

## Review

# The Role of Fossil Fuel Combustion Metals in PM<sub>2.5</sub> Air Pollution Health Associations

Polina Maciejczyk <sup>1</sup>, Lung-Chi Chen <sup>2</sup> and George Thurston <sup>2,\*</sup>

<sup>1</sup> Department of Chemistry and Biochemistry, Eckerd College, St. Petersburg, FL 33711, USA; maciejpb@eckerd.edu

<sup>2</sup> Department of Environmental Medicine, Grossman School of Medicine, New York University, New York, NY 10010, USA; lcc4@nyu.edu

\* Correspondence: george.thurston@nyu.edu

**Abstract:** In this review, we elucidate the central role played by fossil fuel combustion in the health-related effects that have been associated with inhalation of ambient fine particulate matter (PM<sub>2.5</sub>). We especially focus on individual properties and concentrations of metals commonly found in PM air pollution, as well as their sources and their adverse health effects, based on both epidemiologic and toxicological evidence. It is known that transition metals, such as Ni, V, Fe, and Cu, are highly capable of participating in redox reactions that produce oxidative stress. Therefore, particles that are enriched, per unit mass, in these metals, such as those from fossil fuel combustion, can have greater potential to produce health effects than other ambient particulate matter. Moreover, fossil fuel combustion particles also contain varying amounts of sulfur, and the acidic nature of the resulting sulfur compounds in particulate matter (e.g., as ammonium sulfate, ammonium bisulfate, or sulfuric acid) makes transition metals in particles more bioavailable, greatly enhancing the potential of fossil fuel combustion PM<sub>2.5</sub> to cause oxidative stress and systemic health effects in the human body. In general, there is a need to further recognize particulate matter air pollution mass as a complex source-driven mixture, in order to more effectively quantify and regulate particle air pollution exposure health risks.

**Keywords:** particulate matter; air pollution; ambient metals; particulate matter associated metals; fossil fuel combustion; inhalation metals; mortality; hospital admissions; particle acidity



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## 1. Introduction

Air pollution is an important risk factor for global mortality, outpaced only by high systolic blood pressure, tobacco smoking, and poor diet. Exposure to polluted air leads to around 6.7 million premature death annually worldwide according to the latest study of the global burden of diseases [1]. Numerous studies have confirmed a substantial link between ambient particulate matter (PM) and both total and cause-specific mortality [2–6], morbidity, reduced lung function [7], asthma [8], allergic sensitization [9], acute and persistent changes in cardiac rhythm [10–12], vascular dysfunction [13], enhancement of aortic plaque size [13–15], and potentiation of hypertension [16]. Particle size and composition have been identified as major determinants of particle behavior in the mammalian respiratory system. The health effects have been found to be stronger for fine (PM<sub>2.5</sub>, particles with aerodynamic diameter less than 2.5 µm) and ultrafine (UFP, or PM<sub>0.1</sub>, particles with aerodynamic diameter less than 0.1 µm) than coarse mode particles (PM<sub>10–2.5</sub>, referred to as thoracic coarse particles, generally including particles with a nominal mean aerodynamic diameter greater than 2.5 µm and less than or equal to 10 µm) for the following reasons: (1) fine and ultrafine particles contain elevated concentrations of toxic metals; (2) small particles deposit deeper in the lungs; (3) the solubility of metals in small particles is higher than in coarse particles; (4) humans might have longer exposure to small particles, which have long atmospheric residence time (hours for UFPs, and days to weeks for PM<sub>2.5</sub>) [17,18]. While

the specific biological mechanisms as to how exactly PM causes these health effects, and how these effects vary with source and composition, are not yet fully understood, recent studies have pointed towards the oxidative stress potential of ambient metal elements as a key causal factor (e.g., [19]).

What follows is not a systematic review, but instead represents the authors' judgments of the key evidence on this topic. For example, a requirement for inclusion was the consideration of key metal constituents in fossil fuel combustion emissions, with a focus on those potentially contributing to an oxidative stress mechanism of PM<sub>2.5</sub> health effects. It is acknowledged that other health effects are associated with other metals from other sources (e.g., drinking water), as discussed elsewhere (e.g., see [20]).

## 2. Sources and Concentrations of Trace Metals in Ambient Air PM

Overall, PM<sub>2.5</sub> concentrations in the US have decreased considerably in recent decades. The national average PM<sub>2.5</sub> concentration dropped from 20 µg/m<sup>3</sup> of early 1980s [2,21] to 12 µg/m<sup>3</sup> by 2005–2007, and then further to 8.6 µg/m<sup>3</sup> in 2013–2015 (the mean of annual average concentrations based on 24 h samples across all sites during the 3-year period). In 2012, the US Environmental Protection Agency (US EPA) established a new annual PM<sub>2.5</sub> primary standard of 12 µg/m<sup>3</sup> (the annual mean averaged over 3 years) and retained the 24 h PM<sub>2.5</sub> standard of 35 µg/m<sup>3</sup> (the 98th percentile averaged over 3 years) [18]. The substantial concentration decrease at almost all PM<sub>2.5</sub> monitoring sites, with especially large decreases in the eastern US, is primarily attributable to a decrease in sulfate concentrations from the steep decline in SO<sub>2</sub> emissions from 13.9 million metric tons in 2006 to 4.8 million metric tons in 2014 [18]. Interestingly, another consequence of a successful reduction of SO<sub>2</sub> emissions is the observed reduction in summer PM<sub>2.5</sub> concentrations from sulfates in the East, to such an extent that summer is no longer the season with the highest national average PM<sub>2.5</sub> concentrations [18].

Ambient PM originates from both natural and anthropogenic sources. Sources of natural PM include sea salt aerosol, soil and rock erosion, pollen, volcanic eruptions, and wildfires. Mechanical processes (crushing rocks, erosion, and suspensions of dust) predominantly generate the larger sized, coarse mode particles, PM<sub>10–2.5</sub> [22]. Typical metal composition of PM<sub>10–2.5</sub> is oxides of crustal elements (Si, Al, Ti, Fe), sea salts (Na, K, Ca), and metals in tires, brake pads, and road wear debris [18]. In contrast, ultrafine PM<sub>0.1</sub> generally consists of freshly generated particles formed either during combustion or by condensation of semi-volatile gases from heavy traffic, industrial emissions, biomass burning, or cooking [23]. Agglomeration of ultrafine PM and condensation of gases onto them, yield submicron-sized fine PM<sub>2.5</sub>.

Anthropogenic emissions come from a variety of sources, including combustion (e.g., vehicles, fossil fuels in electricity production, and waste incineration), industrial activities, mining, and agricultural activities. In 2020, about 60% of electricity generation in the US was from fossil fuels—coal, natural gas, petroleum, and other gases [24]. Power and heat generation by combustion of these fossil fuels are some of the largest sources of airborne metals, sulfur oxides, and PM<sub>2.5</sub>. Many of the particles resulting from these sources' emissions are also as ultrafine nanoparticles, which can be especially toxic due to their small size and high surface area to mass [25,26]. It has also long been documented that fossil fuel combustion particles are highly enriched, per unit mass, in toxic metals, relative to ambient particles from other sources, such as crustal-derived windblown soil [27]. The metal contents of various fossil fuel combustion emissions are shown in Table 1: it is notable that the metals contained are similar across the various fossil fuels, and, though the total mass emissions differ, the various metals' percentages of mass are similar across the fuels. This suggests that all fossil fuel emissions can have similar metals-related health impacts.

**Table 1.** Metals content of fossil fuel combustion particulate matter emissions [28].

| Pollutant  | PM Emissions (lb/MMBtu) |                       |                      | PM Emissions as % of PM Mass |                |              |
|------------|-------------------------|-----------------------|----------------------|------------------------------|----------------|--------------|
|            | Natural Gas             | Distillate Oil        | Residual Oil         | Natural Gas                  | Distillate Oil | Residual Oil |
| Antimony   |                         |                       | $3.5 \times 10^{-5}$ |                              |                | 0.070        |
| Arsenic    | $2.0 \times 10^{-7}$    | $4.0 \times 10^{-6}$  | $8.8 \times 10^{-6}$ | 0.003                        | 0.017          | 0.018        |
| Barium     | $4.3 \times 10^{-6}$    |                       | $1.7 \times 10^{-5}$ | 0.058                        |                | 0.034        |
| Beryllium  | $<1.2 \times 10^{-8}$   | $3.0 \times 10^{-6}$  | $1.9 \times 10^{-7}$ |                              | 0.013          | 0.001        |
| Cadmium    | $1.1 \times 10^{-6}$    | $3.0 \times 10^{-6}$  | $2.7 \times 10^{-6}$ | 0.014                        | 0.013          | 0.005        |
| Chloride   |                         |                       | $2.3 \times 10^{-3}$ |                              |                | 4.641        |
| Chromium   | $1.4 \times 10^{-6}$    | $3.0 \times 10^{-6}$  | $5.6 \times 10^{-6}$ | 0.018                        | 0.013          | 0.011        |
| Cobalt     | $8.2 \times 10^{-8}$    |                       | $4.0 \times 10^{-5}$ | 0.001                        |                | 0.081        |
| Copper     | $8.3 \times 10^{-7}$    | $6.0 \times 10^{-6}$  | $1.2 \times 10^{-5}$ | 0.011                        | 0.025          | 0.024        |
| Fluoride   |                         |                       | $2.5 \times 10^{-4}$ |                              |                | 0.499        |
| Lead       | $4.9 \times 10^{-7}$    | $9.0 \times 10^{-6}$  | $1.0 \times 10^{-5}$ | 0.007                        | 0.038          | 0.020        |
| Manganese  | $3.7 \times 10^{-7}$    | $6.0 \times 10^{-6}$  | $2.0 \times 10^{-5}$ | 0.005                        | 0.025          | 0.040        |
| Mercury    | $2.5 \times 10^{-7}$    | $3.0 \times 10^{-6}$  | $7.5 \times 10^{-7}$ | 0.003                        | 0.013          | 0.002        |
| Molybdenum | $1.1 \times 10^{-6}$    |                       | $5.2 \times 10^{-6}$ | 0.014                        |                | 0.011        |
| Nickel     | $2.1 \times 10^{-6}$    | $3.0 \times 10^{-6}$  | $5.6 \times 10^{-4}$ | 0.028                        | 0.013          | 1.130        |
| Phosphorus |                         |                       | $6.3 \times 10^{-5}$ |                              |                | 0.127        |
| Selenium   | $<2.4 \times 10^{-8}$   | $15.0 \times 10^{-6}$ | $4.6 \times 10^{-6}$ |                              | 0.063          | 0.009        |
| Vanadium   | $2.3 \times 10^{-6}$    |                       | $2.1 \times 10^{-4}$ | 0.030                        |                | 0.425        |
| Zinc       | $2.8 \times 10^{-5}$    | $4.0 \times 10^{-6}$  | $1.9 \times 10^{-4}$ | 0.382                        | 0.017          | 0.389        |
| Total PM   | $7.5 \times 10^{-3}$    | $2.4 \times 10^{-2}$  | $5.0 \times 10^{-2}$ |                              |                |              |

Table 2 shows the typical concentrations of metals recently found in ambient PM<sub>2.5</sub> around the world. These are usually generated by combustion of fossil fuels and other high-temperature industrial processing as well as by natural sources. In modern cities, wear particles from motor vehicles (e.g., from brake wear) and roads are becoming increasingly more important sources of PM<sub>2.5</sub> mass than vehicle tailpipe exhaust, since the engines are getting cleaner and more cars are e-vehicles, which may lead to a change in the toxicity per unit PM<sub>2.5</sub> mass. Typical metals in fine and ultrafine fractions emitted by combustion processes include compounds of Pb, Cd, V, Ni, Cu, Zn, Mn, and Fe [18]. For an extensive description of properties, production, uses, and sources of these and other metals, see a review by Chen et al. [20]. While metals are found naturally in the environment at various concentrations, and some are physiologically essential, human activity changes the chemical forms of ambient metals, which could lead to greater metal toxicity.

