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Panel discussion review: session two — interpretation of observed associations between multiple ambient air pollutants and health effects in epidemiologic analyses

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Air pollution epidemiologic research has often utilized ambient air concentrations measured from centrally located monitors as a surrogate measure of exposure to these pollutants. Associations between these ambient concentrations and health outcomes such as lung function, hospital admissions, and mortality have been examined in short- and long-term cohort studies as well as in time-series and case-crossover studies. The issues related to interpreting the observed associations of ambient air pollutants with health outcomes were discussed at the US EPA sponsored workshop on December 13 and 14, 2006 in Chapel Hill, North Carolina, USA. The second session of this workshop focused on the following topics: (1) statistical methodology and study designs that may improve understanding of multipollutant health effects; (2) ambient concentrations as surrogate measures of pollutant mixtures; and (3) source-focused epidemiologic research. New methodology and approaches to better distinguish the effects of individual pollutants include multicity hierarchical modeling and the use of case-crossover analysis to control for copollutants. An alternative approach is to examine the mixture as a whole using principal component analysis. Another important consideration is to what extent the observed health associations are attributable to individual pollutants, which are often from common sources and are correlated, *versus* the pollutant mixtures that the pollutants are representing. For example, several ambient air concentrations, such as particulate matter mass, nitrogen dioxide, and carbon monoxide, may be serving as surrogate measures of motor vehicle exhaust. Source apportionment analysis is one method that may allow further advancement in understanding the source components that contribute to multipollutant health effects.
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Introduction

Numerous epidemiologic studies of the association between different ambient air pollutants and various health outcomes have been published in the past few decades since the enactment of the Clean Air Act. Results from these epidemiologic studies, along with human clinical and animal toxicologic studies, have served as the evidence base to inform the setting of the National Ambient Air Quality Standards (NAAQS) in the United States. The six criteria air pollutants that are regulated under NAAQS include particulate matter (PM), ozone (O_3), carbon monoxide (CO), nitrogen oxides (NO_x), sulfur oxides (SO_x), and lead. Air pollution epidemiologists often utilize ambient air concentrations measured from the extensive monitoring sites that exist to regulate these pollutants. These ambient concentrations have been found to be associated with health outcomes such as lung function, hospital admissions, and mortality using various study designs and analysis methods, including short- and long-term cohort studies, time-series analyses, and case-crossover studies. Ambient concentrations from centrally located monitoring sites provide an estimate of exposure to these air pollutants at a relatively low cost to researchers; however, there are several issues related to the interpretation of the results from epidemiologic studies that use such data in their analyses. The issues related to interpreting associations of ambient air pollutants with health outcomes were

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discussed at the US EPA sponsored workshop on December 13 and 14, 2006 in Chapel Hill, North Carolina, USA. This paper briefly summarizes the panel discussion that took place during the second session. This session focused on better understanding the observed associations between multiple, sometimes highly correlated ambient air pollutants and health effects. New methodology and approaches to advance future epidemiologic research in the area of air pollution health effects were also discussed in the panel discussion. The session was chaired by Richard Burnett (Health Canada) and Jee Young Kim (US EPA), and included as panel members Bert Brunekreef (Institute for Risk Assessment Sciences, Utrecht University), Mark Goldberg (McGill University), Lucas Neas (US EPA), Isabelle Romieu (National Institute of Public Health, Mexico), Joel Schwartz (Harvard University), George Thurston (New York University), and Paige Tolbert (Emory University).

