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TECHNICAL PAPER

Long-term particulate matter exposure: Attributing health effects to individual PM components

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While most in the scientific community are of the opinion that the composition of fine particulate matter ($PM_{2.5}$) is an important driver of resultant health effects, there is still some degree of uncertainty regarding those components considered to be most harmful. Reviews of the subject from several perspectives have been published, but to our knowledge a comprehensive review of the epidemiological and toxicological literature related to long-term exposure to $PM_{2.5}$ components does not exist. We reviewed published epidemiological studies that were of a cohort design, included at least one PM component as well as $PM_{2.5}$ mass, and included quantitative analysis to relate health outcomes to individual components. Toxicological studies were included if they were ≥5 months in duration and either included at least one PM component as well as PM mass or focused on a specific PM or emissions type. Overall, we find that epidemiological and toxicological evidence for long-term effects of PM components is limited, in contrast to the short-term literature, which is more plentiful. Epidemiological literature suggests that a number of components are associated with health effects, and that no component is unequivocally not so associated. Toxicological studies that can more easily identify potentially causal components are generally limited to long-term studies using concentrated ambient particles (CAPs), of which few long-term studies exist. Epidemiological study designs that utilize existing monitoring data routinely collected by the U.S. Environmental Protection Agency would be valuable additions to the literature, as would novel toxicological studies that incorporate innovative designs to separate components or groups of components, such as denuders, filtration, or other approaches. From a policy perspective, it is important to more comprehensively investigate this issue so that if particular constituents are determined to be more potent in inducing health effects, their sources can be controlled.

Implications: Understanding the components of $PM_{2.5}$ that are most harmful to human health is a critical policy issue. This review examined the epidemiological and toxicological literature related to long-term exposure to PM components and found that, unlike the literature on short-term health effects, there is insufficient information to make clear inferences about causal components. There is a need for further research in this area to exploit existing PM monitoring data in epidemiological studies and to design experimental studies that are able to tease out the effects of multiple constituents.

Introduction

Since the early 2000s, there has been burgeoning interest in the composition of particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$) and the potential role played by individual components in adverse health effects ascribed to PM. In part, this area of investigation was motivated by a National Academy of Sciences report that highlighted this issue as an important research need (NAS, 2004); other developments, including the initiation of U.S. Environmental Protection Agency (EPA)-funded PM research centers and the development of ambient particle concentrators, have also contributed to active research in this area. However, after close to two decades of research on the differential toxicity of $PM_{2.5}$ components, there is still uncertainty regarding this issue. From a policy perspective, it is important to determine which component(s), or combination of components, are most harmful to human health so that these constituents (and the sources from which they derive) can be controlled.

Currently, the EPA regulates $PM_{2.5}$ mass via a National Ambient Air Quality Standard (NAAQS), with an annual NAAQS of 12 $\mu g/m^3$ and a 24-hr standard of 35 $\mu g/m^3$. There are no constituent-specific standards, with the exception of lead (Pb). The EPA has stated in the Integrated Science Assessment (ISA) related to the last PM NAAQS review that "It remains a challenge to determine relationships between specific constituents, combinations of constituents, or sources of $PM_{2.5}$ and the various health effects observed … many constituents of $PM_{2.5}$ can be linked with multiple health effects, and the evidence is not yet sufficient to allow differentiation of those constituents or sources that are more closely related to specific health outcomes" (EPA, 2009). Similar language can be found in the Agency's Policy Assessment (EPA, 2011): "Staff concludes that there is insufficient information at this time to consider supplementing the mass-based $PM_{2.5}$ indicator by considering a separate indicator for ultrafine

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particles or for a specific $PM_{2.5}$ component or group of components associated with any source categories of fine particles, or for eliminating any individual component or group of components from the mix of fine particles included in the $PM_{2.5}$ mass-based indicator."

Several reviews have concluded that there are components that appear to be playing a comparatively greater role in health effects (Rohr and Wyzga, 2012; Kelly and Fussell, 2012; Lippmann and Chen, 2009). Some investigators have posited a stronger role for carbon-containing PM components, particularly elemental or black carbon. Janssen et al. (2011) conducted a systematic review of the black carbon/health literature and evaluated the value of this constituent as an additional indicator in air quality management. These authors found that the estimated health effects per mass of black carbon (BC) were greater than those for PM_{10} and $PM_{2.5}$. Furthermore, BC effects dominated in two-pollutant models. Janssen et al. calculated that the increase in life expectancy due to reductions in BC in a hypothetical traffic abatement scenario was 4–9 times higher than that due to decreases in $PM_{2.5}$, and concluded that black carbon "is a valuable additional air quality to evaluate the health risks of air quality dominated by primary combustion particles." Grahame et al. (2014) conducted a critical review of epidemiological and toxicological literature regarding carbonaceous combustion emissions, and concluded that BC from various sources appears to be causally involved in all-cause, lung cancer, and cardiovascular mortality, morbidity, and perhaps adverse birth and nervous system effects. These authors applied the causality framework used by EPA in the ISA and concluded that there is a causal relationship between BC/EC for all-cause and various cardiovascular disease (CVD) mortality and morbidity endpoints. Grahame and Schlesinger (2010) had previously concluded in a review of cardiovascular health and vehicular PM emissions that "it may be desirable to promulgate a black carbon $PM_{2.5}$ standard under the National Ambient Air Quality Standards, which would apply to both on and off-road diesels."

Rohr and Wyzga (2012) recently published a review of the short-term health effects of PM components. That review found that the majority of the studies yielded significant findings for specific components of PM, but not for $PM_{2.5}$ mass concentration, suggesting that PM composition is the primary driver of health responses. Overall, no major component of PM studied was unequivocally not associated with health responses. That review motivated the need to examine the long-term effects of PM in the same context; the result is this paper. The current article approaches the issue of long-term health effects of PM components in a similar fashion and summarizes the relevant epidemiological and toxicological literature. Because of the paucity of chronic toxicological studies that consider multiple components—for example, those using concentrated ambient particles (CAPs)—we also consider single-component studies and investigations of specific emissions types. We discuss consistency of the long-term results with those of the previously reviewed short-term studies. Finally, we outline research needs that, if addressed, would facilitate a better understanding of the public health risks associated with long-term exposure to PM constituents.

Methods

We searched the peer-reviewed literature (published as of October 1, 2014) on long-term exposure to $PM_{2.5}$ components and health effects, considering epidemiological and in vivo toxicological studies. The focus on long-term studies eliminated in vitro toxicological studies and controlled human exposure studies from consideration. We used PubMed, entering search terms of "particulate matter," "components," "toxicology," "epidemiology," "sulfate," "carbon," "health," "long term," "chronic," "diesel," "gasoline," "wood smoke," "coal fly ash," and "coal dust" in various combinations.

Our criteria for inclusion in this review were as follows:

(a) Intended to generate information on the long-term effects of $PM_{2.5}$ (since Rohr and Wyzga [2012] covered short-term studies). Therefore, long-term cohort epidemiological studies were included, as were chronic toxicology studies. Time-series epidemiological studies were not included, nor were ecological or cross-sectional studies relying on exposure measures that did not reflect an extended period of time (>5 months). While the true definition of a chronic toxicology study is at least 12 months duration, we expanded the scope to include subchronic studies of at least 5 months duration.

(b) Epidemiological studies included at least one PM component as well as $PM_{2.5}$ mass and included quantitative statistical analyses to relate adverse health outcomes to individual $PM_{2.5}$ components. Toxicological studies included at least one PM component, such as sulfate, or focused on a specific PM type, such as coal dust, engine emissions, or wood smoke.

(c) Studies that only considered groupings of pollutants or source factors were not considered unless they also presented results for individual components.

(d) In an effort to consider more contemporary exposures to PM, epidemiological studies published before 2000 were not considered. $PM_{2.5}$ constituents were rarely considered in studies published before 2000; the only two studies of which we are aware that did consider components prior to 2000 have more recent publications that are included in this review. However, due to the paucity of relevant long-term toxicology studies, we did include pre-2000 toxicological literature. Our cutoff date for inclusion of new material was October 1, 2014.

(e) Several papers reported results of meta-analyses of European cohorts as part of the ESCAPE (European Study of Cohorts for Air Pollution Effects) study. In this review, we only considered the results from the meta-analyses and not from the individual studies, except in the limited cases where a paper was published describing in detail the results of a specific cohort study.

We further note that statistically significant associations are emphasized; nonsignificant associations are generally not reported in this paper.

Results

Epidemiological studies

The epidemiological studies reviewed herein are of a cohort design. These studies generally collect individual-level data, such as education, body mass index, smoking history, and other potential confounding variables. In some cases these data were not available at the individual level, and the studies utilized summary data for the geographic area of study to estimate the impacts of these ancillary factors. For example, in an ideal cohort study, smoking status and history of each study subject would be known, and this information could be factored into the analyses of health status and air quality. In the absence of such data, census tract or other regional estimate of average smoking status and history could be used instead.

Individual-level data are more accurate and are preferred, but their benefits are related to the ways in which they are included in the analyses. For example, the relationship between smoking and health is complex. If the adjustments for smoking are too simple (e.g., do not reflect cumulative smoking history) or do not reflect understanding of this issue, individual-level data may be no more useful than geographic data. The same holds true for the many other variables that are estimated at the individual level. It should be noted, however, that cohort studies have ecological aspects. Air quality data from monitoring stations are most often considered to represent individual exposures, since individual-level exposure data are not available for all members of the cohort. It should be noted that ambient measures are proxies for individual-level doses to the target lung area. To the extent that proxy is incorrect, there is measurement error associated with the exposure variable. This has implications for measures of association, but addressing this issue is beyond the scope of this paper. Some cohort studies also consider contextual variables to characterize the neighborhoods in which individuals live. As these variables are applied to all individuals in that neighborhood, consideration of such variables adds to the ecological aspects of these studies.

Early long-term epidemiological studies of PM considered only $PM_{2.5}$ mass (e.g., Dockery et al., 1993); later studies introduced one component, most typically sulfate (e.g., Jerrett et al., 2007). Consideration of only one component makes it very difficult to make any inference about the relative importance of various components. In this paper, we differentiate between those studies that examined more than one component (Table 1) and those that examined only one component along with PM mass (Table 2). In reviewing the various studies, it is clear that in some cases, the same population database was used to generate many different analyses and results. In these cases, this review emphasizes the most recent results or those that considered the greatest number of PM components.

