Health Effects of Airborne Particulate Matter Trace Elements

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The effects of airborne particulate matter (PM) trace elements on health are widely concerned nowadays. Many achievements have been made while many unknowns exist. This article reports the recent research progresses, describes the effects of exposure to PM trace elements on health epidemiological evidence, toxicology findings, and raises some questions for future studies.

Key words: Health effect; Particulate matter; Trace element

Airborne particulate matter (PM) contains a complex mixture of organic and inorganic fractions. There is a large body of new scientific evidence that has strengthened the link between ambient PM exposure and its effects on health.

Increases in mortality have been observed in studies of the acute and chronic effects of particulate matters. The increase in mortality is attributable to the increases in respiratory and cardiovascular disease mortality. Consistent with the observation of increases in acute mortality, there is also an increase in hospital admissions for respiratory diseases and cardiovascular diseases in association with particulate air pollution. Subpopulations consisting of susceptible individuals show increases in symptoms, medication and physiological parameters consistent with an exacerbation of pre-existing respiratory or cardiovascular diseases[1].

It is believed that the health effects are related to some characteristics of airborne PM, but it is not confirmed what the main causes to health effects are and what roles they play. However, trace elements are thought to be responsible for some of the health effects.

Exposure to PM Trace Elements

In addition to the lighter elements, hydrogen, carbon, oxygen, and nitrogen, the following 49 heavier elements are found in ambient air samples: sodium, magnesium, aluminum, silicon, phosphorus, sulfur, chlorine, potassium, calcium, scandium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, gallium, arsenic, selenium, bromine, rubidium, strontium, yttrium, zirconium, molybdenum, palladium, silver, cadmium, indium, tin, antimony, cesium, barium, lanthanum, cerium, samarium, europium, hafnium, tantalum, tungsten, gold, mercury, thallium, lead, thorium, and uranium[2]. These elements often indicate air pollution sources and several of them are considered to be toxic, such as transition metals, water-soluble metals, and metals in certain valence states, e.g., Fe (II), Fe (III), Cr (III), Cr (VI), As (III), and As (V).

In the atmosphere, most of the trace elements exist in airborne particulate matters. Although the concentration of these elements is low in the atmosphere as shown in Table 1, elements such as Cu, Zn, Pb, As, Fe, Ti, and Al often contribute to 0.01%-2% of the total mass of PM$_{2.5}$[9], and all the trace elements together contribute less than 5% of PM$_{10}$ or PM$_{2.5}$[1] (Si is usually not considered as a trace element), they do play an important role in human health. According to WHO, arsenic, cadmium, fluorides, lead, manganese, mercury, nickel, and vanadium are especially concerned for health effects[10].

Epidemiology of Human Health Effects Associated With PM Trace Elements

Numerous studies have been done on the epidemiology of human health effects associated with airborne PM, but only a few on the human health effects are...
### TABLE 1
Concentration of Some Airborne Particulate Matter Trace Elements (unit: ng/m³)