Methods used to Distinguish Effects of Multipollutant Exposures

Among the various epidemiologic studies that examined the association between short-term exposure to ambient air pollutants and mortality, significant associations have been observed for most pollutants examined, including PM, O_3, NO_2 (nitrogen dioxide), and SO_2 (sulfur dioxide). Using the large multicity studies as an example, significant and robust associations with mortality have been observed for PM_{10} (PM with an aerodynamic mass median diameter of less than or equal to 10 μm) in the National Morbidity and Mortality Air Pollution Study (NMMAPS) of 90 US cities (Samet et al., 2000, reanalyzed by Dominici et al., 2003), O_3 in 95 US communities from NMMAPS (Bell et al., 2004), NO_2 in 12 Canadian cities (Burnett et al., 2004), and SO_2 in 12 European cities ranging from Athens to Wroclaw in the APHEA project (Air Pollution and Health: A European Approach) (Katsouyanni et al., 1997). A meta analysis of 109 time-series studies published since 1985 by Stieb et al. (2003) also indicated significant associations between mortality and all pollutants examined, including PM_{10}, O_3, NO_2, SO_2, and CO, in single-pollutant models.

Multipollutant regression models, in which multiple pollutants are entered simultaneously into the Poisson log-linear model, have often been used in epidemiologic studies in an effort to separate or distinguish the effects from the multiple pollutants. These models provide the estimated marginal effect of one pollutant controlling for the others under a number of assumptions, including linear associations, no measurement error, no overmatching (adjusting for variables that represent the same construct as the exposure variable), no intermediates (variables are not in the causal pathway between the causal exposure and the end point), lack of interactions with other factors (such as season), and lack of seasonal differences in confounding. Unfortunately, not all of these assumptions are met in air pollution epidemiology. For example, if the relationship of one of the pollutants to outcome is not linear, then the multipollutant regression model does not give the independent effect of the other pollutant, since it did not correctly adjust for confounding by the first pollutant. If the relationship with the copollutant varies by season, the multipollutant model also fails to appropriately adjust for confounding. Furthermore, it is unclear as to whether the ambient concentration of each pollutant is a surrogate measure for exposure to that pollutant, rather than for exposure to a different pollutant or the complex mixture. Finding the likely causal pollutant from multipollutant regression models is hindered by the possibility that air pollutants may be acting as surrogates for less-well-measured or unmeasured pollutants, or that the pollutants may all be acting as surrogates for the same mixtures of pollutants.

Multicity hierarchical modeling appears to be a promising approach for evaluating the independent effects of pollutants. Schwartz and Coull (2003) developed a two-stage hierarchical model under the premise that when potential confounding exists, a multilevel model yields better power to assess the independent effects of each predictor. Although these methods do not require the measurement error for different exposures to be independent, the attenuation factor arising from measurement error and the measurement error correlation are assumed to be constant across studies. In a previous analysis of data from six US cities, Schwartz et al. (1996) observed a significant association between mortality and $PM_{2.5}$ (PM with an aerodynamic mass median diameter of less than or equal to 2.5 μm), but not with $PM_{10-2.5}$ (PM with an aerodynamic mass median diameter of between 10 and 2.5 μm) using traditional Poisson regression methods. However, there was concern that greater measurement error in the $PM_{10-2.5}$ measurements could have resulted in a smaller, non-significant effect estimate for $PM_{10-2.5}$ when in fact the effect might be equipotent to $PM_{2.5}$. Simulations were performed using the same data and a two-stage approach that took into consideration measurement error. Results indicated that while the original estimates for $PM_{2.5}$ and $PM_{10-2.5}$ were biased toward the null due to their measurement error, the reanalyzed slope estimator was unbiased and the intercept estimator was free from upward bias. Applying this method to the NMMAPS data, Zeka and Schwartz (2004) reported that reducing the bias from measurement error resulted in a slightly greater PM_{10} effect size compared to the original NMMAPS analysis (Dominici et al., 2003), 0.24% compared to 0.21% increase in mortality per 10 $\mu g/m^3$ increase in PM_{10}.

