative stress induced by particle inhalation in disturbing heart rhythm, Chang et al. (15SQ5.T5.264) demonstrated that oxidative stress induced by nickel sulfate plays a significant role in altering HRV in spontaneous hypertensive rats.

Frasier et al. (15SQ5.T5.266) demonstrated that in some cases the hearts of rats exposed intratracheally to UF ambient particles were more vulnerable to ischemic damage following *in-vitro* ischemia and reperfusion. This effect could be prevented by blocking the mitochondrial permeability transition pore, whose opening has been associated with cell death following ischemia and reperfusion, pointing out that mitochondrial metabolic integrity also interferes with cardiac response to particles. Not only does previous exposure to UF particles amplify ischemic heart damage, but studies performed by Godleski et al. (15SQ5.T5.279) in dogs exposed to concentrated fine particles demonstrated that ischemic episodes amplify the adverse effect of the inhalation of concentrated ambient particles on coronary flow. Both the Frasier et al. and Godleski et al. studies provided compelling evidence that particle exposure increases the risk of myocardial ischemic injury, as previously observed in epidemiological studies (Chuang et al., 2008).

The possible role of $PM_{2.5}$ inhalation in interfering with endothelial layer repair was evaluated by Liberda et al. (15SQ5.T5.275; 2010). Mice exposed to CAPs for up to 4 months had decreased levels of endothelial progenitor cells in both bone marrow and blood. These cells aid in endothelial maintenance and repair, and perturbations of this system may influence the mechanisms of regulation of vascular tone by the endothelium and facilitate the development of atherosclerotic plaques. Madrid et al. (15SQ5.T5.286) and Cuevas et al. (2010) observed that an inhalation exposure of mice to nanoparticles of nickel for 1 to 3 days induced a decrease in the *in-vitro* relaxation capacity of carotid arteries to acetylcholine, pointing towards an increased vascular tone and vasoconstriction. Finally, Wang et al. (15SQ5.T5.291) reported that exposure of a monolayer of human endothelial cells to particles was associated with oxidative damage and subsequent decrease in transendothelial electrical resistance. These findings suggest that particle exposure may affect the integrity of the alveolar-capillary barrier, an event that may favor translocation of particles from the lungs to the bloodstream, as previously proposed by Elder and Oberdörster (2006).

Air pollutant effects on other systems

Several studies provided evidence of effects of PM on the immune system, especially on allergic responses. Li et al. (13A.6) reported that ambient concentrated UF particles administered in combination with OVA exacerbates the allergic recall response in OVA-sensitized mice, including increasing allergic inflammation and OVA-specific antibodies and changing cytokine profiles. As noted earlier (SQ1, Metals), Habre et al. (11SQ1.T5.178) and Wagner

et al. (11SQ1.T5.180) associated increased symptoms of asthma in children or in OVA-sensitized rats to several trace metals in ambient and CAPs $PM_{2.5}$, respectively. Results by Carosino et al. (15SQ5.T5.292) indicated that inhalation of fine CAPs magnifies allergic sensitization in mice. Frampton et al. (15SQ5.T5.280) observed alterations in the number of circulating dendritic cell precursors in asthmatic subjects exposed to UF particles. When dendritic cells isolated from asthmatic subjects were exposed *in-vitro* to urban ambient particles, Williams et al. (15SQ5.T5.268) observed sustained endocytosis of antigens, heightened expression of functionally for important markers, augmented IL-13 secretion, and dampened production of IFN-gamma by naïve CD4+ T cells. These results were interpreted as dysregulation of dendritic cells in asthmatic subjects both before and after exposure to PM. These findings indicate that exposure to particles can enhance allergic response, reinforcing the concept that deregulation of the immune system should be considered a target of ambient pollution.

The work of Hester and Gilmour (15SQ5.T5.283) demonstrated using gene expression analysis that inhalation of diesel exhaust particles alters the networks involved in immune and inflammatory responses in mice sensitized with OVA. Further, a study by McDonald-Hyman et al. (15S.Q5.T5.-272) of children living in areas with different pollution exposures provided the mechanistic insight that exposure to ambient air pollution may induce epigenetic changes. Such changes can affect regulation of the airway immune system, possibly by methylation of CpG islands in the genetic locus of Foxp3 (a key transcription factor that regulates the function of regulatory T cells), thereby increasing the risk of developing allergic responses. Exposure of rat alveolar macrophages, cultured *in-vitro*, to ROFA appears to alter the innate pulmonary defense mechanisms after mycobacterial infection, providing a biological basis for findings of epidemiological studies that report increased susceptibility to develop respiratory infections after exposure to PM (Delfosse et al., 7SQ6.T5.353). Wei and Montoya (15SQ5.T5.281) exposed isolated macrophages co-cultured with $CD4^+$ T cells to TiO_2 (5, 50, and 200 nm) and Al_2O_3 (10 and 50 nm) nanoparticles to evaluate possible immune effects and determine whether nanoparticles impact the antigen presentation mechanism. Results indicated that exposure of nanoparticles impaired the antigen-presenting capacity of macrophages, affecting their ability to elicit a subsequent response of T cells.

Evidence that exposure to particles induces damage to the central nervous system also has been reported (Block and Calderón-Garcidueñas, 2009). Information on neurotoxicity of particles was offered by Kleinman and Campbell (14SQ5.3), who showed that exposure of Apo E -/- mice exposed to PM exhibited reduced counts of dopaminergic neurons in the substantia nigra, as well as altered immune regulation of glial cells, with the latter effect mediated by an increase in nuclear translocation of transcription factors NF-kappa B and AP-1. These mice were prone to develop atherosclerosis and a sustained inflammatory environment, mimicking a frequent condition seen in humans with obesity and high cholesterol levels and showing that metabolic disturbances increase the susceptibility of the central nervous system to inhaled particles.

Biomarkers of air pollution

Biomarkers of exposure have been proposed to reduce exposure misclassification bias in epidemiological studies (Zou et al., 2009). A molecular epidemiology study in the Czech Republic (Sram et al., 13A.5) showed that humans living in Ostrava and exposed to benzo(a)pyrene had higher levels of benzo(a)pyrene-like DNA adducts in peripheral lymphocytes, genomic frequency of translocations, and lipid peroxidation when compared to dwellers of

a cleaner city (Prague). Policemen and bus drivers in Prague (Sram et al., 15SQ5.T5.273) had changes in circulating peripheral lymphocytes that correlated with ambient concentrations of PAHs. In Portugal, Almeida et al. (15SQ5.T3.257) showed the feasibility of using exhaled breath condensate, an indicator of lung inflammation, as a suitable marker to assess occupational exposure to lead.

Biomarkers of oxidative balance and pulmonary and systemic inflammation were employed to assess the effects of air pollution exposure. Ou et al. (15SQ5.T3.352) compared individuals living in two areas, Jinchang and Zhangye, China, where PM concentrations were similar (50.1 vs. 56.5 $\mu g/m^3$, respectively), but Ni concentrations were very different (216 vs. 3.9 ng/m^3, respectively). They observed that serum levels of inflammation activity (CRP, MCP-1, IL-6, ICAM-1, and VCAM-1), thickness of carotid artery wall, and estimators of endothelial repair (circulating endothelial progenitor cells) were effective in distinguishing exposures in the two different populations. All markers of inflammation except ICAM-1, carotid artery wall thickness, and endothelial repair indicated subjects exposed in Jinchang had higher risk of cardiovascular (CV) disease than those from Zhangye, suggesting Ni as an important component in $PM_{2.5}$-induced cardiovascular effects. In Milan, Italy, Zangari et al. (15SQ5.T3.341) found that the thiol redox balance in plasma and erythrocytes and in exhaled breath condensate (EBC) can be effective in monitoring pulmonary oxidative stress in individuals exposed to traffic-derived air pollution. The authors suggest that thiol analysis in EBC can be an early marker of redox imbalance and used to detect early alterations in predisposed subjects. Finally, the determination of enzymes and proteins involved in redox balance (superoxyde dismutase and GSH/GSSG ratio) in nasal lavage has been shown to be of use in characterizing adverse effects of biomass combustion smoke (Padhi et al., 15SQ5.T3.342).

SQ5 Concluding remarks

Recent Advances

Studies presented at the Conference reaffirm the role of ambient particles in eliciting pulmonary and vascular inflammation through mechanisms related to oxidative stress and activation of receptors and transcription factors in inflammatory cells. The Conference results also continue to build confidence that specific PM components, such as transition metals and their valence states, EC, classes of organic carbon compounds adhered to or trapped within particles, UF particles, and particle size distribution, influence particle toxicity and result in adverse health effects. Findings further indicated effects relating, for example, to disturbances of endothelial integrity, cardiac rhythm, and blood pressure, and provided mechanistic support for the epidemiological associations between elevated exposure to particles and premature death due to heart diseases. Studies also provided new evidence linking exposure to particles and disturbances of the immune system by showing that PM enhances allergic responses.

Knowledge Gaps/Research Needs

Despite the new information, future research is needed to better understand the complex nature of interactions and mechanisms between air pollution and human health. Among the key points from the Conference are the following:

- A better understanding is needed of how particle composition relates to toxicity. As noted above, evidence continues to build that specific components influence particle toxicity. Thus, studies using complex mixtures rather than individual components are needed to expand our knowledge in this field.

- Further research is needed to better understand how the combination of multiple components in "real world" air pollution modifies an individual's response to air pollutants.
- Synergistic effects and the possible activation of different pathogenic mechanisms by particles and gaseous pollutants are topics that deserve future exploration.

SQ6. Who are the susceptible populations, what drives different susceptibilities to the same or different air pollutants, and are there susceptibility traits associated with specific health outcomes that are common among the subpopulations?

Introduction

Identifying populations at increased risk for adverse health effects from exposure to air pollution is a central research objective and will supply evidence for informed decision making by EPA for the National Ambient Air Quality Standards (NAAQS) (e.g., *Federal Register*, 2006; Sacks et al., 5D.1). Whether current NAAQS are adequately protective of at-risk populations remains a key question, and factors that determine susceptibility and vulnerability to the health impacts of air pollution are of growing interest (Hubbell, 19SQ9.5).

Susceptibility has been defined differently by various groups depending on the goals of the relevant activity, but, in general, susceptibility refers to biological or intrinsic factors that influence a greater or lesser biological response to exposures (e.g., life stage, gender, race, preexisting diseases, specific genotypes) (EPA, 2003, 2009a (Table 8-1), 2009b). Broadwin et al. (11SQ1.T5.348) have suggested that PM-related health effects are determined as much by individual susceptibility as by the inherent toxicity of the particles. Nonbiological, or extrinsic, factors such as ethnicity and socioeconomic status (SES) are also potential markers of increased risk for adverse health effects related to air pollution. These extrinsic factors are often considered vulnerabilities or conditions under which individuals may become more or less exposed to air pollution (EPA, 2009a, 2009b), but distinguishing susceptibility from vulnerability is not always straightforward. For example, a group characterized as having low SES, usually defined as a vulnerability factor, may have less access to health care, resulting in the manifestation of disease, i.e., a susceptibility factor. They also may reside in a location that results in high exposure to air pollution (e.g., living near a freeway), which also increases their vulnerability.

Susceptibility

Disease status

The impact of air pollution on a number of different diseases has been evaluated, including common outcomes such as asthma (Utell, 8SQ6.1; Rager et al., 7SQ6.T5.364; Mann et al., 5D.4), CV disease (Devlin, 8SQ6.2), and diabetes (Utell, 8SQ6.1), as well as less studied outcomes such as sickle cell disease (Sarnat et al., 7SQ6.T5.134).

Asthma. Asthma is a chronic lung disease characterized by airway inflammation, obstruction, and hyperresponsiveness to allergens. A variety of studies, including epidemiological, controlled human exposure, animal toxicological, and cell culture studies, have been used to investigate the affects of pollution on asthma

(Utell, 8SQ6.1; Habre et al., 11SQ1.T5.178; Yu et al., 2000; Peters et al., 1997; Holguin, 2008). However, while evidence on the whole is convincing, results from individual studies can be difficult to interpret. For example, in an emergency department (ED) visit time-series study in Pittsburgh, PA, Rager et al. (7SQ6.T5.364) found associations between ambient ozone and asthma ED visits in children in the spring (March–May) but not in other seasons. Similarly, positive, although not statistically significant, associations were found for $PM_{2.5}$ in spring and summer but not for fall and winter months.

Within the asthmatic population, there may be subgroups at high risk. For example, asthma exacerbation is the most common medical emergency in children (Moorman et al., 2007), and children have been noted as a susceptible group with regard to exposures to traffic-related air pollution (see SQ1, vehicular emissions) (Costantini et al, 5B.1; HEI, 2010, and references within). In a longitudinal panel study of 315 asthmatic children in Fresno, CA, Mann et al. (5D.4) found that associations between short-term exposures to ambient air pollutants and wheeze were stronger for children who were skin-test positive to various fungi (e.g., *Alternaria, Cladosporium*) or cat dander compared to the full cohort. The authors suggest that atopy to specific antigens may be an indicator of susceptibility to the effects of air pollution among asthmatic children. The possible role of exposure to mold and allergens in the development of asthma was evaluated in the Mechanistic Indicators of Childhood Asthma (MICA) study (Hudgens et al., 7SQ6.T5.138; Williams et al., 7SQ6.T5.133; Cohen Hubal et al., 2010). MICA was an exposure-to-health outcome case-control study that investigated whether genomic data (blood gene expression and single nucleotide polymorphisms), integrated with a range of exposure and effects, and susceptibility markers measured in blood, urine, nails, DNA, and RNA provided a mechanistic explanation for the increased susceptibility of asthmatic children to ambient air pollutants. For example, Cohen Hubal et al. (2010) examined serum from 189 asthmatic and nonasthmatic children in Detroit, MI, for specific IgE antibodies to molds (*Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporum herbarum*, and *Penicillium notatum*), house dust mites, and dog and cat dander. They found that sensitization based on specific IgE antibodies for these antigens was associated with increased odds of an asthma diagnosis.

An interdisciplinary study is planned in Santiago, Chile, that integrates exposure assessment and epidemiological and toxicological design components to further assess and compare the impacts of different PM exposure metrics, including total $PM_{2.5}$ mass, its components, and its toxicological potential, on lung function and respiratory symptoms among asthmatic and nonasthmatic children (Ruiz et al., 7SQ6.T5.350). Studies also are underway to evaluate the factors, including air pollution exposures, that may explain the relatively high incidence of asthma in children (do Carmo Freitas et al., 2C.4) and markers of susceptibility, such as exposure to indoor allergens (Williams et al., 7SQ6.T5.133). Additional research is needed, however, to understand the mechanisms of interaction between air pollutants and exacerbated allergic response.

Cardiovascular disease. CV disease is a common chronic condition in the U.S. adult population that is a leading cause of both morbidity and mortality. Several epidemiological studies have found associations between PM exposure and increased risk of acute CV morbidity and mortality (Devlin, 8SQ6.2; Peel et al., 2C.6; Pope et al., 2004; Delfino et al., 2009; Grahame and Schlesinger, 2010). An extensive array of evidence, including, for example, PM-induced arrhythmias, ST segment changes, systemic inflammation, and HRV

changes, from both human and animal studies provides biological plausibility to support these epidemiological findings (Devlin, 8SQ6.2; Peters et al., 2000; Pekkanen et al., 2002; Delfino et al., 2009). The observation of changes in HRV in relation to PM exposure, for example, suggests PM-induced changes in the autonomic nervous system's control of heart rate as a mechanism by which PM influences acute CV morbidity and mortality (Routledge et al., 2003).

Diabetes. Studies focusing on diabetes and obesity also have provided insight into the observed associations between PM exposure and cardiovascular outcomes (Sacks et al, 5D.1; Utell, 8SQ6.1; Zanobetti and Schwartz, 2002). The incidence of type 2 diabetes, as well as obesity and metabolic syndrome, is increasing in the U.S. population. Diabetes is characterized by increases in CV disease risk factors (e.g., C-reactive protein, fibrinogen, white blood cell count) and endothelial dysfunction that lead to adverse CV disease outcomes (Utell, 8SQ6.1).

Overall, studies suggest that inflammatory and coagulation mechanisms explain increased risk for acute cardiovascular events in diabetics exposed to PM, including impaired endothelial responses and increased blood coagulation (Utell, 8SQ6.1; O'Neill et al., 2007; Liu et al., 2007c; Jacobs et al., 2010). Results from a toxicological study (Yan et al., 7SQ6.T5.131) found that exposure to $PM_{2.5}$, by intratracheal instillation, enhanced insulin resistance in rats with a high-fat diet but not in rats that ate a normal diet, suggesting that obese individuals with insulin resistance may be a susceptible population to $PM_{2.5}$ compared to nonobese individuals. Results from this study were not consistent across PM measures, however, nor were they consistent across markers of inflammation; for example, increased fibrinogen was observed after $PM_{2.5}$ exposure in both types of rats, but no changes were observed for C-reactive protein or white blood cell count.

Age

Disease status and age are often interconnected, with respiratory diseases predominantly affecting the young and cardiovascular diseases affecting the adult and elderly populations. In turn, existing studies suggest that children are at increased risk of PM-related respiratory conditions, while older adults (65+ years old) are at increased risk of PM-related cardiovascular morbidity (Sack et al., 5D.1).

To help explain the observed age-related differences in respiratory effects related to air pollution and to investigate the effects of particle exposure on postnatal lung development at the molecular level, Cormack et al. (7SQ6.T5.136) compared gene expression profiles, using reverse transcription polymerase chain reaction (RT-PCR) methods and bronchoalveolar lavage (BAL) cell counts, in 7- and 14-day-old and adult (> 90 days) rats. The authors found age-dependent lung inflammatory responses to CuO particles, with greater responses in neonatal rats. Correspondingly, Van Winkle et al. (5D.2; 2010) compared the airway antioxidant responses of neonatal (7 days old) and adult rats upon exposure to different PM types (high vs. low PAH content) using RT-PCR gene arrays on airway tissue with focus on genes associated with toxicity and oxidative stress. In general, PM with high PAH content had a more pronounced impact on genes in neonatal rat airways versus the adult rats than PM with low PAH content, particularly in relation to induction of genes associated with oxidative stress. However, adult rats displayed greater airway antioxidant responses to low PAH content PM, suggesting age-related differences in sensitivity depending on particle type.