**Table 2.** Metal concentration mean or range of means in ambient PM<sub>2.5</sub>, as reported in various regions of the world (ng/m<sup>3</sup>).

| Metal | European Union                                                 | North America                                                                                               | Asia                                                                                                                 | Central and South America                                                                           | Africa                                                                                                                   |
|-------|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| Cd    | 0.05–2.9 rural [29]<br>0.1–14.1 urban [29]                     | Less than 0.2 US [30]<br>6 Los Angeles [31]                                                                 | 2.3–55 China [32]<br>0.1–8.4 Beijing [33]<br>0.2 Nagasaki [34]                                                       | 0.1–15.1 Sao Paulo [35]<br>0.05 Bogota [36]<br>0.03–13 Mexico City [37]<br>1–8 Huancayo, Peru [38]  | 5 Harare, Zimbabwe [39]                                                                                                  |
| Pb    | 1–115 rural [29]<br>1–330 urban [29]                           | 32 US [40]<br>5 Los Angeles [31]<br>0.8–17 Houston [41]                                                     | 100–1100 China [32]<br>6–715 Beijing [33]<br>7.8 Nagasaki [34]<br>1.3–12.6 SE Tibetan Plateau [42]<br>37 Mumbai [43] | 3–172 Sao Paulo [35]<br>1.6 Bogota [36]<br>1.1–125 Mexico City [37]<br>5–153 Huancayo, Peru [38]    | 185 Harare, Zimbabwe [39]<br>6–31 Accra, Ghana [44]<br>22 Nairobi, Kenya [45]<br>30–180 Vaal Triangle, South Africa [46] |
| As    | 0.06–3.3 rural [29]<br>0.1–30.2 urban [29]                     | 1–3 US rural [47]<br>20–100 US urban [47]<br>0.46 Toronto [48]<br>0.85 New York City [49]                   | Beijing 0.5–27 [33]<br>0.4–15.7 SE Tibetan Plateau [42]<br>1.4 Nagasaki [34]<br>13.7 Mumbai [43]                     | 0.06–7.1 Sao Paulo [35]<br>0.12 Bogota [36]<br>2–14 Huancayo, Peru [38]                             |                                                                                                                          |
| Fe    | 67–283 [50]:<br>92 Northern<br>119 West/Central<br>1224 South  | 26 rural New York [51]<br>4–488 NYC [49]<br>190 Los Angeles [31]<br>36–1270 Houston [41]<br>42 Toronto [48] | 81–4300 Beijing [33]<br>30–940 SE Tibetan Plateau [42]<br>90 Nagasaki [34]<br>316 Mumbai [43]                        | 140–2056 Sao Paulo [35]<br>124 Bogota [36]<br>350 Mexico City [52]<br>932–5064 Huancayo, Peru [38]  | 346–539 Accra, Ghana [44]<br>530 Nairobi, Kenya [45]<br>90–22870 Vaal Triangle, South Africa [46]                        |
| Ni    | 0.6–4.4 [50]:<br>1.1 Northern<br>0.9 West/Central<br>3.1 South | 3 NYC summer [49]<br>9.8 NYC winter [49]<br>3 Los Angeles [31]<br>0.3–5.7 Houston [41]<br>0.17 Toronto [48] | 6–127 China [32]<br>0.7–257 Beijing [33]<br>0.4–5.1 SE Tibetan Plateau [42]<br>1.3 Nagasaki [34]<br>6.7 Mumbai [43]  | 2.3–16.1 Sao Paulo [35]<br>0.49 Bogota [36]<br>1.2–114 Mexico City [37]<br>4–22 Huancayo, Peru [38] | 180 Harare, Zimbabwe [39]<br>3–4 Accra, Ghana [44]<br>4 Nairobi, Kenya [45]<br>10–2470 Vaal Triangle, South Africa [46]  |

Table 2. Cont.

| Metal | European Union                                                      | North America                                                                                                | Asia                                                                                                                 | Central and South America                                                                           | Africa                                                                                        |
|-------|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Cu    | 1.8–14.2 [50]:<br>3.2 Northern<br>5.3 West/Central<br>10.1 South    | 3 rural New York [51]<br>6.3 NYC [49]<br>10 Los Angeles [31]<br>0.5–36 Houston [41]<br>2.57 Toronto [48]     | 31–231 China [32]<br>2.5–80 Beijing [33]<br>6.7–73.2 SE Tibetan Plateau [42]<br>2.3 Nagasaki [34]<br>6.7 Mumbai [43] | 7–390 Sao Paulo [35]<br>19.4 Bogota [36]<br>0.64–5181 Mexico City [37]<br>12–77 Huancayo, Peru [38] | 2–6 Accra, Ghana [44]<br>11 Nairobi, Kenya [45]<br>10–240 Vaal Triangle, South Africa [46]    |
| Zn    | 11.7–57.8 [50]:<br>13.4 Northern<br>26.5 West/Central<br>34.9 South | 6 rural New York [51]<br>33 NYC [49]<br>10 Los Angeles [31]<br>0.6–53 Houston [41]<br>9.1 Toronto [48]       | 13–748 Beijing [33]<br>0.8–88.3 SE Tibetan Plateau [42]<br>26 Nagasaki [34]<br>61 Mumbai [43]                        | <DL-673 Sao Paulo [35]<br>13 Bogota [36]<br>58 Mexico City [52]<br>145–719 Huancayo, Peru [38]      | 15–45 Accra, Ghana [44]<br>91 Nairobi, Kenya [45]<br>110–690 Vaal Triangle, South Africa [46] |
| Mn    | 2.5–5.6 Paris [53]                                                  | 2 rural New York [51]<br>3.1–4.3 NYC [49]<br>12 Los Angeles [31]<br>0.8–21 Houston [41]<br>1.68 Toronto [48] | 3–223 Beijing [33]<br>1.9–21.5 SE Tibetan Plateau [42]<br>5.6 Nagasaki [34]<br>10.5 Mumbai [43]                      | <DL-64 Sao Paulo [35]<br>1.9 Bogota [36]<br>1.5–567 Mexico City [37]<br>16–182 Huancayo, Peru [38]  | 7–9 Accra, Ghana [44]<br>41 Nairobi, Kenya [45]<br><DL-120 Vaal Triangle, South Africa [46]   |
| V     | 0.7–9.7 [50]:<br>1.9 Northern<br>1.3 West/Central<br>6.1 South      | US mean 11 [54]<br>3 rural New York [51]<br>14.5 NYC [49]<br>1 Los Angeles [31]                              | 5.69 Shanghai [55]<br>0.4–19 Beijing [33]<br>2.6 Nagasaki [34]<br>13.1 Mumbai [43]                                   | 0.2 Bogota [36]<br>0.09–761 Mexico City [37]<br>1–15 Huancayo, Peru [38]                            | 1 Accra, Ghana [44]<br>10–50 Vaal Triangle, South Africa [46]                                 |

### 3. Source Apportionments of Particulate Matter

Source apportionment is a set of statistical techniques by which time-series of air pollution measurements are analyzed to determine the contributions from various sources. A recent review of PM<sub>2.5</sub> and PM<sub>10</sub> source apportionment included 741 PM apportionments that included metals, water-soluble species, and carbon-containing particles [56]. The two types of source apportionment are source-unknown models (e.g., positive matrix factorization (PMF) [57] and absolute principal component analysis (APCA) [58] and source profile dependent models (e.g., chemical mass-balance (CMB)) [59]. To determine the origin of the ambient particles, the PMF and APCA statistical methods are often applied because (1) the CMB emission concentrations/profiles are outdated or were never measured, (2) the emissions are too similar, and do not have a unique element/species for clear source identification, (3) photochemical and aging processes change the initial source profile. Nevertheless, all models rely on existing knowledge of elemental tracers and their principal sources (e.g., [60–63]). Galvão and colleagues have recently reviewed elemental and ionic markers associated with various sources and recommended strategies for interpretations and apportionment [64]. The summary of most common source categories and their usual elemental markers are shown in Table 3. The contribution of each source varies by particle size fraction and geographical location.

Table 3. Summary of PM source categories and their respective elemental tracers.

| Source Category      | Types of Sources                                                                   | Element Markers                                                                                                            |
|----------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Coal combustion      | Coal-fired power plants, coal-fired industrial boilers, and residential combustion | Crustal materials (Na, Ca, Mg, Al, Fe, Cl), OC, EC, sulfate, and trace metals (As, Se, Cd, Cr, Cu, Ni, Pb, Hg, Zn) [64–66] |
| Oil combustion       | Power plants, industrial boilers, maritime/shipping industry                       | Ni and V [58,67]                                                                                                           |
| Industrial emissions | Industrial, mining, and manufacturing processes                                    | Highly dependent on location; EC, OC, Ca, S, Mn, Fe, Cr, Zn, Pb [64]                                                       |

Table 3. Cont.

| Source Category    | Types of Sources                                                                                               | Element Markers                                                                                                                                            |
|--------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Traffic            | (1) Vehicle tailpipe                                                                                           | Ca, Mn, Fe, Cu, Ni, Zn, Cr, and Ba. Specifically: Ca, Cu, and Ni for gasoline-fueled vehicles [68,69], Ti and Ba for diesel-fueled vehicles [70,71]        |
|                    | (2) Vehicle non-tailpipe sources (i.e., tire abrasion, brake and engine wear)                                  | Zn (brake and tire wear, motor oil), Cu (brake wear), Pb (brake, oil, additives, gasoline), Cd (tire wear), Ni (brake wear), Cr (brake and tire wear) [72] |
|                    | (3) Dust resuspension from the roadway                                                                         | Cd, Pb (as legacy soil contamination from Pb-gasoline days), Cu, Ba, and Sb (from brake wear), as well as Ca and Zn from lubricating oil [64]              |
| Fugitive dust      | Crustal/soil and road dust resuspension                                                                        | Si, Al, Ca, Fe, Na, Mg, Ti                                                                                                                                 |
| Biomass burning    | Residential wood combustion other types of solid fuels combustion, wildfires, burning of agricultural residues | K, OC, EC, and organic markers                                                                                                                             |
| Waste incineration | Municipal waste incineration                                                                                   | Pb, Zn [73]                                                                                                                                                |
| Fireworks          | Fireworks                                                                                                      | Pb, Ti, Sr, Ba, Cu [74,75]                                                                                                                                 |

Modeling of the US Chemical Speciation Network data has shown the US nationwide distribution of PM<sub>2.5</sub> source components, including oil burning (highest in New York, NY); coal (highest in Pittsburgh, PA); wood burning (highest in Missoula, MT), traffic (highest in Los Angeles, CA), salt aerosols (highest along the ocean coasts), and steel emissions (highest in Detroit, MI, and Birmingham, AL) [76]. A subsequent analysis of the health effects of these source contributions indicated the coal burning PM<sub>2.5</sub> component to have the greatest health impact per µg/m<sup>3</sup> on ischemic cardiovascular disease [6]. The analysis of relative contributions of specific sources of primary PM<sub>2.5</sub> as reported to the National Emission Inventory, indicated that in contrast to rural areas PM<sub>2.5</sub> is dominated by agriculture and fire emissions, while the major source of primary PM<sub>2.5</sub> in urban settings is often mobile sources [18]. The PM<sub>2.5</sub> source mix has varied over time, however, and an analysis of PM<sub>2.5</sub> from 2004 to 2017 in Toronto [48] showed changes in the chemical composition of PM<sub>2.5</sub>, from inorganic-rich to organic- and metal-rich particles during 2013–2016, mainly due to a reduction of the emissions from coal-fired power plants, with an increase in the non-tailpipe vehicle emissions (road dust and brake wear).

Two seasons of synchronous sampling across 15 sites in Europe (ICARUS EU2020 project) [77] indicated the contributions to PM<sub>2.5</sub> concentration as follows: high traffic sites had the highest contribution of traffic exhausts (23.3%), urban background sites had highest traffic non-exhaust (13.5%) and biomass burning (30%), and rural sites had the highest contribution of oil combustion (18.7%) and soil dust (16%). Overall, the study results showed that, while fuel oil combustion, traffic non-exhausts, and soil dust profiles are varied between sites, biomass burning, sea salt, and traffic exhaust were characterized as relatively homogenous among the sites.

Chemical profiles of the main primary sources of ambient PM across China from 1987 to 2017 were investigated and reviewed by Bi et al. [65]. These are coal combustion sources (coal-fired power plants, industrial boilers, and residential), vehicle emissions (gasoline and diesel engines), industrial process emissions, biomass burning, cooking emissions, fugitive dust, and other localized specific sources. They noted that large variability due to sampling methods. The profiles of vehicle emissions were dominated by organic carbon (OC) and elemental carbon (EC) and varied due to the changing standards of sulfur and additives in gasoline and diesel. The profiles of biomass burning and cooking emissions

were affected by the different biofuel and cooking types. The most complicated profiles were coal combustion and industrial emissions due to a lack of measurements of local emission profiles. Isotope analysis for Pb was used to evaluate the effect of coal-burning heating activities of northern China cities to southern China cities [78].

#### 4. Review of Epidemiologic Studies in Human Populations

PM<sub>2.5</sub> mass composition and source contributions vary over time and space, which likely means that the toxicity of PM<sub>2.5</sub> mass varies from place to place and over time, as well. The common practice of collecting and weighing PM<sub>2.5</sub> mass, and thereby treating all PM<sub>2.5</sub> mass as having the same toxicity, has undermined efforts to address PM air pollution health effects on a more specific constituent or source basis. This has hampered our ability to assess the likely variations in PM<sub>2.5</sub> health effects per  $\mu\text{g}/\text{m}^3$  exposure as its source mix varies over time or space (e.g., [79]).

Ozkaynak and Thurston [2] were the first to associate increased human mortality risk with exposure to fine particulate matter mass (now referred to as FPM or PM<sub>2.5</sub>), but also first to use PM<sub>2.5</sub> compositional information (from the US EPA's Inhalable Particle, IP, Network) to develop source factors (indications of the sources, on the basis of their source-specific elemental profile “fingerprints”). Since then, a growing number of epidemiological studies have also included consideration of the sources and elemental compositions of the PM. These are considered below, subdivided according to whether the exposures effects considered were acute (short-term) or chronic (long-term). Studies of short-term PM<sub>2.5</sub> exposures to constituents and mortality have been reported for the European Union region, North America, South America, the West Pacific, and Asia [80], while long-term exposure and mortality studies have been published mostly in North America and Western Europe [18,81–84]. In this section, we review the history of the development of this field of knowledge, as well as recent meta-analyses summaries of the short-term exposure associations.

