A review of effects of particulate matter-associated nickel and vanadium species on cardiovascular and respiratory systems

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Many epidemiological investigations indicate that excess risks of mortality and morbidity may vary among specific PM\textsubscript{2.5} components. Nickel (Ni) and vanadium (V) particulate metal species may potentially be related to increasing respiratory and cardiovascular mortality and morbidity. This review focuses on exposure concentrations of these two species in various settings, their health effects based on epidemiological and toxicological studies and the underlying mechanisms. The evidence shows that environmental exposure concentrations of Ni and V in general setting are lower than the World Health Organization standard (V, 1 \(\mu\)g/m\(^3\)/day) in 2000, or the European Environment Agency standard (Ni, 1 \(\mu\)g/m\(^3\)/day) in 2003, but their associations with cardiopulmonary diseases can still be found. The toxicological mechanism can be explained by laboratory-based studies. Updated safe guidelines on environmental and human exposure of Ni and V are necessary in order to clarify the associations between them and cardiopulmonary diseases and provide environmental intervention policies.

**Keywords:** particulate matter; cardiopulmonary disease; nickel; vanadium; Air Quality Guidelines

**Introduction**

Particulate air pollutants have been shown associated with increased respiratory, cardiovascular and cancer mortality, and morbidity, as well as with other health problems (Reichhardt 1995; Dockery 2001; Morris 2001). Fine atmospheric particulate PM\textsubscript{2.5} (particles with aero-diameters less than or equal to 2.5 \(\mu\)m) has a closer association with human adverse health effects than either PM\textsubscript{10} (particles with aero-diameters less than or equal to 10 \(\mu\)m) or total suspended particles (TSP, particles with aero-diameters 0.1–100 \(\mu\)m) (Reichhardt 1995). PM\textsubscript{2.5} contains a low level of soil particle components, with the main anthropogenic source being either a product of the combustion related to fossil fuels or biomass materials (Oholström et al. 2000). Nickel and vanadium are two important metal species generated from the combustion of fossil fuels. In this review, we summarize the research findings about environmental versus biological exposures, epidemiological versus toxicological assessments, and the plausible biological mechanisms for the effects of nickel and vanadium on cardiovascular and respiratory mortality, and morbidity.

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Methods
This review draws from peer-reviewed English-language publications and government reports identified from Ovid, Science Direct, Scopus, ProQuest, and EBSCO host electric research databases up to December 2007, in the library of The University of Hong Kong. The time period mainly focuses on the years after 1995. Earlier publications were also included, when they were identified to be important. Search strategies included keywords for various combinations: nickel, vanadium, metal, PM$_{2.5}$, cardiovascular disease, respiratory disease, cardiopulmonary disease, epidemiology, toxicology and exposure. The PubMed “related articles” function was used to search for other relevant articles not retrieved in initial keyword searches. Further searches were done using the names of authors of relevant articles. This review included original epidemiologic and toxicological studies and review articles.

Nickel and vanadium in ambient air and occupational workplace

**Nickel (Ni)**
Natural sources of airborne nickel levels include soil, sea, volcanoes, forest fires and vegetation. Anthropogenic sources include emissions from the combustion of coal and fuel oil and from nickel mining or production plants (mainly in stainless steel and nickel alloy production) (Davies 1974). There are a variety of nickel-containing minerals and compounds, including soluble nickel salts (chloride, nitrate and sulfate), nickel sulfides, and nickel oxides as well as metallic nickel. The daily exposure concentrations in the ambient air are less than 1 $\mu$g/m$^3$, which is the standard of nickel concentration of the European Environment Agency (EEA 2003). Nickel levels in the ambient air are in the range of 1–10 ng/m$^3$ in urban areas, although much higher levels (110–180 ng/m$^3$) have been recorded in heavily industrialized areas and large cities (World Health Organization [WHO] 2000). Estimated mean exposures to inhalable metallic nickel in nickel-producing industries ranged from 0.01–6 mg/m$^3$ compared to 0.05–0.3 mg/m$^3$ in nickel-using industries, except for powder metallurgy in alloy production where mean exposures were estimated to be as high as 3 mg/m$^3$ (Norseth and Piscator 1979).