Case-crossover studies are a version of time-series studies with an alternative methodology for controlling for confounders such as weather and effects of other pollutants. In case-crossover studies, control for these confounders is achieved in the design stage and an implicit model based

on the matching is assumed, compared to the time-series approach where the adjustment is done in the analysis stage and the model is specified. Schwartz (2004) examined whether the association between PM_{10} and mortality was confounded by gaseous pollutants using the case-crossover study design. Using data from 14 US cities, he compared the PM_{10} concentration on the day of death with the pollution level on days before and after the day of death. Control days were selected by matching on season (days in the same month of the same year) and gaseous air pollutant levels (within 1 ppb for SO_2 and NO_2, within 2 ppb for O_3, and within 0.03 ppm for CO) to control for potential confounding by these factors. This method of analysis automatically controls for non-linearities as well as any interactions among the matched variables (e.g., month and O_3). The results indicated that the PM_{10} effect was statistically significant and robust to matching on SO_2, NO_2, O_3, and CO.

An alternative to assessing the effects of individual pollutants is to consider the mixture as a whole. One approach for examining a mixture of pollutants is through principal component analysis. Burnett et al. (2000) applied this method to data from eight Canadian cities to examine the association between acute exposure to ambient air pollutants and mortality. They concluded that PM mass explained 28% of the total health effect of the mixture, with the remaining effects accounted for by the gases. Burnett et al. further observed that sulfate ion, iron, nickel, and zinc from $PM_{2.5}$ were most strongly associated with mortality. A modified version of the principal component analysis was recently proposed by Roberts and Martin (2006) to assess pollutant mixture effects. Supervised principal components analysis uses a subset of the multiple pollutants that are selected on the basis of their association with the adverse health outcomes, unlike the traditional principal component analysis that identifies mixtures of pollutants using only the covariate information without regard to the relationship between the pollutant and the health outcome. Using data from nine US cities, Roberts and Martin observed that specific pollutants (e.g., PM_{10}) were found to be associated with mortality in some cities but not in others. One concern of this approach is the use of single-pollutant models in deciding the importance of individual pollutant effects. Pollutants not associated or only weakly associated with the adverse health outcomes in single-pollutant models have a significant chance of being excluded from the chosen model, which may result in substantial modeling errors if the lack of an association was due to chance or other factors such as measurement error. As in the case of the traditional principal component analysis, there is the implicit assumption that a weighted average across pollutants is appropriate. A more detailed discussion of the air pollution mixture and the use of cluster or latent profile analysis to examine the health effects of the mixture are presented in another publication in this special issue (Goldberg, 2007).

Surrogate Measures of Pollutant Mixtures

An important consideration of these air pollution epidemiologic studies is the extent to which the health effects are attributable to the specific pollutants that they are found to be associated with versus the pollutant mixtures that the pollutants are representing. Consider CO, for example. Studies have shown CO to be associated with emergency department visits and hospital admissions for asthma (Peel et al., 2005). However, ambient levels of CO are not known to have any direct effects on lung tissue (US EPA, 2000). The observed association, therefore, must be because CO is serving as a surrogate for some other set of exposures. The concern is that if this is true for asthma, could it not also be the case for heart disease, where an association is biologically plausible. The database used in Peel et al. (2005) has since been extended and expanded, and Paige Tolbert of Emory University presented analyses of these data at the workshop. The investigators have been conducting an intensive spatio-temporal assessment of the roles of multiple pollutants in cardiorespiratory health outcomes, taking advantage of comprehensive air quality measurements and data on over 10 million emergency department visits for the time period 1993–2004 in Atlanta, GA. This study provides an excellent opportunity to consider major challenges in air pollution epidemiology such as the potential for the pollutants under investigation to act as surrogates of other pollutants or unmeasured factors and the impacts of measurement error. Using daily time-series analyses to examine emergency department visits for all respiratory diseases combined, positive associations were observed for several criteria pollutants (O_3, CO, NO_2, PM_{10}), with the strongest findings for O_3. For all cardiovascular diseases combined, associations were observed for CO, NO_2, and $PM_{2.5}$ elemental and organic carbon fractions. In multipollutant models, CO appears to drive the observed associations for cardiovascular diseases. The investigators concluded that CO may be serving as the best surrogate of vehicular emissions, rather than being itself directly responsible. Additional results from this study are presented by Tolbert et al. (2007) in this special issue.