Studies considering more than one $PM_{2.5}$ component. Relatively few long-term studies considered more than one PM component (Table 1). A straightforward comparison of the relative strengths of the associations between various components and health measures is complicated by the fact that different components have different degrees of measurement errror associated with them. For example, a regional pollutant such as secondary sulfate will have less spatial heterogeneity than a localized pollutant such as elemental carbon (EC). These differences can impact the estimates of association between the component and health event; by and large, the greater the exposure error, the greater is the bias of the estimate toward zero (Szpiro et al., 2011). As mentioned earlier, since the relevant exposure measure is the pulmonary dose, this consideration adds to the measurement error associated with exposure estimates. Only one of the studies considered in the following (Bergen et al., 2013) addressed measurement error explicitly.

Lipfert et al. (2009) considered many different components of $PM_{2.5}$, including arsenic, benzene, chloride, elemental carbon, formaldehyde, manganese, nickel, nitrate, sulfate, and polycyclic organic matter, as well as $PM_{2.5}$ mass, in several analyses. Results varied somewhat depending upon the analysis and available data, but all analyses considered the relationship between PM components and total mortality among a group of U.S. male veterans, who were treated at Veterans Administration hospitals in the United States and diagnosed as hypertensive or borderline hypertensive. By and large, $PM_{2.5}$ mass was not significantly associated with mortality, but several components of $PM_{2.5}$ were. Significant components included "diesel particulate matter," nitrate, elemental carbon (EC), Ni, polycyclic organic matter, and Pb. Sulfate showed a significant negative association with mortality. In addition, several non-PM pollutants, including benzene and formaldehyde, were significantly associated with mortality. When pollutants were considered jointly with measures of traffic density, Pb was no longer significant, while the other species retained significance. In this study, "diesel particulate matter" was defined by the EPA as the weighted average of several pollutants associated with diesel emissions. Except for models that jointly examined air quality variables and traffic density, no multipollutant models were run. Multipollutant models can provide more information about the relative toxicity of components, but the issues of differential measurement error and high correlation among components warrant consideration in the interpretation of results from these models.

Ostro et al. (2010) considered several PM components in a cohort of California teachers; participants were current and former female public school professionals who were enrolled in 1995 and followed through 2007. The resulting cohort consisted of about 45,000 women with about 2600 deaths. In a letter to the journal after publication (Ostro et al., 2011), more limited results were presented, for example, no multipollutant model results and no consideration of alternative exposure metrics. Single-pollutant models indicted all of the components monitored ($PM_{2.5}$ mass, EC, organic carbon [OC], sulfate, Fe, K, Si, Zn) in associations with ischemic heart disease deaths. Fewer pollutants ($PM_{2.5}$ mass, sulfate, nitrate, Si) were significantly associated with cardiopulmonary deaths, and no significant associations were observed for all-cause and pulmonary mortality. No multipollutant model results were presented.

Table 1. Epidemiological studies with $PM_{2.5}$ and two or more components

Reference	Study location	Study period	Study population	Endpoint evaluated	Pollutants studied	Significant results		Comments
						One-pollutant models	Multipollutant models	
Basu et al., 2013	California	2000–2006	646,000+ full-term births	Reduced birth weight	$PM_{2.5}$, Al, ammonium, Br, Ca, Cl, Cu, EC, Fe, Pb, Mn, Ni, OC, K, Si, Na, sulfate, Ti, nitrate, V, Zn	$PM_{2.5}$, Fe, Ti, V, sulfate, EC, Mn, Cu, Br, ammonium, Zn, nitrate, Ni, K, OC	Not reported	Results for full-term exposure; results for trimester exposure generally lower and not consistent
Eeftens et al., 2014	Europe	1995–2006	3 to 5 cohorts with 4800+ participants, trace element dependent	Pediatric lung function	Cu, Fe, K, Ni, S, Si, V, Zn	Not significant	When adjusted for $PM_{2.5}$, Ni significant for FVC	Part of ESCAPE. Single pollutant results presented only for FEV1: Cu 1/5 cohorts; Fe 1/5 cohorts; S 1/5 cohorts, Si 1/5 cohorts
Fuertes et al., 2014	Europe	1994–2008	7 European birth cohorts, 16,000 participants	Early-life pneumonia	Cu, Fe, K, Ni, S, Si, V, Zn	Not significant	Not reported	Part of ESCAPE. Significant positive results for Fe (2/7 cohorts), S (negative, 1/6 cohorts), Si (1/6 cohorts), Zn (1/7 cohorts)
Lipfert et al., 2008	United States	1976–2001	70,000+ male veterans	Mortality	PM2.5, diesel PM, benzene, EC, Ni, As, Cl, Pb, Hg, Mn, sulfate	Benzene, diesel PM, EC, NOx, Ni, As, Cl, Pb, Hg	With traffic only: diesel PM, Cl, sulfate (negative)	
Madrigano et al., 2011	Greater Boston, MA	1999–2007	Older men	DNA methylation	$PM_{2.5}$, BC, sulfate	Not significant for exposures over 90 days	Not reported	Maximum exposure 180 days. Significant associations with BC for exposures of 28, 45, 60, and 90 days; with sulfate for 90 days
Ostro et al., 2011	California	1995–2007	130,000+ female public school professionals	Mortality: total, cardiopulmonary, IHD, pulmonary	$PM_{2.5}$, EC, OC, sulfate, nitrate, Fe, K, Si, Zn	All cause: not significant; cardiopulmonary: $PM_{2.5}$, sulfate, nitrate, Si; IHD: $PM_{2.5}$, EC, OC, sulfate, nitrate, Fe, K, Si, Zn; pulmonary: not significant	Not reported	Corrected update of Ostro et al. (2010); exposure considered 30 km from monitor
Sun et al., 2013	United States	2000–2008	About 6300 subjects in 6 U.S. cities	Subclinical CVD markers: CIMT, CAC	$PM_{2.5}$, EC, OC, Si, S	CAC: not significant; CIMT: $PM_{2.5}$, EC, OC, S	OC most robust	Si results sensitive to model, exposure characterization
Thurston et al., 2013	United States	1982–2004	CPS-II cohort, 445,000+ participants	Mortality: all-cause, pulmonary, IHD, lung cancer	$PM_{2.5}$, As, Ca, Cl, Fe, Pb, Mn, Ni, Se, V, Si, Zn, K, Na, OC, EC, S	All cause: As, Se, S; IHD: PM2.5, As, Cl, Fe, Pb, Ni, Se, Zn, EC, S; pulmonary: PM2.5, Ca, Cl (negative), Ni (negative), OC; lung cancer: S	Not reported	

Vedal et al., 2013	United States	1994–2005	90,000 postmenopausal women in 45 U.S. cities	CVD events, coronary heart disease	$PM_{2.5}$, EC, OC, S, Si	CHD: $PM_{2.5}$, S; cerebrovascular disease: $PM_{2.5}$, OC; MI: S; coronary revascularization: S; stroke: $PM_{2.5}$, OC, S; CVD mortality: OC	Not reported	
Vedal et al., 2013	United States	2000–2007	About 6800 participants in 6 U.S. cities	Subclinical CVD markers: CAC, CIMT	$PM_{2.5}$, OC, EC, S, Si, Cu, Ni, V	CAC; log (CAC): Si, EC (negative and positive), OC, Cu; CIMT: $PM_{2.5}$, S, OC, Cu	Not reported	Bergen et al. (2013) addressed measurement error for this cohort; OC, Si, S all significant after adjustment
Wang et al., 2014	Europe	1985–2007	19 European cohorts with 320,000+ participants	Cardiovascular mortality	Cu, Fe, K, Ni, S, Si, V, Zn	Not reported	Not reported	Part of ESCAPE. Significant positive results for 1/19 cohorts; Si 3/16 cohorts; Zn 4/19 cohorts
Wilhelm et al., 2011	Southern California	6/2004–4/2006	About 111,000 births in Los Angeles County	Preterm birth	Naphthalene, benzo(g,h,i) perylene, total PAHs, OC, EC, nitrate, PM2.5, diesel PM2.5, V, biomass PM2.5	Naphthalene, total PAHs, benzene, OC, EC, nitrate, diesel $PM_{2.5}$, sulfate, biomass $PM_{2.5}$	Multi-pollutant models with ammonium nitrate, ammonium sulfate, geological $PM_{2.5}$: $PM_{2.5}$	PAHs not included in two-pollutant models

Table 2. Epidemiological studies with $PM_{2.5}$ and one component

Reference	Study location	Study period	Study population	Endpoint evaluated	Pollutants studied	Significant results		Comments
						One-pollutant models	Two-pollutant models	
Beelen et al., 2008	Netherlands	1986–1997	114,378 Dutch subjects	Lung cancer risk	BC, $PM_{2.5}$	Only significant result was for BS in never-smokers	Not reported	Included in ESCAPE
Beelen et al., 2014	Europe	1992–2005 (cohort-dependent)	22 European cohorts	Mortality	$PM_{2.5}$, PM_{abs}, PM_{10}, NOx	$PM_{2.5}$	Nonsignificant adjusted for NOx; no $PM_{2.5}$-PM_{abs} joint models	Model 3; most comprehensive set of confounders. Part of ESCAPE.
Cesaroni et al., 2014	Europe	1992–2007 (cohort-dependent)	11 European cohorts	Acute coronary events	$PM_{2.5}$, PM_{abs}, PM_{10}, NOx	$PM_{2.5}$	Not reported	Model 3; most comprehensive set of confounders. Part of ESCAPE.
Dimakopoulou et al., 2014	Europe	1992–2007 (cohort-dependent)	16 European cohorts	Nonmalignant respiratory deaths	$PM_{2.5}$, PM_{abs}, PM_{10}, NOx	Not significant.	Not reported	Part of ESCAPE.
Fuks et al., 2014	Europe	1992–2008 (cohort-dependent)	15 European cohorts	Blood pressure	$PM_{2.5}$, PM_{abs}, PM_{10}, NOx	Systolic BP: PM_{coarse}, PM_{10}, NOx; Diastolic BP: $PM_{2.5}$	Not reported	Part of ESCAPE.
Gan et al., 2010	Vancouver, Canada	1994–2002	Metropolitan Vancouver	Coronary heart disease hospitalizations and mortality	BC, $PM_{2.5}$	BC: hospitalization, mortality	BC remained significant for hospitalization and mortality	
Gan et al., 2013	Vancouver, Canada	1994–2002	Metropolitan Vancouver	COPD hospitalizations and mortality	BC, $PM_{2.5}$	BC: hospitalization, mortality	BC remained significant for hospitalization and mortality	
Gehring et al., 2013	Europe	1995–2006 (cohort dependent)	5 European cohorts	Pediatric lung function	$PM_{2.5}$, PM_{abs}, PM_{10}, NOx	Using address at birth: not significant Using current address: NOx, PM_{abs}, $PM_{2.5}$	Not reported	Part of ESCAPE.
Gruzieva et al., 2014	Europe	1995–2006 (cohort dependent)	5 European cohorts	Allergic sensitization	$PM_{2.5}$, PM_{abs}, PM_{10}, NOx	Not significant	Not reported	Part of ESCAPE.
Guxens et al., 2014	Europe	1997–2008 (cohort dependent)	6 European cohorts	Measures of cognitive and psychomotor development	$PM_{2.5}$, PM_{abs}, PM_{10}, NOx	Not significant	Not reported	Part of ESCAPE. Significant associations with NOx.
Jerrett et al., 2007	United States	1982–2000; five discrete time periods considered (1982–1986, 1987–1990, 1991–1994, 1995–1998, 1999–2000	ACS cohort	Mortality	$PM_{2.5}$, sulfate	$PM_{2.5}$: cardiopulmonary mortality 1982–2000 $PM_{2.5}$: cardiopulmonary mortality 1995–1998, 1999–2000 $PM_{2.5}$: cardiopulmonary mortality 1995–1998, 1999–2000 Sulfate: all cause mortality 1982–1986, 1987–1990; cardiopulmonary mortality 1982–1986, 1999–2000	Not reported	