**Vanadium (V)**
Vanadium is a transition element that is found in nature in oxidation states but not in metallic form. Physiologically relevant forms of vanadium include vanadyl sulfate, sodium metavanadate, sodium orthovanadate and vanadium pentoxide. Sometimes vanadium compounds are used for the treatment of anemia, diabetes, tuberculosis, and syphilis. Athletes use vanadium supplements to improve their performance in weight training. Vanadium also lowers cholesterol and triglycerides and glucose levels. Nevertheless, most vanadium compounds come mainly from the fossil fuel combustion of vehicles and marine vessels. The WHO standard of daily vanadium concentration in the ambient air is 1 $\mu$g/m$^3$ (WHO 2000). For occupational population, the lowest observed adverse effect level for acute exposure is considered to be 60 $\mu$g/m$^3$ whereas that for chronic exposure is regarded as 20 $\mu$g/m$^3$ (WHO 2000).

The general population is exposed to vanadium via the respiratory route in ambient air. It was reported that concentrations of ambient air vanadium from different regions of the world ranged from 1.4–40 ng/m$^3$ (David et al. 2006). In cities during the winter, when fuel oil with a high vanadium content was used for heating, concentrations as high as
2000 ng/m$^3$ were reported. The concentrations of vanadium in workplace air (0.01–60 mg/m$^3$) are much higher than those in the general environment (WHO 2000).

High vanadium concentrations have been found in occupational settings, particularly in boiler-cleaning due to the presence of vanadium oxides in the dust. Boiler repair work in power plants is linked to occupational exposure to vanadium compounds and other complex mixtures of toxic agents (Williams 1952; Woodin et al. 2000).

Sources relevant to general population exposure

Residual oil fly ash (ROFA) produced by the combustion of fuel oil has a high content of Ni and V, as well as other transition metals (e.g. iron and zinc), often at concentrations that can affect health adversely (Huffman et al. 2000). As fuel oil combustion commonly occurs in urbanized populations, Ni and V have been widely studied as tracer components for combustion sources (Juichang et al. 1995; Galbreath et al. 2000; Chen et al. 2004; Thurston et al. 2005). Analysis of the sources of PM$_{2.5}$ in New York City identified Ni and V as indicators of oil combustion not just in vehicles (Li et al. 2004; Zheng et al. 2004), but also in ships (Qin et al. 2006).

Epidemiological studies of nickel and vanadium effects on cardiovascular and respiratory diseases

Vanadium and nickel exist in respiratory ambient particulates in an easily soluble form, which makes them bioavailable through inhalation and are thought to contribute to the incidence of adverse health problems.

Several epidemiologic studies provide evidence of an association between daily mortality and PM$_{2.5}$ (Laden et al. 2000; Ostro et al. 2006). The Six California Counties Study adds to the growing body of evidence linking variation of specific PM$_{2.5}$ components with excess risks of mortality. The study showed that almost all of the pollutants (including PM$_{2.5}$, EC, OC, SO$_4$, Cu, Fe, Mn, V and Zn) were associated with all-cause and cardiovascular mortality except for Al, Br, and Ni during the cooler months (Ostro et al. 2007). Several decades ago, Stocks (1960) demonstrated positive correlations between vanadium concentrations in urban air and mortality from bronchitis, pneumonia, cancer and heart disease.