The availability of ambient air pollution data sets that include PM<sub>2.5</sub> elemental speciation data, and especially of metallic elements that serve as tracers for source apportionments of health effects, has been limited until recent years. The National Research Council (NRC) [85] acknowledged the value of source apportionment models, but it also noted that “a number of approaches have been presented in the literature, but they are typically applied to only a single location or region”. The NRC [85] also noted that, there has not been an extensive enough effort to test the effectiveness of these methods. To address this issue, Thurston et al. [86] organized a 2003 workshop to analyze two sets of PM<sub>2.5</sub> speciation data (Phoenix, AZ, and Washington, DC) by eight research groups applying a variety of multivariate source apportionment techniques, and then followed by air pollution-mortality analyses for each [87–89]. An inter-comparison of modeling approaches found an acceptable degree of agreement of source apportioned PM<sub>2.5</sub> and health effects across a variety of sources and methods considered [86,87]. The mortality analyses of the source apportioned PM<sub>2.5</sub> found common source types that were associated with mortality [88,89]. However, some critical issues were identified needing further investigation, including the consistency of lag structure of associations for a given source type and outcome, and the influence of possibly differential exposure error across source types. More such analyses of PM<sub>2.5</sub> constituent data are still needed using a consistent approach for multiple cities having substantial populations and a variety of PM<sub>2.5</sub> source types.

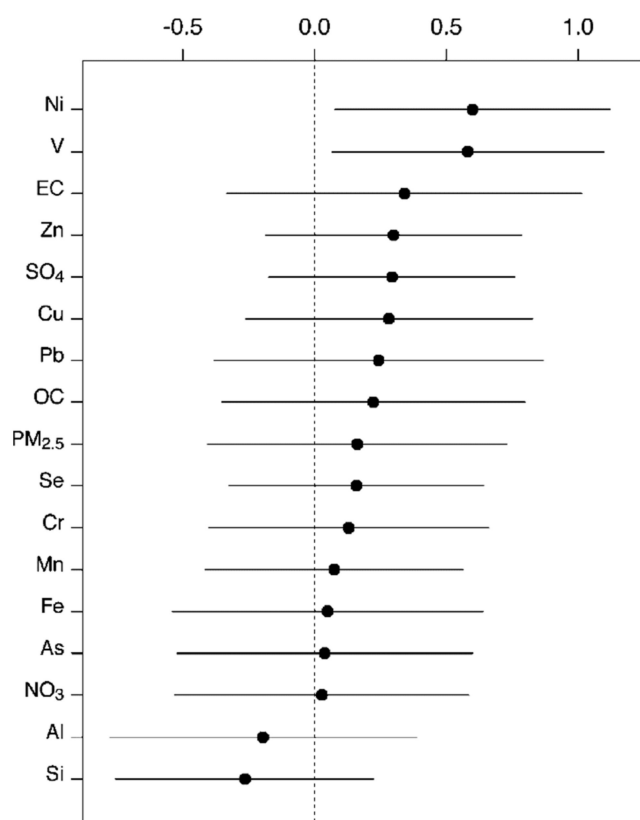
The following discussion of the literature on source apportionment and health-related effects needs to be interpreted with caution, as the studies summarized here did not have the same kind of uniform framework as the workshop comparison discussed above [86]. By contrast, the studies considered below were conducted at various times in a variety of locations that differed in PM metals analyzed, with varying limits of detection, and addressing differing health outcomes. Thus, their ability to clarify the respective roles of specific sources in adverse health effects is still hampered by their numbers and varying approaches. Therefore, the following focuses primarily on studies that consider multiple cities or are meta-analyses of multiple studies using similar methods. Thus, even at this

stage of the development of the art and science of source apportionment for health effects studies, the studies summarized here are still informative as to which PM<sub>2.5</sub> sources are of greatest health concern.

#### *4.1. Health Effects of Short-Term Exposure to PM Metals or Their Source-Related Mass*

Pollution emission interventions have provided real-world insights into which sources and/or particle constituents are of greatest health impact. For example, a mandated switch to burning low sulfur content fossil fuels in Hong Kong (beginning 1 July 1990) provided one of the earlier documentations that varying PM<sub>2.5</sub> mass composition can change its health impacts. Hedley and colleagues [90] documented significant reductions in the concentrations of Ni and V, but not in other metals, in Hong Kong after the policy initiation, consistent with significant effects of residual oil combustion emissions on both daily mortality and bronchial hyperreactivity recorded in Hong Kong.

The results obtained by Hedley et al. [90,91] led Lippmann and colleagues [92] to examine the possible role of PM constituents (i.e., transition metals, ions, and crustal soil tracers) as modifiers of PM<sub>10</sub> mortality risk estimates across the US. For this analysis, they analyzed the association between PM<sub>2.5</sub> constituents from the US EPA IP Network (speciation network and the National Morbidity Mortality Air Pollution Study (NMMAPS)) daily mortality risk estimates for PM<sub>10</sub>. The analysis focused on the 16 key constituents that were most closely associated with major source categories, i.e., Al, As, Cr, Cu, EC, Fe, Mn, Ni, NO<sub>3</sub><sup>-</sup>, OC, Pb, Se, Si, SO<sub>2</sub>, V, and Zn. Metropolitan Statistical Area (MSA)-averaged PM<sub>2.5</sub> constituent values were matched with mortality in the 60 NMMAPS metropolitan areas that had PM<sub>2.5</sub> speciation data. The PM<sub>10</sub> mortality risk estimates (expressed as percent excess deaths per 10-μg/m<sup>3</sup> increase in PM<sub>10</sub>) were then regressed on each of the FPM components. Figure 1 shows the resulting difference in the inhalable particulate matter (PM<sub>10</sub>) mortality risk estimates (in percent change per 5th-to-95th percentile difference in the PM<sub>2.5</sub> constituent). Consistent with the Hong Kong experience, Ni and V, which are most strongly associated with residual oil combustion particles, showed the strongest associations with the variation in PM<sub>10</sub> risk estimates across the NMMAPS MSAs. In contrast, the metals most closely associated with resuspended soil, i.e., in Al and Si, had the lowest values, suggesting that they were unlikely to be influential on daily mortality. Thus, variations in PM<sub>2.5</sub> composition appear to explain some of the MSA-to-MSA variation the NMMAPS PM<sub>10</sub> daily mortality risk coefficients.



**Figure 1.** Percent differences in mortality effect estimates per the 5th to 95th percentile changes in PM<sub>2.5</sub> mass and PM<sub>2.5</sub> constituent concentrations across 60 NMMAP metropolitan areas in the US. Reproduced with permission from [92].

Dominici et al. [93] extended the Lippmann et al. analysis to 69 MSAs and an additional 2 years (through 2005). Their results were consistent with those of Lippmann et al. [92] but noted that excluding the New York City (NYC) metropolitan region (with its much higher levels of Ni and V than other US cities) yielded associations that were no longer statistically significant. Aside from the strong influence of NYC, these results need to be interpreted with some caution, since they compare PM<sub>10</sub>-associated daily mortality for different years than the FPM composition data (1987–1994 vs. 2000–2003 or 2005).

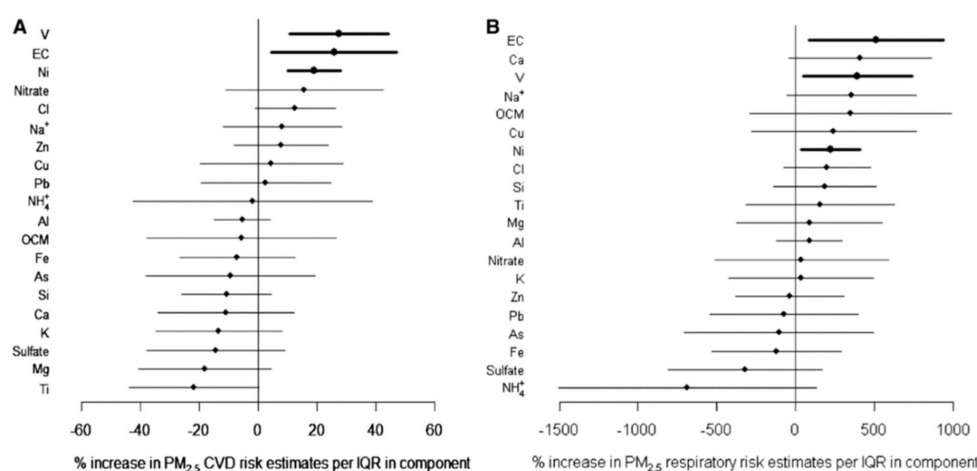
Among the first studies that evaluated the acute (day-to-day) health risks from PM<sub>2.5</sub> constituents and source-specific PM<sub>2.5</sub> used the Harvard Six City Cohort Study's data to evaluate the source-specific PM<sub>2.5</sub> using a single trace element as a marker (or "target") of that source across six US cities [94]. The PM<sub>2.5</sub> sources and their elemental tracers identified in all six cities were crustal (Si as tracer), mobile source (traffic) emissions (Pb as tracer), and coal combustion (Se as tracer). Of these, mobile sources and coal were statistically significant overall, while the crustal component (primarily from windblown soil) was consistently not associated overall with daily mortality, or in any of the individual six cities considered. Overall, the authors concluded that combustion particles in the fine fraction from mobile and coal combustion sources, but not fine crustal particles, were associated with increased mortality.

Burnett et al. [95] also evaluated the associations between pollutant gases and 47 elements within both coarse thoracic PM and PM<sub>2.5</sub> on daily mortality in eight Canadian cities. The strongest associations with mortality found were with four specific components of FPM, i.e., sulfate, Fe, Ni, and Zn. Their collective effect estimate was greater than that for FPM mass. Combining the coarse and fine concentrations for Ni (change = 2.9 ng/m<sup>3</sup>), there was a 1.2% increase ( $t = 2.9$ ), while for Zn (change = 41 ng/m<sup>3</sup>) there was a factor of 1.25 increase ( $t = 3.1$ ). In contrast, a larger study by many of the same authors [96], using

19 yrs. of data from 12 Canadian cities, found that vehicles were the main emission source category associated with daily mortality. These contrasting results do, however, both point to particles from fossil fuel combustion sources as important risks.

Ostro et al. [97] examined the roles of PM<sub>2.5</sub> constituents on short-term mortality in humans in California, and reported associations of traffic markers, sulfate, Ca, Cl, Cu, Fe, Mn, Pb, Ti, V, and Zn in the cool season with all-cause and or cardiovascular short-term mortality, but no significant associations for Al, Br, or Ni.

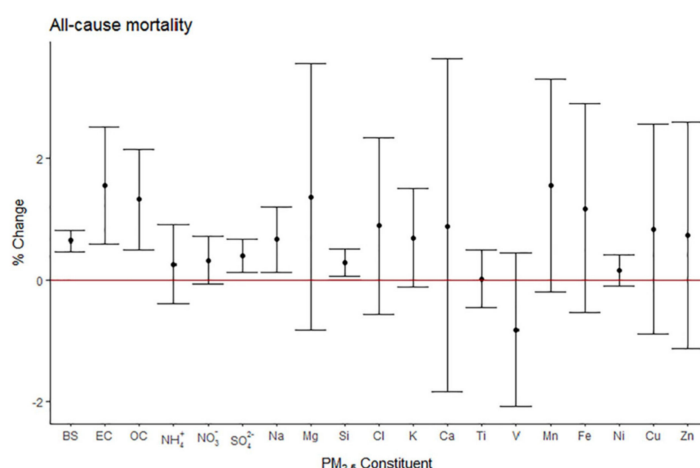
Bell et al. [98] linked two national datasets: (1) a US EPA database used to form long-term average concentrations of PM<sub>2.5</sub> chemical constituents across the US for 2000–2005; (2) daily cardiovascular and respiratory Medicare hospitalizations for persons 65 years or older in 106 US counties from 1999 through 2005. As shown in Figure 2, it was found that communities with generally higher PM<sub>2.5</sub> content of Ni, V, and EC yielded higher risk of hospitalizations associated with short-term exposure to PM<sub>2.5</sub>.



**Figure 2.** PM<sub>2.5</sub> component hospital admissions risk coefficients shown as the 5th–95th percentile difference in concentrations of PM<sub>2.5</sub> constituents for US metropolitan areas (from [98]), where: (A) shows the risk of cardiovascular (CVD) hospitalization per constituent exposure interquartile range (IQR); (B) shows the risk of respiratory hospitalization per constituent exposure IQR. (OCM = Organic Carbonaceous Matter).