Krewski et al., 2012	United States	1982–2000	ACS cohort	Mortality	$PM_{2.5}$, sulfate	$PM_{2.5}$: all cause, cardiopulmonary, CVD mortality Sulfate: all cause, cardiopulmonary, CVD, lung cancer mortality	Not reported	
Lenters et al., 2010	Netherlands	1999–2000	750 young adults	Vascular damage	BC, $PM_{2.5}$	Not significant	Not reported	$PM_{2.5}$ significant for never-smokers
MacIntyre et al., 2014	Europe	1994–2010	10 European cohorts	Pediatric respiratory infections	$PM_{2.5}$, PM_{abs}	Pneumonia: $PM_{2.5}$	Not reported	Part of ESCAPE.
Pedersen et al., 2013	Europe	1994–2011	12 European cohorts	Low birthweight	$PM_{2.5}$, PM_{abs}	$PM_{2.5}$	$PM_{2.5}$ remained significant when adjusted for PM_{abs}, NOx	Part of ESCAPE.
Pope et al., 2002	United States	1982–1988	ACS cohort	Mortality	$PM_{2.5}$, sulfate	$PM_{2.5}$: all-cause, cardipulmonary, lung cancer mortality; sulfate: all-cause, cardiopulmonary, lung cancer, all other cause mortality	Not reported	
Raaschou-Nielson at al., 2013	Europe	Since 1990s (cohort dependent)	17 European cohorts	Lung cancer incidence	$PM_{2.5}$, PM_{abs}	$PM_{2.5}$	Not reported	Part of ESCAPE.
Schikowski et al., 2014	Europe	Pre-2008–2011	4 European cohorts	Prevalence, incidence of COPD	$PM_{2.5}$, PM_{abs}	Not significant	Not reported	Part of ESCAPE.
Stafoggia et al., 2014	Europe	1992–2007	11 European cohorts	Incidence of cerebrovascular events	$PM_{2.5}$, PM_{abs}	Not significant	Not reported	Part of ESCAPE.

The other major U.S. studies that considered several components were the Health Effects Institute (HEI)-funded National Particle and Component Toxicity (NPACT) studies. Two published NPACT studies were relevant to this paper (Thurston et al., 2013; Vedal et al., 2013). These studies were published in an HEI report along with the comments of an HEI review panel of independent experts, who expressed their evaluations of the reported research findings. Thurston et al. (2013) examined the association between mortality among a group of individuals in the American Cancer Society cohort, which has been extensively studied in the past. The analysis identified source factors using positive matrix factorization (PMF); factors were labeled as oil, metals, traffic, salt, residual oil combustion, steel industry, coal combustion, and biomass combustion. The investigators also conducted component-specific analyses, including As, Ca, Cl, Fe, Pb, Mn, Ni, Se, V, Si, Zn, Si, K, Na, EC, OC, and S; they considered $PM_{2.5}$ mass as well. Two general models (standard Cox and random effects models) were applied in this analysis; by and large, both models yielded similar results with exceptions noted in the following. Within these model frameworks the investigators considered models with and without ecological covariates; in this review we emphasize the most complex model that included ecological covariates. For all-cause mortality, significant associations were found for the traffic and coal combustion factors, $PM_{2.5}$ mass, As, Se, EC, and S. Respiratory mortality was significantly associated with the traffic factor, $PM_{2.5}$ mass, Ca, Si, and OC; associations with Cl and Ni were significantly negative. In one model the biomass combustion, salt, and residual oil combustion factors were significantly negatively associated with respiratory mortality. Ischemic heart disease was the only specific cause of cardiovascular mortality considered, as this was found to be the most sensitive cardiovascular endpoint in a previous study; these analyses reported significant associations for the metal, traffic, and coal combustion factors, $PM_{2.5}$ mass, As, Cl, Fe, Pb, Ni, Se, Zn, EC, and S. It would be informative to have considered other specific, and total, cardiovascular causes of death in the analysis. For lung cancer mortality, significant associations were reported for Se and S. No results for multipollutant models were presented. The paper's conclusions emphasized the importance of sulfur and coal combustion as predictors of mortality; however, the HEI review panel felt that significant measurement error associated with organic particles could have biased the associations downward, and felt that overall conclusions should indict this category as well.

Vedal et al. (2013) examined two cohorts. The first was a cohort of 6800 people recruited between 2000 and 2002 in 6 U.S. cities (Vedal et al., 2013) as part of the Multi-Ethnic Study of Atherosclerosis (MESA). The cohort had no previous history of cardiovascular disease and included significant numbers of individuals from four racial–ethnic groups. Subclinical markers that could be precursors for cardiovascular disease were considered, specifically carotid intima-media thickness (CIMT) and coronary artery calcium (CAC). These markers were measured at the time of recruitment and at subsequent examinations. Several components were measured, but the paper presents results for $PM_{2.5}$ mass, OC, EC, S, Si, Al, As, Cu, Fe, K, Ni, V, and Zn. The other elements measured either had few measurements above the level of detection or showed no significant associations with any health parameter. The analyses included several models with different sets of potentially confounding variables, such as age, sex, race, education, income, medical history, as well as city where the subject resided. The investigators specified one model as the primary model, with the others serving to indicate the relative robustness of results. Except for those models that included city of residence, the results were largely similar across models. In the primary model, significant associations were observed between CIMT and $PM_{2.5}$ mass, S, OC, and Cu. When city of residence was included in the model, the confidence limits for the estimated associations increased markedly, and only sulfate and copper remained significant in one of the two models that included city of residence. The investigators considered several methods to estimate individual exposure as accurately as possible. Further analyses considering measurement error in a limited way found significant associations for OC, Si, and S and the CIMT endpoint. The CAC endpoint was significantly associated with Si and EC; in models that adjusted for city of study, nickel and copper were significantly associated with CAC; in other models, vanadium was negatively associated with CAC.

The second cohort studied by Vedal et al. (2013) was comprised of 90,000 women in 45 U.S. cities participating in the Women's Health Initiative (WHI). This was a cohort of postmenopausal women with no prior history of cardiovascular disease from 45 cities in the United States. Women entered the cohort between 1994 and 1998 and were followed through 2005. The analyses considered the total population of women, but focused on the subpopulation of about 70,000 who were free of cardiovascular disease when they entered the study. The health outcomes of interest were cardiovascular deaths and nonlethal cardiovascular events. The components considered in analyses were $PM_{2.5}$, mass, EC, OC, S, and Si, and considerable effort was expended to predict exposures of the individual subjects to the pollutants of interest. All cardiovascular events were associated with $PM_{2.5}$ mass and S. Some subsets of these events (e.g., stroke) also implicated OC. Results with multipollutant models were not presented, and there was no explicit consideration of differential measurement error. CV deaths were associated with OC only. The issue of measurement error was the subject of a comment by the NPACT Review Panel, which was concerned that the effects of EC could be underestimated.

Bergen et al. (2013) considered measurement error in the smaller cohort analyzed by Vedal et al. They corrected for measurement error using new methods that account for the spatial patterns of predicted exposures. The only significant change identified after consideration of this issue was the emergence of Si as being significantly associated with the subclinical markers. Sun et al. (2013) undertook additional analyses of this cohort, examining alternative exposure measures and two-pollutant models. CIMT associations were sensitive to model and exposure characterization, and $PM_{2.5}$ mass, EC, OC, and S showed significant associations with this indicator in at least one model. There were no significant

associations with Si. In joint pollutant models, OC was the most robust predictor of CIMT response. No pollutant measure was significantly associated with either the presence or extent of CAC.

There was a series of analyses/papers that reported the results of the European ESCAPE study of several cohorts. Three of these papers (Wang et al., 2014; Fuertes et al., 2014; Eeftens et al., 2014) considered several trace elements (Cu, Fe, K, Ni, S, Si, V, and Zn) in association with cardiovascular mortality, early-life pneumonia, and lung function in children. Neither the Wang et al. nor the Fuertes et al. studies reported any statistically significant associations. Wang et al. incorporated results from 19 European cohorts; the total population studied was about 322,000, with about 9500 cardiovascular deaths. The Fuertes et al. study was based upon seven birth cohorts from six different European countries; about 16,000 births were included in these cohorts. Eeftens et al. found that Ni was significantly associated with a decline in forced vital capacity.

Two studies considered reproductive endpoints in California cohorts. Wilhelm et al. (2011) studied a cohort of births from about 110,000 women who lived within 5 miles of an air pollution monitor in southern California from June 2004 through March 2006. Preterm births were related to entire pregnancy exposures of several pollutants, including $PM_{2.5}$ mass, ammonium nitrate, ammonium sulfate, V, PAHs, and some gases, as well as PM associated with diesel, gasoline, and sea salt. In one-pollutant models, total PAHs, OC, EC, nitrate, diesel $PM_{2.5}$, sulfate, and biomass $PM_{2.5}$ were associated with preterm birth incidence. In addition, non-PM pollutants, including naphthalene and benzene, were so associated. Two-pollutant models suggested that nitrate and $PM_{2.5}$ mass dominated the effects; however, PAHs were not considered in these models. Basu et al. (2014) studied a cohort of infants born between 2000 and 2006 to mothers living in California. Results were dependent upon the birth-weight variable used; by and large, multiple components (including ammonium, Br, Cl, Cu, EC, Fe, Pb, Mn, Ni, K, Na, sulfate, Ti, nitrate, V, and Zn) and $PM_{2.5}$ mass were associated with low birth weight. However, lack of multipollutant models makes it difficult to identify a subset of components that may be more important. Moreover, interpretation of these results is complicated by the choice of exposure metric, as results differed depending on whether full-term or trimester exposures were considered.