Burnett et al. (2000) found that iron, nickel and zinc, in addition to sulfates, were associated with increased mortality in the study of Canadian cities. In the study of six US cities, sulfur, nickel and lead were significantly associated with all-cause mortality. An increase of nickel by 10.3 ng/m$^3$ was associated with a 1.5% (95% CI, 0.5–2.6%) increase in mortality (Laden et al. 2000). Magari et al. (2002) focused on the association between the metallic component of PM$_{2.5}$ and cardiac autonomic function of boilermakers. There was a statistically significant mean increase in the SDNNi (standard deviation of the normal-to-normal index) of 3.98 msec for every 1 µg/m$^3$ increase in the vanadium concentrations after adjusting for mean heart rate, age and smoking status. Additionally, Cavallari et al. (2007) investigated the association between night heart rate variability and PM$_{2.5}$ exposures among boilermakers and construction workers. It was found that there was an inverse exposure-response relationship, in that a decrease in all heart rate variability (HRV) measures was associated with increasing PM$_{2.5}$ exposure. The decrease was most pronounced at night, where a 1 mg/m$^3$ increase in PM$_{2.5}$ was associated with a change of $-8.32$ msec night time rMSSD, $-14.77$ msec night time SDNNi and $-8.37$ msec night time SDNNi, after adjusting for nonworking night time HRV, age
and smoking. For SDNNi, different findings were shown in the above two studies. The underlying explanation was still unknown. In the National Mortality and Morbidity Air Pollution Study (NMMAPS), daily mortality rates in the 60 cities with recent speciation data were significantly associated with average Ni and V, for which average values (mean ± SE) of annual mean were 1.9 ± 0.4 ng/m³ for Ni and 1.9 ± 0.2 ng/m³ for V, but not with other measured species (Lippmann et al. 2006). Similarly, the Hong Kong sulfur intervention produced sharp drops in sulfur dioxide, Ni and V, but not other components, corresponding to the intervention-related reduction in cardiovascular and pulmonary mortality (Hedley et al. 2002).

There is no epidemiological information on the effects of nickel uptake from the environment on cancer incidence in the general population. However, nickel refinery workers exposed through inhalation to various nickel compounds have a higher risk of lung cancer and nasal cavity cancers than the general population (International Committee on Nickel Carcinogenesis in Man [ICNCM] 1990; WHO 2000). Turning from cancer to non-malignant respiratory disease, it is noteworthy that morbidity studies on such diseases in nickel workers are sparse. Nevertheless, increased mortality from non-malignant respiratory disease has seldom been shown (Sivulka et al. 2007). Boilermakers with high exposure to residual oil fly ash (ROFA) experienced increased respiratory symptoms, airway inflammation, and airway obstruction (Hauser et al. 1995; Woodin et al. 2000). Expired nitric oxide (FENO) was commonly used as a marker of acute airway responses to occupational metal exposure. Kim et al. (2003) studied the association of FENO with urinary metal concentrations in boilermakers exposed to ROFA. Results showed significant inverse exposure-response relationships between FENO and the urinary concentrations of vanadium, manganese, nickel, copper and lead at several lag times, after adjusting for smoking status. Respiratory tract clinical symptoms of acute exposure are reported in workers exposed to vanadium concentrations ranging from 80 μg/m³ to levels in mg/m³, and in healthy volunteers exposed to concentrations of 56–560 μg/m³. Chronic exposure to vanadium compounds revealed a continuum in the respiratory effects, ranging from slight changes in the upper respiratory tract, with irritation and coughing, detectable at 20 μg/m³, to more serious effects such as chronic bronchitis and pneumonitis, which occurred at levels above 1 mg/m³ (WHO 2000).

It is worth considering that there are adverse health outcomes identified from epidemiological studies for associations between Ni and V exposure and cardiovascular and respiratory disease mortality or all-cause mortality. In these studies, Ni and V exposure concentrations in ambient air are below their respective standard. Hence, current standards of Ni and V need to be updated after taking into account these and further epidemiological investigations.