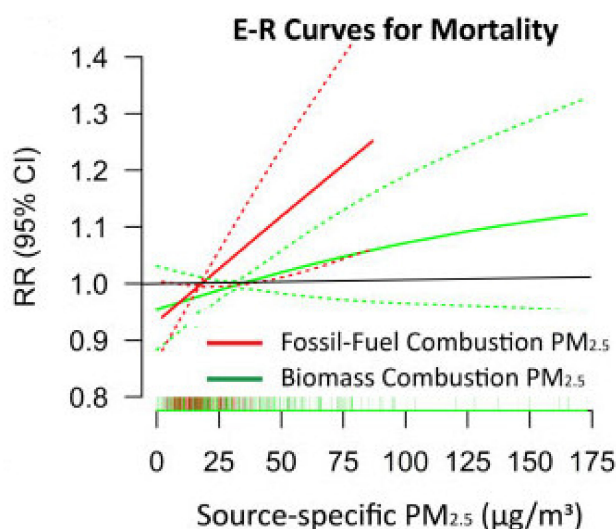
Ostro et al. [97] used city-specific PM<sub>2.5</sub> mass source apportionment in eight major metropolitan areas in California during 2005–2009 to examine the associations of source-specific PM<sub>2.5</sub> exposures from vehicular emissions, biomass burning, soil, and secondary nitrate and sulfate sources with emergency department visits (EDVs) for cardiovascular and respiratory diseases. Using a case-crossover analysis, they observed associations of vehicular emissions with all cardiovascular EDVs. Vehicular emissions, biomass burning, and soil sources were associated with all respiratory EDVs and with EDVs for asthma. The soil source, which includes resuspended road dust, generated the highest risk estimate for asthma. Overall, the authors concluded that their results provide additional evidence of the public health consequences of exposure to specific sources of PM<sub>2.5</sub> and indicate that some source-specific components of PM<sub>2.5</sub> may pose higher risks (per  $\mu\text{g}/\text{m}^3$ ) than the overall PM<sub>2.5</sub> mass.

Achilleos et al. [80] systematically reviewed available epidemiological studies that examined the association between short-term exposure to PM<sub>2.5</sub> constituents and all-cause, cardiovascular, and respiratory mortality, in the general adult population. As shown in Figure 3, all-cause mortality was significantly associated with black smoke (BS), EC, sulfate (SO<sub>4</sub><sup>2-</sup>), Ni, and Si. The authors concluded that the meta-analysis suggested that combustion source-related elements had a stronger association with mortality across the mortality outcomes.



**Figure 3.** PM<sub>2.5</sub> constituent total mortality risk coefficients, shown as the 5th–95th percentile difference in concentrations of PM<sub>2.5</sub> constituents (from [80]). (BS = black smoke; EC = elemental carbon; OC = organic carbon; NO<sub>3</sub><sup>−</sup> = nitrate; SO<sub>4</sub><sup>2−</sup> = sulfate).

Fewer such source specific studies have been conducted in the developing world, especially in Southern Asia. However, Rahman and colleagues [99] recently addressed this gap by evaluating cardiovascular hospital visits, admissions, and deaths at a hospital in Dhaka, Bangladesh. A time-series regression model, adjusted for potentially confounding influences, was applied to cardiovascular disease (CVD) EDVs during January 2014 to December 2017, hospital admissions during September 2013 to December 2017, and CVD deaths during January 2014 to October 2017. Significant associations were confirmed between PM<sub>2.5</sub>-mass exposures and increased risk of cardiovascular EDV (0.27%, (0.07% to 0.47%)) at lag-0, hospitalizations (0.32% (0.08% to 0.55%)) at lag-0 and deaths (0.87%, (0.27% to 1.47%)) at lag-1 per 10 µg/m<sup>3</sup> increase in PM<sub>2.5</sub>. However, the relationship of PM<sub>2.5</sub> with morbidity and mortality effect slopes was less steep and non-significant at higher PM<sub>2.5</sub> concentrations (during crop burning-dominated exposures) and varied with PM<sub>2.5</sub> source. Fossil-fuel-combustion PM<sub>2.5</sub> had roughly a four times greater effect on CVD mortality (see Figure 4) and double the effect on CVD hospital admissions on a per-µg/m<sup>3</sup> basis than did biomass-combustion PM<sub>2.5</sub>.



**Figure 4.** Fossil fuel combustion PM<sub>2.5</sub> vs. biomass PM<sub>2.5</sub> effects on daily mortality in Dhaka, Bangladesh (adapted from [99]) Color dotted lines are 95%ile confidence intervals.

#### 4.2. Adverse Health Effects of Long-Term Exposure to PM Constituent Metals or Source-Related PM Mass

As mentioned above, Thurston et al. and Ozkaynak and Thurston [2,100] were the first to associate an increased risk of death with long-term fine particulate matter mass exposure (then abbreviated as FPM, rather than  $PM_{2.5}$ ), and also were the first to use compositional data (from the US EPA IP Network [101]) to develop source factors (indexes of  $PM_{2.5}$  source impacts, on the basis of their composition profiles) that most strongly influence the site-to-site variations in FPM mass across the nation. The elemental loadings on (correlations with) these factors suggested that five major source groups were most influential: wind-blown soil (Si, Fe); motor vehicle emissions (Pb, Br); residual oil combustion (Ni, V); iron/steel/metals industry emissions (Mn, Zn); coal combustion (Se, S). As shown in Table 4, when the IP Network source factors were entered into a cross-sectional regression of 36 US Metropolitan Statistical Areas (MSAs), the regressions of annual mortality rates on pollution and other mortality, cofactors (age, poverty, etc.) indicated that long-term exposures to the coal and metals/steel FPM components were more significantly associated with increased mortality than the other components identified in this early work [2,102]. Soil particles were clearly shown to be nonsignificant contributors to annual mortality. Thus, these associations of mortality with source-specific FPM contributions, while rudimentary in terms of the mortality assessment method (cross-sectional), were a first indication that  $PM_{2.5}$  from differing sources can have differing impacts on mortality.

**Table 4.** Mean source contributions and their mean effects on 1980 mortality in 36 US MSAs [2,102].

| Emission Source Class | Mean US $PM_{2.5}$ ( $\mu g/m^3$ ) | Percent Mortality Effect Estimate (%) |
|-----------------------|------------------------------------|---------------------------------------|
| Soil                  | 4.4                                | 0.4                                   |
| Auto emissions        | 2.9                                | 0.6                                   |
| Oil combustion        | 3.8                                | 0.6                                   |
| Metals (iron/steel)   | 1.1                                | 1.2 <sup>a</sup>                      |
| Coal burning          | 11.0                               | 7.3 <sup>a</sup>                      |

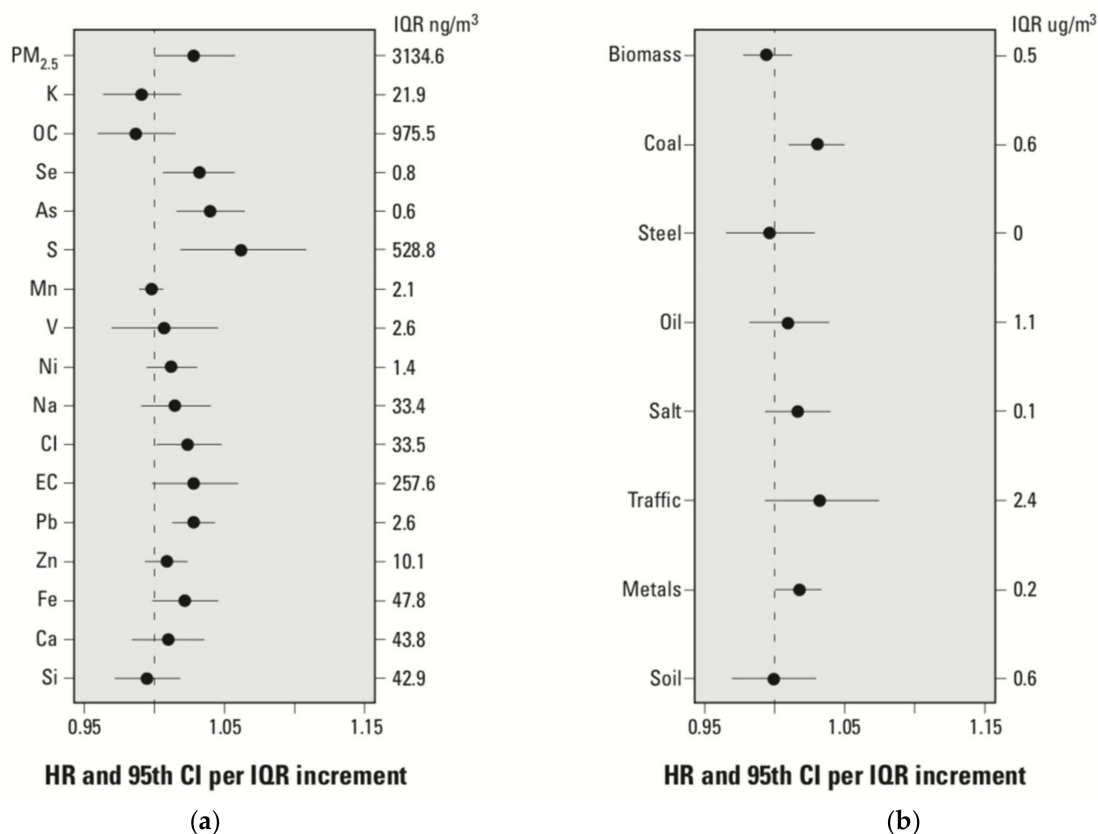
<sup>a</sup> Significant at  $p < 0.01$ .

Lipfert et al. [103] examined the influences of  $PM_{2.5}$  sources on survival in a cohort of male US military veterans using county-level data on  $PM_{2.5}$  composition and vehicular traffic density for 1997–2002 and cohort member mortality for those living in those communities for 1997–2001. Using single-pollutant models, traffic density was the strongest predictor of mortality, but other components also appeared to be influential, including  $NO_2$ , nitrate, EC, Ni, and V. Unlike most other studies, sulfate was not significant in any of the models considered. In multipollutant models, the traffic density variable (which may or may not be related to metals content) was more robust than other emission categories, remaining significant when others ceased to be significant, with loss of significance occurring only when EC (another proxy for vehicular emissions) was also in the model. When traffic density was not in the models, V and Ni were often significant in multipollutant runs. As these oil combustion-related elemental emissions are not nearly as widespread as vehicular emissions, it is possible that their importance might have been understated in this study.

Chung et al. [104] examined 12.5 million Medicare enrollees residing in the eastern United States. A seven-year average from 2000 to 2006 pollution exposures was developed for six major constituents of  $PM_{2.5}$  taken from the US EPA chemical speciation network. The constituents included EC, organic carbon matter (OCM), sulfates, nitrate, Si, and Na. Rather than a traditional Cox regression, the authors used a novel Bayesian hierarchical regression model to determine whether changes in monthly mortality rates were associated with monthly changes in the concentrations of the  $PM_{2.5}$  constituent. The regression model for a given constituent controlled for other constituents by including a term for the annual average of  $PM_{2.5}$ . The authors also examined whether the risk of the seven-year average of

PM<sub>2.5</sub> on mortality was modified by the concentrations of the constituents. In their basic model they found that EC, Si, and nitrates were associated with mortality, and that PM<sub>2.5</sub> mass that contained more sulfates demonstrated significantly greater risk estimates.

A study of a subset of the national American Cancer Society's (ACS) Cancer Prevention Study-II cohort, with more individual level information on participants than in the Medicare data, evaluated the risk of both PM<sub>2.5</sub> constituents and source-related mass components [6]. A total of 446,000 adults in 100 US metropolitan areas were followed from 1982 to 2004. In this case, the average of concentrations from the available US EPA Composition Speciation Network (CSN) monitors in each city were used as a measure of metropolitan area-wide concentrations of the pollutants. Sixteen constituents and eight sources were examined. Four different Cox regression models focusing on ischemic heart disease (IHD) mortality were employed, where additional controls for possible confounding factors were progressively introduced. Among the constituents that contributed significantly to PM<sub>2.5</sub> mass, EC (a tracer for traffic PM<sub>2.5</sub>) and S (a tracer for fossil fuel combustion PM<sub>2.5</sub> in general) and As (a tracer for coal combustion PM<sub>2.5</sub>) were statistically significant in most models, while OC and Si were not. Of note, the risks relating to the coal-related mass component were not altered when other sources were controlled for in models with two sources, similar to the earlier findings of Özkaynak and Thurston [2]. PM<sub>2.5</sub> from both wind-blown soil and biomass combustion were not associated with IHD mortality (see Figure 5). Based on the model including random effects, but no population based contextual variables, mortality risk estimates for PM<sub>2.5</sub> mass, coal combustion, and EC were 1.6% (95% CI = 0.6, 2.5), 4.6% (95% CI = 1.5, 9.1) and 11.5% (95% CI = 0, 22.6), respectively, on a per  $\mu\text{g}/\text{m}^3$  PM<sub>2.5</sub> basis. Overall, this study, similar to the Medicare population study, found that PM<sub>2.5</sub> mass that contained more sulfates demonstrated greater risk estimates, indicating the importance of PM<sub>2.5</sub> resulting from fossil fuel combustion.