Madrigano et al. (2011) considered a DNA methylation measure in 706 older men in the greater Boston area participating in the Normative Aging Study. DNA methylation is associated with aging and could contribute to any long-term effects of air pollution. Madrigano et al. considered exposures of up to 180 days for $PM_{2.5}$ mass, BC, and sulfate. Two measures of methylation were considered: LINE-1 and Alu. There were no significant results for exposures to $PM_{2.5}$ mass for any exposure period. For the longer exposure periods (≥90 days), the only significant associations were for sulfate and LINE-1 at 90 days, but not for 180 days. There was also a significant association between BC and Alu at 90 days, but not at 180 days.

Studies considering only one $PM_{2.5}$ component. Long-term studies that investigated $PM_{2.5}$ mass and only one other component are summarized in Table 2. Several of the more recent studies in this category are part of the European ESCAPE initiative and are meta-analyses of results from several European cohorts. The cohorts considered in each meta-analysis differed by health endpoint, as every cohort did not consider every health endpoint analyzed. The cohorts were from Western Europe and varied in size from about 2400 subjects to over 115,000 subjects. The baseline period of entry and follow-up time also varied across studies although most studies were able to follow subjects for at least 10 years. Many of the ESCAPE studies also considered PM_{10} and NO_x, but these pollutants are not the subject of this review. The only component of $PM_{2.5}$ that was considered was defined as "$PM_{2.5}$ absorbance," often referred to as black smoke (BS) or black carbon (BC), which is highly correlated with EC measures (Eeftens et al., 2012).

The ESCAPE studies considered a wide range of health endpoints, including mortality by several cause categories (Beelen et al., 2014; Dimakopoulou et al., 2014; Wang et al., 2014), several morbidity measures (Cesaroni et al., 2014; MacIntyre et al., 2014; Raaschou-Nielsen et al., 2013; Schikowski et al., 2014; Stafoffia et al., 2014; Fuertes et al., 2014), physiological measures (Fuks et al., 2014; Gehring et al., 2013; Gruzieva et al., 2014), and reproductive measures (Pederen et al., 2013). The results from these studies varied according to the endpoint studied, with cardiovascular endpoints generally showing a significant association with $PM_{2.5}$ mass, but not with $PM_{2.5}$ absorbance (Cesaroni et al., 2014). The same was true for pediatric pneumonia, low birth weight, and lung cancer incidence (MacIntyre et al., 2014; Pedersen et al., 2013; Raaschou-Nielsen et al., 2013). Lung function in children was associated with both $PM_{2.5}$ and $PM_{2.5}$ absorbance (Gehring et al., 2013). Cerebrovascular events, nonmalignant respiratory deaths, prevalence and incidence of chronic obstructive pulmonary disease (COPD), and allergic sensitization measures were not significantly associated with any PM measure (Stafoggia et al., 2014; Dimakopoulou et al., 2014; Gruzieva et al., 2014; Schikowski et al., 2014). None of these studies considered multipollutant models. Beelen et al. (2008) presented the detailed results for one of the cohorts included in the ESCAPE study, a study of approximately 115,000 Dutch subjects. They examined the relationship between lung cancer and $PM_{2.5}$ and BC. The only significant relationship reported was between BC and lung cancer in never smokers; results for other groups were not significant. The authors did not consider any joint models with both $PM_{2.5}$ and BC.

Three papers reported the results for a large U.S. cohort of individuals recruited by the American Cancer Society (Krewski et al., 2005; Pope et al., 2002; Jerrett et al., 2007) and considered $PM_{2.5}$ mass along with sulfate in relation to mortality. Krewski et al. and Pope et al. reported very similar results; the Krewski et al. analyses included two more years of follow-up than Pope et al. All three studies reported significant associations between $PM_{2.5}$ and all-cause, cardiopulmonary, and lung cancer mortality. Krewski et al. and Pope et al. also found

sulfate to be significantly associated with these categories, as well as mortality from all other causes. Krewski et al. reported similar results for cardiovascular disease mortality, but found no significant associations between either pollutant and respiratory mortality, other (nonlung) cancers, and other cause mortality. Jerrett et al. (2007) analyzed five different time periods (1982–1986; 1987–1990; 1991–1994; 1995–1998; 1999–2000) and considered exposure metrics from these periods. $PM_{2.5}$ mass was associated with cardiopulmonary deaths, especially in the latest time period (1999–2000), with both concurrent and lagged exposure variables. Sulfate was associated with cardiopulmonary mortality, but largely in the earliest time period (1982–1986). Sulfate was also associated with all-cause mortality in the two earliest time periods. It is unclear why these differences occurred over time, although there has been a decrease in sulfate levels over time. The number of observations for each time period in the Jerrett et al. paper are smaller, resulting in greater variability of estimated relative risks, but there is a clear demarcation between results of the earlier two periods and the latter three for sulfate. For $PM_{2.5}$, a time trend is less clear.

Two papers investigated hospitalizations and deaths for coronary heart disease (Gan et al., 2010) and for chronic obstructive pulmonary disease (COPD) (Gan et al., 2013) associated with $PM_{2.5}$ and BC in metropolitan Vancouver, Canada. The cohort consisted of all metropolitan Vancouver residents who were registered with the provincial health insurance plan in 1999 and who resided in the study area for 5 years and were 48–85 years old. In the 2010 cohort subjects had no previous diagnosis of coronary heart disease; in the 2013 cohort there was no previous diagnosis of COPD. Both papers reported significant associations with BC for both deaths and hospitalizations for both disease categories. There were no significant associations between $PM_{2.5}$ mass and COPD in any model adjusted for demographic and socioeconomic variables. For coronary heart disease $PM_{2.5}$ mass was significantly associated with hospitalizations but not for mortality. These associations with BC in both studies persisted in joint models with $PM_{2.5}$ mass.

A study of young adults in the Netherlands (Lenters et al., 2010) found no significant associations between either $PM_{2.5}$ mass or BC and vascular damage in a population-based cohort of those born between 1970 and 1973, who attended secondary school in Utrecht, the Netherlands, and who agreed to participate in the study. A subpopulation of never smokers showed significant associations with both $PM_{2.5}$ mass and BC.

Toxicological studies

The toxicological literature on long-term effects of particulate matter components is generally comprised of subchronic studies of concentrated ambient particles; studies evaluating sulfate (in either acidic or neutralized form); studies of coal fly ash and coal dust; and subchronic studies of specific emissions such as gasoline or diesel engine exhaust. Each of these is covered in the subsections that follow.

Studies using concentrated ambient particles (CAPs). There have been a handful of studies involving subchronic (generally 5- to 6-month) exposures to CAPs in various regions of the United States. Many other CAPs studies have investigated short-term effects; however, these fall outside the scope of this paper and have been covered in a previous publication (Rohr and Wyzga, 2012). The reader is also referred to Lippmann and Chen (2009), who published a comprehensive review of the toxicological effects of CAPs and its components.

All of the longer term CAPs studies have been conducted by a group at New York University, and all have evaluated cardiovascular effects. The first subchronic study, conducted in Tuxedo, NY, in spring/summer 2003, consisted of 5–6 months of daily exposures (5 days/week, 6 hr/day) in $ApoE^{-/-}$ mice. Results of this large study were reported in a special issue of *Inhalation Toxicology* (Maciejczyk et al., 2005; Hwang et al., 2005; Chen and Hwang, 2005; Chen and Nadziejko, 2005; Gunnison and Chen, 2005; Veronesi et al., 2005; Maciejczyk and Chen, 2005; Lippmann et al., 2005a, 2005b). However, none of these papers evaluated the potential influence of CAPs composition on long-term biological responses. Lippmann et al. (2005c) used the source apportionment, heart rate (HR), and heart-rate variability (HRV) data generated in this prior research effort to evaluate the associations between PM source factors and changes in cardiac function. However, because associations with individual PM components were not reported, the results are not discussed here.

Lippmann et al. (2006) conducted a 6-month study in Tuxedo, NY, in 2004–2005, also with $ApoE^{-/-}$ mice. They noted that on days when the animals had unusually high HR, the responses were most closely associated with the Ni, Cr, and Fe content of $PM_{2.5}$. Back trajectory analyses indicated that on these days, winds predominantly came from a Ni smelter near Sudbury, Ontario, and avoided heavily populated areas. Further statistical modeling showed that Ni was significantly associated with increases in HR as well as reductions in SDNN, a measure of heart-rate variability. Cr and Fe had nonsignificant associations.

In another study (Chen et al., 2010), $ApoE^{-/-}$ mice were exposed to CAPs in Tuxedo and Manhattan, NY, for 6 months in 2007. Lag structure was investigated as well as component-specific and source factor associations with cardiac function. In single-component analyses with Manhattan CAPs, Br, EC, Na, Ni, P, S, V, Al, and Se were each associated with at least one lag (0 day, 1 day, or both). In Tuxedo, S was associated with a 0-day lag, Br and Zn with 1-day lags, and Si with both 0- and 1-day lags. Bipollutant models were also investigated. With CAPs mass, these models found significant associations for Br, EC, S, and Ni in Manhattan and Br, S, Si, and Zn in Tuxedo. In bipollutant models with EC, the most important components were found to be EC, Ni, and S in Manhattan and Cr, Ni, and V in Tuxedo. Bipollutant models with S revealed that S was not an important predictor of effects, as all elements showed stronger associations than S, except for a 0-day lag in Tuxedo. Source factor analyses indicated that in Manhattan, the largest number of significant effects (all models, all cardiac parameters, all lag times) was observed for a residual oil factor. After that, long-range transport > traffic > Fe/Mn > incineration > soil. The fireworks factor

showed no significant associations. In Tuxedo, long-range transport > Ni refinery > soil > residual oil combustion/traffic.