**Toxicological studies of nickel and vanadium on cardiovascular and respiratory diseases**

**In vivo and in vitro respiratory toxicological studies of nickel and vanadium**

The experiment studies with PM filter extracts sampled in Utah Valley support the epidemiological findings on respiratory problems. The study of tracheal instillation on rats showed that PM, collected during the opening period of the steel mill, induced pulmonary injury and inflammation. However, PM sampled during the closing period of the mill, did not have the same results. The analysis of metal content of the extracts showed that the metal species in the opening period was higher than that in the closing period. It implied that the toxicity of PM extracts mainly came from heavy metal species (iron, copper, nickel, lead and zinc) (Ghio 2004). Similarly, in vitro studies on lung cells also showed that
exacts from the active periods of the steel mill had a higher effect on the biological activity than that from the closure period (Ostro et al. 2007). Deferoxamine and antioxidants have been shown to inhibit the expression of cytokine in human bronchial epithelial cells exposed to residual oil fly ash (ROFA) particles containing vanadium, nickel and iron (Carter et al. 1997). Using an in vitro model to study the effect of ROFA on the antimicrobial mechanism of host defense in the airway, \( \beta \)-defensin-2 and its bovine homologue, tracheal antimicrobial peptide (TAP) induction in response to lipopolysaccharide (LPS) and IL-1 \( \beta \) were determined in bovine tracheal epithelial (BTE) cells and the human alveolar type II epithelial cell line, A549. As little as 2.5 \( \mu \)g/cm\(^2\) of ROFA inhibited LPS-induced TAP gene expression by 30%. Moreover, the inhibitory activity was associated with the soluble vanadium fraction. Also, ROFA inhibited the increase of IL-1 \( \beta \)-induced human \( \beta \)-defensin-2 in A549 cells. These suggest that exposure to ROFA or vanadium compound could result in an impairment of defense against airborne pathogens (Klein-Patel et al. 2006). Salnikow et al. (2004) investigated the effect of nickel and iron co-exposure on the induction of hypoxia-like stress and the production of interleukins (ILs) in minimally transformed human airway epithelial cells (1HAEo\(^{-}\)). The study showed that exposure to soluble nickel sulfate (0.25 mM) resulted in the induction of hypoxia-inducible genes and IL-8 production by the 1HAEo\(^{-}\). The simultaneous addition of iron and nickel completely inhibited IL-8 production, but had no effect on "hypoxia-like" stress caused by nickel, which suggests the existence of two different pathways for the induction "hypoxia-like" stress and IL-8 production. Rice et al. (2001) studied differential ability of transition metals to induce pulmonary inflammation. The rats exposed to 1.0 \( \mu \)mol/kg nickel had the highest lactate dehydrogenase activity in bronchoalveolar lavage (BAL). 0.1 \( \mu \)mol/kg or 1.0 \( \mu \)mol/kg nickel, vanadium and other transition metals could induce rats to produce different levels of neutrophilia and macrophage inflammatory protein-2 (MIP-2) and other proteins in BAL fluid after 0, 4, 16, or 48 h of instillation. Clarke et al. (2000) experimented on canines inhaled concentrated ambient particles (CAPs) for 6 h/day for three consecutive days to detect the changes of hematologic and bronchoalveolar lavage. The results showed that the increase of circulating neutrophils BAL macrophages was associated with the vanadium/nickel factor in the CAPs. This suggests that CAPs inhalation is associated with subtle alterations in pulmonary and systemic cell profiles, and specific components of CAPs may be responsible for these biologic responses.

**In vivo cardiovascular toxicological studies of nickel and vanadium**

Some experimental studies suggested metals play a role in cardiovascular effects caused by PM. Copper, zinc and vanadium had been shown to induce a range of different cardiovascular effects, including decrease in spontaneous beat rate, vasoconstriction and vasodilatation (Bagate et al. 2006). Lippmann et al. (2006) experimented on a mouse model of atherosclerosis (ApoE\(^{-/-}\)) exposed to 85 \( \mu \)g/m\(^3\) fine particulate matter (FPM) containing nickel at an average concentration of 43 ng/m\(^3\) for 6h/day, 5d/wk for 6 months. The electrocardiogram of the mice revealed that Ni was significantly associated with acute changes in heart rate and their variability. Inhalation of Ni (1.2 mg/m\(^3\)) induced delayed hypothermia, Bradycardia and arrhythmogenesis in rats, similar to that following Ni instillation (Campen et al. 2001). On the other hand, V inhalation (2.4 mg/m\(^3\)) produced only mild pulmonary inflammation and minimal physiological response, much unlike the profound hypothermic response seen immediately after V instillation. When combined, Ni and V produced observable effects with a lag a period of time at 0.5 mg/m\(^3\) and potentiated responses at 1.3 mg/m\(^3\), greater than that produced by the highest
concentration of Ni (2.1 mg/m³) alone (Campen et al. 2001). These results help resolve questions regarding the biphasic response to ROFA instillation. They also suggest that PM-associated metals may cause the lag effects commonly reported in epidemiological studies.