<table>
<thead>
<tr>
<th>Element</th>
<th>Location and Concentration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>Downtown L.A. USA</td>
<td>9.2b, 6.6c</td>
</tr>
<tr>
<td></td>
<td>Taejon, Korea</td>
<td>12.2b</td>
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<tr>
<td>Cr</td>
<td>Downtown L.A. USA</td>
<td>42b, 24.7c</td>
</tr>
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<td></td>
<td>Taejon, Korea</td>
<td>16.2b</td>
</tr>
<tr>
<td>Mn</td>
<td>Downtown L.A. USA</td>
<td>6.3b, 42.7c</td>
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<td></td>
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<td>47.1b</td>
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<tr>
<td>Fe</td>
<td>Downtown L.A. USA</td>
<td>2191.8b, 556.6c</td>
</tr>
<tr>
<td></td>
<td>Taejon, Korea</td>
<td>1531b</td>
</tr>
<tr>
<td>Co</td>
<td>Downtown L.A. USA</td>
<td>1.6b</td>
</tr>
<tr>
<td>Ni</td>
<td>Downtown L.A. USA</td>
<td>4.5b, 7.0c</td>
</tr>
<tr>
<td></td>
<td>Athens, Greece</td>
<td>4.70c</td>
</tr>
<tr>
<td></td>
<td>Taejon, Korea</td>
<td>38.6b</td>
</tr>
<tr>
<td>Cu</td>
<td>Downtown L.A. USA</td>
<td>178.3b, 272.8b</td>
</tr>
<tr>
<td></td>
<td>Taejon, Korea</td>
<td>40.8b</td>
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<td></td>
<td>Guangzhou, China</td>
<td>62.6b, 36.2b</td>
</tr>
<tr>
<td>Zn</td>
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<td>293.4b, 298.2c</td>
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<tr>
<td></td>
<td>Taejon, Korea</td>
<td>245b</td>
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<tr>
<td></td>
<td>Guangzhou, China</td>
<td>645b, 248b</td>
</tr>
<tr>
<td>As</td>
<td>Athens, Greece</td>
<td>0.96b</td>
</tr>
<tr>
<td></td>
<td>Taejon, Korea</td>
<td>5.89b</td>
</tr>
<tr>
<td></td>
<td>Ankara, Turkey</td>
<td>1.5±1.9bg</td>
</tr>
<tr>
<td></td>
<td>Guangzhou, China</td>
<td>40.4b, 8.0bg</td>
</tr>
<tr>
<td>Se</td>
<td>Downtown L.A. USA</td>
<td>9.6b, 10.5bg</td>
</tr>
<tr>
<td></td>
<td>Guangzhou, China</td>
<td>10.9b, 2.5bg</td>
</tr>
<tr>
<td>Cd</td>
<td>Cartagena, Spain</td>
<td>10.03±19.05b</td>
</tr>
<tr>
<td></td>
<td>Athens, Greece</td>
<td>0.44b</td>
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<tr>
<td></td>
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<td>0.74b</td>
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<tr>
<td>Ba</td>
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<td>126.7b, 43.0b</td>
</tr>
<tr>
<td></td>
<td>Taejon, Korea</td>
<td>24.0b</td>
</tr>
<tr>
<td>Hg</td>
<td>Ankara, Turkey</td>
<td>0.18±0.19df</td>
</tr>
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<td>Pb</td>
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</tr>
<tr>
<td></td>
<td>Athens, Greece</td>
<td>160b</td>
</tr>
<tr>
<td></td>
<td>Taejon, Korea</td>
<td>259b</td>
</tr>
<tr>
<td></td>
<td>Guangzhou, China</td>
<td>476b, 104b</td>
</tr>
</tbody>
</table>

Note. Element in a. TSP, b. PM10, c. PM2.5, d. PM2.2, e. PM10-2.5.

associated with trace elements. Besides analysis cost, one possible reason is that trace elements in PM are in low concentration, often below detection limit especially for some elements, thus the data base for trace elements is often lack of data. Such data are not suitable for time-series epidemiologic studies. In epidemiologic studies, trace elements are often taken as source indicators to help people find the principal factors that affect human health.

For epidemiologic studies, a factor analysis of trace elements and sulfate was conducted and identified several major source types: motor vehicle (Pb, carbon monoxide), geological elements (Mn, Fe), oil burning elements (V, Ni), industrial elements (Zn, Cu), and sulfate/secondary aerosols (sulfate)[11].

In conducting source-oriented evaluation of PM components, Laden et al. found that increase in daily mortality was associated with mobile source factor[12]. Similar results were also found by Mar et al.[13-14] and Tsai et al.[11]. Mar et al. found that motor vehicle factor (1 day lag) and vegetative burning factor (3 day lag) were significantly positively associated with cardiovascular mortality[13-14]. Coal combustion factor was also positively associated with mortality, while no positive association was found between fine crustal mass factor and mortality[14].

Some other studies showed a qualitative association between PM trace elements and human health effects. For example, the Utah Valley study[16-18] showed that PM10 particles, while the steel mill was operating, were more highly associated with adverse health effects than PM10 while the steel mill was closed.

**Toxicology of PM Trace Elements**

Although there are some uncertainties about the different effects of one transition metal versus another, water soluble metals leached from ambient filter extracts or (residual oil fly ash) (ROFA) have been shown consistently (albeit at high concentrations) to cause cell injury and inflammatory changes in vitro
Conflict findings in cardiovascular and systemic effects and consistent results in respiratory effects

Numerous toxicological studies on the roles of PM trace elements in respiratory, cardiovascular and systemic effects are available. The conflict findings in cardiovascular and systemic effects, and the consistent results in respiratory effects are summarized below.

Godleski et al. performed a series of experiments examining the cardiopulmonary effects of inhaled concentrated ambient PM (CAPs) on dogs. They hardly noticed any biologically-relevant evidence of pulmonary inflammation or injury in normal dogs, while a significant change in heart rate and in T wave alternans was seen, and a potential increase in chemical stress of the cardiac tissue due to repeated ischemic to concentrated ambient PM was observed. They observed a significantly more rapid ST elevation of the ECG waveform, and a greater peak ST-segment elevation after PM exposure\(^2\) [25].