In the Burnett et al. (2004) study, the association between NO_2 and mortality was examined in 12 of Canada's largest cities over a 19-year time period (1981–1999). Gaseous pollutant data were collected daily while PM measurements were taken every sixth day. Significant positive associations were observed for most pollutants in the single-pollutant models, including NO_2, O_3, SO_2, CO, and PM_{10}. No associations with mortality were found for $PM_{2.5}$ and $PM_{10-2.5}$. In two-pollutant models adjusting for NO_2, only O_3 and SO_2 remained significant, whereas the risk estimate for NO_2 was robust to adjustment for each of the various gaseous and particle pollutants. However, as the biological plausibility as to whether NO_2 by itself can cause mortality at the ambient concentrations currently observed in Canada (mean 22.4 ppb across 12 cities [mean range 10.0 ppb in Saint John to

26.4 ppb in Calgary) is unknown, the investigators were unable to definitively implicate NO_2 as a specific causal pollutant. Further, there was concern that the observed effects might be influenced by the availability of data. To examine this, the investigators conducted analyses using data from 1998 to 2000 in 11 of the 12 cities where daily $PM_{2.5}$ measurements were collected. They observed that when daily data were used for both NO_2 and $PM_{2.5}$, the effect estimate for NO_2 was indeed sensitive to $PM_{2.5}$ adjustment, whereas the $PM_{2.5}$ effect was robust to adjustment for NO_2. The investigators noted that in Canadian cities, the major source of nitric oxide (NO) (80–90%) was exhaust from motor vehicles or other forms of transportation, suggesting that ambient concentrations of NO_2 might be serving as a surrogate of primary traffic-related pollutants. An updated analysis of the multicity Canadian study further examining the association of NO_2 and mortality is presented by Brook et al. (2007) in this special issue. The findings suggest that NO_2 may be a better indicator of motor vehicle fine particles than $PM_{2.5}$, thereby offering one explanation as to why some epidemiologic studies have found a stronger association between mortality and NO_2 than with $PM_{2.5}$.

Unlike US or Canadian studies that tend to compare effect estimates between communities, the long-term studies in Europe have focused mostly on within-city contrasts in exposure characterized by deterministic or stochastic modeling. Similar to the multicity Canadian study, results from these studies also seem to implicate traffic-related air pollution components, as identified by NO_2 and soot (black smoke), which are sometimes more robustly associated with mortality than PM mass (Nafstad et al., 2004; Filleul et al., 2005). As spatial correlations among $PM_{2.5}$, soot, and NO_2 are generally high, the observed results do not allow disentanglement of the role of these components in causing mortality effects following long-term exposure. The results from these and additional European studies are discussed further in another publication in this special issue (Brunekreef, 2007).

This question of whether ambient concentrations of gaseous pollutants are serving as surrogates of particulate pollutant mixtures has been considered in two studies conducted by Sarnat and co-workers. They simultaneously measured and compared personal exposure to multiple pollutants with ambient concentrations from community monitors in Baltimore, MD (Sarnat et al., 2001) and Boston, MA (Sarnat et al., 2005). The results showed that in both Baltimore and Boston, ambient concentrations of O_3, NO_2, SO_2, and CO were associated with personal exposure to $PM_{2.5}$ and sulfate. The relationships between personal exposure and ambient concentrations for the gases differed by city, indicating that the results observed in the individual cities may not be generalizable due to possible differences in housing characteristics and population activity patterns. In Baltimore, ambient gas concentrations were not associated with their respective personal exposures, while in Boston, moderately strong associations were observed between personal exposures and ambient concentrations for O_3, NO_2, and SO_2. However, the ambient gas measurements in both cities were more strongly associated with personal exposure to $PM_{2.5}$ than with their respective personal exposures. It is important to note that $PM_{2.5}$ and PM_{10} are also surrogate markers of particle phase pollution. These results, therefore, suggest that multipollutant models using ambient concentrations of gases may be a form of source apportionment of the effects of particle phase pollution and may provide limited information about the effects of gases. A simulation study conducted by Schwartz et al. (2007) using the Baltimore data showed that a significant association with ambient O_3 is much more likely to result from a true association with sulfate than from a true association with exposure to O_3. However, this may not be true in all cities. For example, a study by Kim et al. (2006) conducted in Toronto, Canada, observed a moderately strong correlation (median Spearman correlation coefficient of 0.57) between ambient NO_2 concentrations and personal NO_2 exposures. In contrast to the studies by Sarnat et al., the relationship between ambient NO_2 concentrations and personal $PM_{2.5}$ exposures was considerably weaker (median Spearman correlation coefficient of 0.24). These results further suggest that in some situations, ambient NO_2 concentrations may, to some extent, represent personal NO_2 exposures.