**Biological plausibility of nickel and vanadium producing cardiopulmonary effects**

*Levels of nickel and vanadium on human pulmonary and extrapulmonary organs as well as serum and urinary*

The above epidemiological and toxicological studies make it clear that fine ambient particles containing a variety of metals, including Ni and V, are associated with increased cardiovascular and respiratory morbidity and mortality. The respiratory function lesion is easily recognized because these ambient particles were exposed by natural inhalation. Fortoul et al. (2002) reported that vanadium concentrations in lung tissues from autopsy specimens taken from residents of Mexico City in the 1990s (1.36 ± 0.08 µg/gm) had significantly increased compared with those in the 1960s (1.04 ± 0.05 µg/gm). These results suggest that vanadium in ambient air is increasing, which presents a potential health hazard for residents of Mexico City. As a result, it suggests that we should pay more attention to the chronic diseases related to vanadium.

Wallenborn et al. (2007) found oil combustion particulate matter (HP-12)-associated metals could translocate to systemic circulation and extrapulmonary organs following intratracheal instillation (IT) exposure. And this translocation is dependent upon their levels and water solubility. It is easier for water soluble metals, Zinc, Ni and V to translocate to extrapulmonary organs than for acid soluble and insoluble metals (Wallenborn et al. 2007). Thereby this feature may provide a biological basis on which metals may elicit direct extrapulmonary effects. Tomei et al. (2004) found that there were more elevated serum levels of Ni in traffic policemen than in administrative workers, both in male and female. As Ni is a fuel additive in lead-free fuels and a catalyst in catalytic converters (Masuda et al. 1999; Den Hollander et al. 2002), we may suspect that the general population is also at risk.

Kim et al. (2003) examined urinary metal concentrations in New England boilermakers (n = 32) exposed to ROFA. The concentration of Ni and V pre-workshift is 1.34 µg/g creatinine and 1.29 µg/g creatinine, respectively. The concentration of post-shift is 1.70 µg/g creatinine and 1.49 µg/g creatinine, respectively. Mukherjee et al. (2005) also conducted a repeated-measures cohort study in boilermakers (n = 20) during the overhaul of an oil-fired boiler. The levels of vanadium and nickel in two studies were significantly higher than the range of recorded levels of young residents of an urban area of Rome (nickel 0.2–1.23 µg/g creatinine; vanadium 0.02–0.22 µg/g creatinine). Moreover, the levels of vanadium and nickel in post-workshift (2.07 µg/g creatinine, 8.46 µg/g creatinine) were higher than those in pre-workshift (1.02 µg/g creatinine, 3.44 µg/g creatinine). These findings may suggest that the metabolic removal of metals is unable to keep up with the higher levels of exposure, compared to those found in the general population. Therefore, urine metal concentration may be utilized as a biomarker of occupational metal exposure.

**Mechanisms of vanadium and nickel-induced cardiovascular and respiratory disease**

In an experiment using a custom rat cardiopulmonary cDNA array consisting of 84 cardiopulmonary-related genes, the gene expression profile was measured in Sprague-Dawley (SD) rats at 3 and 24 h following intratracheal instillation of nickel (NiSO₄,
It was observed that Ni induced expression of oxidative stress-responsive genes (Heme oxygenase-2, HO-2; tissue inhibitor of metalloproteinase-2, TIMP-2), injury/inflammation gene (interleulin-6, IL-6), repair/remodeling genes (vascular endothelial growth factor-D, VCAM-1; E-selection, E-sel.), and vascular function gene (Thrombomodulin [TM]) (Srikanth and Urmila 2002). Ni also turned off the expression of thrombospondin (a regulator of angiogenesis) and activated hypoxia-inducible factor-1, which is an important factor in regulating cellular oxygen concentration, and NFκB (nuclear factor kappa B) (Denkhaus and Salnikow 2002). Ni exposure, even when mice are exposed to an ambient mixture containing nickel at only 45 ng/m³ for 30h/wk over 6 months, may play a key role in leukocyte recruitment in the vasculature, which leads to vascular inflammation and dysfunction, resulting in enhanced progression of atherosclerosis (Sun et al. 2005). Ni can also induce apoptosis of Chinese hamster ovary cells and T cell hybridoma cells. The apoptosis is initiated by Fas/FasL. Similarly, increased ROS (reactive oxygen species), decreased GSH and bcl-2 can aid in apoptosis (Pulido and Parrish 2003). Apoptosis may also be involved in the inflammation and the development of both acute health problems and chronic lung diseases. The exposure to high doses of nickel induces respiratory carcinoma which is mediated by the accumulation of ROS. The appearance of nickel-bound abnormal proteins or poisoning of an oxygen sensor is another important aspect of nickel toxicity (Aaron and Kimberley 2003). These changes may lead to the activation of some signaling pathways and subsequent transcription factors and eventually cause alterations in gene expression and cellular metabolism.