**Figure 5.** Cox random effects estimates of the ischemic disease mortality risks associated with (a) PM<sub>2.5</sub> elements and (b) source contributions, per interquartile range (IQR) in the US nationwide American Cancer Society cohort [6].

The ELAPSE Study subsequently examined this issue in Europe [105]. Pooled data from eight cohorts with 323,782 participants, average age 49 y at baseline (1985–2005). Residential exposures to 2010 annual average concentration of eight PM<sub>2.5</sub> constituents (Cu, Fe, K, Ni, S, Si, V, Zn) were estimated. Cox proportional hazards models were applied to investigate associations between these constituents and natural and cause-specific mortality. Most constituents were significantly associated with mortality in single pollutant regressions. Simultaneous inclusion of PM<sub>2.5</sub> mass in the models weakened constituents' associations with mortality except V, which was to be expected, since V was the constituent least correlated with PM<sub>2.5</sub> mass. In cause-specific analyses, the authors noted that "In the present study, we also found robust associations between S and lung cancer mortality, which was observed in ACS CPS-II as well [66]".

Investigating the role of oxidative stress in PM<sub>2.5</sub> metals' associations with health, Zhang and colleagues [106] evaluated the associations of long-term exposure to metal constituents (Fe and Cu) in PM<sub>2.5</sub> with cardiovascular disease incidence in a population-based cohort study in Toronto, Canada. Exposures to Fe and Cu in PM<sub>2.5</sub> and their combined impact on the concentration of reactive oxygen species (ROS) in lung fluid were estimated using land use regression models. Incidence of acute myocardial infarction (AMI), congestive heart failure (CHF) and CVD death was ascertained using health administrative datasets. Mixed-effects Cox regression models were applied to assess associations between the exposures and health outcomes. A series of sensitivity analyses were conducted, including indirect adjustment for individual-level cardiovascular risk factors (e.g., smoking), and adjustment for PM<sub>2.5</sub> and nitrogen dioxide (NO<sub>2</sub>). Consistent with a role by oxidative stress from metals, long-term exposure to Fe and Cu in PM<sub>2.5</sub>, and their combined impact on ROS, were consistently associated with increased CVD death.

The epidemiological evidence for oxidative stress as a likely causal factor in the systemic adverse health effects of PM<sub>2.5</sub> exposures has also been supported by recent research into the influence of diet on health. Lim and colleagues found that participants in the NIH-AARP cohort who ate a diet rich in antioxidants (e.g., fruits) had a much diminished cardiovascular mortality effect from PM<sub>2.5</sub> exposure than those who did not, consistent with a role by oxidative stress in PM<sub>2.5</sub> health impacts [107].

Yang and colleagues [84] searched studies published before 1 August 2018, on the associations of fine particulate matter constituents with mortality and morbidity. Studies were included if they explored the associations between short-term or long-term exposure of fine particulate matter constituents and natural, cardiovascular, or respiratory health endpoints. They applied a random-effects model to derive the risk estimates for each individual constituent. They performed main analyses restricted to studies that adjusted the PM<sub>2.5</sub> mass in their models. Significant associations were observed between several PM<sub>2.5</sub> constituents and different health endpoints. Among them, the authors noted that BC and OC were most robustly and consistently associated with all natural, cardiovascular mortality and morbidity in models including PM<sub>2.5</sub>. Other potential toxic constituents including nitrate, sulfate, Zn, Si, Fe, Ni, V, and K were each associated with adverse cardiovascular health, while nitrate, sulfate and V were relevant for adverse respiratory health outcomes. However, the authors' choice to focus on model results simultaneously including particle mass with constituents would be expected to statistically weaken health associations for those that also comprise a significant percent of the mass (e.g., sulfates), as occurred in the Chen et al. study [105]. In general, models including both constituents and mass simultaneously, such as conducted here, should be avoided, due to the intercorrelation bias introduced for some, but not all, constituents. Additionally, Yang et al.'s reported mixed results for individual metals may also be contributed to by the fact that the metals' chemical form and source-specific co-pollutant mixtures they are emitted with are likely also important to their toxicity, such as the known effect of sulfur on metals' bioavailability in a particle (see Section 5, below), so that using a source-specific elemental groupings approach (e.g., factor analyses) in future may be more informative of potential health impact causality than consideration of single constituents.

Although not examining metals and their specific sources, per se, Vodonos et al. [108] conducted a meta-analysis of published cohort studies examining the association between long term exposure to PM<sub>2.5</sub> and mortality that considered sources of the PM<sub>2.5</sub>. Meta-regression techniques were used to test whether study population or analytic characteristics modify the PM<sub>2.5</sub>–mortality association. Geographical locations with higher percent of PM<sub>2.5</sub> from traffic were significantly associated with higher effect estimates, with a 2.05% increase in mortality rate (95% CI 1.89–2.81) per µg/m<sup>3</sup>. The percent increase in mortality at PM<sub>2.5</sub> = 10 µg/m<sup>3</sup>, calculated based on the 25th and 75th percentile levels of the continuous variables, found that the percent traffic PM<sub>2.5</sub> had the highest range of impacts on the PM<sub>2.5</sub> effect size (19.3–26.5 percent) than did natural, industrial or biomass burning PM<sub>2.5</sub>, consistent with an important contribution to PM<sub>2.5</sub> health effects by PM<sub>2.5</sub> from fossil fuel combustion.

Overall, the results of epidemiological studies indicate that, while many PM<sub>2.5</sub> constituents and sources are associated with adverse health effects, the evidence does not yet conclusively indicate that any one PM<sub>2.5</sub> constituent is uniquely responsible for the health effects associations. However, the source-specific epidemiology is generally consistent with the hypothesis that particles from fossil fuel combustion sources (e.g., coal and traffic) are among those most toxic to human health, especially for systemic health effects by PM<sub>2.5</sub> (i.e., non-respiratory disease, such as cardiovascular).

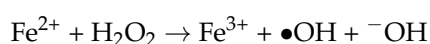
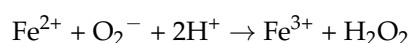
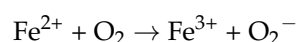
## 5. Toxicology Studies of PM<sub>2.5</sub> Exposure

As described in the above review of relevant epidemiological studies, PM air pollution exposures have been most often associated with adverse cardiopulmonary effects. However, the potential causal mechanism is not well understood, so the biological role(s) of PM constituents needs to also be evaluated using toxicological studies. In this section, we review the current evidence of the toxicology of metals contained in fossil fuel combustion particles.

### 5.1. Role of Metals in Oxidative Stress and Inflammation

Many studies have shown that PM causes oxidative stress and inflammation when a target site does not have enough antioxidant reserve to counteract the ROS [18,109–118]. Molina and colleagues [19] recently reviewed the oxidative potential (OP) of the PM related to the presence of transition metals and organic compounds that can induce the production of reactive oxygen and nitrogen species (ROS and RNS). Some studies of the OP of ambient PM implicated water-soluble metals, including Fe, Cu, and Mn [119–122]. Water-soluble Cr and Zn, as well as water-soluble OC, were also shown to be correlated to OP in PM<sub>2.5</sub> collected in Seoul, Korea [123]. In a comparison study in Calu-3, human bronchial cell line, exposed to NiCl<sub>2</sub> (water soluble) and Ni particles on trans-epithelial electrical resistance and induced oxidative stress, the effect of soluble NiCl<sub>2</sub> both at the barrier level and at the molecular level was more pronounced than the effect of Ni particles [124].

Metals with unpaired electrons, most notably Fe and Cu, can catalyze the production of free radicals via the Haber–Weiss cycle, directly contributing to oxidative capacity of PM. The hydroxyl radicals (•OH, •OOH), superoxide anion (O<sub>2</sub><sup>−</sup>), and H<sub>2</sub>O<sub>2</sub> can interact with several biological molecules to activate cellular signals as well as produce cellular damage. In vivo superoxide-driven Fenton chemistry below explains how O<sub>2</sub><sup>−</sup> and H<sub>2</sub>O<sub>2</sub> synergize to produce •OH [114,125,126]:



The activity of metal is determined by its speciation (type, oxidative states) and is critical in PM toxicity. For example, the magnitude and kinetics of hydroxyl radical

formation was found to vary by the oxidation state of a particular metal, with  $V(II) > V(V) > Fe(II) > Fe(III)$  [122],  $Cu(II)$  was more reactive than  $Fe(II)$  [127].

Another important determinant of OP is the solubility of transition metals. Metal oxides (possibly formed in high-temperature combustion, but also some crustal), chlorides, and carbonates can be generally dissolved in lung fluids, while metal sulfides, phosphates, and silicates (many of crustal origin) are common insoluble compounds. Sholkovitz et al. [128] described a systematic trend of higher solubility of Fe in aerosols derived from anthropogenic and natural combustion sources compared to lithogenic dust derived from arid continental soils. Their combined analysis for total Fe and soluble Fe in ~1100 samples collected by multiple researchers over the open ocean, the coastal, and continental sites revealed the inverse trends for anthropogenic (low total Fe, but high solubility) and lithogenic (high total Fe, but low solubility) PM. This notable trend was observed over regional and global scales, regardless of any differences in when and how the samples were collected and stored, as well as in analytical methods used to define 'soluble' iron. The solubility of Fe (and thus, possibly of other metals) in lithogenic aerosols was noted to increase when mixed with acidic anthropogenic aerosol [128]. This is consistent with earlier toxicological research finding that lung injury from fossil fuel combustion  $PM_{2.5}$  exposures are due to their transition metals (e.g., Cu, Fe, V, Fe, Zn), when solubilized in the co-presence of acidic sulfur [129–131].

Generally, atmospheric processing of  $SO_2$  emitted by burning fossil fuels leads to formation of sulfuric acid and its acidic ions. Previously, Schwartz and Lepeule reasoned that the acid and acidic sulfates coat and migrate through other particles dissolving metal oxides [132]. This may be a key factor in the enhanced toxicity of metals contained in S-rich particles from fossil fuel combustion. Sulfate has been reported to increase the solubility of iron [133]. Fang et al. [119] demonstrated almost in a Venn-diagram way that water-soluble Cu was found only the presence of highly acidic sulfates (see Figure 6). Noticeable correlation between water-soluble Fe, pH, and concentrations of sulfate  $SO_4^{2-}$  in Toronto, Montreal, and Vancouver, which suggested that acid processing contributed to Fe solubility in the aerosol aqueous phase [134]. Similarly, Brehmer et al. [135] confirmed that elements associated with the secondary sulfate source (As, Mo, Zn) had the strongest correlation with increased cellular oxidative potential, while chemical markers of biomass burning (water-soluble K and water-soluble OC) had negligible OP. These studies are evidence that the acidic nature of sulfur compounds in particulate matter (e.g., as ammonium sulfate, ammonium bisulfate, or sulfuric acid) can make insoluble metal oxides more bioavailable and thus more toxic. This suggests that sulfate, while not especially toxic in itself, does contribute to the toxicity of ambient PM, as previously argued by Lippmann and Thurston [136]. In addition, a thin layer of sulfuric acid was shown to be 10× more potent in reducing lung function than equivalent mass of sulfate [137]. The follow-up study of the Harvard Six Cities Study reported that there was no evident change in the estimate of the effect of  $PM_{2.5}$  mass over time, despite the significant reduction in sulfate concentrations when compared with  $PM_{2.5}$  mass during the study period [138]. Thus, it is still unclear from the epidemiology whether removal of  $SO_2$  from the emissions of oil and coal combustion would lead to a significant reduction in the health effects associated with particles from these sources. However, the toxicology indicates that the sulfur acidity itself is not the biologically causal factor, but instead the acid's ability to solubilize the transition metals that cause its adverse health effects associations [131].

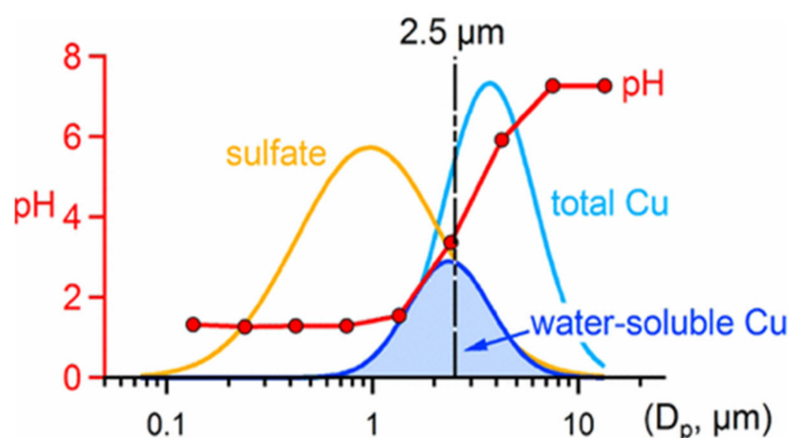


Figure 6. Enhanced metal solubilization induced by acidic sulfates [119].