The elderly are generally considered to be more susceptible to air pollution-related cardiovascular effects than younger age groups (Sacks et al., 5D.1). While most cardiovascular mortality time-series studies have been conducted in North America and Europe, a recent study conducted in the heavily populated city of Seoul, South Korea, also reported an increase in cardiovascular mortality with increases in both fine and coarse PM (Heo and Yi, 3SQ3.T5.60) and showed that the elderly (65+ age group) were more vulnerable to the effects of pollution. Klemm et al. (7SQ6.T5.137) estimated and compared the effects of air pollution on daily circulatory, respiratory, cancer, and other nonaccidental deaths in Atlanta, GA, between 1998 and 2006 among individuals 65–84 and 85+ years of age. While results for $PM_{2.5}$ suggested greater associations among the 85+ age group, associations for other pollutants examined, including CO, NO_2, EC, and OC, were greater among the 65–84 age group.

Gender

In a review of existing studies, Sacks et al. (5D.1) determined that epidemiological studies overall do not suggest differential health effects of PM by gender. Individual studies, however, have noted some differences that can possibly be attributed to dose received in relation to size differences of men and women (see SQ4). For instance, the mortality time-series study in Seoul, South Korea, cited above found stronger associations among males than females (Heo and Yi, 3SQ3.T5.60).

Perinatal health

The potential impact of air pollution on perinatal health, including preterm birth (i.e., babies born before 37 weeks gestation), low birth weight, and birth defects, is gaining attention (O'Neill, 8SQ6.3; Malmqvist et al., 13B.3). Spontaneous abortion in relation to residential vehicular traffic exposure was identified as a novel health outcome (Green et al., 5D.5). The Fresno Asthmatic Children's Environment Study (FACES)–Lifetime Exposure (LiTE) found that prenatal exposures to CO and NO_2 resulted in decreased lung function among asthmatic children aged 6–13 years at the time of evaluation, which suggests that maternal exposure to such air pollutants can have persistent effects on lung function development in children with asthma (Padula et al., 3SQ2.T5.42).

O'Neill (8SQ6.3) conducted an overview of existing birth registry studies on the effects of air pollution on birth outcomes and indicated several important limitations: limited data on confounders and effect modifiers, lack of time-varying and clinical variables, little attention to spatial variation of exposure and time-activity patterns, and few clues about causal mechanisms. While plausible biological mechanisms for air pollutant influence on birth outcomes have been proposed (Slama et al., 2008), including air pollution impacts on maternal inflammation, endothelial function, and host defenses, integration of epidemiological and toxicological study designs may help confirm such hypotheses (O'Neill, 8SQ6.3).

Genetics and epigenetics

Genetic markers are starting to be used to identify susceptible populations. Genetic polymorphisms occurring within biological pathways that are important for disease processes may impact individual responses to pollutant exposure. Sacks et al. (5D1) reviewed results from past epidemiological, controlled human exposure, and toxicological studies and noted in some studies an increase in PM-related health effects in individuals with

certain genetic polymorphisms, for example, in glutathione-S transferase (GST) genes, whereas other studies identified potential protective effects of certain polymorphisms such as hemochromatosis genes (see also EPA, 2009b).

Genetic variations in antioxidant and metabolizing enzymes, for example, heme oxygenase 1 (HMOX1), GSTs, and microsomal epoxide and hydrolase (EPHX1), may make some individuals more susceptible to the effects of oxidative pollutants. These and other candidate genes may play a role in both the development and progression of asthma in response to air pollution exposures as suggested from results observed in the Southern California Children's Health Study (http://www.arb.ca.gov/research/chs/chs.htm) (Breton, 8SQ6.4). In the MICA study, Joubert et al. (5D.3) evaluated single nucleotide polymorphism (SNP) within several genes known for asthma susceptibility, including IL-4, IL-13, and GST, and urinary levels of two PAHs (1-hydroxypyrene and 9-hydroxyphenanthrene) for their association with asthma in a group of mostly African American children living in Detroit, MI. They found that children who had specific SNP within one of their genes as well as higher levels of hydroxyphenanthrene were five times more likely to have asthma. This led the authors to conclude that both genetic and environmental factors contribute to the risk of asthma in children.

Genome-wide association studies are important for discovering novel gene–environment interactions in asthma, but the statistical power needed for identifying interaction in these studies is daunting. Thus, candidate gene studies will likely continue to be important. Candidate gene studies to date have provided evidence of a complex network of potential susceptibility-related genes with respect to air pollution health effects (Breton, 8SQ6.4). These include genes encoding antioxidant enzymes, cytokines, and transcription factors. Additional toxicological and clinical studies that examine these pathways will be needed to further this research (Hubbell, 19SQ9.5).

Epigenetics represents a new and exciting area of air pollution health research that describes transient alterations to gene expression that may also influence susceptibility to air pollution (Breton, 8SQ6.4). The findings of McDonald-Hyman et al. (15SQ5.T5.272), for example, suggested an influence of air pollution exposure on DNA methylation, which controls gene expression with no change of DNA sequence. In this study, children with asthma exposed to higher levels of pollution had greater methylation of a gene that controls regulatory T cells (Foxp3) and correspondingly reduced suppression of regulatory T cell function. Questions remain about whether susceptibility to air pollution varies by epigenetic patterns and whether genetic and epigenetic variations can jointly affect air pollution-induced outcomes.

Studies such as the MICA study (Hudgens et al., 7SQ6.T5.138) are underway that combine genetics data with traditional health endpoints and biomarkers of susceptibility. Such studies will enhance our understanding of mechanisms by which exposure to air pollutants impacts the health of susceptible populations. See SQ5 for details regarding mechanisms of action and biomarkers of exposure.

Vulnerability

Studies conducted in both the U.S. and other countries suggest that social determinants may influence exposure to and effects from air pollution. An increasing number of studies point to greater air pollution–health

associations among certain racial groups (e.g., African Americans [Green et al., 5D.5]) and among those with low educational attainment (Heo and Yi, 3SQ3.T5.60; Sacks et al., 5D.1) or other measures of SES. Research that attempts to explain these results is underway. It is possible that disadvantaged groups are differentially exposed and/or are differentially sensitive to air pollution (O'Neill et al., 2003). Elevated concentrations of UF particles, BC, and nitric oxide were found in the low SES residential Boyle Heights community of Los Angeles, CA, compared to downtown and West Los Angeles (Hu et al., 7SQ3.T2.203). A study in New Dehli, India, also found higher $PM_{2.5}$ exposures in areas where lower SES groups reside (Saraswat and Kandlikar, 5D.7).

Increased sensitivity of individuals with low SES compared to those with high SES may be due to poor nutrition, greater prevalence of co-morbidities, less access to and use of health care, and possibly higher levels of psychosocial stress (O'Neill et al., 2003). Indeed, using a rat model of social stress, concentrated ambient fine particle exposures led to shallow, rapid breathing patterns that were exacerbated under chronic stress (Clougherty et al., 5D.6).

O'Neill (8SQ6.3) indicated that what may appear to be differential individual susceptibility to adverse effects from air pollutants may be related predominantly to differential levels of exposure (vulnerability). For example, an apparent increased effect of PM in a racial/ethnic group may be due to greater residential proximity to major roadways. Often, however, increased effects may be related to both exposure and susceptibility; high prevalence of diabetes and obesity, lack of nutritious food, and high pollutant exposures in some lower-income populations make it difficult to distinguish susceptibility from vulnerability.

SQ6 Concluding remarks

Recent Advances

Research on factors that determine susceptibility and vulnerability to the health impacts of air pollution has made several advances in recent years. It is clear that numerous factors likely influence susceptibility of populations to air pollution exposures, but the strength of underlying evidence varies for each factor. Certain chronic diseases (e.g., asthma, diabetes, and CV disease) appear to enhance susceptibility to acute effects of air pollution. Young children with genetic predisposition to asthma and who are exposed to both air pollution and allergens may be at increased risk of developing the disease, but the evidence is still quite limited. Evidence that older adults with preexisting CV disease are at increased risk of acute CV morbidity and mortality from PM exposure is considerable. Still, the biological plausibility of PM effects on CV outcomes has been enhanced by studies that suggest increased susceptibility to PM exposures of individuals with diabetes, obesity, and metabolic syndrome, which increase systemic inflammation and oxidative stress and, in turn, lead to exacerbation of these diseases. Genetic factors, such as differences in antioxidant enzyme function, have been shown to affect susceptibility to health effects related to PM exposure. Further, recent evidence for this susceptibility is emerging through focused research in the new field of epigenetics.

The concept of vulnerability also is gaining increased research attention. Results of a number of studies indicate that social factors may be important determinants of health risk from air pollution exposures in addition to the biological attributes and health status of individuals.

Knowledge Gaps/Research Needs

While advances in this field have been made over recent years, several knowledge gaps and research needs are evident:

- Additional research is needed to understand the mechanisms of interaction between air pollutants and exacerbated allergic response.
- Epidemiological studies examining outcomes related to *in-utero* exposures and perinatal health are grappling with several methodological limitations that will need to be overcome before consistency in results between studies is likely to be observed.
- Toxicological and clinical studies that examine the pathways controlled by susceptibility-related genes identified by candidate gene studies are needed.
- Questions remain about whether susceptibility to air pollution varies by epigenetic patterns and whether genetic and epigenetic variations can jointly affect air pollution-induced outcomes.
- New methodological tools must be developed to distinguish the effects of social vulnerability factors from individual susceptibility factors.
- Integration of exposure assessment, epidemiological, and toxicological study designs will be useful to help confirm hypotheses regarding biological plausibility and mechanisms of air pollution health impacts among susceptible and vulnerable populations.

SQ7. What roles do confounding or other factors have in increasing, decreasing, or obscuring attribution of the true health effects from ambient air pollutants?

Introduction

In attempts to link air pollutants and sources with adverse human health effects, the concept of "confounding" in observational data is important. As outlined below, the problem of confounding factors in a multipollutant atmosphere is quite complex, but confounders need to be identified to ensure more accurate assessment of health effects from air pollution.

Control of confounding remains a major challenge for air pollution and health study researchers. As a result of the seminal, theoretical work of people like Pearl (2009), Robins et al. (2000), and Robins (2001), quantitative tools now exist to address confounding in health studies related to pollution with more sophistication than those applied previously. Discussions of confounding at the Conference included some basic and important conceptual elements that are particularly relevant to studies of air pollution-related health effects. Key concepts and topics from the Conference are summarized below, with illustrative examples, recent approaches, and explanation of the connections between susceptibility and confounding.

Key concepts

Brunekreef (6SQ7.1) defined potential and actual confounders, two important terms for understanding confounding, as follows: A potential confounder is an independent determinant of the health outcome under study. An actual confounder, in addition to criterion 1, is associated with the air pollution variable(s) under study and can lead to a distortion (bias) in the estimate of the effect of a pollutant(s) on health. Implied, but not stated explicitly, was the

additional criterion that the variable being considered as a potential confounder should not be on the causal pathway, that is, an intermediate between the air pollutant exposure and the health outcome. Failure to make this distinction also can lead to biased estimates of association (Robins et al., 2000).

To make this distinction, an *a priori* hypothesis is essential: A factor on the causal pathway will meet, on superficial inspection, the two criteria described by Brunekreef as well as the criterion for effect modification, that is, effect of an exposure is different at different levels of another factor, but if treated as a confounder can lead to biased estimates. For example, conceptualizing the association between nitrogen dioxide (NO_2) and respiratory health outcomes with ozone (O_3) as a third variable depends on the hypothesis because O_3 meets the definition of a confounder. It also could be the proximate cause of the association, due to the importance of NO_2 in the photochemistry of O_3, or an effect modifier of the direct effect of nitrogen oxides on the respiratory tract.

Each of these concepts necessitates different analytical approaches (Pearl, 2009) and illustrates why statistical testing is not directly relevant to identification of confounding factors and why confounding can be understood only in the context of a hypothetical model (Pearl, 2009, 1998)—a fact not often appreciated or implemented in epidemiological studies in general. This problem extends to the evaluation of the effects of mixtures of air pollutants on human health, as discussed below.

Several key issues need to be considered regarding confounding in real-world studies (Brunekreef, 6SQ7.1): (1) all alternative determinants of a given health outcome may not be known; (2) all known determinants may not be measured or measurable in a given study; (3) confounders often are mismeasured, which leads to residual confounding and even the appearance of spurious effect modification (Greenland, 1980); and (4) all or part of the effect of the apparent confounders actually may be due to their being part of the underlying pathway between exposure and disease, i.e., the air pollutant may partially cause or worsen the state of the confounder and thus is not a confounder in this situation. For example, oxidative stress is associated with exposure to ambient pollution and, independently, with asthma exacerbations (Nel et al., 2001). Therefore, oxidative stress would be viewed as "on the causal pathway" and not as a confounder. Imbedded in this example is the notion of time-dependent confounding—i.e., the exposure alters the intermediate, which then can change the exposure. Time-dependent confounding is important in relation to longitudinal or panel studies of air pollution health effects (Robins et al., 2000). If children with asthma regulate their rescue medication in relation to air quality, then a panel study of the association between exposure to air pollution and asthma exacerbations contains time-dependent confounding (see, for example, Mortimer et al., 2005). This type of confounding cannot be addressed by conventional statistical methods (Robins et al., 2000).

From a practical standpoint, confounders that are problematic for different study designs were identified (Brunekreef, 6SQ7.1). Meteorology (including temperature) and bioaerosols are confounders in ecological time-series studies. Individual-level factors and ecological factors are both relevant in panel studies (time-series studies with individual subjects). Cohort studies are sensitive to confounding from individual-level factors and factors that vary spatially within the cohort or across cohorts that are being compared. Confounding also can arise in cohort studies if exposures and intermediates are not updated with sufficient frequency (i.e., time-dependent confounding). Common approaches to control confounding include statistical adjustment and stratification (Brunekreef, 6SQ7.1),

both of which have limitations. Statistical adjustment, which is by far the most common method currently employed, does not reflect newer concepts on the identification and treatment of confounding variables (Pearl, 2009), and therefore cannot be relied on to provide optimal control of confounding. Stratification, sorting data by a potential confounder or causal agent, on the other hand, is a reasonable but inefficient approach since each of the stratified data sets has a reduced number of observations.

Burnett et al. (6SQ7.2) described the complex problem of confounding in the American Cancer Society (ACS) cohort (Cohen and Pope, 1995; Pope et al., 2004) that has been an important source of information about health effects related to ambient air pollution exposure. The standard Cox proportional hazards model, including only individual-level covariates, was compared with a model developed by Burnett et al. (6SQ7.2) that accounts for spatial random effects and an assessment of the degree to which inclusion of ecological covariates, such as socioeconomic, environmental, and health care variables, changed estimates of association between air pollutants and health outcomes. Spatial variation, alone and in association with ecological variables that describe groups of people in areas, is an important potential confounder in epidemiological studies. Individual-level covariates (e.g., 14 smoking variables, body mass index, diet) accounted for only 5% of the spatial variance, while ecological covariates plus ozone accounted for an additional 45%. Despite this intensive analysis, approximately 50% of the spatial variation between exposure to $PM_{2.5}$ and mortality was not captured by the approaches used. The following conclusions from this analysis are important given the overall significance of the ACS study to our understanding of health effects associated with exposure to air pollution:

- Studies and analyses (i.e., in the ACS cohort) to date have not been able to provide an alternative explanation for the spatial concordance between ambient [particulate (*sic*)] air pollution and mortality.
- Air pollution association remains after exhaustive control for important risk factors measured at the individual and contextual (i.e., ecological) levels.
- Air pollution association remains after incorporating some temporal and spatial aspects of the considered pollutants.

Reasons why associations between air pollution and mortality vary over geographical space were suggested, two of which are of particular importance in the context of confounding: (1) unresolved confounding, that is, What is causing the other 50% of spatial variation?, and (2) spatial dependence of measurement errors as described below (Burnett et al., 6SQ7.2).

Measurement errors can lead to confounding through misclassification of exposure and mismeasurement of confounders (Sheppard, 6SQ7.3). Because studies of human health effects related to air pollution rarely have access to the pertinent exposure measurements (e.g., personal exposure), many studies predict exposure based on some model. Typically these analyses do not account for the uncertainty associated with their predictions, resulting in incorrect inferences. Key to addressing this problem is development of an "exposure model" that relates the measured exposures to the true unknown exposure(s). Recognizing that different study designs pose different challenges for measurement error estimation is also important. A framework to address this issue by considering personal exposure was described by Sheppard (6SQ7.3) as the sum of ambient (E^A) and non-ambient (E^N) sources, where E^A is partitioned into ambient concentration (C^A) times an attenuation factor (α). The latter term, α,

represents the attenuation of exposure to ambient pollution due to less than complete penetration of some pollutants into indoor environments. In addition to any measurements available to provide data on outdoor pollutants directly, time-activity (and location) data and building-specific infiltration factors are needed to properly specify the likely exposures. Data on pollutants not covered by regulatory monitoring networks often are needed as well.

An important distinction was noted between the Berkson error (measure of true exposure) and so-called classical errors (measure of true exposure plus noise) (Sheppard, 6SQ7.3). The former results in unbiased estimates (in linear models) but with increased variance, whereas the latter results in biased but less variable estimates of association. Usually both types of errors occur when using models to predict exposures.