Source-Focused Epidemiologic Research

In response to recommendations by the National Research Council and other extramural groups (NRC, 1998), the US EPA's research on the health effects of particle phase pollution is moving from a focus on particle size through particle constituents to particles from specific sources. The initial focus on the health effects of various particle size fractions was helpful in focusing concern on combustion particles, but relied on rather arbitrarily defined size fractions. Research on particle constituents has been hampered by the large number of identifiable particle constituents and characteristics, and by the high inter-correlations of many constituents. Fortunately, the major sources of PM are less numerous than the particle constituents. Particulate matter from different sources with differing constituents and characteristics is likely to exert adverse health effects over differing modes of action or differing time scales. A research focus on PM sources can also provide guidance in air quality improvements through reductions in emissions from specific sources. However, there is uncertainty as to whether meaningful and reliable source apportionments of PM health effects are possible with currently available data and methods. Source-focused research depends on advancements in three major areas: exposure modeling, air quality monitoring, and epidemiologic study design.

Exposure modeling through the source apportionment of PM may be accomplished through many different methods that have been shown to yield similar results in epidemiologic analyses. The receptor modeling method decomposes the measurement matrix of particle constituents into a matrix of particle source profiles and a matrix of the daily variability in source contributions to particle mass. The chemical mass balance method uses an *a priori* matrix of source profiles that are similar to the source profiles obtained through receptor modeling. Rotational ambiguities and model specification by individual investigators are inherent issues for receptor modeling, but recent publications by Ito et al. (2006) and Mar et al. (2006) have shown that these issues are not crucial to the use of receptor modeling for exposure assessment in epidemiologic studies. The hope is that the source-apportionment of PM may inform the attribution of health effects to PM or gaseous copollutants.

Air quality monitoring is an essential element for receptor modeling and source-focused epidemiologic research. New developments in speciation monitoring, such as STN, IMPROVE, and NCore, will vastly expand the available air quality data on PM constituents and characteristics. Key determinants of monitor location, monitor density, and monitoring frequency are the requirements and funding provided to State, Local and Tribal governments by the US EPA. Recently, EPA and the Health Effects Institute co-sponsored a meeting on the role of air quality monitoring in source-focus epidemiologic research (for additional information regarding this meeting, see http://www.healtheffects.org/AQDNov06/AQDWorkshop.html). The workshop participants expressed a need for more daily speciated air quality monitoring data. Such data are especially necessary for the determination of the lagged or extended health effects of PM from various sources.

Epidemiologic study design will also play a key role in distinguishing between the roles of PM and gaseous copollutants with regard to adverse health effects. For example, consider the essential correlation by air quality measurements of NO_2 and PM from mobile sources. Future epidemiologic studies should take advantage of city-to-city variations in the traffic contribution to ambient concentrations of NO_2 and PM. One approach to distinguishing between these two interrelated pollutants is through epidemiologic studies of indoor NO_2 sources, particularly gas stoves with pilot lights and unvented gas space heaters. Another means of distinguishing between these two pollutants is through an examination of effect modification by indoor sources, such as gas stoves and environmental tobacco smoke, of the associations between ambient concentrations and adverse health effects.