The New York University (NYU) group recently completed a 6-month CAPs exposure study in $ApoE^{-/-}$ mice as part of the Health Effects Institute-funded National Particle Component Toxicity (NPACT) initiative (Lippmann et al., 2013, 2014). Five locations were studied based on their varying air quality profiles and predominant PM sources: Manhattan, NY; Tuxedo, NY; Seattle, WA; East Lansing, MI; and Irvine, CA. Manhattan has Ni, elemental carbon (EC), and organic carbon (OC) in PM along with long-range transported material from several sources; Tuxedo PM is dominated by long-range transport; Seattle has high levels of wood smoke in the winter; East Lansing is influenced by coal-fired power plant emissions; and Irvine $PM_{2.5}$ is predominantly related to mobile sources. Nine source categories were resolved for Manhattan, three for Tuxedo, four for East Lansing, six for Seattle, and six for Irvine. The categories were not the same across locations, with some source factors being present in only some cities, and some similarly labeled source factors across cities having different composition. Three lag structures (0, 1, and 2 days), four times of day (during exposure, afternoons, late evenings, and overnight), and 16 elemental components of PM were considered. Significant differences were found in HR, SDNN, or RMSSD between the CAPs-exposed and control mice—including 29 such differences at Manhattan, 26 at Tuxedo, 9 at East Lansing, 5 at Seattle, and 3 at Irvine. The investigators suggested that certain components of $PM_{2.5}$ (such as sulfur) that were found in much lower concentrations at East Lansing, Seattle, and Irvine were the most efficacious at producing these electrocardiograph (ECG) changes. When the investigators regressed the five-site mean component concentrations with the most significant responses in terms of HR, SDNN, and RMSSD, the largest correlation coefficient was for Ni (r^2 = 0.96), followed by Al (r^2 = 0.81), EC (r^2 = 0.79), P (r^2 = 0.77), S (r^2 = 0.65), V (r^2 = 0.35), Mg (r^2 = 0.30), Zn (r^2 = 0.27), and Se (r^2 = 0.19). In terms of strength of associations, components attributable to source categories for residual oil combustion (Ni, V, and S), coal combustion (S and Se), and traffic (EC, Al, and P) were suggested by the investigators to be the most influential.

Lippmann et al. (2013) also evaluated plaque progression in the carotid artery. Significant plaque progression was found in the mice exposed at Manhattan, Tuxedo, and East Lansing (the investigators noted that at these three sites coal combustion emissions account for a significant fraction of ambient air $PM_{2.5}$) compared with plaque progression in control mice. In Seattle and Irvine, no plaque progression occurred. The investigators stated that these findings suggested that coal combustion as a source category had more influence on plaque progression than other $PM_{2.5}$ source categories. However, they also noted that the small number of sites limited the ability to identify the most influential components or source categories. However, the NPACT Review Panel did not agree with the interpretation that the residual oil combustion and coal combustion source categories were the most important contributors to health effects. In its comments in the report, the panel noted that it is unclear to what extent the larger responses observed in some locations might have reflected higher CAPs exposures, rather than differences in PM composition, since the PM exposure concentrations differed dramatically between cities.

Beyond the concerns noted by the panel, there are other issues that limit interpretation of this study. First, the source apportionment results are highly uncertain and include multiple cases where constituents expected to derive primarily from a specific source category load onto several different factors. For example, the factor analysis in Manhattan resolved a "sulfur-coal" factor and a "secondary aerosol" factor, both with substantial amounts of sulfur. Notwithstanding the fact that the statistical significances of the correlation coefficients between constituent and source factor were not presented, there were commonalities between the two factors, including moderate to high loadings of sulfur as well as OC and EC. Both of these factors represent long-range transported aerosols; thus, they may be more indicative of common atmospheric processing rather than indicating specific sources. In Tuxedo, the "sulfur-coal" factor had only slightly higher sulfur loading than the "soil" factor, and both the sulfur-coal and soil factors had about the same loading of OC. The "sulfur-coal" factor also had by far the highest EC loading of any of the four factors. The East Lansing factor analysis appeared to be more successful at resolving discrete source factors, at least with respect to EC and OC loading predominantly onto an "EC-OC" factor. However, interestingly Se loaded substantially onto both the "sulfur-coal" factor and the "residual oil combustion" factor. The potential misuse of Se as a marker for coal combustion emissions when it may arise from residual oil combustion has been discussed by Grahame and Hidy (2007). Also relevant to the use of Se as a marker for coal-fired power plant emissions (including extensively in this study) is the observation that mean Se concentrations were highest at East Lansing and Irvine (20–21 ng/m^3), intermediate at Manhattan and Tuxedo (9–10 ng/m^3), and lowest at Seattle (6 ng/m^3). Notably, since there are no coal combustion point sources in southern California, the high Se concentrations at Irvine indicate the influence of other sources.

Because very little temporal resolution was possible in terms of assessment of plaque progression over the 6-month exposure periods, the ability to determine which PM components or source factors were most influential on this endpoint was limited. As mentioned earlier, the investigators attributed plaque progression primarily to the coal combustion factor. This conclusion was reached in a qualitative manner by comparing CAPs and S concentrations in the areas where plaque progression was noted (Manhattan, Tuxedo, and East Lansing) and in Seattle and Irvine, where no effect was noted. The authors stated that the fact that S concentrations were highest in the three former cities and lowest in the two latter cities suggests that the coal combustion source factor has a causal role in plaque progression. However, S concentrations in Irvine (7.6 μg/m^3), where no plaque progression was observed, were higher than in Tuxedo (6.5 μg/m^3), where such progression occurred.

In totality, the longer term CAPs studies described here indicate that a number of PM components and source factors are associated with changes in cardiovascular effects. Qualitative evaluation of the data suggests that Ni and the residual oil factor may be more important; indeed, this hypothesis has been forwarded by these investigators (Lippmann et al., 2006).

Studies of neutral and acidic sulfate. The majority of the published data related to individual PM components pertains to sulfate or acidic sulfate, with many of these studies being conducted in the 1970s and 1980s when there was burgeoning interest in acid rain and the potential health effects of acidic air pollution. The focus of these studies has been on the respiratory system; in fact, to our knowledge no long-term studies have investigated extrapulmonary endpoints. We have included pre-2000 studies since little more contemporary literature is available. Overall, while many studies have investigated the short-term impacts of sulfate exposure, longer term studies are less common. It is interesting to note that Amdur et al. (1978) showed that the irritant potency of various sulfate species varied widely, with pure sulfuric acid being the most potent. For this endpoint, such results are not unexpected, given that strongly acidic substances are also strong irritants.

A number of studies have evaluated the toxicological effects of sulfuric acid. Cavender et al. (1978) exposed rats and guinea pigs to 0.5 ppm ozone, 10 mg/m^3 sulfuric acid mist, or their combination for 6 hr/day, 5 days/week, for 6 months. Microscopic alterations were seen in the lungs of guinea pigs exposed to ozone alone or ozone in combination with sulfuric acid; no effects were observed with exposure to H_2SO_4 alone. Schlesinger et al. (1979) exposed donkeys (n = 4) to 102–106 μg/m^3 sulfuric acid mist for 1 hr/day, 5 days/week for 6 months, and monitored mucociliary clearance from the lungs. Clearance became erratic within the first week of exposure, usually slower than controls. Two of the four animals exhibited a sustained impairment of clearance toward the end of the 6-month exposure period and continued to have erratic clearance during the 3-month follow-up period. In another long-term study of sulfuric acid mist, Gearhart and Schlesinger (1988) exposed rabbits to 250 μg/m^3 sulfuric acid mist for 1 hr/day, 5 days/week, for up to 1 year. Bronchial clearance was monitored and was found to become slower during the first month of exposure. The slowing became progressively greater over time. After cessation of exposure, clearance became extremely slow and did not return to normal by the end of a 3-month follow-up period. Histopathological evaluation showed that acid exposure changed the airway diameter distribution compared to controls, with a shift to smaller airways. Exposure also caused an increase in epithelial secretory cell density. Schlesinger et al. (1992) evaluated clearance in rabbits exposed to 125 μg/m^3 sulfuric acid, 0.1 ppm ozone, and their combination for 2 hr/day, 5 days/week, for up to 1 year. Clearance time was affected by sulfuric acid and the mixture, becoming progressively slower following the end of exposures to the pollutant atmospheres. After 12 months of exposure, the number of secretory cells in small airways was increased.

Griese et al. (1999) exposed beagle dogs to 0.36 mg/m^3 of neutral sulfite (16.5 hr/day) and 5.66 mg/m^3 of acidic sulfate (6 hr/day), both for 400 days. Serial bronchoalveolar lavage (BAL) was performed and surfactant-related endpoints, including total phospholipid concentration, were evaluated. Results indicated no significant changes over time and no exposure-related differences.

Heyder and colleagues conducted three long-term studies of sulfur-related air pollution in beagle dogs (Heyder et al., 1992; Heyder et al., 1999; Heyder et al., 2009). In the first, animals were exposed to 0.3 mg/m^3 neutral sulfur(IV) aerosol (sulfite) for 290 days. No indication of chronic bronchitis was observed, but there were some indications of early stages of lung emphysema (Takenaka et al., 1992), as well as changes in the integrity of the alveolar–capillary barrier and reduction in the defense capacity of alveolar macrophages (Maier et al., 1992). Macrophage-mediated particle clearance was also altered (Kreyling et al., 1992), and proliferative changes were observed in the nasal cavity and with ciliated cell development in the trachea (Takenaka et al., 1992).

In the second study, beagle dogs were exposed to 1.5 mg/m^3 neutral sulfite [sulfur(IV)] and acidic sulfate particles carrying 15 μmol/m^3 hydrogen ions for 13 months (Heyder et al., 1999). The objective of the study was to determine whether acidic aerosols modulate adverse effects of neutral sulfate in ambient air. Dogs in the exposure group were exposed to neutral sulfite for 16.5 hr/day and acidic sulfate for 6 hr/day. These concentration–duration combinations were designed such that the dose received by each dog during the entire study was equivalent to the dose received by a person living for about 70 years in an urban environment; thus, the study mimicked lifetime exposure of humans. Evaluation of cellular and molecular parameters of injury (Maier et al., 1999) as evidenced by BAL revealed no clinical symptoms that could be clearly related to exposure. However, the combined neutral + acidic sulfate exposure resulted in some minor biological changes, including proliferation of type II epithelial cells likely caused by minor damage. Overall, findings suggested that possible health effects of neutral sulfate are not enhanced by atmospheric acidity. Kreyling et al. (1999) reported several results indicating alteration in nonspecific respiratory defense capacities, while Schulz et al. (1999) evaluated lung function and found no significant changes in the parameters assessed compared with control animals. Bronchial responsiveness to carbachol was also not affected. Finally, morphological and morphometric changes were evaluated in the test animals (Takenaka et al., 1999). Results indicated no differences between the exposed and control animals, with the exception of a thickening at the entrance to alveoli, which appeared to be due mainly to Type II cell proliferation.