Health effects regression models that ignore measurement errors can be, but are not always, misleading, depending on several factors: (1) study design, (2) underlying exposure distribution, and (3) quality of exposure assignment approach (Sheppard, 6SQ7.3). In particular, exposure models that predict well (e.g., exposures with large spatial structure) perform well in health effects analyses, whereas less predictable exposure models can lead to bias and larger standard errors. Differences in health effects estimates between studies also can be driven by variation in population exposures (all other things being equal), which are compounded by "parameter misalignment"—i.e., different health parameters that result from replacing dose with concentration—an important issue for time-series studies (Sheppard, 6SQ7.3). On the other hand, cohort studies can be hampered by "spatial misalignment," wherein exposure data are not available at the locations of interest for the study. Sources of the latter type of misalignment can be due to nearest monitor interpolation, land-use regression, and geostatistical methods such as kriging and semiparametric smoothing. Also, a better understanding is needed in health studies of the impact of mismeasured confounders that can lead to significant distortions in exposure–outcome associations, as noted above.

Illustrative examples

Selective examples of how confounding is being addressed in epidemiological studies are provided here. Time is an important confounder in epidemiological studies of air pollutant-related health effects and can manifest itself as day-of-week effects, seasonal effects, and long-term trends. Confounders related to time include changes in temperature (O'Neill et al., 2005a; Stafoggia et al., 2008), humidity, air pollution exposure and population characteristics, and seasons, as well as in spatiotemporal distribution of the occurrence of health endpoints (Moore et al., 2008, 2010). A number of time-series studies have examined the control of the confounding of short- and long-term effects of time, along with some of its associated components, such as temperature, humidity, and long-term trends (HEI, 2002). Recent studies have addressed the role of time in relation to relatively long-term exposures (Moore et al., 2008, 2010). However, time also should be considered as an effect modifier (e.g., Stafoggia et al., 2008). Restrepo et al. (3SQ3.T5.63), for example, examined the treatment of season and demonstrated season-specific associations between asthma hospitalizations and $PM_{2.5}$, individually and combined, in different boroughs of New York City. There were differences in these associations across the boroughs, but the treatment of "borough" was that of a confounder in the absence of a specific hypothesis to the contrary. "Borough," being a proxy for population differences under given exposure regimens, could also have been an effect modifier.

To provide estimates of average, individual-level daily exposures, Yap et al. (3SQ2.T5.177) summarized pollutant exposure as a complex trigonometric function that attempts to adjust for seasonal trends and spatial characteristics (topography, housing density, and distance to the urban boundary) that vary over different areas in central Scotland. In the health analysis, smoking, co-pollutants, prior health and physiological factors, and education were recognized as confounders. The identification of these factors in the absence of a model illustrates the problem related to identifying confounders because they all meet the first two criteria noted above (Brunekreef, 6SQ7.1). Smoking, however, could easily be an effect modifier because tobacco smoke contains many of the same constituents found in ambient air pollution. Prior health status also could be an effect modifier as many studies have demonstrated that conditions such as diabetes can modify the associations with other health outcomes and exposure to air pollution (Utell, 8SQ6.1; Devlin, 8SQ6.2; Zanobetti and Schwartz, 2001; O'Neill et al., 2005b). Age as a proxy for altered physiology also has been shown repeatedly to modify these associations (Fischer et al., 2003). The same can be said for education (Krewski et al., 2009).

An investigation of exposure to ambient air pollutants in California showed a complex relationship between high temperature, age and race of the mother, and increased odds of preterm birth (Basu et al., 7SQ7.T5.139). Results illustrated that temperature is not a "fixed" confounder, and its apparent relation to air pollution-associated health outcomes is dependent on outcome, location of the study, and characteristics of the study population. Artamonova et al. (7SQ7.T5.141) provided an approach to better understand how to summarize severe changes in meteorology (anticyclonic, cyclonic, and frontal), including air pollution, in relation to meteorologically sensitive patients in whom variations in weather can cause changes in blood pressure and other adverse reactions.

Recent approaches

Two newer approaches are described here: (1) use of multiple pollutants in the analysis and (2) inclusion of sources to represent a mix of pollutants rather than a single pollutant. The distinction between confounding and the more complex consideration of air pollution-associated health effects is embodied in the current emphasis on "multipollutant" exposure estimates (EPA, 2008b; Dominici et al., 2010; Greenbaum and Shaikh, 2010). Most epidemiological studies of air pollution and health have focused on a single pollutant, with other pollutants treated as potential confounders in "two-pollutant" models (e.g., McConnell et al., 2003). This approach undoubtedly has been guided by the NAAQS regulatory focus on single pollutants. While the "other pollutants" meet the definition of a confounder as noted above (Brunekreef, 6SQ7.1), a more realistic concept is a mixture in which a given pollutant's biological/health effects are determined in whole or part by the other components and the attendant meteorology regimen. Delfino (9C.2) described a "two-pollutant" approach in which primary and secondary organic aerosols had differential effects on markers of adverse effects in elderly subjects with a history of heart disease. Traffic-related POA (measured as PAHs from fresh emissions) was associated with increases in the inflammatory marker IL-6 but not with fractional exhaled NO (F_{eNO}), but the opposite was the case with SOA measured as *n*-alkanoic acids and water-soluble carbon.

The use of "sources" in a multipollutant context has received considerable attention recently (Jongbae et al., 11SQ1.T2.123; Wilson, 2C.1; do Carmo Freitas et al., 2C.4; Peel et al., 2C.6; Thurston et al., 9C.7; Wichers Stanek et al., 11SQ1.T5.166; Gluskin et al., 11SQ1.T5.366; Kirrane et al., 13B.6; Ito et al., 2006; EPA 2008b,

2009a). Sources are usually identified and quantified at the receptor (ambient or human) using a variety of source apportionment approaches (e.g., Watson et al., 2008; Solomon et al., 2008; and references within). Kirrane (13B.6) examined a number of studies included in EPA's Integrated Science Assessment (ISA) (EPA, 2009a) with the aim of considering effect estimates for PM, CO, and NO_2 in a multipollutant context. Kirrane (13B.6), however, did not treat pollutants as mixtures to identify associations within the mixture, since study designs and analysis approaches were different among the studies examined, but did show the importance of the multipollutant approach. It is clear from these studies, however, that new statistical methods will have to be developed and applied to deal with problems of colinearity between pollutants in a mixture.

Connections between concepts of susceptibility and confounding

Many of the factors that are treated as confounders also can be viewed as susceptibility factors (described in SQ6) according to the definition provided within EPA's current ISA (EPA, 2009a); as such, a hypothesis must be developed to determine if a factor is a confounder or a susceptibility factor. Devlin (8SQ6.2) made this point explicitly while addressing the evidence for CV disease as a risk factor for enhanced susceptibility to air pollutants: "Their [people with CV disease] responses may not be different than people without CV disease, but that response may be sufficient to cause adverse affects (*sic*) because of their underlying disease." Furthermore, in this context, one has to distinguish statistical interaction from susceptibility, e.g., the need to include an interaction term in a Cox proportional hazards model to ensure that the proportional hazards assumption is met and is not *prima facia* grounds for the conclusion that a susceptibility factor has been identified. Susceptibility also has to be distinguished from mediation. The latter refers to a factor that is not a direct consequence of the exposure (i.e., on the causal pathway), but one whose presence or absence affects the magnitude of the association. Mann (5D.4) provided an example of the test of an *a priori* hypothesis about a susceptibility factor: For the hypothesis that atopic children, measured by skin prick testing to aeroallergens, would be at increased risk of daily wheeze with exposure to air pollution, children with a positive skin test showed greater increases in wheeze upon exposure to air pollution in Fresno, CA than those without positive skin tests.

Joubert et al. (5D.3) explored examples of enhanced susceptibility due to genetic and epigenetic factors. They described various approaches to studying genetic susceptibility of asthmatics to exposures of pyrene and phenanthrene as indicators of exposure to PAHs. Breton (8SQ6.4), who described the potential effects on health outcomes of epigenetic modification of a gene important in the metabolism of air pollutants, showed an increase in methylation of the micro epoxide hydrolase gene in relation to distance from traffic, indicating that genetic variation can alter susceptibility to air pollution-related outcomes. Consideration of epigenetic modifications as susceptibility factors can be problematic, however. If air pollutant exposure leads to epigenetic modification of important genes (Perera et al., 2009; McDonald-Hyman et al., 15SQ5.T5.272), then the epigenetic change is a mediator (i.e., on the causal pathway) and the susceptibility factors are those biological factors that support such changes in the face of exposure. Here, clarity of terminology and hypotheses are critical for understanding the implications of any associations between epigenetic modification of genes and susceptibility to health effects.

SQ7 Concluding remarks

Recent Advances

Confounding in observational data was noted at the Conference to be an important issue that needs to be addressed when trying to link air pollutants and sources to adverse human health effects. Properly identifying and measuring the impact of confounding is critical given the very small quantitative risks being assessed and the need to strive for high accuracy as ambient pollutant levels approach design values. Confounding is not a statistical issue, but an issue related to the hypothesis being tested. Understanding how to identify and address confounding through proper data analysis and use of *a priori* hypotheses to facilitate distinctions between confounders, susceptibility factors, and mediators is essential for application of epidemiological results to risk assessment.

Spatial influence and time were specifically identified as important potential confounders. Considerable advances have been made in statistical methodology to control confounding due to temporal and spatial factors. Conceptual progress also has been made with respect to sources of measurement error and methods to address the impact of such errors on strength of associations. The single most important step that can be taken to reduce problems related to confounding is more widespread adoption of the use of directed acyclic graphs to encode hypotheses to be tested (Pearl 2009) and the application of methods based on counterfactual concepts that can provide less biased estimates of associations and more realistic and accurate estimates of population-level impacts.

Knowledge Gaps/Research Needs

The complexity of the overall problem of confounding and the full range of methods available to address confounding remain areas for further research, including the following specific areas:

- Although health and physiological factors that can alter response to air pollutant exposure have been studied, a modern quantitative method to address effect modification and factors on the causal pathway remains an area of importance for future discussion.
- The importance of measurement errors as a source of bias and imprecision must remain a central area of concern for studies of air pollution-related health effects. This focus places demands on study designs for more dense spatiotemporal data over long enough periods of time to facilitate a more accurate assessment of the health effects from long-term exposures to ambient concentrations of pollutants across widely differing geographical areas and populations.
- Studies need to state *a priori* specific hypotheses and the *a priori* specific variables that are confounders, effect modifiers, or mediators. More objective methods to link hypotheses with statistical analyses need to be adopted—e.g., directed acyclic graph (Pearl 2009). When mediators are considered, standard statistical methods may not be adequate.
- Pollutants in mixtures should not be considered as true confounders, since their association with health outcomes are evaluated as part of complex mixtures, even if not stated explicitly.
- New statistical methods need to be developed to tease out the health effects associated with individual pollutants within the context of mixtures.
- All future epidemiologic studies of air pollution-related health effects need to address specifically the impact of measurement errors on the reported results.

- The problem of confounding in the assessment of health effects from mixtures of pollutants (i.e., a multipollutant atmosphere) in which a given pollutant can be found needs continued research to ensure the correct confounders are identified.

SQ8. Do actions taken to improve air quality result in reduced ambient concentrations of relevant pollutants, exposure, and health effects, and have we encountered unintended consequences?

Introduction

Protection of public health from adverse environmental impacts of air pollution often involves voluntary or required regulatory actions to mitigate sources of emissions or exposures to pollutants of health concern. Evaluating the effectiveness of these source controls and air quality interventions is typically referred to as "accountability" assessment (van Erp et al., 4SQ8.1, 2008; van Erp and Cohen, 2009). As illustrated in Figure 4, the chain of accountability involves examination of the relationships between regulatory and other actions designed to reduce pollution levels through a series of steps along the source-to-health effects continuum, with feedback at each step to help ensure reduction efforts are working as intended (HEI, 2003; van Erp et al., 4SQ8.1; Kelly, 4SQ8.3). The linkages between each of the key components of the accountability chain are quantified by a combination of measurements and models. The benefits derived from emissions reductions, ranging from associated improvements in air pollution concentrations to improvement in health, can be examined under two broad categories of actions: (1) those that take effect over short to intermediate time periods and (2) those that are implemented over multiple years (van Erp et al., 4SQ8.1; Kelly, 4SQ8.3). The link then needs to be developed to validate the impact of emissions reductions on air quality and that reductions in emissions and air quality result in anticipated improvements in health effects, thus cycling back to confirm that the correct regulatory action or other intervention was appropriate.

Short- to medium-term interventions

Short- to medium-term actions are implemented over a few weeks to a year by banning the use of a specific fuel, for example, or by enforcing emissions reductions from selected facilities or areawide sources. Referred to as "natural interventions" or "natural experiments," these actions are not always the result of regulatory actions, but may result from nonregulatory planned or unplanned events such as a temporary plant shutdown as in the case of the Utah Valley steel mill closure (Pope, 1989). Interventions are often local- or city-scale actions that result in step changes in concentrations such as temporary measures taken during the Olympic Games (Atlanta and Beijing) to reduce traffic-related pollution and congestion (Lin et al., 13A.3; Huang et al., 2A.7; Friedman et al., 2001; Peel et al., 2010). In other instances, implementation occurs in phases, such as in a series of coal sale bans in multiple cities in Ireland (Clancy et al., 2002) or the London Low Emission Zone (LEZ) experiment (Kelly, 4SQ8.3). These and other interventions have included introduction of cleaner fuels or combustion systems (Hong Kong and Libby, MT) and/or measures to reduce traffic congestion and emissions (London Congestion Charging scheme) (Kelly, 4SQ8.3; van Erp et al., 4SQ8.1; Hedley et al., 2002; Tonne et al., 2008).

Interventions over extended periods

Interventions over extended periods include, for example, the U.S. Clean Air Act regulations (e.g., *Federal Register*, 2006) implemented through State Implementation Plans or the new vehicle emission standards (e.g., the diesel rules)

now in place in the U.S. These longer implementation periods make it difficult to isolate the effects of changing pollutant concentrations on health from parallel changes in a multipollutant environment, health risk factors, SES, and demographic factors over the same time period (van Erp et al., 4SQ8.1; Demerjian et al., 4SQ8.2; Pope et al., 4SQ8.4; Burnett et al., 2005; Jerrett et al., 2007). In spite of these challenges, credible analyses can be carried out. For example, life-expectancy methods were used to assess whether reductions in $PM_{2.5}$ (ranging from 1 to 14 $\mu g/m^3$) over the time period 1980–2000 contributed to improved life expectancy in the U.S. (Pope et al., 4SQ8.4). Specifically, results from these long-term cohort studies have shown that a 10 $\mu g/m^3$ decrease in $PM_{2.5}$ was associated with an increase in life expectancy of approximately 0.6 to 1.6 years (Pope, 2000; Pope et al., 2009; Krewski, 2009, and references within). These results directly confirm the population health benefits resulting from declines in air pollution and support the value of effective air pollution policies (Craig et al., 2008). On a much smaller geographical scale, researchers have assessed the feasibility of performing an accountability study focused on air quality in New Haven, CT, for pollutants such as NO_x, PM, and benzene by relying on hybrid regional- and local-scale models (CMAQ and AERMOD, respectively) (Özkaynak et al., 3SQ8.T3.68).

Effects of changes in source-specific emissions on air quality improvements

Temporal changes in the use, and consequent emissions, of a wide variety of sources as a result of either regulatory or technological changes were evaluated in terms of their contribution to air quality. Source categories included emissions from mobile sources (diesel vehicles and diesel or biodiesel fuels), wood stoves, residential heating, and dust from roads.

Studies that examined mobile source emission inventories and ambient pollution data in California between 1970 and 2010 suggested that mobile source emissions are far more important than inventories suggest and that projected emission reductions are often more optimistic than achieved (Lawson, 2A.1). Photochemical modeling (e.g., CMAQ) used to assess air quality impacts of increased planned use of ethanol fuel in the U.S., for example, predicted small overall impacts for most air toxics, with the exception of some significant local impacts and limitations on stationary sources (ethanol plant) and vehicle emissions affecting hydrocarbon species (Cook et al., 2A.3). Millstein and Harley (2A.2) used the CMAQ photochemical model to analyze the effects of retrofitting emission control systems on all in-use heavy-duty diesel trucks in southern California between the 2005 baseline and 2014 alternative baseline, with fleet turnover and with retrofits (on-road diesel only). The results predicted a greater impact of retrofits on BC than on PM (12–14% vs. < 1% reductions, respectively) and small reductions in NO_2 (2–4%), with a corresponding 3–7% increase in ozone concentrations.

While modeled predictions such as these can be useful, it also is important to evaluate the real-world effects of actual interventions. Reductions in emissions and associated improved air quality and health benefits due to episodic controls (burn bans) on residential wood burning were estimated in the San Joaquin Valley in California (Lighthall et al., 2A.5). Burn bans were projected to be responsible for reducing $PM_{2.5}$ concentrations, particularly in the evening. The substantial estimated air quality improvements due to episodic wood-burning bans, together with BenMap, predicted mortality benefits and led to further tightening of the original ban in 2008. Control of PM_{10} levels in two towns in New Zealand exhibited similar effects through various restrictions on the use of solid fuel burners for residential heating and on open fires (Scott and Lucas, 2A.4). Measurements and modeling data

(CALPUFF PM_{10}) indicated larger reductions in residential heating emissions in Christchurch than in Timaru, where restrictions were less stringent.

The London LEZ accountability study, beginning in 2005, was designed to establish a baseline of PM_{10} and BC levels in advance of the 2008–2012 restrictions on the most polluting diesel vehicles in targeted highly populated areas in London (Kelly and Kelly, 2009). The objective of the LEZ experiment was to evaluate the effects of these motor vehicle restrictions on pollutant levels. Initial results indicated measurable reductions in BC concentrations but not in PM_{10} levels (Barratt et al., 3SQ8T1.65). Other studies included an investigation in Spain that demonstrated the benefits of street washing for reducing on-road dust resuspension and toxic components (Karanasiou et al., 3SQ8.T1.66) and a U.S. study that found no significant differences in PM impacts due to petroleum diesel versus biodiesel used at waste transfer recycling facilities in Keene, NH, USA (Traviss et al., 3SQ8.T3.69).