There is also growing evidence of the importance of coexistence of metals and organics in generation of OP of aerosols [139–141]. Indeed, freshly formed sulfuric acid or ammonium sulfate particles enhance the photochemical processing of organic vapors and serve as a condensation sink for primary and secondary organic components. Water-soluble Cu, Fe, and Mn have been found to be correlated with PM oxidative activity, and the association was higher in summer due to enhanced photochemical reactions [114,142]. Non-redox active metals, such as K, Ca, Mg, and Zn, have also been associated with oxidative activity and may result from co-emitted redox active constituents, such as quinones [143].

Nitrates, which, like sulfates, are components of PM<sub>2.5</sub> resulting from fossil fuel combustion sources that are acidic and can therefore engender similar potentiation of metals' solubility and bioavailability. Indeed, a recent analysis of cardiovascular mortality in the Catheterization Genetics (CATHGEN) cohort found that PM<sub>2.5</sub> from both ammonium bisulfate (pH = 1.42 at 0.1 M) and ammonium nitrate (pH = 5.22 at 0.1 M) were associated with increased prevalence of myocardial infarction per IQR exposure in the population (OR = 1.20; 95% CI = 1.10, 1.29, and OR = 1.35; 95% CI = 1.20, 1.53, respectively [144]).

Once deposited into lungs, particle-bound soluble metals can dissolve into the fluid lining of the airway, and then directly act as reducing agents to biological molecules extracellularly to produce ROS. Oxidative stress may disturb cellular machinery by increased production of oxidant species or decreased levels of free radical scavengers (e.g., ascorbate or glutathione) or antioxidant enzymes (e.g., catalase, superoxide dismutase or glutathione peroxidase), altered function of mitochondria, NADPH-oxidases, disrupted intracellular calcium homeostasis or through activation of inflammatory cells by activation of redox sensitive signaling pathways, including activator protein 1 (AP-1), mitogen-activated protein (MAP) kinases and nuclear factor kappa B (NF-κB) activation with subsequent changes in pro-inflammatory gene expression and production of cytokines [115]. The three approaches in ascertaining oxidative properties of PM (cell-free assays, cellular assays, and in vivo assays) were recently reviewed by Molina et al. [19]. Below we provide examples of some relevant studies.

Correlations of ROS activity with mass concentration of PM<sub>2.5</sub>, prevalent components (EC, OC, SO<sub>4</sub><sup>2−</sup>, NO<sub>3</sub><sup>−</sup>, and NH<sub>4</sub><sup>+</sup>), and select trace metals (Cu, Fe, Ni, V, Zn) have been presented by the US EPA [18]. Correlations between PM<sub>2.5</sub> mass concentration and DTT activity (a measure related to ROS) ranged from Pearson *R* = 0.49 to 0.88. Most correlations were greater than 0.3 for EC, OC, SO<sub>4</sub><sup>2−</sup>, NO<sub>3</sub><sup>−</sup>, and NH<sub>4</sub><sup>+</sup>. In contrast, correlations between trace metals and ROS macrophage assay showed variation in responses ranging from positive to negative.

The radical generating capacity of PM<sub>10</sub> from both gasoline and diesel engine exhaust was significantly higher when compared to that of PM<sub>10</sub> from ambient or indoor air; in urban PM<sub>10</sub> and PM<sub>2.5</sub>, ROS-generating capacity significantly correlated with concentrations of polycyclic aromatic hydrocarbon content and particular transition metals [145]. In

a prospective birth cohort, asthma incidence, prevalence of asthma symptoms and rhinitis in adolescents were more strongly associated with the DTT activity than with PM<sub>2.5</sub> mass or PM ESR activity and these associations were sensitive to adjustment for NO<sub>2</sub> [146]. An intracellular fluorescent dye dichlorofluorescein (DCFH) was used as a measure of intracellular ROS production by Ni as a tracer of traffic emissions in ambient PM<sub>2.5</sub> in Athens, Greece [147]. Increases in PM DCFH activities were directly related to decreases in cell viability in PM-exposed BEAS-2B bronchial epithelial cells [148].

Alternatively, the extent of ROS causation of lung inflammation can be studied by using free radical scavengers (e.g., dimethylthiourea), antioxidants (e.g., glutathione or N-acetylcysteine), or antioxidant enzymes (e.g., superoxide dismutase). The diminished response to PM after treatment with these antioxidants indicates the involvement of ROS. For example, a study of the nasal mucosa of rats following PM<sub>2.5</sub> exposure found increased levels of malondialdehyde and several pro-inflammatory mediators, a decrease in the activities of antioxidant enzymes, changes in expression of specific mitochondrial fission/fusion genes, and abnormal alterations of mitochondrial structures [149]. Thus, although ROS production and inflammation are common responses induced by PM, they may not be correlated with each other, since ROS production can be neutralized by antioxidant defense system. Inflammation may occur via other signaling pathways, perhaps by different PM components. For example, in a study of the associations of cellular responses with PM components for seasonal samples collected from five cities in North China, Pb, Cu, Zn, Cd in autumn and winter samples were more related to the PM-induced oxidative stress, while Al, Fe, Mg, Co, V, Mn, and Ca in the spring and summer samples were more related to PM-induced inflammation and cytotoxicity [150]. These studies indicate that physiochemical properties other than the mass concentration, such as oxidative stress potential, can be very important in the extent of health impacts induced by particulate air pollution.

### 5.2. Role of Metals in Cardiovascular Disease (CVD)

The collective evidence of PM and metals causation of oxidative stress and inflammation lead to a hypothesis of pathways for CVD health effects of PM air pollution. Inhaled PM can instigate extrapulmonary effects on the cardiovascular system by three general “intermediary” pathways: (1) the release of proinflammatory mediators (e.g., cytokines, activated immune cells, or platelets) or vasoactive molecules from lung-based cells; (2) a systemic perturbation of autonomic nervous system (ANS) balance or heart rhythm by particle interactions with lung receptors or nerves; (3) potential physical translocation of fine PM or particle constituents (organic compounds, metals) into the systemic circulation (see review [151]).

Ambient particles and its metal constituents can also stimulate resident or newly recruited alveolar macrophages or polymorphonuclear leukocytes (PMNs) to undergo oxidative stress, resulting in ROS production and subsequent cell response (e.g., proinflammatory cytokines/chemokines) and injury in the pulmonary system. The resulting increase in circulating proinflammatory mediators (e.g., activated immune cells, cytokines) could thus serve as a pathway to instigate adverse effects on the heart and vasculature. Furthermore, a small fraction of PM or its constituents may penetrate into the systemic circulation (as free PM, incorporated intracellularly within circulating cells, or bound to molecules such as lipoprotein) or via lymphatic spread to cause systemic inflammation or inflammation/injury in other organ systems (review by [151]).

Particle stimulation of irritant and afferent ANS fibers may also play a role in local and systemic oxidative stress formation. PM exposure also enhances the known interconnection between inflammation and thrombosis, induces platelet activation and increases peripheral vascular thrombosis in both arteries and veins. In addition, PM exposure disrupts normal vascular homeostasis and vasoactive mediator balance through ROS-dependent mechanisms and sensitizes the vessel toward vasoconstrictors and causes hypertension [151].

Transition metals in PM<sub>2.5</sub> (e.g., Ni) have been shown to alter heart rhythms by inhibiting the transient receptor potential vanilloid receptor in the lungs. This suggests that the

relevant neural mechanism that leads to alterations in HRV or heart rhythm may be induced by activation of receptor-mediated autonomic reflexes in the lung. Circulating PM or its constituents may also directly interact with myocardial ion channels or electrophysiology to alter the cardiac rhythm (review by [151]).

Chronic PM<sub>2.5</sub> exposure, in conjunction with a high fat diet, accelerated the progression of atherosclerosis in atherosclerosis-prone mice by inducing oxidative stress and heightened vascular inflammation [15]. In a later study, transition metals derived from coal and oil combustion were found to be responsible for these effects [152].

Finally, longer-term exposure to PM air pollution may promote the chronic development of insulin resistance, obesity, and the metabolic syndrome. High fat diet fed mice exposed to PM<sub>2.5</sub> exhibited marked worsening of whole-body insulin resistance, systemic inflammation (increased IL-6 and TNF- $\alpha$ ), and higher levels of adipokines, such as resistin and plasminogen activator inhibitor-1. PM<sub>2.5</sub> increased visceral adiposity and inflammation (F4/80<sup>+</sup> cells), with stromal vascular cells expressing higher TNF- $\alpha$  and IL-6 and lower IL-10 levels. Exposure also induced insulin-signaling abnormalities and reduced phosphorylation of Akt and endothelial nitric oxide synthase in aortic tissue, accompanied by abnormalities in vascular relaxation to insulin. Additionally, there was evidence that PM<sub>2.5</sub> exaggerated adhesion of monocytes in mesenteric microvessels, culminating in accumulation in visceral adipose [153].

### 5.3. Translocation of Inhaled Metals from Lungs to Other Organs

Comparison studies of soluble and insoluble metal compounds showed that besides a localized induced oxidative stress [124] and toxicity [154] in the lungs, bioavailable metals enter systemic circulation and may be important in producing direct impact on multiple organs. For example, PM<sub>2.5</sub> inhalation study in mice found that PM<sub>2.5</sub>-bound metals could reach and gather in secondary off-target tissues (liver, heart and brain) [155]. After intratracheal instillation of mice with coal and coal fly-ash, Cr, Fe and Ni were detected in liver, spleen and brain [156]. PM and associated metals have been linked to neurotoxicity and mental health [157]. Excess brain exposure to either essential or non-essential elements can result in brain dyshomeostasis, which has been implicated in both neurodevelopmental disorders (NDDs; autism spectrum disorder, schizophrenia, and attention deficit hyperactivity disorder) and neurodegenerative diseases [158]. After prenatal exposure of mice to concentrated ambient particles via inhalation, Fe, Al, and Si were metabolically distributed to the CNS [159]. The same study demonstrated the PM effect on the development of CNS of prenatally exposed mice, specifically, induced neuropathologies characteristic of autism spectrum disorder, including ventriculomegaly and aberrant corpus callosum myelination.

### 5.4. Evidence from Concentrated Ambient Particles (CAPs) Inhalation Studies in Animals

It is critical to systematically investigate the potential effects of components of ambient PM in different regions, since PM of different composition and from different sources may vary markedly between regions, and in their potency for producing adverse health effects. However, it is toxicologically difficult to investigate the health effects of mixtures because each compound has its own pharmacokinetics/toxicokinetics. In response to this need, short term experimental toxicology studies using “real-world” CAPs, under controlled conditions, were employed in the early 2000s to provide some evidence that certain ambient PM mixtures or specific PM components may be responsible for reported health effects of ambient PM. Unfortunately, those early short-term CAPs inhalation studies, as described in 2004 US EPA Particulate Matter Criteria Document (PMCD) [160], had limited statistical power, and were not able to delineate the specific characteristics of PM in producing toxicity, and associated potential underlying mechanisms.

After the release of the 2004 PMCD [160], a series of more informative longer-term subchronic PM CAPs inhalation studies were conducted at NYU. The studies’ lengths and types of concurrent data collected (PM<sub>2.5</sub> composition, electrocardiographic data in

mice, and in vitro endpoints) allowed investigations of both acute and cumulative effects of inhalation exposures, and thus, had more to identify possible causal components of ambient PM<sub>2.5</sub>. The first NYU subchronic CAPs inhalation study involved 5 months of warm-season daily exposures to inertially concentrated ambient-air PM<sub>2.5</sub> (CAPs) in Sterling Forest, NY in a mouse model of atherosclerosis (ApoE<sup>-/-</sup>) (5 d/wk, 6 h/d to an average CAPs concentration = 110 µg/m<sup>3</sup>) [10,12,14,51,161–165]. These papers documented CAPs exposure-associated acute and chronic effects on HR and HRV, formation of aortic plaque, and changes in brain cell distribution and in gene expression markers, as well as data on the effects of daily CAPs exposures in vitro on NF-κB activation. The composition analysis of daily CAPs samples was used for the source apportionments to determine the PM source categories (secondary sulfate, suspended soil, residual oil combustion, and a remainder category, which was largely due to long-range transported motor vehicle traffic) [51]. The associations of daily source apportionment, elemental composition data, and both heart rate (HR) and heart rate variability (HRV) were examined for three different daily time periods: (1) during exposure; (2) the afternoon following exposure; (3) late at night [10,12]. They found significant associations of HR with secondary sulfate during exposure, and with residual oil combustion (predominantly V and Ni) in the afternoon. For HRV, there were comparable associations with suspended soil (predominantly Si, Al, Ca) in the afternoon and for both residual oil combustion and traffic (Br, Fe, elemental carbon) late at night.

The extent of metals' ability to mediate biological response was demonstrated by Kodavanti and colleagues [166], in which stain-specific systemic effects were not linked to high mass, but instead appeared to be dependent on CAP chemical composition. Using similar exposure protocol, the results of more recent HEI-NPACT CAPs studies were consistent with evidence from earlier studies in Tuxedo NY that exposure to CAPs leads to acute changes in heart rate and HRV, as well as chronic changes in atherosclerotic plaques and markers of inflammation [152]. Presumably, the effects observed at Tuxedo resulted from long-range transport of air pollutants from the Ohio Valley (e.g., coal burning PM<sub>2.5</sub> and associated sulfates). Surprisingly, few changes were observed at Seattle and Irvine, two major urban areas dominated by traffic-related pollution.