Contrary to the study of Godleski, Muggenburg et al. reported that inhalation exposure to high concentrations of ROFA produced no consistent changes in amplitude of the ST-segment, form of the T wave, or arrhythmias in dogs. Although the study did not specifically address the effect of PM trace elements, it suggested that inhalation of high concentrations of trace elements might not have obvious effects on the cardiovascular system of a healthy individual\(^3\) [26]. In a further study, Muggenburg et al. evaluated the effects of a short-term inhalation exposure to aerosols of transition metals. Heart rate and electrocardiogram were studied in conscious beagle dogs inhaling respirable particles of oxide and sulfate forms of transition metals (manganese, nickel, vanadium, iron, and copper oxides, and nickel and vanadium sulfates at concentrations of 0.05 mg/m\(^3\)). No significant effects of exposure to the transition metal aerosols were observed\(^4\) [27].

Thus, no certain conclusion could be drawn up till now. The conflict results suggest that more experiments on the cardiovascular and systemic effects of PM and its trace elements are needed. On the other hand, a lot of consistent evidence has been found for respiratory effects of PM trace elements.

Intratracheal instillation of various doses of ROFA suspension has been shown to produce severe inflammation, an indicator of pulmonary injury that includes recruitment of neutrophils, eosinophils, and monocytes into the airway. The biological effects of ROFA on rats have been shown to depend on aqueous leachable chemical constituents of the particles\(^5\) [28-29]. Leachate prepared from ROFA, containing predominant Fe, Ni, V, Ca, Mg, and sulfate, produced similar lung injury to that induced by the complete ROFA suspension. Depletion of Fe, Ni, and V from the ROFA leachate eliminated its pulmonary toxicity. A surrogate transition metal sulfate solution containing Fe, V, and Ni largely reproduced the lung injury induced by ROFA\(^6\) [28].

Thus, intratracheally instilled high doses of ROFA, in which water soluble trace elements play a key role, may produce acute lung injury and inflammation have been widely accepted. These ROFA studies have clearly shown that combustion-generated particles with high trace element content can cause substantial lung injury, but whether the similar phenomena will appear in ambient PM is not sure, since the trace elements in ambient PM are different from those in ROFA.

The Utah Valley PM experiments showed the similar results. Utah Valley PM treated with Chelex, an agent that removes transition metals from solution, produced no change (relative to control) in the inflammatory mediator interleukin-8 (IL-8), while untreated extract showed a significant concentration-dependent increase in IL-8 when compared to the control cells. Thus, the authors concluded that removal of metal cations could attenuate cellular responses to the aqueous extract and suggested a role of transition metal involvement in PM-associated increases in morbidity and mortality\(^7\) [30].

In addition to the above experimental studies, autopsy data suggests that chronic exposure to urban air pollution could lead to an increased retention of trace elements in human tissues. A comparison of autopsy cases in Mexico City from the 1950s with those from the 1980s indicated substantially higher (5- to 20-fold) levels of Cd, Co, Cu, Ni, and Pb in lung tissues from the 1980s\(^8\) [31]. Similar studies have examined the trace element content in human blood and lung tissues, with similar results\(^9\) [32-33].