Effects of changes in emissions or air quality concentrations on health improvements

Kelly (4SQ8.3) and van Erp et al. (4SQ8.1) summarized a number of studies that assessed health benefits of various emission control actions (e.g., Atlanta Olympic Games, Ireland coal sale ban, London Congestion Charging scheme). These studies employed a variety of epidemiological methods to quantify the health improvements resulting from these emission control measures. The pollutants covered a wide variety of PM and gaseous species, but as indicated by Pope et al. (4SQ8.4), determining which pollutant(s) among multiple pollutants are most relevant in causing the health impacts remains a challenge. Nonetheless, as noted above, reductions in pollutant concentrations appear to result in an increase in life expectancy (i.e., an increase by approximately 0.6 to 1.6 years per 10 $\mu g/m^3$ decrease in $PM_{2.5}$ levels).

In some cases, observed changes in air pollution concentrations may not be the result of the local control efforts but due to some other factor. Initial results on emergency room visits (Friedman et al., 2001) versus those of a more recent analysis (Peel et al., 2010) indicated that caution is needed in linking air pollution control measures to reductions in adverse health effects due to specific source emissions control efforts. During the Atlanta 1996 Olympic Games, initial results suggested a reduction in emergency room visits were due to reductions in ozone concentrations as a result of local traffic emissions control measures. However, a more recent analysis (Peel et al. 2010) indicates the ozone reductions were probably due more to a regional phenomenon, likely driven by meteorology. These results indicate the importance of choosing appropriate control periods and locations as well as understanding potential confounding factors in accountability studies.

A case-crossover analysis was used to estimate impacts of $PM_{2.5}$ air pollution reduction strategies on respiratory hospitalizations in Minnesota. Shinoda et al. (2A.6) compared hospitalization rates before implementation of controls (2002–2004) with rates during the early implementation period (2005–2007). Respiratory hospitalization effect estimates, per 10 $\mu g/m^3$ increases in $PM_{2.5}$, were larger in the pre-controls period. Taken at face value, findings such as this, in which one compares effects of fixed PM increments (essentially controlling for any change in concentration), suggest that something about the PM, perhaps its composition, changed due to the emissions controls to account for the different effect estimates by time period. This type of study design in the accountability context does not readily allow one to directly assess effects due to multipollutant exposures.

Fann and Risley (3SQ8T2.67) conducted a risk assessment-based accountability evaluation of health impacts associated with trends in ozone and $PM_{2.5}$ levels in the U.S. between 2000 and 2007 using EPA's BenMap software. Results indicated that the number of premature deaths related to ozone and $PM_{2.5}$ in the U.S. was estimated to decrease cumulatively. While analyses such as these may be helpful in providing information on what might be expected, they apply a risk function to observed declines in pollutant concentrations that does not directly test the link between reductions in pollutant concentrations and improvements in health outcomes. This linkage is assumed in the risk function, so that the "observed" changes in health outcomes are preordained.

Spatially and temporally resolved multiscale air quality modeling (CMAQ and AERMOD) and exposure modeling (HAPEM and SHEDS) tools were used along with air quality data and other information in New Haven, CT, a small urban area (population ~128,000), to evaluate the feasibility of conducting a local (e.g., city level) accountability study of the public health impacts of voluntary federal, state, and local cumulative air pollution reduction activities to estimate multiyear pollution levels and related health effects (Özkaynak et al., 3SQ8.T3.68). While new methodologies were developed to better link reductions and regulations with health effects, the ability to conduct a monitoring-based accountability study successfully in such a small town was deemed unlikely for many of the air pollutants. In New York City, source apportionment using PMF was first used to estimate impacts of restricting residual oil, and then BenMap was used to estimate mortality impacts (Cromar et al., 3SQ3.T5.326). Results indicated that converting residual oil to distillate oil or natural gas would result in 67.4 (± 18.9) or 204.0 (± 57.7) avoided deaths per year, respectively. Again, in these two cases, effects on health were assumed in the risk function employed rather than observed.

SQ8 Concluding remarks

Recent Advances

Studies have already made important contributions to evaluating the links in the accountability chain that connect emission reductions to health impacts. As detailed earlier, these have included studies of changes in air quality resulting from reduced emissions, studies of health impacts of reductions in concentrations, and studies that have assessed the entire set of links from emission reductions to health impacts. These studies have augmented our knowledge of accountability and provided sound guidance for future accountability studies (van Erp et al., 2010):

- Before starting a health study directed at achieving a particular air quality change, investigators need to estimate the size of air quality impacts through model simulations or other means.
- Public health benefits gained from slow, incremental changes in emissions over a long period of time, in conjunction with gradual changes in concentrations, become more difficult to discern as other factors that affect the same outcomes may change during the same time period).
- Studies of short-term interventions have shown the need to account for other determinants of pollutant concentrations (e.g., confounding factors such as meteorology, as discussed in SQ7) and/or parallel changes in other pollutant sources (e.g., increased bus or taxi traffic in concert with reduced automobile traffic).

Knowledge Gaps/Research Needs

The studies presented at the Conference have also highlighted a number of research needs that, if addressed, should allow more definitive accountability studies to be carried out:

- Evaluation of effects of multiple regulations on improvements in air quality and health effects over the long-term remains challenging and requires new or more sophisticated approaches.
- A number of methodological challenges and issues remain regarding accountability, i.e., validating that interventions, designed to reduce emissions from sources, result in the anticipated improvements in air quality and reductions in adverse health effects.
- A key question that must be addressed in relation to accountability is, How much change in air quality is needed to observe or detect changes in health outcomes? Generally, the improvements in air quality as a result of interventions are modest, and they often have implications regarding our ability to identify the associated health benefits.
- The unintended consequences of air-pollution regulations also need to be evaluated, yet they are easier to list than to quantify. When targeted pollutants are individually controlled, the changes in air chemistry (and possibly toxicity) are largely unstudied. Decreasing the levels of some air pollutants, or their properties (e.g., fine particle mass) can increase the levels of others (e.g., ultrafine particle count). Decreasing ammonia levels can result in increased acidity in the air.
- Finally, the economic effects of air quality regulations need greater evaluation, especially since low socioeconomic status is a known risk factor.

SQ9. What findings presented at the Conference provide policy-relevant insights that can lead to an improved understanding of the source-to-health effects paradigm and more knowledgeable policy decisions?[5]

Introduction

The previous sections presented selected findings from "Air Pollution and Health: Bridging the Gap from Sources to Health Outcomes" and laid out the scientific evidence in response to the eight policy-relevant science questions that formed the basis of the Conference. Those sections should be referred to for details supporting the policy-relevant insights, based on the findings outlined below for each SQ. It should be noted that a number of the policy-relevant findings reaffirm past results, thus strengthening and providing further guidance for policy decisions. However, the science continues to move incrementally forward, helping reduce uncertainties in our understanding across the source-to-health effects continuum.

SQ1. Pollutants and sources associated with health effects

- Exposure to PM is associated with adverse respiratory and cardiovascular effects including premature mortality and morbidity, but the PM mass metric alone appears to be insufficient to fully and effectively evaluate the health effects of PM. Recent results indicate factors including concurrent gases, particle size and composition, or other physical properties, perhaps several in concert, affect the relationship between PM and health effects.
- Studies with limited air quality or exposure measurements often find associations with the air quality parameters measured; however, as more recent studies measure multiple components of air pollution new

[5]Modified from the SQ9 conference question: What are the policy implications of our improved understanding of the source to health effect paradigm?

associations are being found with additional variables and, in some cases, replacing the previously noted associations.

- Depending on the source of PM, different size fractions (typically UF, fine, or coarse) appear to elicit a range of effect responses, perhaps due to the different chemical and physical properties observed in these empirically defined PM size fractions.
- Epidemiological studies consistently associate adverse health effects with components of PM. Specifically noted in the Conference were EC, Ni, and V. Studies also have found associations with other metals, including Zn, Al, Cd, Fe(II), and Pb, as well as organic carbon components such as PAH species like anthracene.
  - Diesel emissions are the major source of EC in most urban areas. Ni and V are indicators of oil combustion.
  - EC may be associated with health effects due to both its own characteristics and its association with other pollutants emitted from the same or associated sources, including components adsorbed onto the EC particles.
- Motor vehicle emissions appear to be linked with adverse health effects, from premature mortality to cardiovascular and respiratory morbidity. Studies of motor vehicle emissions indicate that PM mass, certain PM components, and related gases are associated with adverse health effects, suggesting the need for multipollutant research approaches.
- Toxicological studies are focusing more on specific sources in addition to motor vehicles. A recent study, for example, indicated that the toxicity of emissions from coal-fired plants may vary from plant to plant.

SQ2. Reliability of methods and approaches for linking pollutants and sources to health effects

- Interpretation of results from measurements, models, dosimetric, toxicological, and epidemiological studies must be taken into account by a weight-of-evidence approach rather than relying on a single method.
- Uncertainty still exists regarding the extent to which the right compounds are being measured, in terms of both measuring the correct health-relevant pollutants and measuring what is actually in the air, because the measurement itself (collection and analysis methods) can bias the result. Routine monitoring networks provide consistent, repeatable data, but are limited in their ability to quantify spatial and temporal variations and levels of metals and particulate organic carbon species that may be of most interest to health researchers.
  - Continuous PM speciation monitoring can provide improved temporal data for health studies investigating the role of specific components as well as effects due to short-term changes in pollution.
  - Significant uncertainty remains in characterizing exposure to the carbonaceous fraction of PM (OC, EC, and organic carbon species) because current sampling methods not only affect the measurement, but different methods provide inconsistent answers when compared.
  - The actual composition of the organic fraction of the PM remains poorly characterized, so it is not apparent which compounds and their respective sources may have the most significant health effects.
- Air quality model uncertainties, particularly with respect to quantifying source impacts or the species that are not directly measured (e.g., OC), are poorly characterized, and it is not apparent which approaches are preferable for use in exposure assessments. Recent advances have been made in modeling semivolatile compound formation, but significant uncertainty remains in the formation of secondary OC.

- The different approaches to assess exposure noted throughout the Conference have strengths and weaknesses, but recent results indicate that hybrid approaches that combine multiple measurement methods and models provide results that bracket uncertainty and provide more confidence in exposure estimates than using a single approach.
- The comparative importance of indoor and outdoor exposure remains one of the major uncertainties in characterizing human exposure. In part, this is because penetration of pollutants into indoor spaces varies by pollutant as well as geographically and temporally, and once indoors, pollutants initially outdoors can undergo additional physical and chemical changes.
- A variety of toxicological approaches are being used to establish the underlying causality of associations identified by epidemiological studies. However, considerable uncertainty remains in linking air pollutants to human health effects because of interspecies extrapolation and the difficulty of simulating real-world exposures under controlled conditions.

SQ3. Pollutant characterization[6] and population exposure

- Air pollution consists of a complex mixture of gases and particles that vary in space and time, the sources of which include both primary and secondary emissions. PM composition can vary widely by size and location depending on the sources affecting the area and the age of the aerosol. These factors add difficulty to estimating exposures and linking sources to health effects.
  - Primary pollutants tend to be more heterogeneous across urban areas than secondary pollutants. Coarse and UF particles also are more spatially heterogeneous relative to fine particles.
  - Intraurban pollution variability and near-roadway studies reinforce the need to measure pollutants on a range of spatial scales to better understand differences in exposure and health impacts.
- The mass of UF particles is very small, so other metrics such as count and surface area are needed to define their relationship to health effects. Particle number may be a surrogate for UF PM mass or vice versa, but not for $PM_{2.5}$ mass.

SQ4. Relationship between exposure and dose

- Particle deposition in the lungs is not uniform, especially in diseased individuals but also in healthy ones, resulting in "hot spots" within the lung and partially explaining why small doses may have large biological impacts.
- Breathing pattern, rate of ventilation, and presence of lung disease appear to be more important than age or gender in affecting the dose of particles received and deposited within the respiratory tracts of individuals with consistent exposures.
- Recent studies have indicated that the clearance of slowly solubilized particles from the tracheobronchial region of the respiratory tract may be much slower than previously thought, providing more time for interactions of particles with epithelial cells and possible translocation to other organs in the body.

[6] See special issues by Solomon and Hopke (2008a, 2008b).

- Direct transfer of UF particles to the brain via olfactory nerves and to other organs via the lungs through the blood raises the need to better understand the chemical, physical, and toxicological characteristics of UF PM.
- Newly identified dendritic cells (see Figure 3) that bridge across the air-blood barrier of the lung may affect respiratory responses to inhaled pollutants and help explain interspecies differences in response to pollutants.

SQ5. Mechanisms of action and biomarkers of exposure and effects

- Oxidative stress and inflammation resulting from the generation of ROS appear to be closely linked to adverse cardiovascular and respiratory effects. A number of biomarkers have been identified that relate to oxidative stress and inflammation. Validation of these biomarkers will help reduce uncertainties in source-to-health effects relationships. The following are examples of pollutants believed to generate ROS:
  - transition metals (e.g., V, Ni, Mn, Fe, Ni, Co) and/or the specific oxidation state of the transition metal;
  - various carbonaceous components, in particular EC and certain organic species; and
  - different fractions of diesel exhaust particles.
- New mechanisms for the movement of pollutants to other body systems are being identified. For example, exposure to particles was associated with a decrease in transendothelial electrical resistance that may affect the integrity of the alveolar-capillary barrier, allowing translocation of particles from the lungs to the bloodstream.
- Mechanistic evidence is developing that better links air pollution exposures with altered immune function, resulting in increased allergic response and asthma and inducing epigenetic changes that affect the regulation of the airway immune system.
- Uncertainty remains in the synergism among pollutants that, once inhaled, might result in more severe responses than the separate pollutants themselves.

SQ6. Susceptible populations

- Susceptibility to adverse health effects is influenced by biological factors such as age, gender, or preexisting disease that increase risk due to exposure to air pollution. In addition, vulnerability related to risk for greater exposure to health effects is affected by environmental factors such as poor diet, lack of access to health care, or increased exposure to air pollution such as living near a major roadway. Distinguishing between these factors, as well as confounding, as noted later, is important for study design to obtain the most accurate estimate of causal associations between air pollutants and human health.
- Individuals with existing disease, either cardiovascular or respiratory, are at increased risk of adverse effects from air pollution compared to healthy people. Diabetes also appears to enhance susceptibility to the acute effects of air pollution. The related problems of obesity and metabolic syndrome also are being studied.
- An increasing number of studies suggest that air pollution has a greater impact on public health among certain racial groups and those with lower SES. Determining whether these effects are due to greater exposure or greater sensitivity to air pollution would facilitate more effective policy decisions.
- A variety of studies have shown that asthma exacerbation increases with increased air pollution.
  - Evidence is sufficient to support a causal association between traffic-related air pollution and exacerbation of asthma in children.

- Children sensitive to a variety of allergens may be more sensitive to a worsening of their asthmatic condition by air pollution than those who are not sensitive to these and other tested allergens.
- While results are inconclusive, some studies of asthmatics have shown seasonal variation in response to air pollution, with ambient ozone levels more strongly associated with asthma emergency room visits by children in the spring and $PM_{2.5}$ in the spring and summer.

- Age may indirectly affect susceptibility through the presence of disease. The risk of PM-related respiratory effects appears to be greater for children than adults, and those adults 65 and older experience greater risk of PM-related cardiovascular morbidity.
- Animal studies indicate that air pollution may affect perinatal health, resulting in, for example, preterm birth, low birth weight, or birth defects.
- Genetic makeup may influence a person's response to exposure to air pollutants, possibly either increasing or reducing susceptibility. Studies of candidate genes suggest that a variety of genes may influence susceptibility to air pollution health effects.
- A relatively new area of study called epigenetics describes genetic changes other than to the genetic code that may also influence susceptibility to air pollution.

SQ7. Confounding or other factors

- A distortion in the estimate of the effect of a pollutant on health effects can result from not properly identifying and controlling for confounders, which are independent factors associated with the pollutant(s) or effect(s) being studied. Control of confounding factors remains a major challenge for air pollution and health studies because they are not often recognized, included in, and/or correctly formulated in air pollution health studies.
- Clear definition of hypotheses to differentiate confounders from variables of interest (e.g., effect modifiers, causal intermediates) is essential for accurate estimation of causal associations between air pollutant agents and human health. Directed acyclic graphs, which provide a method to state hypotheses and probability-based rules to identify which variables are confounders, should be used whenever possible. Lack of such a strategy could lead to an ineffective emissions management strategy.
- How confounders, susceptibility factors, and mediators are considered in a study can influence results and the basis for policy decisions.
  - The distinction between confounders and susceptibility factors depends on the frame of reference of the study: Is the focus on the effects of an individual pollutant or a group of pollutants? Mixtures of pollutants from a variety of sources may be considered confounders if the study is focused on the effect of a particular source or type of source.
  - Confounders also need to be distinguished from mediators, which are defined as consequences of exposure that, in turn, lead to the health outcome under study.
  - Study designs also must account for colinearity among pollutants from a common source or sources.
  - The validity of estimates of health impacts from exposures depends on the estimation of measurement errors and the incorporation of these errors into analyses.

- More dense spatiotemporal data will be required to support health-based standards as they move closer to background levels of pollutant mixtures.

- More sophisticated tools are beginning to be used in air pollution studies to control for the effects of confounding factors, but a discussion of these methods was outside the scope of this Conference.