The third and final study was designed to specifically investigate the effects of acidic sulfate, Heyder et al. (2009) exposed beagle dogs to acidic sulfate particles (25 μmol H^+/m^3 or 4.5 mg/m^3) for 13 months), and measured pulmonary responses, including lung function, cell and tissue integrity, redox balance, and nonspecific respiratory defense capacity. The sulfate particles were generated by nebulizing an aqueous sodium hydrogen sulfate at pH 1.5. The paper reported only subtle exposure-

related changes. A significant increase in alveolar macrophage respiratory burst function was observed, along with slightly increased tracheal mucous velocity and reduced in vivo dissolution of semisoluble test particles. Histological analysis revealed no hypertrophy or hyperplasia of bronchial epithelia, but increase in volume density of bronchial glands and a change in pH in epithelial secretory cells in distal airways. The authors concluded that the exposure had no pathophysiological consequences even at a high concentration of 4.5 mg/m^3, and that it is unlikely that long-term inhalation of acidic particles is associated with a health risk.

Overall, the long-term acidic or neutral sulfate exposure studies indicate no or only mild effects on respiratory parameters.

Studies of coal fly ash and coal dust. There is a relatively large literature related to acute or sub-acute inhalation of coal fly ash (CFA), although the published research on chronic studies is sparse. Raabe et al. (1982) exposed rats to 0.6 mg/m^3 and 4.25 mg/m^3 CFA for 8 hr/day for up to 180 days. No effects were observed at the lower exposure level, and only minor effects were observed at the higher level. The authors reported more and larger macrophages in BAL fluid, and minor changes in glycoprotein secretion or viability, adherence, and macrophage phagocytic index. The paper concluded that the changes observed were not coal fly ash-specific and would be expected with any inhaled particle. It should be pointed out, however, that no negative or positive controls were studied. Golden hamsters were exposed to 2 mg/m^3 coal fly ash for 180 days, and phospholipid levels in the lung were measured as an indicator of surfactant accumulation, which is a nonspecific response to inhaled particles (Nishimura and Negishi, 1995). The exposure was found to increase the phospholipid levels in pulmonary tissue but not in the lung surfactant, suggesting that type II cells were accumulating surfactant.

Some studies have investigated effects of exposure to coal dust in an effort to relate findings to occupational mining exposures. Rats exposed for 20 months (6 hr/day, 5 days/week) at 6.6 and 14.9 mg/m^3 of coal dust developed lesions similar to coal worker's pneumoconiosis in humans (Busch et al., 1981). No advanced lesion types, such as micro- or macronodules or infective granulomas, were observed in these animals. Focal bronchiolization occurred. Ross et al. (1962) showed that increasing quartz content of coal dust led to more severe pathology. Rats were exposed to coal dust at 60 mg/m^3 for 16 hr/day for 10 months and quartz content was varied from 5 to 40%. At the lowest quartz content of 5% and 10%, little fibrosis was observed. However, at 20% and 40% quartz, considerable pathology was reported in fibrosis-grade and collagen content. Both of these parameters were correlated with total silica in the lung postexposure. A long-term inhalation study was carried out with coal dust and/or diesel exhaust (Castranova et al., 1985) in which rats were exposed to 2 mg/m^3 coal dust 7 hr/day, 5 days/week, for 2 years. Exposure to coal dust had little effect on oxygen consumption, membrane integrity, lysosomal enzyme activity, or protein content of alveolar macrophages. However, exposure did increase macrophage yield, enhanced chemiluminescence, and increased the activity of the cell membrane (i.e., increased cellular spreading and surface ruffling). In addition, there was no effect on influenza infection in mice (Hahon et al., 1985). Overall, these findings suggest a mild activation of alveolar macrophages, but no impact on viability.

Overall, the available long-term studies of coal fly ash and coal dust exposure report minor changes in biological responses.

Studies of specific emissions. Few studies have involved long-term exposure (for the purposes of this review, considered ≥5 months in duration) to emissions, with the exception of diesel emissions, for which more published papers are available. There is some literature related to gasoline emissions, wood smoke, and coal combustion emissions, discussed in the following. Mauderly (1994) published a review of the health risks of engine emissions, which covers much of the early literature. Additional information on the short-term effects of diesel emissions (as well as epidemiological studies) can be found in the EPA's Health Assessment Document for Diesel Engine Exhaust (EPA, 2002) and in a recent review by the Health Effects Institute (HEI, 2010). Similarly, a review of the health effects of wood smoke exposure has been published by Naeher et al. (2007).

Arguably the most comprehensive toxicological evaluation of various emissions sources was carried out by the National Environmental Respiratory Center (NERC). NERC conducted subchronic (6-month) exposures to four emissions types—hardwood smoke, diesel exhaust, gasoline exhaust, and simulated downwind coal combustion emissions—with the goal of creating a composition-concentration-response database that could be examined for causal components (Mauderly, 2014). For all the emissions, F344 and spontaneously hypertensive (SH) rats, and A/J, C57BL/6, and BALB/*c* mice were exposed 6 hr/day, 7 days/week, for 6 months to the various atmospheres. Different dilutions were performed to allow exposures normalized by particulate matter concentration (30, 100, 300, and 1000 $\mu g/m^3$). Toxicological endpoints included organ weight, histopathology, hematology, serum chemistry, bronchoalveolar lavage, cardiac electrophysiology, micronuclei in circulating cells, DNA methylation and oxidative injury, clearance of *Pseudomonas aeruginosa* from the lung, and development of respiratory allergic responses to ovalbumin. A comparison of the responses to the four exposure scenarios is provided by Mauderly et al. (2014a); individual study results are described in the following in brief. Overall, diesel exhaust induced the largest number of significant responses (33), followed by gasoline exhaust (30), coal combustion emissions (27), and wood smoke (18). It is important to note that these values differ from the results reported in the individual studies, as these reflected an "exposure effect" trend statistic, not *p*-values as reported in the previous reports.

Diesel emissions were generated from a commonly used 2000 model 5.9-L, 6-cylinder turbo diesel engine operated on a variable-load heavy-duty test cycle burning national average certification fuel (Reed et al., 2004). Male and female F344 rats

and A/J mice were exposed by whole-body inhalation to clean air (control) or the different dilutions of whole emissions. Only mild effects on clinical observations, body and organ weights, serum chemistry, hematology, histopathology, bronchoalveolar lavage, and serum clotting factors were observed. Some significant exposure-related effects were found, including decreases in serum cholesterol and clotting Factor VII and slight increases in serum gamma-glutamyl transferase. Several other responses met screening criteria for significant effects but were not consistent between genders or exposure times and were not corroborated by related parameters. Carcinogenic potential was evaluated as micronucleated reticulocyte counts and proliferation of adenomas in A/J mice; however, these parameters were unaffected by 6 months of exposure. In general, findings showed few and only modest health hazards from subchronic exposures to realistic concentrations of diesel emissions.

The gasoline exhaust findings were reported by Reed et al. (2008). Emissions were obtained from 1996 General Motors 4.3-L engines burning national average fuel on a simulated urban operating cycle. PM concentrations were as previously described, with the exception that filtered exhaust at the highest concentration was also evaluated. The most coherent and consistent effects were those related to increased red blood cells; this finding was interpreted to be linked with carbon monoxide exposure (13–107 ppm) in the emissions. Other effects supported by multiple variables included mild lung irritation and depression of oxidant production by alveolar macrophages. The lowest exposure level caused no significant effects. An interesting observation was that only 6 of the 20 significant effects were substantially reversed by filtering PM, which suggests that most of the effect was due to gaseous components of the exhaust.

Hardwood smoke was generated from an uncertified woodstove burning wood of mixed oak species, and F344 rats, SHR rats, A/J mice, and C57BL/6 mice were exposed to the standard dilutions. Effects of exposure on general indicators of toxicity, bacterial clearance, cardiac function, and carcinogenic potential were mild (Reed et al., 2006). There were some exposure-related effects, including increases in platelets and decreases in blood urea nitrogen and serum alanine aminotransferase. As with the diesel exhaust exposures, several other endpoints met screening criteria for significant exposure effects but lacked consistency between genders or exposure times and were not corroborated by related parameters. Very little hardwood smoke-related PM was found to accumulate in lung tissue. In general, only few and mild effects were observed in response to realistic concentrations of hardwood smoke.

Finally, the coal emissions study involved generation of a mixture simulating key components of a “downwind” coal atmosphere (Mauderly et al., 2011). Emissions from low-sulfur subbituminous coal were modified to create a mixture recommended by an expert workshop, with SO_2, NOx, and PM (comprised primarily of partially neutralized sulfate) being the dominant components. F344 and SHR rats and A/J, C57BL/6, and BALB/*c* mice were exposed to the same normalized PM concentrations as in the other three studies; in addition, the highest concentration exposure was filtered to remove PM. Findings showed few significant changes in biological outcomes; in some models, no effects were observed. Results of the filtered atmospheres showed that PM was a significant contributor to response for only three endpoints. Overall, on a total mass or PM mass basis, the coal emissions atmosphere was less toxic than diesel and gasoline exhausts or wood smoke.

While interesting findings were generated from the four individual studies, the power of the NERC program was the ability to exploit the composition, concentration, and response variability to determine which component(s) of air pollution as a whole were driving the responses observed. Mauderly and Seilkop (2014) used Multiple Additive Regression Tree (MART) analysis, which grouped the hundreds of NERC exposure analytes into 45 predictor variables; these were then fitted to each of 47 significant biological responses. Results gave suggestive to strong evidence of causation of 19 of the 47 responses. The top two predictors of the 19 responses included 12 organic and 6 inorganic species or classes. The 12 organic predictor classes included 3 particulate predictors: total particulate organic carbon, particle-borne alkanes, and particle-borne polycyclic aromatics. The 9 nonparticulate organic classes included three classes of carbonyls (aliphatics, alkanals, and ketones), four classes of nonmethane volatiles (alkanes, alkenes, furans, and oxygenated), volatile aliphatic acids, and vapor-phase semivolatile alkanes. The inorganic species included elemental carbon, ammonia, SO_2, NO, NO_2, and nitrate. The strongest evidence for causation was related to an increase in red blood cell count in rats by ammonia, and proatherosclerotic vascular responses in mice by inorganic gases. Overall, responses to PM components were not as strong, although EC, OC, nitrate, particle alkanes, and particle PAHs were among the top predictors, as noted earlier.