#### 5.5. Bioactivity of PM Associations with Elements and Sources

Usually, equal mass of PM is used in toxicological studies to evaluate the biological response. The diverse characteristics of PM samples collected from different regions and at different sampling times is expected to produce different responses. Several studies demonstrated that the biological responses elicited by exposure to fossil fuel combustion sources are more significant than of other sources. For example, in a comparison study of wintertime PM<sub>2.5</sub> from Beijing and Guangzhou, two megacities in China, PM<sub>2.5</sub> from Beijing resulted in higher oxidative stress at equal mass concentrations due to their higher burden of metals (Fe, Cu, and Mn) and PAHs per unit mass of PM<sub>2.5</sub>. The disparity was attributed to significant contributions from coal combustion and vehicular emissions in Beijing [167]. In another study, a mouse macrophage cell line (RAW264.7) was exposed to a total of 66 PM<sub>2.5</sub> samples collected in Beijing. Both ROS and secretion of inflammatory cytokines IL-1β were positively correlated with transition metals; components from vehicle emissions promoted both ROS and TNF-α, while IL-1β secretion was induced mainly by those from coal combustion [168]. In a comparison study of fine (PM<sub>2.5-0.2</sub>) and coarse (PM<sub>10-2.5</sub>) samples collected from six European cities, cytotoxicity responses increased up to 2-fold after repeated exposures to PM<sub>2.5-0.2</sub> samples and up to 6-fold after repeated exposures to PM<sub>10-2.5</sub> samples. The constituents with major contributions to the inflammatory responses were oxidized organic compounds and transition metals in PM<sub>2.5-0.2</sub> samples, Cu and soil minerals in PM<sub>10-2.5</sub> samples, and Zn in both size ranges. In contrast, biomass and coal combustion were associated with elevated levels of PAHs, as well as a consistent inhibitory effect on the inflammatory activity of PM<sub>2.5-0.2</sub> samples [169].

An in vitro and in vivo toxicity assessment of coarse and fine PM simultaneously collected at three rural and two urban sites within the metropolitan New York City (NYC) region during two seasons found that the aerodynamic size, locale (i.e., urban versus rural), and site of PM samples affected the ROS response in vitro, and the inflammatory response in vivo. In addition, these responses were dependent upon the chemical composition of the PM samples [170]. A similar study of in vitro and in vivo toxicity was conducted for coarse (PM<sub>10-2.5</sub>) and fine (PM<sub>2.5</sub>) PM samples collected simultaneously at five diverse sites (two rural and three urban) within California during the summer. Particle size, locale, and location were important parameters that influenced these responses. In this case, trace elements associated with soil and traffic markers were most strongly linked to the adverse effects in vitro and in vivo [171].

Size-fractionated particles collected in Windsor, Canada, in the vicinity of industrial (steel mills and associated coking operations, wastewater treatment), high traffic, and residential areas showed systematic differences in biological potency in human A549 lung epithelial and murine J774A.1 macrophage-like cells using cytotoxicity bioassays, cytokine production, and transcript profiles [172,173]. Cytotoxic potency varied across size fractions and within a fraction across sites and sampling periods, suggesting that particle composition, in addition to size and mass, affected particle toxicity. Chemical speciation varied in relation to prevailing winds, consistent with enrichment of source emissions (e.g., higher metal and PAH content downwind of the industrial site). In addition, greater potency of coarse fractions at the industrial site and of ultrafine particles at the traffic site were observed. Regression of potency against particle constituents revealed correlations between resazurin reduction, induction of metal-responsive genes, and metal content, which were particularly strong for the coarse fraction (composed primarily of Fe and Al), and between cytokine release and endotoxin, suggesting that these factors were important drivers of biological effects that explain, at least in part, the contrasting potencies of particles, when compared on an equivalent mass basis [172].

In contrast, ultrafine and fine (PM<sub>0.1-2.5</sub>) fractions displayed considerable variability in metal composition (especially water-soluble metals) across collection sites consistent with source contributions. Fine and coarse PM collected near metal industry were enriched in semi-volatile and PM-associated PAHs. At equivalent mass basis, cell responses to exposure displayed striking differences among sites, suggesting that particle composition, in addition to size, impacted particle toxicity [173]. The in vitro study of exposure to PM<sub>10</sub> collected in three different sites (urban traffic, industrial area, rural background location) showed that on an equal mass basis, PM<sub>10</sub> induced toxicological effects differ due to differences in PM<sub>10</sub> characteristics. The main determinants for the observed biological responses were metals (Cd, Cu, Ni and Zn), BC, and endotoxin [174].

As discussed previously, there is evidence that PM metals emitted from different sources could vary by their bioavailability. For example, the soluble fraction (in simulated lung fluid) of As, Pb, Cr, Mn, Cd, Cu, Ni, and Zn varied drastically among PM originated from coal combustion, biomass combustion, fugitive dust, road dust, construction dust, cement and soil [175]. The authors calculated that when considering bioaccessibility of metals examined in their study, coal combustion PM exhibited the highest carcinogenic and noncarcinogenic risks among all source particles, whereas when based on total metal content, cement PM would be the source with highest risk. This means that when total PM or total metal concentrations, rather than bioavailable metals, are considered, the health risk of PM could be incorrectly estimated, and attributed to incorrect pollution sources.

### 5.6. Effects of Metal Removal or Addition

A key question is the extent to which metals mediate the biological responses of PM. To test this, the effects of metals have been evaluated by differences, via treatment with metal chelators, antioxidant enzymes, or antioxidants. Several studies on ROFA and air pollution particles show decreased cytokine secretion (TNF, IL6, IL8) or gene expression in macrophages, BEAS-2B, and microvascular endothelial cells by treatment with transition

metal chelators [115]. The cell viability of A549 increased significantly (12.3%) after metal removal in PM (SRM1648a), demonstrating an important contribution of metal components to PM toxicity. Among 11 elements examined (Zn, Cr, Mn, Fe, Ni, Cu, As, Se, Sr, Cd, and Pb), six heavy metals (Zn, Cr, Mn, Fe, Cu, and Pb) might account for PM toxicity in A549 cells, and their co-exposure led to a high mortality of A549 cells. Using mixtures of six heavy metal in a permutation, cell mortality caused by single or multiple metal mixtures was usually alleviated by Fe addition, while it was often aggravated in the presence of Mn. The varying effects of other metals (Zn, Cu, Pb and Cr) on different metal mixtures might be explained by their interactions (e.g., similar or dissimilar membrane transporters and intracellular targets) [176].

PM rich in metal components, such as nickel (Ni), has been linked to adverse cardiopulmonary effects in mice [92]. To further explore the mechanisms of Ni induced cardiovascular effects, male FVB/N mice received oropharyngeal aspiration of water or PM<sub>2.5</sub> from JC (Jinchang, China, city near Ni refinery), ZH (Zhangye, China, city with no refinery), or ZH spiked with one of the following elements at the same concentrations found in the JC PM (Ni = 4.76; As = 2.36; Se = 0.24; Cu = 2.43 µg/mg) followed by evaluation of markers of pulmonary and systemic inflammation. Significant pulmonary inflammation was observed in mice exposed to PM from ZH and JC and ZH + NiSO<sub>4</sub> as compared to control and a significant decrease in mesenteric artery relaxation and this decrease is blunted in the presence of NADPH oxidase inhibitors. Significant increases in other end-points (TNF-α, IL-6, NOS3, NOX4) were observed in JC and ZH + NiSO<sub>4</sub>, as well as significantly higher concentrations of VEGF and IL-10. These results showed that the specific toxicity observed in PM from JC is likely due to the nickel component in the PM [177].

To investigate the effects of Ni as a varying component of ambient PM<sub>2.5</sub> exposures, male ApoE knockout mice were exposed to filtered air, fine-sized nickel sulfate particles alone (Ni) at 0.44 µg/m<sup>3</sup>, PM<sub>2.5</sub> CAPs at a mean of 70 µg/m<sup>3</sup>, or CAPs + Ni in Tuxedo, NY, 6 h/day, 5 days/week, for 3 months. Exposure to Ni, irrespective of co-exposure to CAPs, resulted in body weight gain, while exposure to CAPs + Ni significantly enhanced fasting glucose and worsened insulin resistance measures (HOMA-IR), when compared with exposure to CAPs alone. CAPs + Ni exposure induced a significant decrease in phosphorylation of AMPK-α. Exposure to Ni or CAPs + Ni significantly induced microcirculatory dysfunction and increased monocytic cell infiltration into lung and adipose and decreased uncoupling protein 1 expression at gene and protein levels and several brown adipocyte-specific genes in adipose tissue [178].

In experiments, Ni exposure also decreased endothelial nitric oxide synthase (eNOS) dimers in the aorta, which was potentiated by co-exposure with CAPs. CAPs alone did not reduce NOS dimers but was more effective than Ni in decreasing phosphorylation of eNOS (S1177) and Akt (T308). Ni had minimal effects on the expression of vascular inflammatory genes, but it synergized with CAP in marked upregulation of TNF-α and monocyte chemotactic protein-1. Ni also synergized with lipopolysaccharide, another bioactive component of CAP in reducing eNOS dimerization in cultured endothelial cells. Ni exposure induced endothelial dysfunction through oxidative stress-dependent inhibition of eNOS dimerization [179]. These studies have shown that the interaction of a specific component, in this case Ni, with other components of CAP, may significantly modify the adverse cardiovascular effects of CAP exposure.

Field studies around the globe have yielded consistent conclusions. Water-soluble extracts from PM collected at a roadside site in London were used to elucidate potential components that drive pulmonary inflammatory, oxidative, and defense mechanisms and their systemic impacts. Multiple exposures of the London PM led to an increase in cytokine levels in both BALF and in the blood serum, indicating a systemic reaction. Lung mRNA levels of antioxidant/phase II detoxifying enzymes decreased by exposure to the PM extract, but not when metals were removed by chelation [180]. To investigate the influence of metals on the bioassays, a series of pure metal solutions were prepared to mimic the concentration of metals in the extracts of the PM samples. The specific metal mixtures were

(a) major cations/anions to ensure that we captured the bulk metals and ion-strength (Ca, Mg, Na, K, Ba, Sr, S, P), (b) major and minor cationic/anionic redox-active transition metals (Fe, Mn, Cu, V, Ni, Cr), (c) major non-redox active metals (Zn, Pb, Al), and (d) several minor elements of significance in roadway emissions (Y, Ce, Pt and Pd). An artificial metal mixture solution was able to reproduce the ambient PM extract response, thus excluding a major role for other chelatable (e.g., organic) materials [181]. In a different study using PM<sub>10</sub> collected in Beijing, China, removal of metals through chelation significantly reduced water extracted-PM<sub>10</sub>-mediated inflammatory, carcinogenic and metastatic responses [182].

## 6. Discussion

As documented above, epidemiological and toxicological research focusing on the influence of PM<sub>2.5</sub> composition and source on health-related responses has clearly shown that spatial or temporal differences in PM composition, notably metals from fossil fuel combustion, are driving the reported variations in its health effects and that, for the same ambient level of PM mass, the health implications of exposure to ambient air depend on the PM source and composition. As a result, some components of the PM mixture are clearly of a greater public health threat than others.

### 6.1. Where Do Metals Fit in the Larger Picture of PM-Associated Health Effects?

There is clearly emerging evidence that the inhalation of transition metals in ambient air PM is associated with adverse health effects at concentrations near or not much higher than current ambient levels. These include Ni, V, and Pb, and suggestive evidence exists for others, such as Zn, Cu, and Fe. There is also a rapidly growing literature implicating motor vehicle related pollution in human health effects, as indexed by EC, OC, and ultrafine particle number. However, there are also metals in motor vehicle exhaust whose role, if any, in association of their concentrations in ambient air with human health effects, has not been determined. Furthermore, there is a great deal of evidence that adverse health effects of metals are significantly contributed to by aerosol acidity, which is likely due to its role in solubilizing transition metals within the particles.

### 6.2. Are There Specific Metals That Can Account for Health Effects Associated with PM Mass?

Toxicological studies investigating the biological effects of constituents of ambient air have not, with one exception, identified an individual metal as being the definitive cause for an effect of concern with respect to human health. The one exception is the demonstration that acute peaks of Ni within PM CAPs were significantly associated with short-term increases in heart rate (HR) and decreases in heart rate variability (HRV) in a mouse model of atherosclerosis [92]. Lippmann et al. [92] also discussed evidence that both Ni and V, which, together, are markers for the residual oil combustion source, have been significantly associated with excess daily mortality in time-series mortality studies. In these time-series studies the separate influences of Ni and V cannot be determined because their air concentrations are usually highly correlated. In a previous subchronic (six-month) CAPs exposure studies in this animal model at NYU, we reported that total PM was associated with effects on HR and HRV, as well as on the progression, during exposure, on aortic plaque growth and invasiveness, and on the gene expression and brain cell distribution [163]. However, it is not known whether Ni, or any other specific component of the PM CAPS, played any major role in these effects of prolonged series of daily exposures. Furthermore, there have been no previous studies of people in urban areas, or in working populations, that have related Ni exposure to cardiovascular disease.