SQ8. Accountability

- It has been demonstrated that reducing air pollution levels reduces adverse health effects from air pollution. Results presented at the Conference reaffirm that a decrease of 10 $\mu g/m^3$ of $PM_{2.5}$ can decrease morbidity and mortality and increase life expectancy up to 1.5 years. These results provide direct confirmation of population health benefits resulting from declines in air pollution and support the value of effective air pollution control policies.
- Insufficient monitoring (space, time, and components) and uncertainty in air quality modeling results in inadequate exposure and dose estimates, limiting our ability to assess the effectiveness of air pollution controls.
- It is difficult to quantify uniquely the health benefits from multiple emission reductions implemented over extended time periods, e.g., the Clean Air Act regulations in the U.S. Other variables such as SES, health risk factors, and weather that may influence health also change over time.
- Even when step change reductions occur in exposure and health improvements are noted, for example, during the Atlanta and Beijing Olympics or the Utah Valley steel mill strike, significant challenges still exist in linking specific sources or pollutants to health effect(s) because multiple sources can be reduced at once and any single source emits multiple pollutants. In addition, health data may be insufficient to draw definitive conclusions because of the short duration of the emissions reduction period or limited population size.
- While analyses that apply concentration-response functions obtained from epidemiological studies to estimate health impacts of air pollution interventions may be helpful in providing information on what might be expected, they do not substitute for direct assessment of health impacts.
- Effects on air quality due to targeted pollutant reductions need to be well understood so that reducing one component does not cause an increase in another with adverse health implications. This also emphasizes the need for a multipollutant approach to air pollution study and emissions control.

SQ9 Concluding remarks

Scientific evidence is fundamental to sound public policy development. Communication between the scientific and regulatory communities with regard to ambient air quality standards and regulatory approaches within or outside the current regulatory framework is critical to developing policies to reduce the human health risks due to air pollution. Together with a greater focus on multiple pollutants (i.e., gases and particulate matter mass, components, and physical properties), interactions among disciplines cutting across the source-to-health effects continuum and among measurement and modeling scientists will help reduce uncertainty and provide more confident direction for policy decisions.

At the same time that greater emphasis is being placed on multipollutant approaches and studying the effects of pollutant mixtures from specific types of sources, interest is increasing in identifying specific toxic components or characteristics of PM and/or gaseous pollutants that are the primary determinants of health effects

from the air pollution mixture. To allow improved source apportionment and exposure estimates for use in epidemiological studies, measurement methods and models must more accurately estimate individual exposures in both time and space, thus the need to continue to refine these approaches. Community-based monitoring systems to supplement routine compliance measurements may become increasingly important, along with methods to track individual exposure using new GPS and sensor technologies, and refined capabilities to model concentrations of multiple pollutants, including individual PM species, to small areas across a region. New U.S. requirements for near-roadway monitoring provide an opportunity to clarify the spatial effects of motor vehicle emissions and to better understand near-roadway exposures. Further development, validation, and application of continuous methods will help fill temporal gaps currently experienced in routine networks.

Agencies must consider the needs of health researchers in designing air quality monitoring networks. The effects of air pollution on public health and on global climate change are linked by overlapping variables of interest (e.g., EC; BC; biologically active chemicals such as PAHs; sulfate; metals such as Ni, V, Fe, Cu; markers for roadway dusts such as Si; CO_2; primary and secondary organics; ozone). Related pollutants must be monitored across multiple spatial and temporal scales to integrate studies of their effects ranging from microenvironmental to global and from less than an hour to decades.

More information also is needed regarding the susceptibility and vulnerability of various populations and the influences of confounding factors to hide or enhance effects. Policy is improved by a greater understanding of both the mechanisms that link pollution to adverse health effects (e.g., from toxicology and human panel studies) and the impact of pollutants on populations (from population-based epidemiology). Variation in exposure and susceptibility within urban areas also is an important area of study.

Policy decisions of the past have reduced air pollution and improved public health, even in the face of significant population growth over the last 30 years. Improved scientific understanding of the links between air pollution and health effects will help both to sustain this progress and to improve it by better targeting the most toxic emissions.

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KEY TERMS

AAAR	American Association for Aerosol Research
ACS	American Cancer Society
AD	aerodynamic diameter
AER	air exchange rate
AERMOD	American Meteorological Society/EPA Regulatory Model
AOD	aerosol optical depth
BAD	brachial artery diameter
BAL	bronchoalveolar lavage
BALF	bronchoalveolar lavage fluid
BC	black carbon
CAPs	concentrated ambient particles
CMAQ	Community Multiscale Air Quality model
CMB	chemical mass balance
COD	coefficient of determination
CRF	concentration–response function
CV	cardiovascular
DEARS	Detroit Exposure and Aerosol Research Study
DTT	dithiothreitol
EBC	exhaled breath condensate
EC	elemental carbon
ED	emergency department
EF	effect factor
ETC	electron transport chain
F_{eNO}	fractional exhaled NO
GST	glutathione-S transferase
HAP	hazardous air pollutant

HEI	Health Effects Institute
HRV	heart rate variability
ICRP	International Commission on Radiological Protection
iF	intake fraction
ISA	Integrated Science Assessment
ITR	integrated transdisciplinary research
LBNL	Lawrence Berkeley National Laboratory
LEZ	low emission zone
LUR	land-use regression
MICA	Mechanistic Indicators of Childhood Asthma
NAAQS	National Ambient Air Quality Standards
NO_x	nitrogen oxides
NRC	National Research Council
OC	organic carbon
ORD	Office of Research and Development
OVA	ovalbumin
PAH	polycyclic aromatic hydrocarbon
PCA	principal components analysis
PM	particulate matter
$PM_{0.1}$	ultrafine particles usually considered less than 0.1 μm AD; also referred to as UF
PM_{10}	particles in the size range equal to or less than a nominal 10 μm AD
$PM_{2.5}$	fine particles in the size range less than a nominal 2.5 μm AD; also referred to as PMf
PMc	coarse particles in the size range between a nominal 2.5 μm and a nominal 10 μm AD
PMf	fine particles in the size range less than a nominal 2.5 μm AD; also referred to as $PM_{2.5}$
PMF	positive matrix factorization
PMN	polymorphonuclear neutrophil
POA	primary organic aerosol
RH	relative humidity

ROFA	residual oil fly ash
ROS	reactive oxygen species
RT-PCR	reverse transcription polymerase chain reaction
SADI	surface area deposition index
SES	socioeconomic status
SNP	single nucleotide polymorphism
SOA	secondary organic aerosol
SQ	science question
SRM	Standard Reference Material
T	temperature
TBARS	thiobarbituric reactive substance
TOA	thermal-optical analysis
UF	ultrafine particles usually considered less than 0.1 μm AD; also referred to as $PM_{0.1}$
USC	University of Southern California
UV	ultraviolet
VOC	volatile organic compound
WSOC	water-soluble organic carbon

REFERENCES

Alexander DJ, Collins CJ, Coombs DW, Gilkison IS, Hardy CJ, Healey G, Karantabias G, Johnson N, Karlsson A, Kilgour JD, McDonald P (2008) Association of Inhalation Toxicologists (AIT) Working Party recommendation for standard delivered dose calculation and expression in nonclinical aerosol inhalation toxicology studies with pharmaceuticals. Inhal Toxicol 20:1179–1189.

Allen DT, Turner JR (2008) Transport of atmospheric fine particulate matter: part 1 - findings from recent field programs on the extent of regional transport within North America. J Air Waste Manage Assoc 58:254–264.

Anderson, HR (2009) Air pollution and mortality: a history. Atmos Environ 43:142–152. (doi:10.1016/j.atmosenv.2008.09.026)

Bailey MR, Ansoborlo E, Guilmette RA, Paquet F (2007) Updating the ICRP human respiratory tract model. Radiat Prot Dosimetry 127 (1-4): 31-34. doi: 10.1093/rpd/ncm249

Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, Armstrong B, Brunekreef B (2008) Long-term exposure to traffic-related air pollution and lung cancer risk. Epidemiol 19:702–710.

Bell ML, Ebisu K, Peng RD, Samet JM, Dominici F (2009) Hospital admissions and chemical composition of fine particle air pollution. Am J Respir Crit Care Med 179:1115–1120.

2429 Block ML, Calderón-Garcidueñas L (2009) Air pollution: mechanisms of neuroinflammation and CNS disease.
2430 Trends Neurosci 32(9):506–516.
2431 Braniš M, Vyškovská J, Malý M, Hovorka J (2010) Association of size-resolved number concentrations of
2432 particulate matter with cardiovascular and respiratory hospital admissions and mortality in Prague, Czech
2433 Republic. Inhal Toxicol 22(S2):21–28.
2434 Brauer M (2010) How much, how long, what, and where: air pollution exposure assessment for epidemiologic
2435 studies of respiratory disease. Proc Am Thorac Soc 7:111–115.
2436 Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV,
2437 Mittleman MA, Peters A, Siscovick D, Smith SC Jr, Whitsel L, Kaufman JD, on behalf of the American
2438 Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular
2439 Disease, and Council on Nutrition, Physical Activity and Metabolism (2010) Particulate matter air pollution
2440 and cardiovascular disease: an update to the scientific statement from the American Heart Association.
2441 Circulation 121:2331–2378.
2442 Brown JS, Wilson WE, Grant LD (2005) Dosimetric comparisons of particle deposition and retention in rats and
2443 humans. Inhal Toxicol 17:355–385.
2444 Burke JM, Zufall MJ, Özkaynak H (2001) A population exposure model for particulate matter: case study results for
2445 $PM_{2.5}$ in Philadelphia, PA. J Expo Anal Environ Epidemiol 11:470–489.
2446 Burnett RT, Bartlett S, Jessiman B, Blagden P, Samson PR, Cakmak S, Steib D, Raizenne M, Brook JR, Dann T
2447 (2005) Measuring progress in the management of ambient air quality: the case for population health. J
2448 Toxicol Environ Health A 68(13–14):1289–1300.
2449 Buset KC, Evans GJ, Leaitch WR, Brook JR, Toom-Sauntry D (2006) Use of advanced receptor modelling for
2450 analysis of an intensive 5-week aerosol sampling campaign. Atmos Environ 40(S2):482–499.
2451 Cahill TA, Cahill TM, Barnes DE, Spada NJ, Miller R (2011) Inorganic and organic aerosols downwind of
2452 California's Roseville Railyard. Aerosol Sci Technol 45(9):1049–1059.
2453 Canagaratna MR, Jayne JT, Jimenez JL, Allan JD, Alfarra MR, Zhang Q, Onasch TB, Drewnick F, Coe H,
2454 Middlebrook A, Delia A, Williams LR, Trimborn AM, Northway MJ, DeCarlo PF, Kolb CE, Davidovits P,
2455 Worsnop DR (2007) Chemical and microphysical characterization of ambient aerosols with the Aerodyne
2456 Aerosol Mass Spectrometer. Mass Spec Rev 26:185–222.
2457 Chen LC, Lippmann M (2009) Effects of metals within ambient air particulate matter (PM) on human health. Inhal
2458 Toxicol 21:1–31.
2459 Chow JC (1995) Measurement methods to determine compliance with ambient air quality standards for suspended
2460 particles. J Air Waste Manage Assoc 45:320–382.
2461 Chow JC, Yu JZ, Watson JG, Ho SSH, Bohannan TL, Hays MD, Fung KK (2007) The application of thermal
2462 methods for determining chemical composition of carbonaceous aerosols: a review. J Environ Sci Health
2463 Part A 42(11):1521–1541.

2464 Chow JC, Doraiswamy P, Watson JG, Chen L-WA, Ho SSH, Sodeman DA (2008) Advances in integrated and
2465 continuous measurements for particle mass and chemical composition. J Air Waste Manage Assoc
2466 58(2):141-163.
2467 Chow JC, Watson JG, Chen L-WA, Rice J, and Frank NH (2010) Quantification of $PM_{2.5}$ organic carbon sampling
2468 artifacts in U.S. networks. Atmos Chem Phys 10(12):5223–5239.
2469 Chuang K-J, Chan C-C, Su T-C, Lin L-Y, Lee C-T (2007) Associations between particulate sulfate and organic
2470 carbon exposures and heart rate variability in patients with or at risk for cardiovascular diseases. J Occup
2471 Environ Med 49:610–617.
2472 Chuang KJ, Coull BA, Zanobetti A, Suh H, Schwartz J, Stone PH, Litonjua A, Speizer FE, Gold DR (2008)
2473 Particulate air pollution as a risk factor for ST-segment depression in patients with coronary artery disease.
2474 Circulation 118(13):1314–1320.
2475 Clancy L, Goodman P, Sinclair H, Dockery DW (2002) Effect of air-pollution control on death rates in Dublin,
2476 Ireland: an intervention study. Lancet 360(9341):1210–1214.
2477 Clarke RW, Coull B, Reinisch U, Catalano P, Killingsworth CR, Koutrakis P, Kavouras I, Murthy GG, Lawrence J,
2478 Lovett E, Wolfson JM, Verrier RL, Godleski JJ (2000) Inhaled concentrated ambient particles are
2479 associated with hematologic and bronchoalveolar lavage changes in canines. Environ Health Perspect
2480 108:1179–1187.
2481 Cohen AJ, Pope CA 3rd (1995) Lung cancer and air pollution. Environ Health Perspect 103(Suppl 8):219–224.
2482 Cohen Hubal EA, Richard AM, Shah I, Gallagher J, Kavlock R, Blancato J, Edwards SW (2010) Exposure science
2483 and the U.S. EPA National Center for Computational Toxicology. J Expo Sci Environ Epidemiol 20:231–
2484 236.
2485 Craig L, Brook JR, Chiotti Q, Croes B, Gower S, Hedley A, Krewski D, Krupnick A, Krzyanowski M, Moran MD,
2486 Pennell W, Samet JM, Schneider J, Shortreed J, Williams M (2008) Air pollution and public health: a
2487 guidance document for risk managers. J Toxicol Environ Health A 71:588–698.
2488 Crouse DL, Goldberg MS, Ross NA (2009) A prediction-based approach to modelling temporal and spatial
2489 variability of traffic-related air pollution in Montreal, Canada. Atmos Environ 43(32):5075–5084.
2490 doi:10.1016/j.atmosenv.2009.06.040.
2491 Cuevas AK, Liberda EN, Gillespie PA, Allina J, Chen LC (2010) Inhaled nickel nanoparticles alter vascular
2492 reactivity in C57BL/6 mice. Inhal Toxicol 22(S2):100–106.
2493 Delfino RJ, Staimer N, Tjoa T, Polidori A, Arhami M, Gillen DL, Kleinman MT, Vaziri ND, Longhurst J, Zaldivar
2494 F, Sioutas C (2008) Circulating biomarkers of inflammation, antioxidant activity, and platelet activation are
2495 associated with primary combustion aerosols in subjects with coronary artery disease. Environ Health
2496 Perspect 116:898–906.
2497 Delfino RJ, Staimer N, Tjoa T, Gillen DL, Polidori A, Arhami M, Kleinman MT, Vaziri ND, Longhurst J, Sioutas C
2498 (2009) Air pollution exposures and circulating biomarkers of effect in a susceptible population: clues to
2499 potential causal component mixtures and mechanisms. Environ Health Perspect 117:1232–1238.

Demerjian KL, Mohnen VA (2008) Synopsis of the temporal variation of particulate matter composition and size. J Air Waste Manage Assoc 58(2):216–233.

Dominici F, Peng RD, Ebisu K, Zeger SL, Samet JM, Bell ML (2007) Does the effect of PM_{10} on mortality depend on PM nickel and vanadium content? A reanalysis of the NMMAPS data. Environ Health Perspect 115:1701–1703.

Dominici F, Peng RD, Barr CD, Bell ML (2010) Protecting human health from air pollution: shifting from a single-pollutant to a multipollutant approach. Epidemiol 21:187–194.

Dubowsky SD, Suh H, Schwartz J, Coull BA, and Gold DR (2006) Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. Environ Health Perspect 114:992–998.

Elder A, Oberdörster G (2006) Translocation and effects of ultrafine particles outside of the lung. Clin Occup Environ Med 5(4):785–796.

EPA (2003) Framework for cumulative risk assessment. Risk Assessment Forum, EPA/630/P-02/001F. U.S. Environmental Protection Agency, Washington, DC. http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=36941. Accessed 19 July 2011

EPA (2008a) Ambient air quality monitoring and health research: summary of April 16-17, 2008, workshop to discuss key issues. U.S. Environmental Protection Agency, Office of Research and Development and Office of Air Quality Planning and Standards, Research Triangle Park, NC.

EPA (2008b) Clean air research multi-year plan 2008–2012 (EPA 620R-08/001). U.S. Environmental Protection Agency, Office of Research and Development, Research Triangle Park, NC. http://www.epa.gov/research/npd/pdfs/Air-MYP-narrative-final.pdf. Accessed 19 July 2011

EPA (2009a) Integrated science assessment for particulate matter (EPA/600/R-08/139F). U.S. Environmental Protection Agency, Office of Research and Development, Research Triangle Park, NC. http://www.epa.gov/ncea/pdfs/partmatt/Dec2009/PM_ISA_full.pdf. Accessed 19 July 2011

EPA (2009b) Susceptible populations. U.S. Environmental Protection Agency, Office of Research and Development, Research Triangle Park, NC. http://www.epa.gov/nerl/goals/health/populations.html. Accessed 19 July 2011

Faiola C, Johansen AM, Rybka S, Nieber A, Thomas C, Bryner S, Johnston J, Engelhard M, Nachimuthu P, Owens KS (2011) Ultrafine particulate ferrous iron and anthracene associations with mitochondrial dysfunction. Aerosol Sci Technol 45(9):1109–1122.

Federal Register (2006) National ambient air quality standards for particulate matter: final rule, 40 CFR Part 50 *Federal Register* 71(200):61144. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, NC. Part 50 available at http://www.gpo.gov/fdsys/pkg/FR-2006-10-17/pdf/06-8477.pdf#page=1. Accessed 19 July 2011

Fehsenfeld F, Hastie D, Chow J, Solomon P (2004) Particle and gas measurements. In: McMurry P, Shepherd M, Vickery J (eds) Particulate matter science for policy makers: a NARSTO assessment, Cambridge University: Cambridge, UK, pp 159–189.