Other than the NERC study described earlier (Reed et al., 2006), we were only able to identify two long-term exposure studies to wood smoke. Liang et al. (1988) conducted a field study in which mice and rats were placed in an indoor environment to inhale either air or smoke generated from burning wood or coal. Exposures were 15 months in duration for the mice, and 19 months for the rats. Total suspended particulate (TSP) in these exposures was very high (14.4 and 14.9 mg/m^3 in the coal and wood smoke rooms, respectively). After exposure, incidence of nonmalignant and malignant lung tumors was evaluated. Tumor incidence in mice in the wood smoke group was 45.8%, in the coal smoke group 89.5%, and control mice had a rate of 17%. In rats, 0% of controls had lung cancer, 0% of animals exposed to wood smoke, and 67.2% in the coal smoke group. It should be noted that these exposures were intended to simulate indoor exposure of villagers in Xuan County, China, and the coal used for this domestic purpose differs substantially from coal used for electricity generation. More recently, Zou et al. (2014) assessed small-airway remodeling in rats exposed to wood smoke for 4 to 7 months in an effort to increase mechanistic understanding of chronic obstructive pulmonary disease (COPD) associated with chronic wood smoke exposure. Lung tissues were examined with morphometric measurements, immunohistochemistry, and Western

blotting. Serum concentrations of MMP-9 and TIMP-1 were also measured. Results showed that the area of collagen deposition was significantly increased in the small airway walls of animals exposed to wood smoke for 7 months. Gelatinase expression was increased in whole lung tissue, and MMP-9 and TIMP-1 were increased in serum.

As mentioned earlier, there is more information on the toxicological effects of engine emissions. Mauderly (1994) published a review of the health risks from inhaled engine emissions. In the toxicology section of this paper, he concluded that (1) animal studies have shown that heavy, chronic exposures to both diesel exhaust and gasoline exhaust can cause lung pathology and associated physiological effects; (2) gasoline exhaust has not been shown to be carcinogenic in animals; and (3) chronically inhaled diesel exhaust at high concentrations is a pulmonary carcinogen in rats, but the response is questionable in mice and negative in Syrian hamsters. The current review summarizes the more recent literature (post-1994), but also includes some information on individual studies published prior to that date. It does not discuss all available studies, which date back to 1936.

In the study, mentioned earlier, by Castranova et al. (1985), rats were exposed to 2 mg/m^3 of diesel exhaust for 7 hr/day, 5 days/week, for 2 years. As with coal dust, exposure to diesel exhaust had little effect on oxygen consumption, membrane integrity, lysosomal enzyme activity, or protein content of alveolar macrophages. However, exposure depressed chemiluminescence and decreased the ruffling of the cell membrane. An exposure was also conducted to coal dust and diesel exhaust simultaneously, and the combination resulted in phagocytic activity that was an average of the effects of the separate exposures; that is, no multiplicative effect was observed.

Brightwell et al. (1989) examined the carcinogenicity of automobile engine exhausts using rats and hamsters. Animals were exposed to emissions from (1) a gasoline engine, (2) a gasoline engine fitted with a three-way catalytic converter, (3) a diesel engine, and (4) a diesel engine with particle filtration. Exposures were for 16 hr/day, 5 days/week, for 2 years. No increase in lung tumor incidence was observed in hamsters exposed to emissions. There was also no increase in lung tumors in rats exposed to filtered diesel exhaust or to the exhaust from the gasoline or gasoline-catalyst engines. However, incidence of lung tumors was significantly elevated in rats exposed to diesel engine emissions compared to controls, with a clear dose-response relationship in both males and females.

Mauderly et al. (1994) exposed F344/N rats to diesel exhaust and carbon black at 2.5 and 6.5 mg particles/m^3 for 16 hr/day, 5 days/week, for up to 24 months. The carbon black particles were similar to the soot particles in the diesel engine exhaust; however, they contained markedly lower amounts of adsorbed organic compounds. Toxicological endpoints over a wide variety, as well as tumor incidence, were evaluated at varying points during the exposure. Results indicated that prolonged exposure to diesel engine exhaust and carbon black produces nearly identical carcinogenic and noncarcinogenic effects. Both exposures caused injury to lung tissue, including inflammation, cell proliferation, and fibrosis. The lesions progressed in number and size with increasing particle dose. At both exposure concentrations, particles accumulated in lungs and lymph nodes over time. Lung DNA adducts were slightly increased by diesel exhaust exposure, and DNA adducts in type II cells were increased by both diesel exhaust and carbon black exposure. No exposure-related chromosome damage was found in circulating lymphocytes. Primary lung neoplasm incidence was increased significantly and related to dose.

Gallagher et al. (1994) conducted a long-term (2-year) exposure study in rats using diesel emissions, carbon black, and titanium dioxide particles. The objective was to determine whether the polycyclic aromatic hydrocarbons (PAHs), nitro-PAHs, or other polycyclic organic matter adsorbed to diesel particles induces the formation of DNA adducts in the lung when compared to particles with little or no adsorbed organic matter. Wistar rats were exposed to diesel emissions containing particles with over 30% solvent-extractable adsorbed organic matter and to particles with <0.1% adsorbed organic matter (carbon black particles and TiO_2). Adducts possibly resulting from exposure to nitro-PAHs were detected in diesel-exposed rats but not in rats exposed to TiO_2 and carbon black. No significant elevation in PAH-derived adducts, relative to the filtered air controls, was observed in the rodents exposed to diesel emissions.

A long-term study by Ishihara and Kagawa (2003) involved exposure of Wistar rats to "low," "medium," and "high" concentrations of diesel exhaust for 6, 12, 18, or 24 months. The "medium" concentration was also filtered to remove particles. Bronchoalveolar lavage fluid and blood from the right ventricle were collected and various biomarkers of inflammation and components of mucus and surfactant were determined. Changes in total cell counts and cell differentiation, total protein, mucus and surfactant components, and prostaglandin E2 in BAL fluid, but not biomarkers in plasma, showed statistical differences among the exposure groups, with the highest response in the "high" exposure group, less response in the "medium" group, and no response in the "low" group. The onset of significant changes in inflammatory cells and these biomarkers in BAL fluid for the medium and high groups was at 6 to 12 months of exposure. The filtered atmosphere induced significantly fewer effects.

Quan et al. (2010) exposed ApoE$^{-/-}$ mice to one of five different exposure atmospheres: (1) filtered air; (2) CAPs (105 μg/m^3); (3) whole diesel exhaust (WDE; PM = 436 μg/m^3); (4) diesel exhaust gases (DEG; equivalent to gas levels in whole diesel exhaust group); and (5) CAPs + DEG ($PM_{2.5}$ = 113 μg/m^3, with DEG equivalent to WDE group). Animals were exposed for 5 hrs/day, 4 days/week for 5 months. Results indicated that vascular changes occurred in response to all inhalation exposures. Further, atherosclerosis was most notable in response to CAPs, followed by WDE. The atherosclerotic response to DEG was the same as filtered air, suggesting that PM components in the diesel exhaust are responsible for plaque development.

Investigators at Lovelace Respiratory Research Institute conducted the Advanced Collaborative Emissions Study

(ACES), which involved exposure of rats and mice to diesel exhaust from engines compliant with the 2007 on-road emissions standard in the United States. Animals were exposed for 1, 3, 12, and 24–30 months in a carcinogenicity bioassay, with additional assessment of pulmonary toxicity. The methods and exposure characterization results are described by McDonald et al. (2012); concentrations tested averaged 0.1, 0.8, and 4.2 ppm NO_2. More than 100 biological response indicators were evaluated, with the majority showing no significant differences from control animals. No pre-neoplastic lung lesions or primary lung neoplasia were observed in rats exposed to diesel emissions, although some lung lesions, primarily related to epithelial proliferation, did occur at the highest exposure level. There was also a subtle accumulation of pulmonary alveolar macrophages, coupled with slight bronchiolization in some animals. The findings in the lung progressed from 3 months to 12 months, but showed only modest progression between 12 months and the final sacrifice. In addition to the histologic findings, a number of biochemical changes in the lung tissue and lavage fluid indicated mild inflammation and oxidative stress. These findings were generally only observed at the highest exposure level, and there was a stronger response in females than in males. There was also a mild progressive decrease in respiratory function that was also greater in females. Overall, the findings of this study demonstrated markedly less severe biological responses to 2007-compliant engine emissions than observed previously in rats exposed to traditional diesel exhaust (McDonald et al., 2015).

Discussion

We reviewed both epidemiological and toxicological evidence related to the role played by PM components in long-term health effects. Epidemiological studies either considered $PM_{2.5}$ mass along with one component (sulfate or black carbon), or considered more than one PM component. The extent of any conclusions from these studies is limited by the components of particulate matter that were analyzed in individual studies. Table 2 summarizes the results from studies that examined $PM_{2.5}$ and one component and shows that there is a distinct difference in the components considered between U.S. and non-U.S. studies. The U.S. studies considered sulfate as the only $PM_{2.5}$ component, and found significant associations between sulfate and most mortality categories, as well as associations between mortality and $PM_{2.5}$ mass. No joint model results including both $PM_{2.5}$ mass and sulfate were presented. The closest to a detailed consideration of both of these pollutants is the paper by Jerrett et al. (2007), which found differences in the associations of these two pollutants with mortality over time. Sulfate was significantly associated with all-cause and cardiopulmonary mortality in the earliest two time periods, and $PM_{2.5}$ was significantly associated with cardiopulmonary mortality in the last two time periods. It is unclear whether this finding is the result of chance, changes in the concentrations of sulfate over time, or changes in the composition of $PM_{2.5}$ over time. More investigation of temporal changes in concentrations and composition would be helpful. With such detail, it would be beneficial to undertake the analyses of other data sets for subsets of time to determine whether there are changes over time similar to those found by Jerrett et al. (2007).

The non-U.S. epidemiological papers consider PM_{abs} or BC as the only component of $PM_{2.5,}$ and joint analyses of this component and $PM_{2.5}$ mass are few. A European paper that examined low birth weight (Pedersen et al., 2013) reported a significant association with $PM_{2.5}$ mass in a joint model with BC. Two Canadian papers found the opposite for both cardiovascular and COPD endpoints (Gan et al., 2010; Gan et al., 2013); in their joint models, BC dominated $PM_{2.5}$. Several of the European papers reported significant associations with $PM_{2.5}$, but not with PM_{abs} in single-pollutant models (Beelen et al., 2014; Cesaroni et al., 2014; Fuks et al., 2014; MacIntyre et al., 2014; Pedersen et al., 2013; Raascshou-Nielsen et al., 2013); hence, within Europe the ESCAPE study appears to suggest that $PM_{2.5}$ mass is a better indicator of pollution of concern than PM_{abs}. The Canadian studies suggest the opposite.