A source apportionment analysis of nationwide US EPA speciation data was briefly presented by George Thurston of New York University at the workshop. Using the 2000–2003 EPA Speciation Network data (including 233 monitoring sites in 125 Metropolitan areas), Thurston and co-workers conducted a factor analysis of the entire nation. Quarterly mean site averages of the elemental and mass data were used. The absolute principal components method was applied, as developed by Thurston and Spengler (1985), in which factor analysis was conducted, absolute zero values were calculated and applied to give absolute factor analysis scores, followed by a regression of the mass to apportion $PM_{2.5}$ to source categories and locations around the US. The $PM_{2.5}$ source categories identified (and their key elements) were: metals industry (lead, zinc); soil particles (calcium, silica); motor vehicles (organic carbon, elemental carbon, nitrate); steel industry (iron, manganese); coal combustion (arsenic, selenium); oil combustion (vanadium, nickel); salt particles (sodium, chloride); and other sulfate. Nationwide spatial plots of the impacts confirmed the factor interpretations: motor vehicle impacts highest in Southern California; soil impacts highest in the desert Southwest; steel impacts highest in cities with major steel works (e.g., Detroit, MI, USA); and, coal impacts highest in the Ohio Valley region (e.g., Pittsburgh, PA, USA). It was noted that residual oil burning impacts were highest in cities with deep ports (e.g., Los Angeles, CA; Savannah, GA, and Newark, NJ – New York City, NY, USA), suggesting a major impact in these port cities from cargo ships burning "bunker fuel." This work revealed US source factors similar in character to those reported for the 1979–1983 IP Network (Özkaynak and Thurston, 1987). Results indicate that applying source apportionment methods to the EPA Speciation Network can be a useful avenue to identify source-related $PM_{2.5}$ mass components impacting the nation, and for the determination of source-specific health effects, potentially allowing a more efficient regulation of $PM_{2.5}$.

Interpretation of the Available Epidemiologic Evidence

Given the limitations of the epidemiologic data, an important consideration is what conclusions can be drawn from the available epidemiologic evidence. For some pollutants, most notably O_3, the epidemiologic evidence was greatly informed by human clinical and animal toxicology data. In the absence of strong supporting data from human clinical and animal toxicology studies, even with strong epidemiologic data, the determination of causal associations between specific air pollutants and health effects is difficult.

In epidemiologic studies of multiple pollutants, it is important to consider whether the copollutants, which are often from common sources and are correlated, are confounders or act as surrogates. More informed approaches may be necessary in interpreting the results for pollutants such as NO_2, SO_2, and CO. Ambient concentrations of these gaseous pollutants may be serving as surrogate measures for vehicular traffic, in the case of NO_2 and CO, or power plant emissions, in the case of SO_2; thus, observed associations with these pollutants may indicate health effects resulting

from the pollutant mixtures from these sources rather than the individual pollutant *per se*. The results from Sarnat et al. (2001, 2005), which observed that ambient concentrations of gaseous pollutants were more strongly associated with personal exposure to $PM_{2.5}$ than with their respective personal exposures, suggest that these copollutants are likely serving as surrogates of particle phase pollution. However, as indicated in the Toronto study by Kim et al. (2006), in other cities, ambient gas concentrations may also represent personal exposures to these gases.

Multipollutant regression models, which may have limited effectiveness in controlling for confounding by copollutants, may be useful in determining which of several potential surrogates for a putative risk factor is the best predictor for a given health outcome. Source apportionment has been proposed as another approach to dealing with some of the challenges of studying roles of multiple pollutants, particularly in the case of PM components. While source apportionment introduces an additional layer of uncertainty into epidemiologic analyses, it is complementary to more traditional modeling approaches. In the Atlanta study by Tolbert and co-workers, $PM_{2.5}$ source apportionment work corroborated the impression provided by the single-pollutant models that the cardiovascular disease visits were related to vehicular emissions (both diesel and gasoline). Spatial heterogeneity might have been a factor in the differences across pollutant associations with morbidity.

Despite its limitations, the currently available epidemiologic data still provide valuable information regarding the health effects of air pollutants. Recent studies using advanced methodology have informed the interpretation of the epidemiologic literature and may assist in the development of effective public health policies.

Disclaimer

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