2537 Finlay WH, Martin AR (2008) Recent advances in predictive understanding of respiratory tract deposition. J Aerosol
2538 Med Pulm Drug Deliv 21:189–206.
2539 Fischer P, Hoek G, Brunekreef B, Verhoeff A, van Wijnen J (2003) Air pollution and mortality in The Netherlands:
2540 are the elderly more at risk? Eur Respir J 21(Suppl 40):34s–38s.
2541 Frampton MW, Ghio AJ, Samet JM, Carson JL, Carter JD, Devlin RB (1999) Effects of aqueous extracts of PM_{10}
2542 filters from the Utah Valley on human airway epithelial cells. Am J Physiol 277:L960–L967.
2543 Franklin M, Koutrakis P, Schwartz J (2008) The role of particle composition on the association between $PM_{2.5}$ and
2544 mortality. Epidemiol 19:680–689.
2545 Freney EJ, Heal MR, Donovan RJ, Mills NL, Donaldson K, Newby DE, Fokkens PH, Cassee FR (2006) A single-
2546 particle characterization of a mobile Versatile Aerosol Concentration Enrichment System for exposure
2547 studies. Part Fibre Toxicol 24(3):8. doi:10.1186/1743-8977-3-8
2548 Friedman MS, Powell KE, Hutwagner L, Graham LM, Teague WG (2001) Impact of changes in transportation and
2549 commuting behaviors during the 1996 Summer Olympic Games in Atlanta on air quality and childhood
2550 asthma. J Am Med Assoc 285:897–905.
2551 Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Kuenzli N, Lurmann F,
2552 Rappaport E, Margolis H, Bates D, Peters J (2004) The effect of air pollution on lung development from 10
2553 to 18 years of age. N Engl J Med 351:1057–1067.
2554 Gehr P, Geiser M, Im Hof V, Schurch S (2000) Surfactant-ultrafine particle interactions: what we can learn from
2555 PM 10 studiesPhil Trans R Soc Lond A 358:2707-2718.
2556 Gent JF, Koutrakis P, Belanger K,Triche E, Holford TR, Bracken MB, Leaderer BP (2009). Symptoms and
2557 medication use in children with asthma and traffic-related sources of fine particle pollution. Environ Health
2558 Perspect 117:1168–1174.
2559 Gerlofs-Nijland ME, van Berlo D, Cassee FR, Schins RP, Wang K, Campbell A (2010) Effect of prolonged
2560 exposure to diesel engine exhaust on proinflammatory markers in different regions of the rat brain. Part
2561 Fibre Toxicol 17(7):12. doi:10.1186/1743-8977-7-12
2562 Ghio AJ, Kim C, Devlin RB (2000) Concentrated ambient air particles induce mild pulmonary inflammation in
2563 healthy human volunteers. Am J Respir Crit Care Med 162:981–988.
2564 Grahame TJ, Schlesinger RB (2007) Health effects of airborne particulate matter: do we know enough to consider
2565 regulating specific particle types or sources? Inhal Toxicol 19:457–481.
2566 Grahame TJ, Schlesinger RB (2010) Cardiovascular health and particulate vehicular emissions: a critical evaluation
2567 of the evidence. Air Qual Atmos Health 3(1):3–27.
2568 Greenland S (1980) The effect of misclassification in the presence of covariates. Am J Epidemiol 112:564–569.
2569 Greenbaum D, Shaikh R (2010) First steps toward multipollutant science for air quality decisions. Epidemiol
2570 21:195–197.
2571 Gupta P, Christopher SA, Wang J, Gehrig R, Lee Y, and Kumar N (2006) Satellite remote sensing of particulate
2572 matter and air quality assessment over global cities. Atmos Environ 40:5880–5892.

Gurgueira SA, Lawrence J, Coull B, Krishna Murthy GG, Gonzalez-Flecha B (2002) Rapid increases in the steady-state concentration of reactive oxygen species in the lungs and heart after particulate air pollution inhalation. Environ Health Perspect 110:749–755.

Hedley AJ, Wong CM, Thach TQ, Ma S, Lam TH, Anderson HR (2002) Cardiorespiratory and all-cause mortality after restrictions on sulphur content of fuel in Hong Kong: an intervention study. Lancet 360:1646–1652.

Hedley AJ, Chau PYK, Wong CM (2004) The change in sub-species of particulate matter [PM_{10}] before and after an intervention to restrict sulphur content of fuel in Hong Kong. Poster presented at Better Air Quality/Asian Development Bank Meeting, Agra, India.

HEI (2002) Understanding the health effects of the particulate matter mix: progress and next steps. HEI Perspectives. Health Effects Institute, Boston, MA, USA.

HEI (2003) Assessing health impact of air quality regulations: concepts and methods for accountability research. Communication 11. Executive summary, HEI Accountability Working Group. Health Effects Institute, Boston, MA.

HEI (2010) Traffic-related air pollution: A critical review of the literature on emissions, exposure, and health effects. Special Report 17. Health Effects Institute, Boston, MA, USA. http://pubs.healtheffects.org/view.php?id=334. Accessed 19 July 2011.

Hering S, Cass G (1999) The magnitude of bias in the measurement of $PM_{2.5}$ arising from volatilization of particulate nitrate from Teflon filters. J Air Waste Manage Assoc 49(6):725–733.

Hidy GM, Pennell WT (2010) Multipollutant air quality management. J Air Waste Manage Assoc 60:645–674.

Hoff RM, Christopher SA (2009) Remote sensing of particulate matter air pollution from space: have we reached the promised land? J Air Waste Manage Assoc 59:642–675. doi:10.3155/1047-3289.59.6.642

Holguin F (2008) Traffic, outdoor air pollution, and asthma. Immunol Allergy Clin North Am 28:577–588.

ICRP (1994) Human respiratory tract model for radiological protection, Publication 66. International Commission on Radiological Protection, Task Group of Committee 2. Pergamon Press, New York, USA.

ICRP (1995) Human respiratory tract model for radiological protection: a report of a task group of the International Commission on Radiological Protection. Ann ICRP 24:1–482.

Ito K, Christensen WF, Eatough DJ, Henry RC, Kim E, Laden F, Lall R, Larson TV, Neas L, Hopke PK, Thurston GD (2006) PM source apportionment and health effects: 2. an investigation of intermethod variability in associations between source-apportioned fine particle mass and daily mortality in Washington, DC. J Expo Sci Environ Epidemiol 16(4):300–310.

Jacobs L, Emmerechts J, Mathieu C, Hoylaerts MF, Fierens F, Hoet PH, Nemery B, Nawrot TS (2010) Air pollution related prothrombotic changes in persons with diabetes. Environ Health Perspect 118:191–196.

Jalava PI, Tapanainen M, Kuuspalo K, Markkanen A, Hakulinen P, Happo MS, Pennanen AS, Ihalainen M, Yli-Pirilä P, Makkonen U, Teinilä K, Mäki-Paakkanen J, Salonen RO, Jokiniemi J, Hirvonen MR (2010) Toxicological effects of emission particles from fossil- and biodiesel-fueled diesel engine with and without DOC/POC catalytic converter. Inhal Toxicol 22(S2):48–58.

Janssen NAH, Schwartz J, Zanobetti A, Suh HH (2002) Air conditioning and source-specific particles as modifiers of the effect of PM_{10} on hospital admissions for heart and lung disease. Environ Health Perspect 110:43–49.

Jarabek AM, Asgharian B, Miller FJ (2005) Dosimetric adjustments for interspecies extrapolation of inhaled poorly soluble particles. Inhal Toxicol 17:317–334.

Jerrett M, Newbold KB, Burnett RT, Thurston G, Lall R, Pope CA 3rd, Ma R, De Luca P, Thun M, Calle J, Krewski D. (2007) Geographies of uncertainty in the health benefits of air quality improvements. Stochastic Environ Res Risk Assess 21(5):511–522.

Kane DB, Asgharian B, Price OT, Rostami A, Oldham MJ (2010) Effect of smoking parameters on the particle size distribution and predicted airway deposition of mainstream cigarette smoke. Inhal Toxicol 22:199–209.

Kaskaoutis DG, Kambezidis HD, Hatzianastassiou N, Kosmopoulos PG, Badarinath KVS (2007) Aerosol climatology: dependence of the Angstrom exponent on wavelength over four AERONET sites. Atmos Chem Phys Discuss 7:7347–7397.

Kelly FJ, Kelly J (2009) London air quality: a real world experiment in progress. Biomarkers 14(Suppl 1):5–11.

Kim SY, Sheppard L, Kim H (2009) Health effects of long-term air pollution: influence of exposure prediction methods. Epidemiol 20(3):442–450.

Kleinman MT, Sioutas C, Froines JR, Fanning E, Hamade A, Mendez L, Meacher D, Oldham M (2007) Inhalation of concentrated ambient particulate matter near a heavily trafficked road stimulates antigen-induced airway responses in mice. Inhal Toxicol 19(Suppl 1):117–126.

Kleinstreuer C, Zhang Z (2010) Airflow and particle transport in the human respiratory system. Ann Rev Fluid Mech 42:301–334.

Kodavanti UP, Schladweiler MC, Ledbetter AD, Watkinson WP, Campen MJ, Winsett DW, Richards JR, Crissman KM, Hatch GE, Costa DL (2000) The spontaneously hypertensive rat as a model of human cardiovascular disease: evidence of exacerbated cardiopulmonary injury and oxidative stress from inhaled emission particulate matter. Toxicol Appl Pharmacol 164:250–263.

Krewski D (2009) Evaluating the effects of ambient air pollution on life expectancy. N Engl J Med 360(4):413–415.

Krewski D, Jerrett M, Burnett RT, Ma R, Hughes E, Shi Y, Turner MC, Pope CA III, Thurston G, Calle EE, Thun MJ (2009) Extended follow-up and spatial analysis of the American Cancer Society Study linking particulate air pollution and mortality. Report 140. Health Effects Institute, Boston, MA, USA.

Kreyling WG, Semmler-Behnke M, Moller W (2006) Health implications of nanoparticles. J Nanoparticle Res 8:543–562.

Kumar N, Chu AD, Foster AD, Peters T, Willis R (2011) Satellite remote sensing for developing time and space resolved estimates of ambient particulate in Cleveland, OH. Aerosol Sci Technol 45(9):1090–1108.

Laden F, Schwartz J, Speizer FE, Dockery DW (2006) Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. Am J Respir Crit Care Med 173:667–672.

Langrish JP, Mills NL, Chan JK, Leseman DL, Aitken RJ, Fokkens PH, Cassee FR, Li J, Donaldson K, Newby DE, Jiang L (2009) Beneficial cardiovascular effects of reducing exposure to particulate air pollution with a simple facemask. Part Fibre Toxicol 13:6–8.

Lanki T, de Hartog JJ, Heinrich J, Hoek G, Janssen NAH, Peters A, Stolzel M, Timonen KL, Vallius M, Vanninen E, Pekkanen J (2006) Can we identify sources of fine particles responsible for exercise-induced ischemia on days with elevated air pollution? The ULTRA study. Environ Health Perspect 114:655–660.

Lanz VA, Alfarra MR, Baltensperger U, Buchmann B, Hueglin C, Prevot ASH (2006) Source apportionment of submicron organic aerosols at an urban site by linear unmixing of aerosol mass spectra. Atmos Chem Phys Discuss 6:11681–11725.

Liberda EN, Cuevas AK, Gillespie PA, Grunig G, Qu Q, Chen LC (2010) Exposure to inhaled nickel nanoparticles causes a reduction in number and function of bone marrow endothelial progenitor cells. Inhal Toxicol 22(S2):95–99.

Lipfert FW, Baty JD, Miller JP, Wyzga RE (2006) $PM_{2.5}$ constituents and related air quality variables as predictors of survival in a cohort of U.S. military veterans. Inhal Toxicol 18:645–657.

Lipfert FW, Wyzga RE, Baty JD, Miller JP (2009) Air pollution and survival within the Washington University-EPRI Veterans Cohort: risks based on modeled estimates of ambient levels of hazardous and criteria air pollutants. J Air Waste Manage Assoc 59:473–489.

Lippmann M (2009) Semi-continuous speciation analyses for ambient air particulate matter: an urgent need for health effects studies. J Expos Sci Environ Epidemiol 19:235–247.

Lippmann M, Chen LC (2009) Health effects of concentrated ambient air particulate matter (CAPs) and its components. Crit Rev Toxicol 39(10):865–913.

Lippmann M, Hwang JS, Maciejczyk P, Chen LC (2005) PM source apportionment for short-term cardiac function changes in ApoE-/- mice. Environ Health Perspect 113:1575–1579.

Lippmann M, Ito K, Hwang JS, Maciejczyk P, Chen LC (2006) Cardiovascular effects of nickel in ambient air. Environ Health Perspect 114:1662–1669.

Liu Y, Koutrakis P, Kahn R (2007a) Estimating fine particulate matter component concentrations and size distributions using satellite-retrieved fractional aerosol optical depth: part 1 - method development. J Air Waste Manage Assoc 57:1351–1359.

Liu Y, Koutrakis P, Kahn R, Turquety S, Yantosca RM (2007b) Estimating fine particulate matter component concentrations and size distributions using satellite-retrieved fractional aerosol optical depth: part 2 - a case study J Air Waste Manage Assoc 57:1360–1369.

Liu L, Ruddy TD, Dalipaj M, Szyszkowicz M, You H, Poon R, Wheeler A, Dales R. (2007c) Influence of personal exposure to particulate air pollution on cardiovascular physiology and biomarkers of inflammation and oxidative stress in subjects with diabetes. J Occup Environ Med 49:258–265.

Liu Y, Schichtel BA, Koutrakis P (2009a) Estimating particle sulfate concentrations using MISR retrieved aerosol properties. IEEE Journal of Selected Topics in Applied Earth Observations and Remote Sensing. 2:176–184.

Liu Y, Paciorek CJ, Koutrakis P (2009b) Estimating regional spatial and temporal variability of $PM_{2.5}$ concentrations using satellite data, meteorology, and land use information. Environ Health Perspect 117:886–892.

2683 Maejima K, Tamura K, Nakajima T, Taniguchi Y, Saito S, Takenaka H (2001) Effects of the inhalation of diesel
2684 exhaust, Kanto loam dust, or diesel exhaust without particles on immune responses in mice exposed to
2685 Japanese cedar (Cryptomeria Japonica) pollen. Inhal Toxicol 13:1047–1063.
2686 Maimone F, Turpin BJ, Solomon P, Meng Q, Robinson AL, Subramanian R, Polidori A (2011) Correction methods
2687 for organic carbon artifacts when using quartz-fiber filters in large particulate matter monitoring networks:
2688 the regression method and other options. J. Air Waste Manage Assoc 61(6):696–710.
2689 Mauderly JL, Chow JC (2008) Health effects of organic aerosols. Inhal Toxicol 20:257–288.
2690 Mauderly JL, Burnett RT, Castillejos M, Özkaynak H, Samet JM, Stieb DM, Vedal S, Wyzga RE (2010) Is the air
2691 pollution health research community prepared to support a multipollutant air quality management
2692 framework? Inhal Toxicol 22(S1):1–19.
2693 Maciejczyk P, Zhong M, Lippmann M, Chen LC (2010) Oxidant generation capacity of source-apportioned $PM_{2.5}$.
2694 Inhal Toxicol 22(S2):29–36.
2695 McConnell R, Berhane K, Gilliland F, Molitor J, Thomas D, Lurmann F, Avol E, Gauderman WJ, Peters JM (2003)
2696 Prospective study of air pollution and bronchitic symptoms in children with asthma. Am J Respir Crit Care
2697 Med 168(7):790–797.
2698 McCreanor J, Cullinan P, Nieuwenhuijsen MJ, Stewart-Evans J, Malliarou E, Jarup L, Harrington R, Svartengren M,
2699 Han IK, Ohman-Strickland P, Chung KF, Zhang J (2007) Respiratory effects of exposure to diesel traffic in
2700 persons with asthma. N Engl J Med 357:2348–2358.
2701 Méndez LB, Gookin G, Phalen RF (2010) Inhaled aerosol particle dosimetry in mice: A review. Inhal Toxicol
2702 22(S2):15–20.
2703 Meyer T, Müllinger B, Sommerer K, Scheuch G., Brand P, Beckmann H, Haussinger K, Weber N, Siekmeier R
2704 (2003) Pulmonary deposition of monodisperse aerosols in patients with chronic obstructive pulmonary
2705 disease. Exp Lung Res 29:475–484.
2706 Mills NL, Robinson SD, Fokkens PHB, Leseman DLAC, Miller MR, Anderson D, Freney EJ, Heal MR, Donovan
2707 RJ, Blomberg A, Sandstrom T, MacNee W, Boon NA, Newby DE, Cassee FR (2008). Exposure to
2708 concentrated ambient particles does not affect vascular function in patients with coronary heart disease.
2709 Environ Health Perspect 116:709–715.
2710 Moore KF, Ning Z, Ntziachristos L, Schauer JJ, Sioutas C (2007) Daily variation in the properties of urban ultrafine
2711 aerosol—Part I: Physical characterization and volatility. Atmos Environ 41:8633–8646.
2712 Moore K, Neugebauer R, Lurmann F, Hall J, Brajer V, Alcorn S, Tager I (2008) Ambient ozone concentrations
2713 cause increased hospitalizations for asthma in children: an 18-year study in Southern California. Environ
2714 Health Perspect 116: 1063–1070.
2715 Moore K, Neugebauer R, Lurmann F, Hall J, Brajer V, Alcorn S, Tager I (2010) Ambient ozone concentrations and
2716 cardiac mortality in Southern California 1983–2000: application of a new marginal structural model
2717 approach. Am J Epidemiol 171: 1233–1243.

Moorman JE, Rudd RA, Johnson CA, King M, Minor P, Bailey C, Scalia MR, Akinbami LJ (2007) National surveillance for asthma – United States, 1980–2004. Morbidity and Mortality Weekly Report 56(SS08):1–14;18–54.