The epidemiological papers that considered two or more components fall into two groups based on study location. The European studies focused on elemental composition and did not present results for carbon-containing components (i.e., OC, EC, and/or BC or black smoke). None of the elements studied, including S, which can serve as a marker for sulfate, was significantly related to pediatric respiratory outcomes (Fuertes et al., 2014; Eeftens et al., 2014) or to cardiovascular mortality (Wang et al., 2014). The U.S. papers that considered mortality or adverse cardiovascular outcomes, with the exception of Lipfert et al. (2009), reported significant associations with sulfate; all of these papers reported significant associations with some organic components. Several elements were also significantly associated with these endpoints, but there are insufficient results from these studies to allow any overall inferences about which elements are of greatest concern. There were also two U.S. epidemiological studies of reproductive effects, and several pollutants, including organic components, sulfate, and elements, were indicted in single-pollutant models. One study (Wilhelm et al., 2011) included some multipollutant models; in these, $PM_{2.5}$ mass appeared to be the best predictor of reproductive outcomes.

The results of this review, like those of a review of short-term studies (Rohr and Wyzga, 2012) suggest that no major component of $PM_{2.5}$ can be dismissed as being unequivocally not associated with adverse health responses. This review of the associations between acute health responses and components (Rohr and Wyzga, 2012) suggested that that more scrutiny needs to be given to carbon-containing PM components (elemental and organic carbon). Rohr and Wyzga (2012) found that of the 28 epidemiological studies reviewed, the great majority (24) reported a significant association between acute cardiovascular effects and at least one carbonaceous component. Acute respiratory outcomes as a whole showed fewer associations with carbon-containing constituents (15 of 26 studies), while for asthma-specific endpoints, 7 of 10 studies showed such an association. Far fewer long-term studies considered cardiovascular outcomes, but five of eight that did reported significant associations with organic components. It

should be noted that there is no clear understanding of the relationship between short-term and long-term health effects. There are too few long-term epidemiological studies of pulmonary endpoints to allow any reasonable compilation of results. Relatively few acute epidemiological studies considered elemental species. Those that did yielded mixed results, with Ni, V, Zn, Cu, Si, and K showing the greatest number of significant results. All of these elements identified in the short-term epidemiological studies, except possibly Al, were indicted in at least one long-term study; however, the limited number of available studies prevents any inferences. Among the acute studies, results for sulfate were mixed, with some studies reporting significant positive associations, some significant negative associations, and others reporting nonsignificant associations. Curiously the non-U.S. acute studies found relatively more significant associations with sulfate than the U.S. studies, yet by and large, non-U.S. chronic studies did not consider this component, probably because much of the focus in Europe is on diesel emissions, which are rich in organic components. A limited number of long-term studies considered sulfate, but the evidence for sulfate being of concern is greater in the long-term studies than in the acute studies. Clearly, additional long-term studies that consider several components of $PM_{2.5}$, singly and in multipollutant models, are needed to make inferences with greater confidence.

The toxicological literature pertaining to long-term studies is rather scarce, perhaps unsurprisingly, given the high cost of conducting animal exposures over long periods of time. Moreover, the study designs are somewhat disparate. From a PM component perspective, the two designs that are likely to yield the most valuable data on the relative health effects of individual constituents are studies incorporating CAPs exposures and studies similar to the NERC model, where multiple exposures are conducted to allow construction of a source-composition-concentration database. The CAPs studies reviewed herein (Lippmann et al., 2006; Chen et al., 2010; Lippmann et al., 2013; Lippmann, 2014) have yielded valuable information, with a common finding being the identification of Ni and/or V in adverse cardiovascular responses. Indeed, these authors have proposed Ni as a potential putative factor in health effects (Lippmann et al., 2006).

The NERC program was a highly ambitious research effort that endeavored to employ advanced statistical methods to identify the causative pollutants in a wide range of biological responses. Despite having completed only four of the planned 8 to 10 pollution source exposures, Mauderly and Seilkop (2014) were able to identify the top predictors of a variety of responses. These included 12 organic classes and 6 inorganic classes or species. Interestingly, many of the important predictors were nonparticulate in nature, including carbonyls, nonmethane volatiles, volatile aliphatic acids, vapor-phase semivolatile alkanes, ammonia, SO_2, NO, and NO_2. In fact, the strongest evidence for a causal effect was evident for ammonia, SO_2, NO, and NO_2. These findings are intriguing and are consistent with some other toxicological results, where filtration of particular emissions sources did not appreciably change the biological responses (e.g., Reed et al., 2008; Mauderly et al., 2011). Furthermore, in a subset of epidemiological studies reviewed herein, gas-phase organic compounds were measured (Lipfert et al., 2009; Wilhelm et al., 2011) and were significantly associated with health endpoints. The literature on short-term effects, both epidemiological and toxicological, contains more information on the contribution of non-PM pollutants to health impacts (e.g., Rumchev et al., 2004; Wolkoff et al., 2008). However, some studies discussed herein have shown that the PM contribution is important (Quan et al., 2010; Ishihara and Kagawa, 2003).

In comparing the findings of the long-term CAPs studies cited herein with the short-term studies previously reviewed by these authors (Rohr and Wyzga, 2012) as well as others (Lippmann et al., 2009; Kelly and Fussell, 2012), there is some consistency. It should be noted that while the traditional definition of a "chronic" toxicology study is 2 years in duration, we relaxed this criterion here to include studies of at least 5 months duration. Thus, two studies were reviewed in both the current paper as well as short-term review by Rohr and Wyzga (2012). The overall conclusions from the short-term CAPs studies reviewed by Rohr and Wyzga (2012, p. 149) were:

> Overall, the focus of the toxicological studies has been more on metal species than other components; of the elements studied, V and Ni have appeared with greater frequency as being associated with health endpoints, both in relation to cardiovascular endpoints as well as respiratory outcomes. Associations with Al and Si have also been observed frequently, particularly for respiratory effects. Other elements, including Fe, Zn, S, and Pb have shown some, but fewer, associations. Associations with carbonaceous components have been observed for both respiratory and cardiovascular outcomes; this issue is discussed further in the next section. Associations with sulfate (or sulfur) were noted in 7 of the 18 studies that included this component.

These conclusions compare favorably with those from the current long-term study review. Ni and V appear most frequently, with several other trace elements—Fe, Cr, and Al, in particular—showing positive associations or correlations with cardiovascular endpoints. Elemental carbon, although not organic carbon, showed a high correlation with cardiac function changes in research reported by Lippmann et al. (2013). Sulfur has also been associated with some outcomes in long-term studies, although in one (Chen et al., 2010), two-pollutant models with sulfate revealed that all other associations with trace elements increased in strength, suggesting that S was not a significant predictor of response.

The non-CAPs toxicological literature was limited to those PM components, types, and emissions sources that are generally well studied and that thus include long-term exposure experiments. This body of literature included studies of individual PM components in isolation (i.e., sulfate), studies of specific PM types (i.e., coal fly ash and coal dust), and studies of specific emissions (i.e., engine emissions, wood smoke, coal combustion emissions). From the first category, sulfate in both its neutral and acidic forms was studied. Toxicological evidence suggests either no or minor effects from these exposures, as discussed earlier, with responses generally occurring only at high concentrations. The fact that epidemiological studies (and some CAPs studies) find associations with sulfate (or elemental

sulfur as a marker) at low concentrations leads one to speculate on possible reasons for this inconsistency. Several hypotheses have been forwarded, including catalysis of reactions involving volatile organic compounds with a resultant increase in the mass of secondary organic aerosol, increased bioavailability of metals complexed to sulfur, and adsorption of volatile gases and subsequent transport into lower pulmonary regions (Kelly and Fussell, 2012, and references therein). However, insufficient evidence currently exists to advance these potential mechanisms.

The literature related to specific PM types also shows responses only at high concentrations. Examination of the one study reporting on chronic exposure to coal fly ash at 2 concentrations revealed no effects at 0.6 mg/m^3 and few effects at 4.5 mg/m^3 (Raabe et al., 1982). The paper also concluded that the changes observed were not coal fly ash-specific and would be expected with any inhaled particle. Coal dust exposures revealed similar results, with effects generally being noted only at high concentrations. In contrast, engine emissions and wood smoke appear to induce toxicity at lower concentrations, with varying degrees of effects depending on the endpoint. However, these types of studies do not lend themselves easily to the examination of specific PM (or non-PM) components that may be responsible for health effects, since even with extensive exposure characterization there is no variability in exposure and thus statistical modeling to relate changes in health parameters to varying composition cannot be done. In these cases, removal of specific components, for example, filtration to remove PM or the use of denuders to remove gas-phase components, can allow some evaluation of the role played by different phases in the effects. Different types of denuders can also be used to remove different components of the emissions; for example, a honeycomb denuder can be used to remove reactive gases and hydrocarbons (McDonald et al., 2010), while a spent carbon denuder will only remove reactant gases and will allow hydrocarbons to pass through (Campen et al., 2010).

Another strategy that could be employed is longer term exposure to specific components of emissions that are hypothesized to contribute to effects. For example, following on from the NERC findings of significant response prediction by certain gases, Mauderly et al. (2014b) conducted exposures to CO, NO, NO_2, SO_2, and NH_3 to evaluate whether vascular effects of diesel or gasoline exhaust could be reproduced by this mixture. The results were generally supportive of the idea that these five gases drove the effects of the emissions.

Conclusions

Examination of the literature related to long-term exposure to PM components reveals relatively little information in both the epidemiological and toxicological realms. The epidemiological studies are limited by consideration of few components and a lack of multipollutant models. Toxicological studies are limited by lack of long-term CAPs studies, complex data sets that are difficult to interpret, and lack of ability of long-term emissions experiments to inform the role played by specific constituents.

In the epidemiological arena, the EPA Chemical Speciation Network conducts systematic measurements for major PM components (sulfate, nitrate, elemental carbon, organic carbon) as well as trace elements at a large number of U.S. sites. Even though these measurements may not be made on a daily basis, periodic measurements throughout the year could give a reasonable estimate of annual concentrations for various PM species, although the number of monitors in a given geographic area is limited and may not allow adequate consideration of spatial heterogeneity. We encourage investigators to utilize these data when planning long-term epidemiological studies. Similar networks or measurements can also be made outside of the United States. As more data become available, it is important that future studies make as great a use of these data as possible to inform the role of various components of $PM_{2.5}$ in our understanding of the long-term health effects of air pollution.

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