If there are health-related effects of specific metals, other than the effects of Ni in ambient PM on cardiac function, they are not yet confirmed by careful toxicological studies. However, it is important to remember that the absence of evidence for effects of specific metals does not demonstrate an absence of effects, and that both Ni and V were more closely associated with mortality than other metals in the NMMAPS re-analyses [92,93], and in the Hong Kong sulfur-in-fuel intervention study [90,91]. In particular, the role of

ambient air As in the coal combustion PM<sub>2.5</sub>–CVD mortality association (e.g., as found in Thurston et al. [6]) needs further investigation: is As involved in the mechanistic pathway of CVD effects (as found for drinking water [183]), or is it instead serving as a tracer of other coal combustion PM<sub>2.5</sub> constituents?

Metal concentrations are usually measured by XRF or ICP-MS. However, both analytic methods provide no information on their chemical or physical form or solubility in biological fluids. Solubility, in turn, may depend not only on the associated cations and particle size, but also on whether they exist as dry particles, or as particles within aqueous droplets and, if so, on the pH of those droplets, which strongly affects transition metals' solubility and potential for toxicity (e.g., [119]). In most cases, ionic forms of the metals will be most bioavailable, and therefore most likely to affect cells and organs beyond their deposition sites in the lung airways. Thus, even when quantitative data on metallic component concentrations were available, there were additional constraints on their utility as individual indicators of exposure to potentially causal components, and consideration of groupings of elements, such as by source, is seen as a potentially more productive approach.

### 6.3. Acidic Sulfur as a Potentiator of Health Risks from Particulate Metals

In the observational epidemiologic results discussed above, many past studies have indicated that sulfate-associated particles (i.e., fossil fuel combustion products) are among the combustion-related elements that are most associated with annual mortality rates [2,3,6,136,184]. Although sulfate, per se, is an unlikely causal factor for mortality or morbidity, as previously discussed by [136], its central role in the toxicity of particulate matter is likely due to the fact that sulfates do not occur as pure chemicals in the air, but in intimate mixtures with other compounds, including transition metals, in fossil fuel combustion emissions. Indeed, decades ago, Dreher and colleagues [131] proposed such a causal role by sulfates and soluble transition metals (V, Fe, Ni) on the basis of studies in which rats were exposed by intratracheal instillation to oil combustion fly ash. In addition, Chen and colleagues demonstrated that particles emitted from western US low sulfur and high alkaline coal had none of the adverse lung function effects on guinea pigs exposed to particles resulting from the combustion of eastern US high sulfur coal [185].

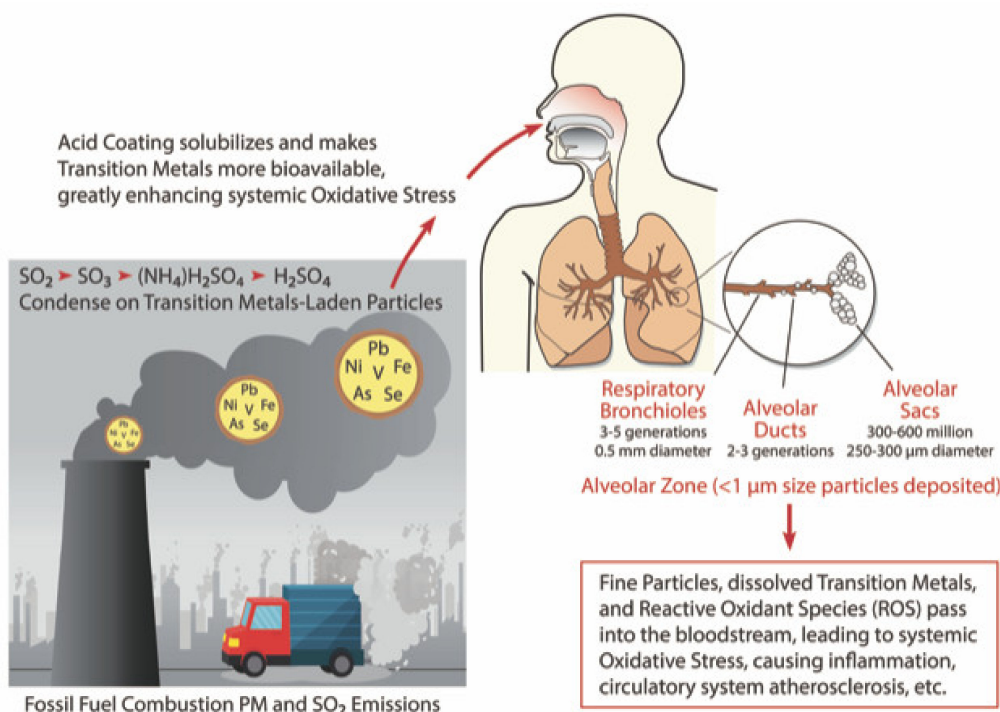
Thus, the inclusion of sulfate measurement in routine regulatory PM<sub>2.5</sub> monitoring networks would seem essential for the most effective control of the health effects of particulate matter. Overall, as previously discussed by Lippmann and Thurston [136], the advantages of also measuring particulate sulfur or sulfate as an index of fossil fuel combustion particulate matter are many. They include:

1. It often has correlated with adverse health effects as well or better than other widely used PM metrics in epidemiological studies for which comparisons were possible.
2. It is stable and nonvolatile on sampling substrates.
3. It can be analyzed easily and economically both continuously and in virtually all analytical laboratories.
4. There is an existing body of historic sulfate epidemiology justifying its monitoring and regulation, along with PM<sub>2.5</sub> mass.

### 6.4. Role of Fossil Fuel Combustion Sources in Adverse Health Effects of PM

As discussed above, and summarized in Figure 7, both toxicological and epidemiological evidence to date have primarily pointed to oxidative stress and its associated systemic inflammation as major pathways of effects from particulate matter exposures, those sources that emit both transition metals (e.g., V, Ni, Fe) and oxidative stress potentiating acidic sulfur, notably fossil fuel combustion, should therefore be more toxic. Indeed, the ubiquitous burning of fossil fuels, including diesel, residual oil, and coal combustion have been indicated by various studies to be among the most toxic in both toxicological, and epidemiological studies. In contrast, those PM<sub>2.5</sub> sources that result in particles lacking this oxidative stress inducing combination of transition metals and sulfur, such as soil and biomass burning, have tended to be less toxic on a per mass basis in both toxicological

and epidemiological analyses. Indeed, the available source apportionment epidemiology generally confirms that fossil fuel combustion sources are more toxic than particles in general, on a per mass basis (e.g., see [6,94]).



**Figure 7.** A causal pathway for systemic effects of fossil fuel combustion particles.

Among the best documented examples of the elevated toxicity of fossil fuel combustion  $\text{PM}_{2.5}$  is effluents from residual oil combustion. The concentrations of Ni and V in ambient air PM were associated with significant differences in mortality rates, while all other measured PM components were not [91,92]. Both Ni and V are present at relatively high concentrations in residual oil combustion effluents from oil-fired power plants and/or from ocean-going ship boilers consuming high sulfur fuel when operating in or near port cities [186–188]. Thus, residual oil combustion effluents, as a source-related mixture, or of the Ni and/or the V in that mixture, may be responsible for a disproportionate contribution to excess PM-associated mortality in coastal cities. These results alone do not indicate the relative contributions of Ni and V to the overall mortality impact, or whether they have differential effects on mortality due to cardiovascular and/or respiratory causes. However, these findings, when considered together with the statistically significant short-term cardiac function changes in mice suggest that Ni is the more likely causal factor for the effects associated with reduced mortality in humans in the NMMAPS, for which longer-term Ni concentrations extended down from  $19 \text{ ng/m}^3$  in NYC to a national average of  $1.9 \text{ ng/m}^3$ .

Similarly, coal combustion particles have been indicated as especially toxic, based on both toxicological and epidemiological investigations. As noted above, using elemental tracers of coal combustion (e.g., As, Se, and S), studies [2,6,66] have shown coal  $\text{PM}_{2.5}$  to be the most important contributor to PM toxicity across the US in the late 20th century. This was not just because of their large contribution to the mass, but also because of their greater inherent toxicity on a per  $\mu\text{g/m}^3$  basis. In addition, studies noted above by Chen and colleagues have demonstrated the impacts of coal particles, especially when present with acidic sulfur [185].

Motor vehicle emissions air pollution have also been identified by many studies as most associated with adverse PM<sub>2.5</sub> health effects in the above discussed epidemiological literature, as well as by an HEI Special Report on the health impacts of traffic air pollution [189]. In addition to the above discussed studies relating the urban traffic pollution tracer (especially for diesel vehicle emissions), elemental carbon, when measured, many studies also have found associations with nitrogen dioxide (NO<sub>2</sub>), which also serves as a more routinely measured tracer for PM<sub>2.5</sub> from traffic in urban areas.

Overall, as discussed above, particles resulting from the combustion of various fossil fuels, from coal to residual oil to distillate and diesel fuel oil, and natural gas, all have key shared toxicity characteristics: enrichment in transition metals and a co-presence of sulfur. Since these are seen from the above discussions as key actors in the adverse health effects of PM<sub>2.5</sub>, it is logical that these ubiquitous fossil fuel combustion emissions are among the greatest contributors to the adverse health effects of PM<sub>2.5</sub> air pollution.

## 7. Conclusions

While the above makes clear that particles resulting from fossil fuel combustion emissions are dominant contributors to the adverse health effects associated with particulate matter exposures, there are multiple reasons why past research has not more definitively accepted the key role that fossil fuel emissions of metals play. These include: (1) most available research considers only the PM<sub>2.5</sub> mass concentration, especially in the Low and Middle Income Countries (LMICs), which ignores wide variations in composition, leading to uncertainty in the PM<sub>2.5</sub> effects per unit mass (e.g., as acknowledged for the Burden of Disease mortality estimates [79]); (2) concentrations of metals in ambient air PM generally range from a few  $\mu\text{g}/\text{m}^3$  in some refractory metals to less than 10  $\text{ng}/\text{m}^3$  for transition metals that are known to generate ROS, raising the issue of biological plausibility when the potentiating effects of co-exposure to acidic sulfur is ignored; (3) when PM<sub>2.5</sub> constituent data are available, epidemiologic research too often considers associations with individual constituents, rather than more appropriately addressing the fact that it is complex source-specific mixtures of constituents that lead to the greatest toxicity; (4) few toxicologists or clinical researchers have had the resources needed to perform CAPs studies that include speciation data on the PM in the exposure samples; (5) controlled exposures to pure compounds at concentrations of environmental relevance have been uniformly negative, even when sensitive animal models were used; (6) a lack of studies defining the relationship between personal exposure and ambient air levels for most metal species; (7) most controlled exposure studies have been limited to one or a few days, which may not be sufficient to elicit responses of concern.

To further address the above-noted uncertainties that remain by policy makers regarding the key role of fossil fuel combustion in the world's PM<sub>2.5</sub> health impacts, more source and composition research is needed. While CAPs studies have concluded that Ni is a particularly influential component of fossil fuel combustion PM in terms of cardiac responses to the inhalation of ambient air PM, further research is also needed on the less well documented impacts of other toxic metals, and their interactions with other constituents, such as acidic compounds like sulfur, in real world ambient air. In addition, more epidemiological studies need to consider source-specific mixture effects, rather than overall mass or individual constituents. As discussed above, the constituent mixtures in particles can vary greatly, and so mass alone is a useful, but only an imprecise metric of a particle's toxicity. Epidemiological consideration of more extensive characterizations and source-specific mass can be expected to provide more consistent estimates of particulate matter toxicity and will also provide better guidance to regulators as to which PM<sub>2.5</sub> mass sources to focus their control efforts on in future.

Finally, the inadequacies of present day PM<sub>2.5</sub> routine air monitoring must be addressed if we are to better understand, and more efficiently regulate, the most health threatening particulate matter air pollution. This is especially the case in the LMIC's, where the sources of PM<sub>2.5</sub> and compositions differ greatly from that in the western world, where

most studies of PM<sub>2.5</sub> toxicity have been conducted in the past. Based on the above discussions, it is of paramount importance to regularly monitor the transition metals (e.g., by relatively inexpensive XRF), as well as key indices of fossil fuel combustion sources, such as EC and S, both of which can be routinely measured continuously or semi-continuously [190]. We must move beyond mass as a sole metric of PM<sub>2.5</sub> exposure: more routine measurement of PM<sub>2.5</sub> constituents and characteristics must be added to allow more detailed research and more efficient regulation of PM<sub>2.5</sub> exposures and their human health risks.

Overall, this review highlights the critical role played by fossil fuel combustion-derived metals and their chemical interactions, including with sulfates, in air pollution health effects, as well as the need to further study air pollution as a complex mixture in order to more effectively quantify and minimize air pollution exposure health risks.

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