Toxicological effects of different elements and different chemical species

Controlled inhalation exposure to high concentrations (up to 6400 mg·m\(^-3\)/min cumulative dose) of MgO had no effect on lung function, symptoms of metal fume fever, or changes in inflammatory mediators or cells recovered by bronchoalveolar lavage (BAL). However, lower concentrations of ZnO fume (166 to 1110 mg·m\(^-3\)/min) induced a neutrophilic inflammatory response in the airways 20 h postexposure. Lavage fluid polymorphonuclear leukocytes (PMNs), tumor necrosis factor \(\alpha\) (TNF-\(\alpha\)), and IL-8 were increased after ZnO exposure\(^10\) [34-35]. Although the concentrations used in these exposure studies exceeded ambient levels by more than 1000-fold, the absence of a response to an
higher death rate and more rapid development of lung oedema in mice than inhalation of an equivalent concentration of hydrogen chloride, and titanium tetrachloride could also cause purulent conjunctivitis and corneal opacity in rabbit eyes\textsuperscript{38}\textsuperscript{39}. Sometimes toxicological effects are related to the bioavailability, e.g. water-solubility, of PM trace elements. Ghio et al. found that water soluble fractions caused greater release of IL than insoluble fractions\textsuperscript{39}, and Pierce et al. found that soluble vanadium induced greater chemokinesis mRNA expression than insoluble vanadium\textsuperscript{40}. Lay et al. and Ghio et al. found that iron-oxide-induced inflammatory responses both in alveolar fractions and in bronchial fractions of the lavage fluid 1 day postinstillation. When the same iron oxide preparation containing a small amount of soluble iron, produced similar pulmonary inflammation in rats, the instillation of rats with two iron oxide preparations containing no soluble iron failed to produce injury or inflammation, suggesting that soluble iron is responsible for the observed intrapulmonary changes\textsuperscript{41-42}. Interaction of different PM trace elements Some studies have shown that the toxicological effects of PM trace elements are not only decided by the elements, nor their concentration or chemical species, but also affected by the combination effects. Dreh er et al. found that ferric sulfate and vanadium sulfate antagonized the pulmonary toxicity of nickel sulfate, when a surrogate transition metal sulfate solution containing Fe, V, and Ni largely reproduced the lung injury induced by ROFA\textsuperscript{28}. Kodavanti et al. found that ROFA-induced PMN influx was associated with its water-leachable V content, but protein leakage was associated with water-leachable Ni content. ROFA-induced in vitro activation of alveolar macrophages (AMs) was the highest with ROFA containing leachable V but not with Ni plus V, suggesting that the potency and mechanism of pulmonary injury may differ between emissions containing bioavailable V and Ni\textsuperscript{43}. Cam pen et al. examined the responses to Ni and V in conscious rats by whole-body inhalation exposure. Results showed while Ni caused delayed bradycardia, hypothermia, and arrhythmogenesis at concentrations > 1.2 mg/m\textsuperscript{3}, V failed to induce any significant change in heart rate (HR) or core temperature (T\textsubscript{CO}), even at the highest concentration. When combined, Ni and V produced delayed bradycardia and hypothermia at 0.5 mg/m\textsuperscript{3} and potentiated these responses at 1.3 mg/m\textsuperscript{3}, to a greater degree than those by the highest concentration of Ni (2.1 mg/m\textsuperscript{3}) alone. Although these studies were performed at element concentrations that were orders of magnitude greater than ambient concentrations, the
results indicated a possible synergistic relationship between inhaled Ni and V\(^44\).

Possible mechanism for PM trace element toxicological effects

Reactive oxygen species (ROS) generated by transition elements is considered to be one of the main mechanisms of toxicity.

Fenton and iron-catalyzed Haber-Weiss reactions have been used to describe this process\(^{45}\):
\[
\begin{align*}
\text{Fe (II) + O}_2 &\rightarrow \text{Fe (III) + O}_2^- \quad (1) \\
\text{Fe (II) + O}_2^- + 2\text{H}^+ &\rightarrow \text{Fe (III) + H}_2\text{O}_2 \quad (2) \\
\text{Fe (II) + H}_2\text{O}_2 &\rightarrow \text{Fe (III) + OH}^- + \text{OH}^- \quad (3) \\
\text{Fe (II) + OH} &\rightarrow \text{Fe (III) + OH}^- \quad (4)
\end{align*}
\]

When bio-reductant is available, Fe (III) is likely to act with these kinds of matters to form Fe (II) and increase damage to biological molecules:
\[
\text{Fe (III) + Reductant } \rightarrow \text{Fe (II) + Oxidized Reductant} \quad (5)
\]

Meanwhile, Fe (II) in equation (4) is likely to be replaced by bio-receptors, thus various types of lesions are caused, including oxidation DNA damage.

Soluble fractions of transition elements from inhaled PM can react directly with biological molecules to produce ROS in the fluid lining of airway lumen. Other transition elements like copper, manganese, cobalt are also able to catalyze this reaction, so under certain conditions when these metal ions are not bound to proteins or chelators, Fenton and Haber-Weiss reactions may take place and cause site specific accumulation of free radicals and initiate biomolecule damage processes.

Other mechanisms may be associated with the characters of specific element. For example, inhaled PM manganese could reach areas of the central nervous system and produce the characteristic neurotoxic effects, because of its ability to cross the blood-brain barrier\(^{10}\). The kidney deposition following exposure to mercury vapour elicited nephrotic syndrome, because Hg\(^0\) could cross cell membranes, including blood-brain and placental barriers, to blood where it was oxidized to mercuric mercury catalysed by catalase, and then Hg\(^{++}\) ions (or complexes) were distributed in the body via the blood to its target organs like kidney\(^{10}\).