Morris RE, Koo B, Guenther A, Yarwood G, McNally D, Tesche TW, Tonnesen G, Boylan J, Brewer P (2006) Model sensitivity evaluation for organic carbon using two multi-pollutant air quality models that simulate regional haze in the southeastern United States. Atmos. Environ 40(26):4960–4972.

Mortimer KM, Neugebauer R, van der Laan M, Tager IB (2005) An application of model-fitting procedures for marginal structural models. Am J Epidemiol 162(4):382–388.

NCRP (1997) Deposition, retention and dosimetry of inhaled radioactive substances, NCRP Report No. 125. National Council on Radiation Protection and Measurements. Bethesda, MD, USA.

Nel AE, Diaz-Sanchez D, Li N (2001) The role of particulate pollutants in pulmonary inflammation and asthma: evidence for the involvement of organic chemicals and oxidative stress. Curr Opin Pulm Med 7:20–26.

NRC (1991) Human exposure assessment for airborne pollutants: advances and opportunities. National Research Council, National Academies Press, Washington, DC, USA.

NRC (1998) Research priorities for airborne particulate matter. I. Immediate priorities and a long-range research portfolio. National Research Council, National Academies Press, Washington, DC, USA.

NRC (2004a) Air quality management in the United States. National Research Council, National Academies Press, Washington, DC, USA.

NRC (2004b) Research priorities for airborne particulate matter: IV. Continuing research progress. National Research Council, National Academies Press, Washington, DC, USA, pp. 95–98.

Oberdörster G (2010) Safety assessment for nanotechnology and nanomedicine: concepts of nanotoxicology. J Internal Med 267: 89–105.

Oberdörster G, Sharp Z, Atudorei V, Elder A, Gelein R, Kreyling W, Cox C (2004) Translocation of inhaled ultrafine particles to the brain. Inhal Toxicol 16:437–445.

Oberdörster G, Elder A, Rinderknecht A (2009) Nanoparticles and the brain: cause for concern? J Nanosci Nanotechnol 9(8):4996–5007.

O'Neill MS, Jerrett M, Kawachi I, Levy JI, Cohen AJ, Gouveia N, Wilkinson P, Fletcher T, Cifuentes L, Schwartz J (2003) Health, wealth, and air pollution: Advancing theory and methods. Environ Health Perspect 111(16):1861-1870.

O'Neill MS, Hajat S, Zanobetti A, Ramirez-Aguilar M, Schwartz J (2005a) Impact of control for air pollution and respiratory epidemics on the estimated associations of temperature and daily mortality. Int J Biometeorol 50(2):121–129.

O'Neill MS, Veves A, Zanobetti A, Sarnat JA, Gold DR, Economides PA, Horton ES, Schwartz J (2005b) Diabetes enhances vulnerability to particulate air pollution-associated impairment in vascular reactivity and endothelial function. Circulation 111(22):2913–2920.

O'Neill MS, Veves A, Sarnat JA, Zanobetti A, Gold DR, Economides PA, Horton ES, Schwartz J (2007) Air pollution and inflammation in type 2 diabetes: a mechanism for susceptibility. Occup Environ Med 64:373–379.

Ostro B, Broadwin R, Green S, Feng W, Lipsett M (2006). Fine particulate air pollution and mortality in nine California counties: results from CALFINE. Environ Health Perspect 114:29–33.

Özkaynak H, Frey HC, Burke J, Pinder RW (2009) Analysis of coupled model uncertainties in source-to-dose modeling of human exposures to ambient air pollution: a $PM_{2.5}$ case study. Atmos Environ 43:1641–1649.

Patel MM, Chillrud SN, Hoepner L, Reyes A, Garfinkel R, Perera FP, Miller RL (2009) Effects of ambient nickel, vanadium, and zinc on wheeze and cough in early childhood. J Allergy Clin Immunol 123:S172.

Pearl J (1998) Why there is no statistical test for confounding, why many think there is, and why they are almost right. Tech Report R-256. Los Angeles, CA, USA. http://preprints.stat.ucla.edu/233/233.pdf. Accessed 19 July 2011.

Pearl J (2009) Causality: models, reasoning, and inference, 2nd edn. Cambridge University Press, New York.

Peel JL, Klein M, Flanders WD, Mulholland JA, Tolbert PE (2010) Impact of improved air quality during the 1996 Summer Olympic Games in Atlanta on multiple cardiovascular and respiratory outcomes. Res Rep Health Eff Inst 2010:148:3–23.

Pekkanen J, Brunner EJ, Anderson HR, Tiittanen P, Atkinson RW (2000) Daily concentrations of air pollution and plasma fibrinogen in London. Occup Environ Med 57:818–822.

Pekkanen J, Peters A, Hoek G, Tiittanen P, Brunekreef B, de Hartog J, Heinrich J, Ibald-Mulli A, Kreyling WG, Lanki T, Timonen KL, Vanninen E (2002) Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease: the Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study. Circulation 106:933–938.

Peltier RE, Lippmann M (2010) Residual oil combustion: 2. distribution of airborne nickel and vanadium within New York City. J Expo Sci Environ Epidemiol 20:342–350.

Perera FP, Tang W-y, Herbstman J, Tang D, Levin L, Miller RL, Ho S (2009) Relation of DNA methylation of 5'-CpG island of $ACSL_3$ to transplacental exposure to airborne polycyclic aromatic hydrocarbons and childhood asthma. PLoS One 4:e4488 (4481–4414). doi: 10.1371/journal.pone.0004488.

Peters A, Dockery DW, Heinrich J, Wichmann HE (1997) Short-term effects of particulate air pollution on respiratory morbidity in asthmatic children. Eur Respir J 10:872–879.

Peters A, Liu E, Verrier RL, Schwartz J, Gold DR, Mittleman M, Baliff J, Oh JA, Allen G, Monahan K, Dockery DW (2000) Air pollution and incidence of cardiac arrhythmia. Epidemiology 11:11–17.

Peters A, Dockery DW, Muller JE, Mittleman MA (2001) Increased particulate air pollution and the triggering of myocardial infarction. Circulation 103:2810–2815.

Phalen RF, Méndez LB (2009) Dosimetry considerations for animal aerosol inhalation studies. Biomarkers 14(S1):63–66.

Phalen RF, Oldham MJ, Wolff RK (2008) The relevance of animal models for aerosol studies. J Aerosol Med Pulm Drug Deliv 21:113–124.

2790 Phalen RF, Mendez LB, Oldham MJ (2010) New developments in aerosol dosimetry. Inhal Toxicol 22(S2):6–14.
2791 Pope CA 3rd (1989) Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am
2792 J Public Health 79:623–628.
2793 Pope CA 3rd (2000) Epidemiology of fine particulate air pollution and human health: biologic mechanisms and
2794 who's at risk? Environ Health Perspect 108(suppl 4):713–723
2795 Pope CA III, Dockery DW (2006) Health effects of fine particulate air pollution: lines that connect. J Air Waste
2796 Manage Assoc 56:709–742.
2797 Pope CA III, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ (2004) Cardiovascular
2798 mortality and long-term exposure to particulate air pollution: epidemiological evidence of general
2799 pathophysiological pathways of disease. Circulation 109:71–77.
2800 Pope CA 3rd, Muhlestein JB, May HT, Renlund DG, Anderson JL, Horne BD (2006) Ischemic heart disease events
2801 triggered by short-term exposure to fine particulate air pollution. Circulation 114:2443–2448.
2802 Pope CA 3rd, Ezzati M, Dockery DW (2009) Fine-particulate air pollution and life expectancy in the United States.
2803 N Engl J Med 360(4):376–386.
2804 Pun BK, Wu S-Y, Seigneur C, Seinfeld JH, Griffin RJ, Pandis SN (2003) Uncertainties in modeling secondary
2805 organic aerosol: three-dimensional modeling studies in Nashville/western Tennessee. Environ Sci Technol
2806 37(16):3647–3661.
2807 Rao ST, Mobley JD (2010) Moving toward an integrated transdisciplinary approach to solving environmental
2808 problems. Special Issue of *Environmental Manager*, Air and Waste Management Association, EM
2809 November:5–42.
2810 Rhoden CR, Wellenius GA, Ghelfi E, Lawrence J, Gonzalez-Flecha B (2005) PM-induced cardiac oxidative stress
2811 and dysfunction are mediated by autonomic stimulation. Biochim Biophys Acta 1725:305–313.
2812 Riediker M, Devlin RB, Griggs TR, Herbst MC, Bromberg PA, Williams RW, Cascio WE (2004) Cardiovascular
2813 effects in patrol officers are associated with fine particulate matter from brake wear and engine emissions.
2814 Particle Fibre Technol 1:2. http://www.particleandfibretoxicology.com/content/1/1/2
2815 Robins JM (2001) Data, design, and background knowledge in etiologic inference. Epidemiology 12:313–320.
2816 Robins JM, Hernan MA, Brumback B (2000) Marginal structural models and causal inference in epidemiology.
2817 Epidemiology 11:550–560.
2818 Robinson AL, Donahue NM, Shrivastava MK, Weitkamp EA, Sage AM, Grieshop AP, Lane TE, Pierce JR, Pandis
2819 SN (2007) Rethinking organic aerosols: semivolatile emissions and photochemical aging. Science
2820 315(5816):1259–1262.
2821 Routledge HC, Ayres JG, Townend JN (2003) Why cardiologists should be interested in air pollution. Heart
2822 89:1383–1388.
2823 Russell AG (2008) EPA Supersites Program-related emissions-based particulate matter modeling: initial
2824 applications and advances. J Air Waste Manage Assoc 58:289–302.
2825 Russell AG, Brunekreef B (2009) A focus on particulate matter and health. Environ Sci Technol 43:4620–4625.

Saldiva PHN, Clarke RW, Coull BA, Stearns RC, Lawrence J, Krishna Murthy GG, Diaz E, Koutrakis P, Suh H, Tsuda A, Godleski JJ (2002) Lung inflammation induced by concentrated ambient air particles is related to particle composition. Am J Respir Crit Care Med 165:1610–1617.

Samet JM (2007) Traffic, air pollution, and health. Inhal Toxicol 19:1021–1027.

Samet J, Krewski D (2007) Health effects associated with exposure to ambient air pollution. J Toxicol Environ Health, Part A 70(3):227–242.

Sarnat JA, Marmur A, Klein M, Kim E, Russell AG, Sarnat SE, Mulholland JA, Hopke PK, Tolbert PE (2008) Fine particle sources and cardiorespiratory morbidity: an application of chemical mass balance and factor analytical source-apportionment methods. Environ Health Perspect 116(4):459–466.

Scheuch G, Kohlhäufl M, Möller W, Brand P, Meyer T, Haussinger K, Sommerer K, Heyder J (2008) Particle clearance from the airways of subjects with bronchial hyperresponsiveness and with chronic obstructive pulmonary disease. Exp Lung Res 34:531–549.

Schwartz J, Litonjua A, Suh H, Verrier M, Zanobetti A, Syring M, Nearing B, Verrier R, Stone P, MacCallum G, Speizer FE, Gold DR (2005) Traffic related pollution and heart rate variability in a panel of elderly subjects. Thorax 60:455–461.

Seinfeld JH, Pandis SN (1998) Atmospheric chemistry and physics from air pollution to climate change; John Wiley and Sons, New York.

Sioutas C, Delfino RJ, Singh M (2005) Exposure assessment for atmospheric ultrafine particles (UFPs) and implications in epidemiologic research. Environ Health Perspect 113(8):947–955.

Slama R, Darrow L, Parker J, Woodruff TJ, Strickland M, Nieuwenhuijsen M, Glinianaia S, Hoggatt KJ, Kannan S, Hurley F, Kalinka J, Sram R, Brauer M, Wilhelm M, Heinrich J, Ritz B (2008) Meeting report: atmospheric pollution and human reproduction. Environ Health Perspect 116:791–798. doi:10.1289/ehp.11074.

Solomon PA, Costa DL (2010) Ambient tropospheric particles. In: Gehr P, Rothen-Muhlfeld B, Blank F. (eds) Particle-lung interactions, 2nd edn. Informa Healthcare, New York, pp 17–37.

Solomon PA, Tolocka MP, Norris G, Landis M (2001) Chemical analysis methods for atmospheric aerosol components. In: Baron P, Willeke K (eds) Aerosol measurement: principles, techniques, and application, 2nd edn. John Wiley & Sons, Inc, New York, pp 261–293.

Solomon PA, Sioutas C (2008) Continuous and semicontinuous monitoring techniques for particulate matter mass and chemical components: a synthesis of findings from EPA's Particulate Matter Supersites Program and related studies. J Air Waste Manage Assoc 58:164–195.

Solomon PA, Hopke PK (2008a) Special Issue Supporting Key Scientific and Policy- and Health-Relevant Findings from EPA's Particulate Matter Supersites Program and Related Studies: an Integration and Synthesis of Results. J Air Waste Manage Assoc 58(2):137-139.

Solomon PA, Hopke PK (2008b) Introduction: EPA's Particulate Matter Supersites Program: an integrated synthesis of findings and policy- and health-relevant insights. J Air Waste Manage Assoc 58(13):S-1 – S-2.

2861 Solomon PA, Hopke PK, Froines J, Scheffe R (2008) Key scientific findings and policy- and health-relevant insights
2862 from the U.S. Environmental Protection Agency's Particulate Matter Supersites Program and related
2863 studies: an integration and synthesis of results. J Air Waste Manage Assoc 58(13):S3–S92.
2864 Solomon, P.A., Gehr, P., Bennett, D., Phalen, R., Rothen-Rutishauser, B., Clift, M., Blank, F., Brandenberger, C.,
2865 Lehmann, A., Müller, L., Gasser, M., Raemy, D., Mendez, L., and Oldham, M. (2011). Dosimetry: From
2866 source to fate of air pollutants in the body. Air Quality, Atmos and Health; Submitted for publication
2867 August.
2868 Sorensen M, Schins RPF, Hertel O, Loft S (2005) Transition metals in personal samples of $PM_{2.5}$ and oxidative
2869 stress in human volunteers. Cancer Epidemiol Biomarkers Prevent 14:1340–1343.
2870 Stafoggia M, Schwartz J, Forastiere F, Perucci CA (2008) Does temperature modify the association between air
2871 pollution and mortality? A multicity case-crossover analysis in Italy. Am J Epidemiol 167(12):1476–1485.
2872 Stanier CO, Khlystov AY, Pandis SN (2004a) Nucleation events during the Pittsburgh Air Quality Study:
2873 description and relation to key meteorological, gas phase, and aerosol parameters. Aerosol Sci Technol
2874 38(1):253–264.
2875 Stanier CO, Khlystov AY, Pandis SN (2004b) Ambient aerosol size distributions and number concentrations
2876 measured during the Pittsburgh Air Quality Study. Atmos Environ 38:3275–3284.
2877 Subbarao P, Becker A, Brook JR, Daley D, Mandhane PJ, Miller GE, Turvey SE, Sears MR (2009) Epidemiology of
2878 asthma: risk factors for development. Expert Rev Clin Immunol 5(1):77–95.
2879 Sullivan RC, Prather KA (2005) Recent advances in our understanding of atmospheric chemistry and climate made
2880 possible by on-line aerosol analysis instrumentation. Anal Chem 77:3861–3886.
2881 Thurston GD, Ito K, Mar T, Christensen WF, Eatough DJ, Henry RC, Kim E, Laden F, Lall R, Larson TV, Liu H,
2882 Neas L, Pinto J, Stolzel M, Suh H, Hopke PK (2005) Workgroup report: workshop on source
2883 apportionment of particulate matter health effects—intercomparison of results and implications. Environ
2884 Health Perspect 113:1768–1774.
2885 Tonne C, Beevers S, Armstrong B, Kelly F, Wilkinson P (2008) Air pollution and mortality benefits of the London
2886 Congestion Charge: spatial and socioeconomic inequalities. Occup Environ Med 65(9):620–627.
2887 Turner JR, Allen DT (2008) Transport of atmospheric fine particulate matter: part 2 - findings from recent field
2888 programs on the intraurban variability in fine particulate matter. J Air Waste Manage Assoc 58:196–215.
2889 Turpin BJ, Lim HJ (2001) Species contributions to $PM_{2.5}$ concentrations: revisiting common assumptions for
2890 estimating organic mass. Aerosol Sci Technol 35:602–610.
2891 Tzamkiozis T, Stoeger T, Cheung K, Ntziachristos L, Sioutas C, Samaras Z (2010) Monitoring the inflammatory
2892 potential of exhaust particles from passenger cars in mice. Inhal Toxicol 22(S2):59–69.
2893 Urch B, Brook JR, Wasserstein D, Brook RD, Rajagopalan S, Corey P, Silverman F (2004). Relative contributions
2894 of $PM_{2.5}$ chemical constituents to acute arterial vasoconstriction in humans. Inhal Toxicol 16:345–352.
2895 van Erp AM, Cohen AJ (2009) HEI's research program on the impact of actions to improve air quality: interim
2896 evaluation and future directions. Communication 14. Health Effects Institute, Boston, MA, USA.

van Erp AM, O'Keefe R, Cohen AJ, Warren J (2008) Evaluating the effectiveness of air quality interventions. J Toxicol Environ Health A 71(9–10):583–587.

van Erp AM, Kelly FJ, Demerjian KL, Pope CA III, Cohen AJ (2010) Progress in research to assess the effectiveness of air quality interventions towards improving public health. Air Qual Atmos Health, DOI 10.1007/s11869-010-0127-y.

Van Winkle LS, Chan JKW, Anderson DS, Kumfer BM, Kennedy IM, Wexler AS, Wallis C, Abid AD, Sutherland KM, Fanucchi MV (2010) Age specific responses to acute inhalation of diffusion flame soot particles: cellular injury and the airway antioxidant response. Inhal Toxicol 22(S2):70–83.