In contrast to Ni, V is capable of disrupting tyrosine protein phosphorylation and activating of the three major branches of the mitogen-activated protein kinase (MAPK) signaling pathways (extracellular signal-regulated kinases – ERK1/2, C-jun amino-terminal kinases – JNK, and P38) in human airway epithelial cells (HAECs). V may also be largely responsible for the pulmonary toxicity of ROFA, which induced a rapid and marked increase in protein tyrosine phosphate accumulation in HEAC (Robert et al. 2000). The rennin-angiotensin system plays an important role in many types of inflammatory and cardiovascular diseases. Urban particles consisting of water-soluble copper and vanadium, produced acute vasoconstriction in pulmonary artery and a time-and-dose-dependent increase in phosphorylation of ERK1/2 and P38 in human pulmonary artery endothelial cells (HPAECs), which are dependent on activating the angiotensin type 1 receptor (AT1R). So, the angiotensin-AT1R signaling pathway may be important in mediating vascular effects induced by PM (Li et al. 2005). In the gene expression profile study, SD rats were exposed to vanadium (VSO₄, 5.7mmol/kg) at 3 and 24 h by intratracheal instillation. It is found that V could induce increased expressions of injury/inflammation gene (macrophage inflammatory protein-2, MIP-2) and vascular function gene (endothelin-1, ET-1) (Srikanth and Urmila 2002).

Epidemiologic studies demonstrate increased lung cancer incidence among boiler-makers, probably caused by cumulative oxidative DNA damage in response to carcinogens. The level of 8-hydroxy-2′-deoxyguanosine (8-OH-dG) is an oxidative injury biomarker. Mukherjee et al. (2004) found that metal-by-cotinine interactions terms for nickel, vanadium, chromium and copper were significantly associated with the 8-OH-dG level, the effects depending on the types of metal. This study suggests that the damage of oxidative DNA in boilermakers is influenced by the interaction of occupational exposures and smoking status. Similarly, Sorensen et al. (2005) reported that vanadium and chromium present in PM₂.₅ could have an effect on oxidative DNA damage, which is independent of particle mass and other possible toxic compounds contained within the particulate mixture.
Conclusion and implications

Considering all findings on nickel and vanadium of exposure, epidemiological, and toxicological studies, we can confidently conclude that nickel and vanadium are positively correlated with human cardiovascular and respiratory diseases. However, further studies are needed towards better understanding of their health effects. Firstly, as different species of nickel related particulate can lead to different toxicity, so species-specific exposure data on nickel is very important to further research and establishment of exposure limits. Secondly, epidemiological studies on Ni and V in general populations are scarce, and laboratory-based studies of nickel and vanadium on cardiovascular and respiratory toxicity carried out in recent years have involved exposures at concentrations well within those considered to be relevant to ambient air exposures. In the US (Lippmann et al. 2006) and Hong Kong (Hedley et al. 2002), the excess human mortality effects associated with ambient air exposures were at concentrations of Ni and V more than an order of magnitude below the Air Quality Guidelines, as well as the effects of CAPs in mice (Sun et al. 2005; Lippmann et al. 2006). Although the results do not indicate the relative contributions of nickel and vanadium to the overall health impact of air pollution, and do not show whether their effects on mortality are specific to cardiovascular and respiratory mortality, it is important for us to understand more on the dose-response relationship. Thus, more extensive epidemiological investigations on nickel and vanadium for effects on cardiopulmonary systems are needed. Thirdly, researches on standards for workplace exposures and general environment exposures utilizing the most up-to-date health data and exposure data are much needed, in the best interests of both the workers and the industry of nickel and vanadium as well as of the general populations.

References