Guidelines for PM Trace Elements

The WHO Guidelines for Air Quality provides a basis for protecting public health from the adverse effects of environmental pollutants and for eliminating or reducing to a minimum, contaminants that are known to be harmful to human health and well-being. Some of the PM trace elements were discussed in this guideline, and the health- or environment-based levels were summarized below (Tables 2-4)\(^{46}\).

No guideline values are provided for other PM trace elements, e.g. mercury, platinum, barium, mainly because of their low concentrations in the ambient atmosphere, which lead to no direct effects on human health at these air levels.

### TABLE 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>Annual Ambient Air Concentration [µg/m(^3)]</th>
<th>Health Endpoint</th>
<th>Observed Effect Level [µg/m(^3)]</th>
<th>Uncertainty Factor</th>
<th>Guideline Value [µg/m(^3)]</th>
<th>Averaging Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>0.01-2</td>
<td>Critical Level of Pb in Blood &lt; 100-150 µg Pb/L</td>
<td>N. A.</td>
<td>N. A.</td>
<td>0.5</td>
<td>1 Year</td>
</tr>
</tbody>
</table>

Note. N. A.: not applicable.

### TABLE 3

<table>
<thead>
<tr>
<th>Compound</th>
<th>Annual Ambient Air Concentration [µg/m(^3)]</th>
<th>Health Endpoint</th>
<th>Observed Effect Level [µg/m(^3)]</th>
<th>Uncertainty Factor</th>
<th>Guideline Value [µg/m(^3)]</th>
<th>Averaging Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadmium</td>
<td>(0.1-20)×10(^3)</td>
<td>Renal Effects in the Population</td>
<td>N.A.</td>
<td>N.A.</td>
<td>5×10(^-3)</td>
<td>1 Year</td>
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<tr>
<td>Manganese</td>
<td>0.01-0.07</td>
<td>Neurotoxic Effects in Workers</td>
<td>0.03 (NOAEL)</td>
<td>200</td>
<td>0.15</td>
<td>1 Year</td>
</tr>
<tr>
<td>Vanadium</td>
<td>0.05-0.2</td>
<td>Respiratory Effects in Workers</td>
<td>0.02 (LOAEL)</td>
<td>20</td>
<td>1</td>
<td>24 Hours</td>
</tr>
</tbody>
</table>

Note. N. A.: not applicable.
Research Deficiency and Needs in the Near Future

Public exposure to PM trace elements needs more concern. Compared with occupational exposure, studies on public exposure to PM trace elements are deficient. Obviously, there are great differences between these two kinds of exposure, so the data collected during occupational exposure may have no meaning on public exposure. For public exposure study, more epidemiological evidence for ambient PM trace element exposure-response to public health and identification of sensitive subpopulations is needed.

Potential health effects at low levels of exposure to trace element especially to mercury, platinum, elements are needed, which have not received the controlling recommendation values, but are thought to have adverse health effects.

The exposure to PM trace elements in some developing countries needs to be concerned, since the PM concentration in these countries may be much higher than that in most developed countries. The life styles in developing countries may be quite different from those in developed countries which may lead to different chemical fractions.

Toxicology of PM trace elements needs further investigation. Since the toxicity of PM trace elements is closely associated with their chemical species, characterization of exposure to different element species are needed. But before this, classification of the bioavailability and toxicity of different element species is needed, while the analysis methods for these species need improvement.

The interaction between different elements needs further investigation, and particularly, biological effects may be different at various ratios of even the same elements.

REFERENCES

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<table>
<thead>
<tr>
<th>Compound</th>
<th>Annual Ambient Air Concentration [µg/m^3]</th>
<th>Health Endpoint</th>
<th>Unit Risk [µg/m^3]</th>
<th>IARC Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>(1-30) x 10^{-5}</td>
<td>Lung Cancer in Exposed Humans</td>
<td>1.5 x 10^{-3}</td>
<td>1</td>
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<tr>
<td>Chromium (VI)</td>
<td>(5-200) x 10^{-5}</td>
<td>Lung Cancer in Exposed Workers</td>
<td>(1.1-13) x 10^{-2}</td>
<td>1</td>
</tr>
<tr>
<td>Nickel</td>
<td>1-180</td>
<td>Lung Cancer in Exposed Humans</td>
<td>3.8 x 10^{-4}</td>
<td>1</td>
</tr>
</tbody>
</table>

TABLE 4
Guidelines for Air Pollutants With Carcinogenic Health Endpoints


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