Verma V, Ning Z, Cho AK, Schauer JJ, Shafer MM, Sioutas C (2009) Redox activity of urban quasi-ultrafine particles from primary and secondary sources. Atmos Environ 43(40):6360–6368.

Watson JG, Zhu T, Chow JC, Engelbrecht J, Fujita EM, Wilson WE (2002) Receptor modeling application framework for particle source apportionment. Chemosphere 49(9):1093–1136.

Watson JG, Chen L-WA, Chow JC, Doraiswamy P, Lowenthal DH (2008) Source apportionment: findings from the U.S. Supersites Program. J Air Waste Manage Assoc 58:265–288.

Wellenius GA, Coull BA, Godleski JJ, Koutrakis P, Okabe K, Savage ST, Lawrence JE, Krishna Murthy GG, Verrier RL (2003) Inhalation of concentrated ambient air particles exacerbates myocardial ischemia in conscious dogs. Environ Health Perspect 111:402–408.

Wexler A, Johnston M (2008) What have we learned from highly time-resolved measurements during EPA's Supersites Program and related studies? J Air Waste Manage Assoc 58:303–319.

WHO (World Health Organization) (2005) WHO air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide. WHO Press, Geneva, Switzerland. http://whqlibdoc.who.int/hq/2006/WHO_SDE_PHE_OEH_06.02_eng.pdf. Accessed 19 July 2011.

Yu O, Sheppard L, Lumley T, Koenig JQ, Shapiro GG (2000) Effects of ambient air pollution on symptoms of asthma in Seattle-area children enrolled in the CAMP study. Environ Health Perspect 108(12):1209–1214.

Zanobetti A, Schwartz J (2001) Are diabetics more susceptible to the health effects of airborne particles? Am J Respir Crit Care Med 164:831–833.

Zanobetti A, Schwartz J (2002) Cardiovascular damage by airborne particles: are diabetics more susceptible? Epidemiology 13(5):588–592.

Zheng W, Zhao Q (2001) Iron overload following manganese exposure in cultured neuronal, but not neuroglial cells. Brain Research 897(1–2):175–179.

Zhu Y, Hinds WC, Shen S, Sioutas C (2004) Seasonal trends of concentration and size distribution of ultrafine particles near major highways in Los Angeles. Aerosol Sci Technol 38(S1):5–13.

Zou B, Wilson JG, Zhan FB, Zeng Y (2009) Air pollution exposure assessment methods utilized in epidemiological studies. J Environ Monit 11(3):475–490.

2932 Table 1 Science questions and list of contributors by question

Science question	Contributing authors
SQ1. Pollutants and sources associated with health effects (overarching theme). How does our understanding of the health effects of air pollutants (singly or in mixtures) help identify pollutants that can be linked to sources the control of which would provide maximal health benefits?	Thomas J. Grahame Miriam E. Gerlofs-Nijland Paul A. Solomon
SQ2. Reliability of methods and approaches. How reliable are methods (measurements and models) and approaches (epidemiological and toxicological) for studying and quantifying the links between air pollutants (species and/or sources) and adverse health effects?	Flemming Cassee Armistead G. Russell Jeffrey R. Brook
SQ3. Pollutant characterization and population exposure. How do relevant pollutant properties vary in space and time from sources and in ambient air, and what are the implications of these variations for population exposure?	Philip Hopke George Hidy
SQ4. Relationship between exposure and dose. What advances have been made in understanding the relationships between exposure, both spatially and temporally, and estimates of dose that tie to health outcomes?	Robert F. Phalen
SQ5. Mechanisms of action and biomarkers of exposure and effects. Are patterns emerging that relate component(s) of air pollution and/or source types to mechanisms? What is the status of identifying and measuring biomarkers of exposure and/or adverse health effects from air pollution?	Paulo Saldiva
SQ6. Susceptible populations. Who are the susceptible populations, what drives different susceptibilities to the same or different air pollutants, and are there susceptibility traits associated with specific health outcomes that are common among the subpopulations?	Stefanie Ebelt Sarnat John R. Balmes
SQ7. Confounding or other factors. What roles do confounding or other factors have in increasing, decreasing, or obscuring attribution of the true health effects from ambient air pollutants?	Ira B. Tager
SQ8. Accountability. Do actions taken to improve air quality result in reduced ambient concentrations of relevant pollutants, exposure, and health effects, and have we encountered unintended consequences?	Halûk Özkaynak Sverre Vedal
SQ9. Regulatory and policy implications. What findings presented at the Conference provide policy-relevant insights that can lead to an improved understanding of the source-to-health effects paradigm and more	Susan Wierman Paul Solomon Maria Costantini

knowledgeable policy decisions?* Dan Costa

*Modified from original Conference question SQ9: What are the policy implications of our improved understanding of the source to health effect paradigm?

2935 Table 2. Associations of $PM_{2.5}$ sources and components with nonfatal health effects (from Lippmann and Chen,
2936 1SQ1.T5.163)[a]

Exposed	Exposure	Associations	Reference
Human adults	2 h CAPs (Chapel Hill, NC)	Fe/Se/SO_4^{2-} with > PMNs[b] in BALF[c]; Cu/Zn/V with > fibrinogen in blood	Ghio et al., 2000
Human adults	2 h CAPs + O_3 (Toronto, Canada)	OC with BAD[d] ($p = 0.04$); EC, Cd, K, Zn, Ca, and Ni ($p = 0.06$-0.17); OC with > blood pressure	Urch et al., 2004
Human adults	Ambient air (Copenhagen, Denmark)	V and Cr with oxidant stress and DNA damage	Sorensen et al., 2005
Human adults	Ambient air (Amsterdam, Netherlands; Helsinki, Finland; Erfurt, Germany)	Traffic with ST-segment depression EC with oxidative stress	Lanki et al., 2006
Human adults	Ambient air (Taipei, Taiwan)	SO_4^{2-} (but not OC or EC) with < heart rate variability (HRV)	Chuang et al., 2007
Asthmatic children	Ambient air (New Haven, CT)	Motor vehicle exhaust with wheeze; road dust with shortness of breath	Gent et al., 2009
Asthmatic infants	Ambient air (Bronx, NY)	Ni, V, and Zn with wheeze and cough; EC with cough	Patel et al., 2009
Healthy children	Ambient air (Southern California)	EC with lung growth (10 to 18 years)	Gauderman et al., 2004
Human adults	Ambient air (Hong Kong, China)	Ni and V with bronchial hyperreactivity	Hedley et al., 2002, 2004
Human adults	Ambient air (London, England)	Black smoke with plasma fibrinogen	Pekkanen et al., 2000
Human adults	Ambient air (14 U.S. cities)	Motor vehicles, oil combustion, and metals processing with CV disease hospital admissions	Janssen et al., 2002
Human adults	Ambient air (106 U.S. counties)	Ni, V, and EC with CV disease hospital admissions (single pollutant); only Ni in multipollutant	Bell et al., 2009
Dogs	CAPs (Boston, MA)	Al/Si with > PMNs in BALF, peripheral white blood cell count, and circulating lymphocytes; Ni/V with PMNs and BALF macrophages; Br/Pb with PMNs	Clarke et al., 2000

		in BALF	
Rats	CAPs (Boston, MA)	Si, V, Pb, SO_4^{2-}, and Br with > PMNs	Saldiva et al., 2002
Rats	CAPs Boston, MA	Al, Si, and Fe with > TBARS[e]; Cr, Zn, and Na with PMNs in BALF	Rhoden et al., 2005
Rats	CAPs (Boston, MA)	Fe, Mn, Cu, and Zn with lung oxidants Fe, Al, Si, and Ti with heart oxidants	Gurgueira et al., 2002
Dogs	CAPs (Boston, MA)	Crustal elements with occlusion-induced ST-segment depression	Wellenius et al., 2003
Rats	CAPs (Research Triangle Park, NC)	Zn with plasma fibrinogen levels	Kodavanti et al., 2000
Mice	CAPs (Tuxedo, NY)	Ni, Cr, and Fe with > HR and < HRV	Lippmann et al., 2006
Mice	CAPs (Tuxedo, NY)	SO_4 with HR during exposure; Ni and V with HR following exposure; soil elements with HRV following exposure; Br, Fe, and EC with HRV later in the day	Lippmann et al., 2005
Mice	CAPs (Los Angeles, CA)	EC and OC with IL-5 and IgG1 @ 50 m from freeway	Kleinman et al., 2007

[a.] Based on material presented in Lippmann and Chen (2009). Reprinted with permission from M. Lippmann, New York University School of Medicine, Tuxedo, NY, USA.

[b]polymorphonuclear neutrophil

[c]bronchoalveolar lavage fluid

[d]brachial artery diameter

[e]thiobarbituric reactive substance

2944 Table 3. Associations of $PM_{2.5}$ sources and components with mortality (from Lippmann and Chen, 1SQ1.T5.163)[a]

Exposed	Exposure	Associations	Reference
Human adults	Ambient air (Hong Kong)	Ni and V intervention with less annual mortality	Hedley et al., 2002 and 2004
Human adults	Ambient air (60 U.S. cities)	Ni and V variation with average daily mortality	Lippmann et al., 2006
Human adults	Ambient air (72 U.S. counties)	Ni and V variation with average daily mortality	Dominici et al., 2007
Human adults	Ambient air (25 U.S. cities)	Intercity variation in $PM_{2.5}$ mortality associated with Al, As, Ni, and SO_4^{2-}	Franklin et al., 2008
Human adults (males only)	Ambient air (U.S. cities)	Traffic density, Ni, and V with annual mortality	Lipfert et al., 2006
Human adults	Ambient air (9 California counties)	OC and EC with daily mortality	Ostro et al., 2006

2945 [a] Based on material presented in Lippmann and Chen (2009). Reprinted with permission from M. Lippmann, New
2946 York University School of Medicine, Tuxedo, NY, USA.

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2948 Table 4. Pros and cons of toxicological methods (Cassee, 1SQ2.3)[a]

Features of methods	A-cellular	*In-vitro* cell	*Ex-vivo*	*In-vitro* animal	Human volunteers
Predictive human health: the extent to which a test can predict the adverse health effects of air pollutants in the human population.	**??**	-/+	-/+	++	++
Acute effects: possibility of assessing outcomes associated with short-term exposure.	**+?**	++	++	++	++
Chronic effects: possibility of assessing outcomes associated with long-term exposure.	-	-	-	++	--
Susceptibility: options to mimic susceptibility of human subjects such as respiratory diseases, e.g. allergy induced in mice (a-cellular systems are inadequate for this purpose).	-	-	-/+	+	++
Biological mechanisms: options to study the biological mechanism, i.e., interactions of a substance with cells and tissue and the sequence of events that follows.	-	++	++	++	++
Coherence epidemiology: options to explain outcomes of observational studies with studies that focus on causal relationships between pollutants and toxic responses.	**??**	**??**	**??**	+	++
Costs: the costs to perform a test or experiment.	++	+	+	-/+	--
Dosimetry and kinetics: possibilities of retrieving information on internal (deposited) dose and distribution of pollutants in the body.	-	-	-/+	+	++
Risk assessment: usefulness for and application in risk assessment.	-	-	-/+	++	++
The 3Rs: replacement, refinement, and reduction—a widely accepted ethical framework for conducting scientific experiments using animals humanely.	++	++	+	-	++

2949 ++ = very good; + = good; +/- = moderate; - = poor or impossible

[a]Reprinted with permission from F.R. Cassee, RIVM (National Institute for Public Health and the Environment), Bilthoven, the Netherlands.

FIGURES

Figure 1. Normalized ROS activity by PM size range at two urban (Bronx and Manhattan) and three rural (Goshen, Tuxedo, and Wallkill) locations in New York. *In-vitro* PMc exposures were measured using human pulmonary microvascular endothelial cells (HPMEC-ST1.6R) and bronchial epithelial cells (BEAS-2B). Ultracoarse refers to PM > 10 µm and was collected at two sites to examine its relative toxicity. Figure reprinted from Gordon et al. (15SQ5.T5.359) with permission from M. Lippmann (New York University School of Medicine, Tuxedo, NY, USA).

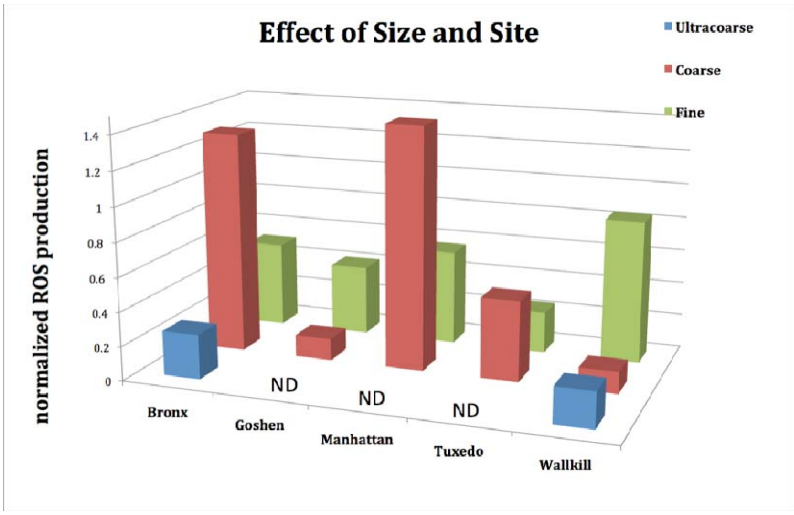


Figure 2. Putative mechanism of Mn-induced cytotoxicity. Increased intracellular Mn alters iron regulatory protein (ACO1) in Step 1, leading to up-regulation of TfR in Step 2 and down-regulation of Fe storage protein ferritin in Step 3. Increased TfR and decreased Fe storage elevate intracellular free Fe as shown in Step 4. The latter catalyzes the formation of highly reactive hydroxyl free radicals via the Fenton reaction and provokes oxidative stress, ultimately resulting in cell damage. (Kleinman and Campbell, 14SQ5.3; Figure from Zheng and Zhao, 2001) Reprinted with permission from Elsevier from Zheng W, Zhao Q (2001) Iron overload following manganese exposure in cultured neuronal, but not neuroglial cells. Brain Research 897(1–2):175–179. Copyright (2001).

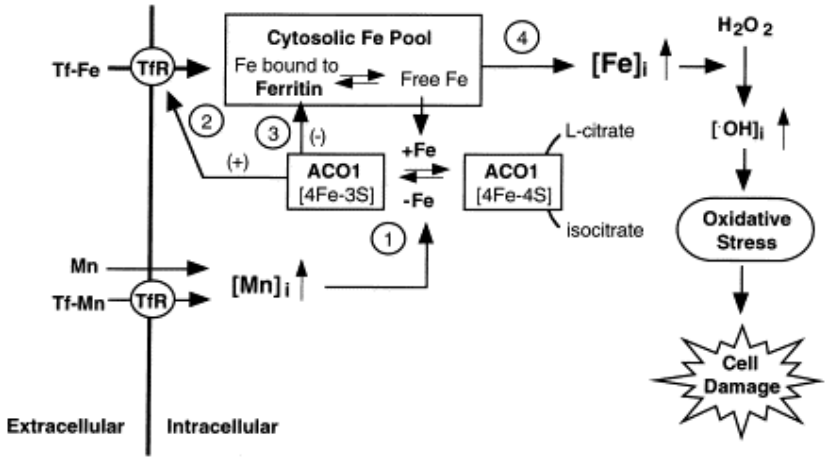
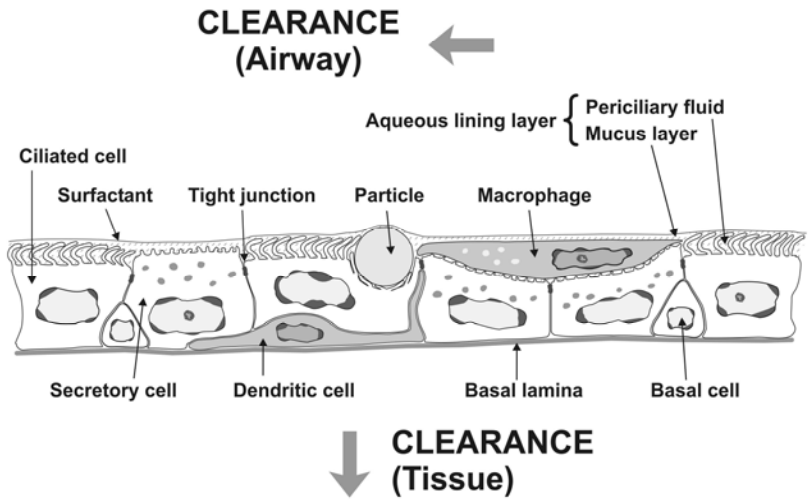


Figure 3. Location of a dendritic cell in normal tracheobronchial epithelium and its relationship to a deposited air-pollutant particle (Gehr et al. 2000). Reprinted with permission from the Royal Society of London, Copyright 2000.



2977 Figure 4. The accountability chain (modified from van Erp et al., 4SQ8.1; Figure from HEI, 2003). Revised figure
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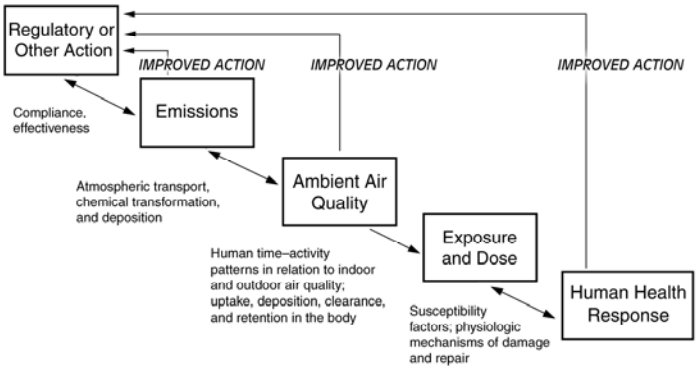

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